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SCORE Study Report 1: Baseline Associations between Central Retinal Thickness and Visual Acuity in Patients with Retinal Vein Occlusion

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Abstract

Objective—To investigate the relationship between baseline center point retinal thickness measured by optical coherence tomography (OCT) and best-corrected visual acuity in eyes with macular edema associated with retinal vein occlusion and to investigate other factors associated with baseline visual acuity letter score.

Design—The Standard Care versus COrticosteroid for REtinal Vein Occlusion (SCORE) Study includes 2 multicenter, randomized clinical trials: one evaluating participants with central retinal vein occlusion (CRVO) and the other evaluating participants with branch retinal vein occlusion (BRVO).

Participants—After omitting 17 participants with missing or unreliable OCT measurements, analyses proceeded with 665 enrolled SCORE Study participants (665 eyes), including 262 with CRVO and 403 with BRVO.

Methods—At baseline, center point thickness was measured by OCT (Stratus OCT 3 [n = 663] and OCT2 [n = 2]; Carl Zeiss Meditech, Dublin, CA), and visual acuity was measured by the electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) methodology.

Main Outcome Measures—Center point thickness and best-corrected E-ETDRS visual acuity letter score.

Results—The correlation coefficient for the association between baseline OCT-measured center point thickness and best-corrected E-ETDRS visual acuity letter score is -0.27 (95% confidence limit: -0.38 to -0.16) for participants in the CRVO trial and -0.28 (95% confidence limit: -0.37 to -0.19) in the BRVO trial. Regression modeling estimated the following decrease in baseline visual acuity letter score for every 100- μ m increase in OCT-measured center point thickness: 1.7 letters ($P = 0.0007$) for CRVO and 1.9 letters ($P < 0.0001$) for BRVO. On the basis of multivariate regression

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models, baseline factors significantly associated ($P < 0.05$, after adjusting for multiple testing) with baseline visual acuity letter score include age and duration of macular edema for CRVO participants and center point thickness and presence of cystoid spaces for BRVO participants.

Conclusions—The correlation between OCT-measured center point thickness and visual acuity letter score is modest. OCT-measured center point thickness represents a useful tool for the detection and monitoring of macular edema in retinal vein occlusion, but it cannot reliably substitute for visual acuity measurements.

Since optical coherence tomography (OCT) became commercially available in 1995, it has provided useful information on vitreoretinal morphologic changes associated with a variety of posterior segment diseases.¹ OCT has been used to assess the outcomes of various treatments for macular edema associated with central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).^{2–10} OCT measurements are secondary outcome variables in the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study, which consists of 2 multicenter, prospective, randomized, US-based, phase III clinical trials funded by the National Eye Institute and designed to investigate the safety and efficacy of standard care versus intravitreal triamcinolone acetonide injection(s) for the treatment of vision loss associated with macular edema from retinal vein occlusion; one trial is conducted among participants with CRVO, and a second trial is conducted among participants with BRVO.

Treatments for macular edema, such as photocoagulation, intravitreal triamcinolone acetonide, and intravitreal antivascular endothelial growth factor therapy, are aimed at reducing retinal thickness, with the assumption that a reduction in retinal thickness will be associated with an improvement in visual acuity. Previous studies have shown an inverse relationship between OCT-measured retinal thickness and visual acuity, with correlation coefficients, either reported or calculated from the literature reports, ranging from 0.16 to 0.64 among patients with diabetic macular edema.^{11–18} Only one study¹⁸ identified from a literature search of the Medline database examined OCT-measured retinal thickness and visual acuity in patients with CRVO; although no correlation was presented, the authors note that the correlation was not statistically significant among the 18 patients with CRVO. No studies were identified that reported this correlation among patients with BRVO. The purpose of the current study is to investigate, using baseline data from the SCORE Study, the association between OCT-measured center point thickness and best-corrected electronic Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity letter score in eyes with macular edema associated with CRVO and in eyes with macular edema associated with BRVO, and to investigate other baseline characteristics that may be associated with baseline visual acuity.

Materials and Methods

The SCORE Study design and methods, previously described in detail,^{19,20} are summarized here. The SCORE Study protocol and informed consent forms were approved by the respective clinical center institutional review boards or a centralized institutional review board, where applicable. Data and safety monitoring are provided by an independent data and safety monitoring committee appointed by the National Eye Institute. The current article analyzes baseline data collected from 262 CRVO study participants and 403 BRVO study participants enrolled in the SCORE Study from 84 clinical sites throughout the United States between November 4, 2004, and February 29, 2008.

Study Population

Major study ocular eligibility criteria include the following: (1) center-involved macular edema secondary to CRVO, BRVO, or hemiretinal vein occlusion (for the purposes of the SCORE Study, eyes with hemiretinal vein occlusion are treated as eyes with BRVO and analyzed with

the BRVO group); eyes could be enrolled as early as the time of diagnosis of the macular edema, but not more than 24 months after diagnosis (by patient history or ophthalmologic diagnosis); (2) best-corrected E-ETDRS visual acuity letter score of ≥ 19 ($\sim 20/400$) and ≤ 73 ($\sim 20/40$) by the E-ETDRS visual acuity protocol; and (3) mean retinal thickness (central subfield) on 2 OCT measurements ≥ 250 μm . In cases where the study eye presented with a visual acuity at the low end of eligibility, between 19 ($\sim 20/400$) and 33 letters ($\sim 20/250$), the investigator must also have judged the study eye to be perfused to prevent nonperfused eyes from being enrolled in the study. Table 1 provides a more detailed description of major study eye inclusion and exclusion criteria.

Study Procedures

Baseline visual acuity was measured by a certified examiner using the electronic visual acuity tester according to ETDRS (E-ETDRS) procedures²¹ at a test distance of 3 m at the screening visit after a standardized refraction.

Two OCT images were obtained at screening from each study eye after pupil dilation by a certified operator using the OCT2 (Carl Zeiss Meditech, Dublin, CA) (2 eyes) or OCT3 (Stratus OCT, Carl Zeiss Meditech, Dublin, CA) (663 eyes) system, and the mean of the central subfield thickness was used for eligibility. The OCT scans were subsequently sent to the University of Wisconsin Fundus Photograph Reading Center (UW-FPRC) for further evaluation. Of the 682 participants randomized, 665 (98%) had screening OCT images evaluated by the UW-FPRC. Of these images that were evaluated, 29% were identified by reading center personnel as having errors that required center point thickness to be measured manually with calipers from the axial OCT scans. The source of the errors was mostly due to the computer algorithm incorrectly defining the inner retina or outer retina boundaries (these errors result in an inaccurate center point thickness measurement), and in fewer cases the errors were due to decentration. The mean of center point thickness from the 2 OCT images at screening is the measure used for analysis presented in this report rather than central subfield thickness, which was used for eligibility determination. Of note, on the basis of reliable scans in the SCORE Study, the OCT-measured center point thickness and central subfield thickness are highly correlated ($r = 0.99$). When subretinal fluid is present at the center point, all OCT-measured center point values, whether determined by the computer algorithm or measured manually at the UW-FPRC, include the height of the subretinal fluid. The visual acuity among those participants who, because their OCT images could not be evaluated manually by the reading center, were excluded from OCT-measured center point thickness calculations did not differ from the visual acuity among those participants who were included.

Retinal morphology on OCT was assessed using a 3-step grading scale for size of cystoid spaces measured axially at the center point. The presence or absence of central subretinal fluid and total macular volume were assessed by OCT. The height of subretinal fluid at the center point was also measured at the UW-FPRC. In cases where subretinal fluid was present under the center point, an exploratory analysis of the relationship of OCT and visual acuity letter score was also performed recalculating center point thickness after subtracting the height of the subretinal fluid.

Area of retinal thickening and area of retinal hemorrhage were measured within the ETDRS macular grid (a circle 2 disc diameters in radius centered on the fovea) from color stereoscopic fundus photographs sent to the UW-FPRC. The area within the grid represents 16 disc areas, includes the majority of the macula, and is responsible for the central 30 degrees of vision.

Fluorescein angiograms were obtained at baseline for all eyes and graded at the UW-FPRC for capillary loss and fluorescein leakage. The area of fluorescein leakage within the grid was used for analysis and ranges from 0 to 16 disc areas. There were 641 baseline images (96%) gradable

for fluorescein leakage, and the visual acuity among those participants with ungraded images was similar to those with graded images. For capillary loss, the area within the entire fundus was used for analysis and ranges from 0 to 210 disc areas. There were 477 baseline images (72%) gradable for capillary loss. Inability to grade capillary loss was likely due to hemorrhage in the macula, confirmed by the finding that eyes with ungradable images had a mean of 4.5 disc areas of retinal hemorrhage compared with 2.6 disc areas of hemorrhage among eyes with a calculated capillary loss ($P<0.0001$). The difference in retinal hemorrhage between eyes with and without gradable images for capillary loss translates into a 4.7-letter mean increase in baseline visual acuity letter score in those eyes with images gradable for capillary loss compared with those eyes without gradable images for capillary loss ($P<0.0001$).

Statistical Methods

Wilcoxon 2-sample tests were used to test differences in baseline continuous variables between participants with CRVO and participants with BRVO, and the Pearson's chi-square test was used to test differences for baseline categorical variables. The Pearson correlation coefficient (r) was used to measure the linear association between baseline visual acuity letter score and OCT-measured center point thickness. As r approaches 1 or -1 , the data indicate a strong positive or negative linear relationship, respectively, between the variables, whereas an r of 0 indicates no linear relationship. The confidence interval for the Pearson correlation coefficient is calculated using a Fisher transformation.

Univariate and multiple linear regression models were used to describe the associations of baseline demographic, ocular, and reading center variables with baseline E-ETDRS visual acuity letter score. Beta coefficients represent estimates from the regression model of change in the baseline visual acuity letter score associated with a unit increase of a continuous independent variable (e.g., 10-year increase for age) or an increase of 1 level of a categorical or binary independent variable (e.g., prior grid laser compared with no prior grid laser). A beta coefficient of 5 indicates a 1 line change in the visual acuity letter score. Coefficients from the regression models for OCT-measured center point thickness show letters of change per 100- μ m difference in OCT-measured central retinal thickness. R^2 statistics from the regression models are also presented. An R^2 of 0.2 would indicate that only 20% of the variability in the outcome (e.g., visual acuity letter score) is explained by the independent factors (e.g., OCT-measured center point thickness). SAS version 9.1.3 (SAS Institute Inc., Cary, NC) was used to conduct all statistical analyses. Numerous P values are presented in this report to investigate differences between retinal vein occlusion groups and factors associated with baseline visual acuity letter score. With so many P values, we expect some statistical tests to be "significant" even if the null hypothesis of no difference is true. That is, if we compare the original P value unadjusted for multiple testing to 0.05, we expect a family-wide error (i.e., the likelihood of making at least one type I error over all tests) to be greater than 0.05. To control family-wide error, we adjust the P values by Hochberg's sequentially rejective method.²² For each comparison in the tables, we present both the unadjusted P value, denoted as P_{unadj} , and the Hochberg-adjusted P value, denoted as P_{hoch} . The reader can consider as statistically significant those tests for which P_{hoch} is less than 0.05.

Results

Relevant baseline characteristics of the study populations are displayed in Table 2. The SCORE Study included 262 participants (39%) in the CRVO trial and 403 participants (61%) in the BRVO trial. The mean visual acuity letter score was significantly lower in patients with CRVO compared with patients with BRVO (52 and 57, respectively; $P_{\text{hoch}}<0.0001$); 41% of eyes in the CRVO trial had a visual acuity letter score less than 48 (~20/125 or worse) compared with

24% of eyes in the BRVO trial ($P_{\text{hoch}} = 0.0006$). There was no statistically significant difference among participants in the CRVO and BRVO trials with respect to duration of macular edema.

Baseline macular edema characteristics differed between the 2 retinal vein occlusion groups. Study eyes of participants in the CRVO trial had a higher mean OCT-measured center point thickness (656 μm), proportion of eyes with large cystoid spaces (35%), mean area of retinal thickening (12.3 disc areas), and mean fluorescein leakage (10.9 disc areas), lower mean capillary loss (0.3 disc areas), and lower percentage with more than 5 disc areas of capillary loss (2.0%) compared with eyes of study participants with BRVO (mean OCT-measured center point thickness of 526 μm [$P_{\text{hoch}} < 0.0001$], 17% with large cystoid spaces [$P_{\text{hoch}} < 0.001$ based on a χ^2 test and the 4-level response categories for cystoid spaces], mean retinal thickening of 7.5 disc areas [$P_{\text{hoch}} < 0.0001$], mean fluorescein leakage of 6.2 disc areas [$P_{\text{hoch}} < 0.0001$], mean capillary loss of 2.5 disc areas [$P_{\text{hoch}} < 0.0001$], and percentage with more than 5 disc areas of capillary loss of 13.9% [$P_{\text{hoch}} = 0.0003$], respectively).

Figure 1 shows a scatter plot of OCT-measured center point thickness against best-corrected E-ETDRS visual acuity letter score for eyes of participants in the CRVO and BRVO trials. The Pearson correlation coefficient for the linear association between baseline OCT-measured center point thickness and visual acuity letter score is -0.27 for participants in the CRVO trial (95% confidence limit [CL]: -0.38 to -0.16) and -0.28 for participants in the BRVO trial (95% CL: -0.37 to -0.19). The slope of the linear regression line for participants in the CRVO trial is -1.67 , which indicates an estimated 1.67 lower baseline visual acuity letter score for a 100- μm increase in OCT-measured center point thickness, with the slope statistically significantly different from zero ($P_{\text{hoch}} = 0.0007$, Table 3). The slope for participants in the CRVO trial is less than for participants in the BRVO trial, at -1.93 letters, indicating an estimated 1.93 lower baseline visual acuity letter score for a 100- μm increase in center point thickness ($P_{\text{hoch}} < 0.0001$). Adjustment for other demographic, medical history, and ocular disease characteristics did not materially change the estimates.

Figure 2 graphically presents Pearson correlation coefficients between OCT-measured center point thickness and visual acuity letter score, with 95% CLs about the coefficient for different groups (i.e., with and without cystoid spaces, with and without dense macular hemorrhage for participants in the BRVO trial only, and in all eyes after subtracting subretinal fluid height at the center point from center point thickness). Confidence limits of all correlation coefficients exclude zero, indicating a statistically significant linear relationship between center point thickness and visual acuity letter score. The strongest negative correlation was observed in eyes without cystoid spaces ($r = -0.45$ for participants in the CRVO trial and $r = -0.41$ for eyes in the BRVO trial). The correlation coefficients do not statistically differ among each other, shown by the overlapping CLs in Figure 2.

The relationship between visual acuity letter score and OCT-measured center point thickness across disease groups is explored in Table 4, which demonstrates that within broad visual acuity categories, there is greater OCT-measured center point thickness in CRVO than BRVO eyes. For example, 39% of eyes in the CRVO trial with a baseline visual acuity letter score between 49 and 58 (20/80 to 20/100) had an OCT-measured center point thickness greater than 725 μm compared with only 11% of eyes in the BRVO trial.

The CRVO and BRVO study populations contained approximately equivalent proportions of men and women, with approximately 90% of the participants white, a mean age of 68 years (range, 27–91 years) in the CRVO trial and 67 years (range, 22–94 years) in the BRVO trial, and a mean duration of macular edema of 4 months (range, 1–24 months) in both trials. There were no statistically significant differences among participants in the CRVO and BRVO trials

in terms of demographic characteristics, duration of macular edema, or prevalence of hypertension, coronary artery disease, or diabetes mellitus at baseline (Table 2).

Table 3 displays results of univariate and multivariate regression analyses of baseline visual acuity letter score on baseline characteristics. Of the characteristics analyzed in univariate models among participants in the CRVO trial, significant predictors at the 0.05 level include participant age, OCT measurements of center point thickness, presence of subretinal fluid, and total macular volume, disc areas of retinal hemorrhage measured by fundus photography, and disc areas of leakage within the grid measured by fluorescein angiography. In the multiple regression analysis, only age and duration of macular edema remained statistically significant at the 0.05 level, with older age and longer duration of macular edema associated with a lower visual acuity letter score.

Among participants in the BRVO trial, significant predictors at the 0.05 level from the univariate models include center point thickness measured by OCT, disc areas of retinal thickening, disc areas of retinal hemorrhage, and disc areas of fluorescein leakage within the grid. In the multiple regression analysis, greater OCT-measured center point thickness and absence of cystoid spaces based on OCT were associated with lower visual acuity letter score. Note that total macular volume and capillary loss within the eye were excluded from the multiple regression analyses because of the large number of missing data points.

The R^2 for the multiple regression model was 27% for the CRVO trial and 23% for the BRVO trial. The multivariate models provide improvement over the univariate models that included only OCT-measured center point thickness, which had an R^2 of less than 10% for both the CRVO and BRVO trials.

Discussion

Current treatment for macular edema associated with CRVO and BRVO is aimed at reducing retinal thickness, with the expectation that reduction in retinal thickness will positively affect visual acuity. However, the relationship between central retinal thickening and visual acuity has not been well established in the disease areas of CRVO and BRVO. The SCORE Study provides an opportunity to investigate the relationship between visual acuity and morphologic variables such as OCT-measured center point thickness, as well as other factors, in a large study population of 665 participants. The present report examines these relationships in a cross-sectional manner using baseline data captured in the SCORE Study.

As presented in Table 2, participants in the CRVO trial are more likely than participants in the BRVO trial to have worse baseline visual acuity letter score, a higher OCT-measured center point thickness, a larger mean area of retinal thickening as measured on fundus photography, and a larger mean area of fluorescein leakage. These differences are not unexpected and are consistent with what has been reported among patients with retinal vein occlusion. The Central Vein Occlusion Study Group M (the group of Central Vein Occlusion Study eyes in which grid pattern photocoagulation for macular edema associated with CRVO was evaluated) included 155 eyes of 155 patients with a median baseline visual acuity of 20/160 in treated eyes and 20/125 in control eyes; 23 in the Branch Vein Occlusion Study, 56 (79%) treated eyes and 54 (79%) control eyes had a baseline visual acuity between 20/40 and 20/100.²⁴ It is not surprising that in the SCORE Study, eyes with CRVO had a higher mean OCT-measured center point thickness, a larger mean area of retinal thickening measured on fundus photography, and a larger mean area of fluorescein leakage compared with eyes with BRVO given that CRVO affects a larger portion of the retina and retinal circulation (and involves both halves of the macula), whereas BRVO affects a smaller portion of the retina and retinal circulation. Thus, the worse baseline visual acuity in patients with CRVO compared with patients with BRVO

(consistent with previously reported findings of the Eye Disease Case Control Study, Central Vein Occlusion Study, and Branch Vein Occlusion Study^{23–26}) and the other aforementioned differences between the SCORE Study CRVO and BRVO study populations that have been shown in this analysis support the SCORE Study statistical plan to analyze the CRVO and BRVO trials separately.

To our knowledge, and on the basis of a literature search of the Medline database, there is only 1 published study that examined the relationship between OCT-measured retinal thickness and visual acuity among patients with CRVO; this study¹⁸ reported a nonsignificant correlation coefficient, although the exact coefficient was not provided. There are no reports examining such a correlation among patients with BRVO. The current study represents the first to evaluate the relationship between OCT-measured center point thickness and E-ETDRS visual acuity letter score in a large series of patients with CRVO and BRVO. The SCORE Study results demonstrate a statistically significant but modest correlation, with a correlation coefficient (r) between OCT-measured center point thickness and E-ETDRS visual acuity letter score of -0.27 for participants in the CRVO trial and -0.28 for participants in the BRVO trial. The proportion of the variance in visual acuity letter score explained by OCT-measured center point thickness (R^2) is less than 10% in both study populations. Thus, although OCT-measured center point thickness represents a useful tool for the detection and monitoring of macular edema in retinal vein occlusion, it cannot substitute reliably for visual acuity measurements.

The correlation between visual acuity letter score and OCT-measured center point thickness was also investigated in subgroups. The strongest correlation coefficient was observed in eyes without cystoid spaces, which was -0.45 for participants in the CRVO trial and -0.41 for participants in the BRVO trial, perhaps because eyes with retinal cystoid spaces may have factors that may add more variability to the visual acuity letter score, thereby weakening the OCT-measured center point thickness-visual acuity letter score association. Such factors may include compression of retinal neuronal tissue and increased disorganization of retinal neuronal connections. We suspected that the correlation between OCT-measured center point thickness and visual acuity letter score may be stronger in patients without dense macular hemorrhage (this was assessed in the BRVO trial only) and in patients without subretinal fluid, because dense hemorrhage and subretinal fluid may add more variability to visual acuity, with the amount of visual acuity variability possibly related to the thickness of the hemorrhage or the height of the subretinal fluid. However, the correlation coefficient in eyes with and without dense macular hemorrhage for participants in the BRVO trial matched the overall correlation, and subtracting subretinal fluid height at the center point from center point thickness did not have an effect on the correlation in either the CRVO or the BRVO trial.

The SCORE Study also provides the opportunity to investigate the relationship between baseline visual acuity letter score and other morphologic features of the retina, in addition to OCT-measured center point thickness, measured according to a standardized protocol by a centralized reading center. These factors include cystoid spaces, total macular volume, and subretinal fluid assessed with OCT, area of retinal thickening and area of retinal hemorrhage assessed with color fundus photographs, and fluorescein leakage and capillary loss assessed with fluorescein angiograms. In participants in the BRVO trial, in addition to lower center point thickness, the presence of cystoid spaces was statistically significantly ($P_{\text{hoch}} = 0.01$) associated with higher visual acuity letter score from the multiple regression models of the BRVO trial, but not in the CRVO trial ($P_{\text{hoch}} = 0.98$). This finding may be due to chance. Of note, an analysis of presence or absence of cysts with duration of disease showed no significant association.

In the CRVO trial, baseline demographic and clinical characteristics that were associated with better baseline visual acuity letter score included younger age and shorter duration of macular

edema. No demographic or clinical characteristics were significantly associated with visual acuity letter score for participants in the BRVO trial. Younger age was associated with better baseline visual acuity score in both trials (although this association was statistically significant only in CRVO participants). This is not unexpected, because visual acuity may decline with older age because of factors such as cataract. Shorter duration of macular edema was significantly associated with better visual acuity letter score in CRVO participants, but poorer visual acuity letter score in BRVO participants, although the latter association did not reach statistical significance. This different direction of effect of macular edema duration on visual acuity letter score between the 2 disease groups may be explained by the fact that in BRVO eyes with a macular edema duration of ≤ 3 months, the mean area of retinal hemorrhage was greater than in BRVO eyes with a macular edema duration > 3 months ($P < 0.0001$). In contrast, in CRVO eyes, the mean area of retinal hemorrhage did not differ as much with respect to duration of macular edema ($P = 0.03$). Mean disc areas of capillary loss and percentage of participants with > 5 disc areas of capillary loss were significantly higher in the BRVO group than in the CRVO group. This may be explained by the larger area of hemorrhage measured within the grid as well as outside the grid in the CRVO participants compared with the BRVO participants. These areas of blocked fluorescence could not be evaluated for capillary loss and may account for the differences in the capillary loss measurements between the 2 groups. Similarly, the larger area of fluorescein leakage in CRVO compared with BRVO eyes may have contributed to the difference in ischemic measurements between these 2 groups because the larger area of fluorescein leakage in CRVO eyes may have obscured visualization of ischemia in the areas of fluorescein leakage.

A limitation of the current report is that the analyses describe only baseline information, and all results are, therefore, based on cross-sectional analyses. Subsequent SCORE Study reports will be able to describe changes from baseline in these relationships in a prospective manner with 1 to 3 years of study participant follow-up. Interest also lies in examining the effects of intravitreal triamcinolone acetonide versus standard care treatments on these relationships.

The correlation between OCT-measured center point thickness and visual acuity letter score is statistically significant but modest in participants with macular edema associated with CRVO and BRVO. OCT-measured center point thickness represents a useful tool for the detection and monitoring of various posterior segment diseases but cannot reliably substitute for visual acuity measurements. The same can be said for the other potential predictors investigated. This information may be important when planning clinical trials involving patients with retinal vein occlusion, as well as in the clinical management of patients with retinal vein occlusion.

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Figure 1.

Scatter plots of baseline OCT-measured center point thickness (microns) and baseline visual acuity letter score for participants in the CRVO (**A**) and BRVO (**B**) trials. Correlation coefficient is -0.27 ($P < 0.0001$; 95% CL = -0.38 to -0.16) for CRVO and -0.28 ($P < 0.0001$; 95% CL = -0.37 to -0.19) for BRVO. Regression line (*solid line*) is displayed with the 95% confidence interval lines (*dotted lines*) about the mean predicted values. Horizontal reference lines represent visual acuity letter score inclusion criterion of 19 and 73 letters.

Figure 2.

Pearson correlation coefficients between baseline OCT-measured center point thickness and visual acuity letter score, with 95% CIs about the coefficient, for eyes in the CRVO and BRVO trials, respectively, overall, without and with cystoid spaces, without and with dense macular hemorrhage (BRVO only), and in all eyes after subtracting subretinal fluid height at the center point from center point thickness.

Table 1**Study Eye Major Inclusion and Exclusion Criteria**

Inclusion Criteria
<ul style="list-style-type: none"> • Best-corrected electronic E-ETDRS visual acuity letter score of ≤ 73 (approximate Snellen equivalent of 20/40 or worse) and ≥ 19 (approximate Snellen equivalent of 20/400 or better). Note: the original lower limit of visual acuity was expanded from >34 letters to >24 letters 5 mo after accrual began and then from >24 letters to >19 letters 12 mo after accrual began. • Center-involved macular edema caused by CRVO or BRVO present on clinical examination • Mean CST of 2 optical OCT fast macular scans ≥ 250 μm • Media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs
Exclusion Criteria
<ul style="list-style-type: none"> • Presence of macular edema due to a cause other than CRVO or BRVO • Presence of an ocular condition such that visual acuity would not improve from resolution of the edema (e.g., foveal atrophy) • Substantial cataract estimated to have reduced visual acuity by ≥ 3 lines • Prior treatment with intravitreal corticosteroids at any time or peribulbar steroid injection within 6 mo before randomization • History of focal/grid macular photocoagulation within 15 wk (3.5 mo) <i>or</i> panretinal photocoagulation within 4 mo before randomization <i>or</i> anticipated need for PRP within the 4 mo after randomization • Prior pars plana vitrectomy • Major ocular surgery (including cataract extraction) within prior 6 mo or anticipated within the next 6 mo after randomization • Yttrium Aluminum Garnet capsulotomy performed within 2 mo before randomization • IOP ≥ 25 mmHg, open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma), steroid-induced IOP elevation that required IOP-lowering treatment or pseudoexfoliation • Aphakia

E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; CST = central subfield thickness; OCT = optical coherence tomography; IOP = intraocular pressure.

Table 2**Baseline Characteristics of Study Participants**

Characteristics	CRVO	BRVO	P_{unadj}	P_{hoch}
No. of participants	262	403		
Demographic Characteristics				
Age (y) (mean [SD])	68 (12)	67 (11)	0.26	0.98
Women (%)	47	49	0.48	0.98
White (%)	91	89	0.28	0.98
Study Eye Characteristics and Prior Interventions				
Mean (SD) E-ETDRS visual acuity letter score [†]	52 (14)	57 (13)	<0.0001	<0.0001
59–73 (20/40–20/63) (%)	38	53	<0.0001	0.0006
49–58 (20/80–20/100) (%)	21	24		
19–48 (20/125–20/400) (%)	41	24		
Duration of macular edema in months (mean [SD])	4.2 (3.5)	4.5 (3.8)	0.36	0.98
Prior lens extraction (%)	19	19	0.96	0.98
Dense macular hemorrhage (%)	—	30	—	
Prior grid photocoagulation (%)	0.4	7.2	—	
OCT Characteristics				
OCT center point thickness* (microns) (mean [SD])	656 (227)	526 (186)	<0.0001	<0.0001
Subretinal fluid (%)	N = 257 43	N = 394 30	0.0013	0.09
Subretinal fluid height at center point among those with subretinal fluid (microns) (mean [SD])	N = 105 178 (120)	N = 113 199 (156)	0.51	0.98
Participants categorized by size of cystoid spaces (%)	N = 262	N = 399	<0.0001	<0.0001
Absent	11	18		
Small (≤ 200 μm)	13	22		
Medium (201–400 μm)	41	43		
Large (> 401 μm)	35	17		
Total macular volume (mm^3) (mean [SD])	N = 171 10.5 (2.0)	N = 250 9.8 (1.8)	0.0012	0.08
Color Fundus Photograph Characteristics				
Area of retinal thickening within the grid (DA) (mean [SD])	N = 252 12.3 (4.8)	N = 388 7.5 (2.9)	<0.0001	<0.0001
Area of retinal hemorrhage within the grid (DA) (mean [SD])	N = 257 3.4 (3.2)	N = 390 3.0 (2.4)	0.46	0.98
Fluorescein Angiogram Characteristics				
Area of fluorescein leakage within the grid (DA) (mean [SD])	N = 248 10.9 (4.9)	N = 393 6.2 (2.4)	<0.0001	<0.0001
Capillary loss within the eye (disc areas) (mean [SD])	N = 190 0.3 (1.4)	287 2.5 (6.4)	<0.0001	<0.0001
>5 disc areas of capillary loss—ischemia (%)	2.0	13.9	<0.0001	0.0003
Other Clinical Characteristics				
Diabetes mellitus (%)	23	14	0.0025	0.17
Hypertensive (%)	70	69	0.77	0.98
Coronary artery disease (%)	19	18	0.56	0.98

CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; P_{unadj} = unadjusted P value; P_{hoch} = adjusted Hochberg P value; SD = standard deviation; E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study; OCT = optical coherence tomography; DA = disc area.

* Center point thickness is based on the mean of the 2 screening OCT measurements.

[†] Visual acuity is measured at the screening visit.

Table 3
Univariate and Multivariate Regression Analyses of Baseline Visual Acuity on Baseline Demographic and Clinical Characteristics

	Central Retinal Vein Occlusion					Branch Retinal Vein Occlusion				
	Univariate			Multivariate (N = 232)		Univariate			Multivariate (N = 374)	
	N	Beta*	P _{unadj}	P _{hoch}	Beta*	P _{unadj}	P _{hoch}	N	Beta*	P _{hoch}
Baseline Demographic and Clinical Center Characteristics										
Age (per 10-y interval)	262	-2.41	0.0006	0.04	-2.96	0.0004	0.03	403	-1.39	0.02
Female gender	262	-1.81	0.30	0.98	-0.18	0.92	0.98	403	-2.60	0.04
White	262	0.90	0.77	0.98	2.28	0.46	0.98	403	1.74	0.39
Duration of macular edema (per month)	262	-0.49	0.05	0.98	-0.83	0.0006	0.04	403	0.27	0.11
With prior grid laser								403	-0.85	0.73
With dense macular hemorrhage								403	-3.58	0.01
With prior lens extraction	262	-1.17	0.60	0.98	1.16	0.63	0.98	403	-0.44	0.79
Prior diabetes mellitus	262	-1.15	0.58	0.98	-0.76	0.72	0.98	403	-0.99	0.59
Prior hypertension	262	-3.52	0.06	0.98	-0.78	0.68	0.98	403	0.35	0.80
With coronary heart disease	262	-2.88	0.19	0.98	-0.07	0.98	0.98	403	-3.60	0.03
Optical Coherence Tomography Characteristics										
Center point thickness (per 100 μ m)	262	-1.67	<0.0001	0.0007	-1.40	0.0033	0.22	403	-1.93	<0.0001
With subretinal fluid	257	6.24	0.0003	0.02	5.05	0.0036	0.24	394	1.33	0.34
With any cystoid spaces	262	-0.43	0.87	0.98	3.80	0.22	0.98	399	3.07	0.07
Size of cystoid spaces	262							399		
Absent (reference)	30	-						72	-	
Small (≤ 200 μ m)	33	-1.02	0.77	0.98				89	1.76	0.38
Medium (201–400 μ m)	108	0.89	0.76	0.98				171	4.81	0.0072
Large (≥ 401 μ m)	91	-1.79	0.54	0.98				67	0.37	0.86

	Central Retinal Vein Occlusion						Branch Retinal Vein Occlusion							
	Univariate			Multivariate (N =232)			Univariate			Multivariate (N = 374)				
	N	Beta*	P _{unadj}	P _{hoch}	Beta*	P _{unadj}	P _{hoch}	N	Beta*	P _{unadj}	P _{hoch}	Beta*	P _{unadj}	P _{hoch}
Total macular volume (mm ³)	171	-2.45	<0.0001	<0.0001				250	-0.84	0.05	0.98			
Color Fundus Photograph Characteristics														
Retinal thickening within the grid (per DA)	252	-0.53	0.0037	0.24	0.10	0.69	0.98	388	-1.34	<0.0001	<0.0001	-0.65	0.03	0.98
Retinal hemorrhage within the grid (per DA)	257	-1.23	<0.0001	0.0003	-0.44	0.18	0.98	390	-1.14	<0.0001	0.0011	0.12	0.73	0.98
Fluorescein Angiogram Characteristics														
Leakage within the grid (per DA) [†]	248	-0.77	<0.0001	0.0012	-0.66	0.0052	0.33	393	-1.34	<0.0001	<0.0001	-0.48	0.15	0.98
Capillary loss within the eye (per DA) [†]	190	-0.72	0.31	0.98				287	-0.08	0.49	0.98			
>5 DA of capillary loss within the eye [†]	190	1.68	0.84	0.98				287	-0.50	0.81	0.98			

DA = disc area; P_{unadj} = unadjusted P value. P_{hoch} = adjusted Hochberg P value.

* Estimate of change in the baseline visual acuity letter score associated with a unit increase of a continuous independent variable (e.g., 10-y increase for age) or an increase in level of a categorical or binary independent variable (e.g., prior grid laser compared to without prior grid laser) (5 letters is 1 line on the electronic Early Treatment Diabetic Retinopathy Study [E-ETDRS] chart).

[†] Total macular volume and capillary loss within the eye were excluded from the multiple regression analyses because of the large number of missing data points. Bolding within the cells identifies factors significant at P_{hoch} < 0.05.

E-ETDRS Visual Acuity Letter Score and OCT-Measured Center Point Thickness by Categories

Table 4

E-ETDRS visual Acuity Letter Score	OCT-Measured Center Point Thickness (microns)					
	CRVO (% of row total)			BRVO (% of row total)		
	≤325	326-725	>725	≤325	326-725	>725
59-73 (20/40-20/63)	12%	64%	24%	99	16%	7%
49-58 (20/80-20/100)	4%	57%	39%	56	7%	11%
19-48 (20/125-20/400)	7%	47%	47%	107	5%	29%
Total	8%	55%	37%	262	11%	13%
						403

DRS = electronic Early Treatment Diabetic Retinopathy Study; OCT = optical coherence tomography; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion.