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Baseline Predictors of Visual Acuity and Retinal Thickness Outcomes in Patients with Retinal Vein Occlusion. SCORE Study Report 10

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Abstract

Objective—To investigate baseline factors significantly associated with visual acuity and central retinal thickness outcomes in patients with macular edema secondary to retinal vein occlusion in the **S**tandard Care versus **CO**rticosteroid for **RE**tinal Vein Occlusion (SCORE) Study.

Design—Two 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—Participants with ≥1 year follow-up data, including 238 with CRVO and 367 with BRVO.

Methods—Visual acuity was measured by the electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) method and central retinal thickness by optical coherence tomography (OCT). Logistic and ordinary least squares regression related these outcomes to 20 baseline measures. Multiple p-values were adjusted to control the false discovery rate.

Main Outcome Measures—Outcome measures of visual acuity letter score included absolute change from baseline, a gain of ≥15 from baseline, and a loss of ≥15 from baseline. Outcome measures of center point thickness included absolute change from baseline, a measurement of ≤250 microns, and a measurement of ≥500 microns. Outcomes were assessed at 1 and 2 years.

Results—For CRVO and BRVO, younger age was significantly associated with improved visual acuity and central retinal thickness outcomes. For CRVO, treatment with triamcinolone and less severe anatomical abnormalities of the retina (center point thickness and areas of retinal

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This article contains online-only material. The following will appear online-only: Table 2 and Table 4.

hemorrhage, thickening, and fluorescein leakage) were predictive of better visual acuity outcomes. For BRVO, lack of a history of coronary artery disease was predictive of improved visual acuity outcomes. For center point thickness outcomes based on OCT, shorter duration of macular edema was significantly associated with improvement in both disease entities. For CRVO, higher baseline visual acuity letter score, and for BRVO, lower baseline visual acuity letter score, presence of dense macular hemorrhage and no prior grid photocoagulation were predictive of favorable OCT outcomes.

Conclusions—Several factors were predictive of better visual acuity outcomes, including younger age, and predictive of more favorable OCT outcomes, including shorter duration of macular edema. These baseline factors may assist clinicians in predicting the course of disease for patients with CRVO and BRVO.

Introduction

Between November 2004 and February 2008, 271 patients with central retinal vein occlusion (CRVO) and 411 patients with branch retinal vein occlusion (BRVO) were enrolled into the Standard Care versus COrticosteroid for REtinal Vein Occlusion (SCORE) Study, which was designed to compare 1 mg and 4 mg intravitreal triamcinolone acetonide with standard care (SC) treatment for vision loss associated with macular edema secondary to retinal vein occlusion.[1] In patients with CRVO (the SCORE-CRVO trial), SC was observation. In patients with BRVO (the SCORE-BRVO trial), SC was grid photocoagulation in eyes with no dense macular hemorrhage, and, in eyes with dense macular hemorrhage, deferred photocoagulation until the hemorrhage cleared sufficiently for grid photocoagulation to be performed. In the SCORE-CRVO trial, the odds of experiencing an improvement in visual acuity letter score of 15 or more from baseline to 12 months was approximately 5 times higher in the 1 mg and the 4 mg intravitreal triamcinolone groups than the SC group, and the 1 mg dose demonstrated a safety profile superior to that of the 4 mg dose.[2] In the SCORE-BRVO trial, there was no difference in visual acuity at 12 months for the triamcinolone groups compared with the SC group, and the rates of adverse events (particularly intraocular pressure [IOP] elevation and cataract) were highest in the 4 mg triamcinolone group.[3] The purpose of the current report is to investigate baseline factors significantly associated with visual acuity and central retinal thickness outcomes in patients with macular edema secondary to retinal vein occlusion in the SCORE Study.

Methods

The SCORE Study design and methods are described in detail elsewhere[1] and summarized here. The study adhered to the tenets of the Declaration of Helsinki. Institutional Review Board (IRB) approval for the protocol was obtained from either a central IRB (Jaeb Center for Health Research) or from institutional IRBs, and informed consent was obtained from all participants prior to eligibility screening and again prior to randomization into the study. The eligible eye of each participant was randomized to one of three equally-sized parallel arms in either the CRVO trial or the BRVO trial; SC, 1 mg intravitreal triamcinolone, and 4 mg intravitreal triamcinolone. Participants in the CRVO trial assigned to SC were observed. Participants in the BRVO trial assigned to SC were treated with grid photocoagulation if a dense macular hemorrhage did not preclude treatment. If a dense hemorrhage was present, grid photocoagulation was postponed until clearing of the hemorrhage permitted grid photocoagulation treatment. Participants were treated with the randomly assigned treatment at baseline and at 4-month intervals except when study-defined criteria to defer additional treatment or to employ the alternate treatment regimen were satisfied. Once randomized, all participants were expected to be followed for 1 to 3 years. Actual length of follow-up

depended on the randomization date relative to the common closeout date of February 28, 2009.

Study visits were scheduled every 4 months following randomization. At all 4-Month study visits, participants had visual acuity testing at 3 meters (including manifest refraction using the electronic Early Treatment of Diabetic Retinopathy Study [E-ETDRS] visual acuity testing method[4]), IOP measurement, an eye examination and an optical coherence tomography (OCT) scan. Stereoscopic color fundus photographs (7 fields) were taken of the study eye at baseline and at the annual visits. Three-field photographs of the study eye were taken at the 4, 8, 16, 20, 28, and 32 month visits. Fluorescein angiography (FA) was performed at baseline, 4 months, 12 months and 24 months. All imaging tests (color fundus photographs, FA and OCT) were sent to the University of Wisconsin Fundus Photograph Reading Center (Reading Center).

The Reading Center graders, without knowledge of treatment assignment or participant clinical data, followed a standardized protocol to grade degree of macular edema and retinal hemorrhage using stereoscopic fundus photographs.[5] OCT scans were evaluated for both quantitative data (e.g., central subfield thickness), using the macular fastmap scan consisting of 6 radially oriented scans, and qualitative data (e.g., presence or absence of vitreomacular traction, subretinal fluid and cystoid spaces), using the two scan crosshair images.[6] Center point thickness was used for analysis instead of central subfield thickness, since this permitted correction of errors in the measurement of the inner and outer retinal boundaries. The correlation between center point thickness and central subfield thickness is 0.98.[7] Fluorescein angiograms were graded for amount of non-perfusion and leakage in disc areas (DA).

Statistical methods

The primary goal of this paper is to predict outcomes for change from baseline in visual acuity letter score and OCT-measured center point thickness at two follow-up time points: 1 year and 2 years. For visual acuity, we investigated 3 outcomes: change from baseline in visual acuity letter score (i.e., the baseline score subtracted from the follow-up score) and a gain and a loss of 15 or more from baseline in visual acuity letter score. For OCT-measured center point thickness, we investigated 3 outcomes: change from baseline in center point thickness (i.e., the baseline thickness subtracted from the follow-up thickness), a measurement of ≤250 microns and a measurement of ≥500 microns at the follow-up visits. For the binary outcomes in these prediction analyses (e.g., indicator for a visual acuity letter score gain of 15 or more), the log odds of the outcome was modeled as a linear function of the baseline variable using logistic regression, testing the hypothesis that the slope of the relationship is zero. For continuous outcomes (e.g., change from baseline in visual acuity letter score), a standard linear regression was performed.

The 20 baseline variables considered in the prediction analyses for the BRVO analyses and 17 for the CRVO analyses (baseline dense macular hemorrhage status, prior grid photocoagulation, and hemiretinal vein occlusion status are not relevant to CRVO participants) include: (1) treatment group (1 mg vs 4 mg vs standard care [observation, grid photocoagulation]); (2) demographic characteristics: age, gender, race; (3) clinical characteristics: diabetes, hypertension, coronary artery disease; (4) study eye characteristics: E-ETDRS VA, duration of macular edema, prior lens extraction, dense macular hemorrhage, prior grid photocoagulation, hemiretinal vein occlusion; (5) OCT characteristics: center point thickness, subretinal fluid (present versus absent/questionable), center point thickness after subtracting out height of subretinal fluid height at center point, diameter of cystoid spaces measured axially at the center point (no cystoid space, ≤ 200 microns, 201-≤400 microns, and > 400 microns); (6) Color fundus photograph characteristics: area of retinal

thickening within the grid, area of retinal hemorrhage within the grid; and (7) FA characteristics: area of fluorescein leakage within the grid.

Statistical tests of the univariate relationships between these baseline predictor variables and the six outcome variables at each of the 2 follow-up visits resulted in 204 (CRVO analyses) and 240 (BRVO analyses) p-values. If so many hypotheses are tested without special precautions, some relationships would likely appear significant due to chance alone (i.e., type I error). To mitigate this, we controlled the False Discovery Rate[8,9] (FDR) at 5% separately within the CRVO and BRVO disease areas analyses.

Modern clinical trials may feature multiple, co-primary endpoints, with the statistical significance of any one of the endpoints potentially serving as a basis for a claim of efficacy. In that situation, one typically controls family-wide type I error (FWE). However, the aim of this paper is not to claim efficacy of a particular treatment, but to nominate important predictive relationships. Here, controlling FDR is more appropriate. Controlling FWE at a level of 0.05 ensures that the probability of incorrectly rejecting at least one null hypothesis is only 5%. In contrast, controlling FDR at a level of 0.05 ensures that the expected proportion, among all rejected null hypotheses, of incorrectly rejected ones is only 5%. FDR is often implemented in genomics research areas such as gene chips, where multiplicity is a well-recognized phenomenon of concern. Benjamini and Hochberg[8] introduced FDR methodology for independent hypothesis tests. Benjamini and Yakuteili[9] later showed that the original method suffices for some types of dependence, and introduced a conservative correction that works for all types of dependence. We chose the FDR criterion to try to ensure that no more than 5% of the results we claim to be significant would fail to be confirmed if subsequently investigated with new data, consistent with recommendations by Benjamini et al.[10]

We refer to baseline predictors as significant if the FDR is less than 0.05. In each disease area for the multivariate analyses, we used stepwise regression analyses to predict each of the 12 outcomes of interest, each time offering to the algorithm only the variables indicated as significant for that outcome using the FDR criterion, and retaining those factors statistically significant at $p<0.05$. In a typical setting, stepwise regression using many potential predictors may greatly overestimate the usefulness of the selected predictors in an independent sample. But as used in this paper, stepwise regression can only reject predictors previously validated by FDR and, thus, cannot increase FDR or FWE. The results of the stepwise regression analyses suggest which baseline predictors could be included in a parsimonious predictor equation.

Results

Table 1 provides a summary of the three visual acuity and three OCT-measured center point thickness outcome measures at 1 and 2 years examined in this report. Note that the number of participants at these follow-up visits is less than the number of enrolled eyes due to participant drop out and death prior to year 1. In eyes of CRVO participants, more eyes had a loss in visual acuity letter score of 15 of more (31-34%) than a gain (20-23%) at years 1 and 2, respectively, with a mean loss in visual acuity letter score of approximately 5 at both time points. In eyes of BRVO participants, more eyes had a gain in visual acuity letter score of 15 of more (27-35%) than a loss (12-13%) at years 1 and 2, with a mean gain in visual acuity score of approximately 5-7. In terms of OCT-measured center point thickness, both CRVO and BRVO eyes had decreasing center point thickness over follow-up, with 40-50% of CRVO eyes ≤250 microns and 50-60% BRVO eyes ≤250 microns at years 1 and 2.

CRVO Results

Table 2 (available at http://aaojournal.org) provides the results of univariate analyses for prediction of visual acuity and center point thickness outcomes in CRVO participants. Note that baseline predictors noted above that are insignificant are excluded from Tables 2-5 (Table 4, available at http://aaojournal.org). Plus (+) superscripts in Tables 2-5 indicate beneficial effects on vision, and minus superscripts (--) indicate detrimental effects. For visual acuity letter score, an effect on vision was considered beneficial if it increased the odds of gain of ≥15, decreased the odds of loss of ≥15, or increased the odds of a positive change from baseline. For center point thickness, an effect was considered beneficial if it increased the odds of center point thickness ≤250 microns, decreased the odds of a center point thickness ≥500 microns, or decreased the odds of a positive change from baseline. There was a beneficial treatment effect of the 1 mg and 4 mg triamcinolone groups compared with observation for the visual acuity outcomes of gain of ≥15 and change from baseline at year 1. Older age made a gain of ≥15 in visual acuity letter score less likely in year 1, and increased the likelihood of loss of ≥15 in year 2. Table 2 (available at http://aaojournal.org) also showed evidence at year 1 of negative effects upon visual acuity of a thicker center point, larger areas within the grid of retinal thickening and hemorrhage (for loss of ≥15 and mean change), and larger area of fluorescein leakage (loss of ≥15 only). Larger area of retinal hemorrhage also predicted visual acuity loss at year 2.

Table 2 (available at http://aaojournal.org) also summarizes the univariate analyses for center point thickness outcomes at years 1 and 2 in CRVO participants. Baseline center point thickness and adjusted center point thickness after removing subretinal fluid height had significant associations with follow-up center point thickness for all three outcomes at year 1. Specifically, higher baseline center point thickness and adjusted center point thickness after removing subretinal fluid height predicted a decreased likelihood of a ≤250 micron outcome, an increased likelihood of a ≥500 micron outcome, and a greater decrease in center point thickness from baseline. Other significant baseline predictors noted in only one of the three center point thickness outcomes at 1 year in CRVO participants include: for increased likelihood of ≥500 microns, lower visual acuity letter score and larger area within the grid of retinal hemorrhage; and, for decreased center point thickness, shorter prior duration of macular edema, greater size of cystoid spaces, and larger area of fluorescein leakage.

For predicting the magnitude of change in visual acuity letter score at year 1 from baseline, the results of the stepwise regression (Table 3) models included larger areas of retinal thickening and hemorrhage as important baseline predictors of a negative (detrimental) visual acuity change. For predicting gain of ≥15 at year 1, the stepwise multivariate models selected only younger age; for loss of ≥15 at year 1, important predictors included larger areas of retinal thickening and hemorrhage. Fewer significant results were found at year 2, perhaps because of reduced sample size, with only older age only predicting loss ≥15, and larger area of retinal hemorrhage predicting both loss ≥15 and decrease from baseline in visual acuity letter score.

The multivariate analyses of OCT-measured center point thickness outcomes consistently selected baseline center point thickness as an important predictor at years 1 and 2. Higher baseline center point thickness predicted an increased likelihood of a ≥500 micron outcome, a decreased likelihood of a ≤250 micron outcome, and greater decrease in center point thickness. Longer duration of macular edema was associated with increased center point thickness at year 1. Higher visual acuity letter score decreased the likelihood of the ≥500 micron outcome at year 1 in the stepwise regression model.

In summary, considering findings identified as significant based on the FDR criteria (Table 2, available at http://aaojournal.org), 1mg and 4mg triamcinolone, younger age, lesser center point thickness, and decreased areas of retinal thickening, hemorrhage, and fluorescein leakage were all predictive of better visual acuity outcomes in CRVO participants. For OCT-measured center point thickness, thicker center point and adjusted center point thickness after removing subretinal fluid height were important factors in predicting lower mean OCT-measured center point thickness, increased likelihood of the ≥500 micron outcome, and decreased likelihood of the ≤250 micron outcome at years 1 and 2. In addition, at year 1, higher visual acuity letter score, shorter duration of macular edema, larger size of cystoid spaces, decreased area of retinal hemorrhage and increased area of fluorescein leakage were important in predicting better OCT-measured center point thickness outcomes.

BRVO Results

Table 4 (available at http://aaojournal.org) displays analyses of baseline predictors of visual acuity letter score for BRVO participants. Age and baseline visual acuity score showed significant effects in almost all analyses, with older age and higher baseline visual acuity both predicting more negative (detrimental) changes in visual acuity during follow-up. Presence of coronary artery disease and longer prior duration of macular edema also predicted worse mean change in visual acuity score at year 1, and coronary artery disease remained significant at year 2.

Table 4 (available at http://aaojournal.org) also summarizes the univariate analyses for baseline associations with center point thickness outcomes in BRVO participants. There were many strongly statistically significant predictors for increase in center point thickness from baseline at 1 year. Older age, better visual acuity letter score, longer duration of macular edema and prior grid photocoagulation predicted a higher center point thickness at year 1. Presence of dense macular hemorrhage, thicker center point, presence of subretinal fluid, higher adjusted center point thickness after removing height of subretinal fluid, and larger areas within the grid of retinal thickening, hemorrhage, and fluorescein leakage predicted a lower center point thickness at year 1. Year 2 findings were mostly consistent those at year 1.

Fewer baseline factors were significantly associated with the ≤250 and ≥500 micron center point thickness outcomes. For the ≥500 micron center point thickness outcome at year 1, thicker center point and higher adjusted center point thickness after removing subretinal fluid height at center point were significant predictors. For ≤250 micron center point thickness outcome, only lower adjusted center point thickness after removing subretinal fluid height at center point was a significant predictor.

The stepwise multivariate analyses were quite consistent across the 3 visual acuity outcomes (Table 5). For predicting visual acuity letter score gain of ≥15, only younger age and lower baseline visual acuity letter score were significant at years 1 and 2. Older age was important for predicting loss of ≥15 at year 1, and presence of coronary artery disease for predicting loss at year 2. For mean change in visual acuity letter score from baseline, there were four important predictors associated with a decrease: older age, presence of coronary artery disease, higher baseline visual acuity letter score, and (for year 1) longer duration of macular edema.

For the OCT-center point thickness outcome (change in center point thickness from baseline), many of the statistically significant univariate variables were no longer significant in the stepwise regression procedures (Table 5). However, higher baseline center point thickness was consistently associated with a greater decrease from baseline in center point

thickness in the stepwise analyses at years 1 and 2. Other factors variably associated with better center point thickness outcomes included: standard care treatment at year 2, younger age, higher adjusted center point thickness after subtracting height of subretinal fluid at center point (although this also predicted less likely ≤250 micron center point thickness), and greater areas of retinal hemorrhage and fluorescein leakage within the grid.

In summary, considering findings identified as significant based on the FDR criteria (Table 4, available at http://aaojournal.org), the analyses suggested that younger age, lack of history of coronary artery disease, lower baseline visual acuity letter score, and shorter duration of macular edema are all predictive of better visual acuity outcomes at years 1 and 2 in BRVO participants. For OCT-measured center point thickness, the analyses suggested that higher baseline center point thickness consistently predicted lower OCT-measured center point thickness changes at years 1 and 2, but also that younger age, lower visual acuity letter score, shorter duration of macular edema, presence of a dense macular hemorrhage, absence of prior grid photocoagulation, presence of subretinal fluid, higher adjusted center point thickness after subtracting out height of subretinal fluid, and larger areas of retinal thickening, hemorrhage, and fluorescein leakage within the grid all showed associations with beneficial changes from baseline in OCT-measured center point thickness at year 1. At year 2, additionally, triamcinolone at either dose was associated with detrimental center point changes in comparison with standard care.

Discussion

This analysis was conducted to identify factors associated with visual acuity and with OCT-measured central retinal thickness outcomes in patients treated with standard care or intravitreal triamcinolone for macular edema secondary to CRVO or BRVO in the SCORE Study. Because of the large number of variables evaluated, only associations with a FDR <5% were considered significant.

Age was the only predictive factor that was significant across both disease entities (CRVO and BRVO) for predicting visual acuity outcomes, with younger age associated with a gain in 15 or more in visual acuity letter score. Younger patients may have better visual acuity outcomes due to generally healthier ocular tissue with improved likelihood for recovery following an acute insult such as a retinal vein occlusion; for example, irreparable damage to photoreceptors may be associated with age. Although the Branch Vein Occlusion Study (BVOS)[11] and Diabetic Retinopathy Clinical Research Network (DRCR.net)[12] did not find age to be a significant predictor of visual acuity outcome following treatment for macular edema in patients with BRVO and diabetic retinopathy, respectively, in the Central Vein Occlusion Study (CVOS) there was an interaction between treatment effect and age.[13] For patients treated with grid photocoagulation in the CVOS, visual acuity tended to be better for younger patients although this interaction between treatment effect and age was not statistically significant, perhaps due to the limited sample size.[13] The smaller number of patients studied in the BVOS compared with the SCORE-BRVO trial may explain, at least in part, why the BVOS found no effect of age on treatment outcome while the SCORE-BRVO trial did find such an effect since the SCORE-BRVO trial (due to its larger sample size) had a higher power to detect such an effect. As SC may be the preferred treatment over intravitreal triamcinolone for eyes with macular edema from BRVO, we conducted univariate regressions of visual acuity outcomes upon age within the SC group only (data not shown). The results were similar to those for all 3 treatment groups combined (Table 2, available at http://aaojournal.org), but were mostly not significant, which we attribute to the smaller sample size.

For OCT outcomes, both duration of macular edema and baseline center point thickness were predictive across both CRVO and BRVO disease entities. Shorter duration of macular edema was associated with a greater reduction from baseline in OCT-measured center point thickness in participants with either type of retinal vein occlusion, perhaps because retinal anatomic changes of shorter duration are more likely to be reversible compared with more chronic changes in the retinal architecture. Although the association between shorter duration of macular edema and a greater reduction in OCT-measured center point thickness suggests that earlier treatment results in better outcomes, this is a secondary finding and was not one of the primary objectives of the SCORE Study. For baseline center point thickness, a higher baseline thickness was associated with a greater reduction in mean OCT-measured center point thickness. This finding of retinal thinning over time in eyes with high baseline center point thickness may be due to the natural course of the disease in both CRVO and BRVO eyes. This hypothesis is supported by the fact that central retinal thickness progressively decreased over time in all treatment groups in the SCORE-CRVO[2] and SCORE-BRVO[3] trials, including study participants who were observed in the SCORE-CRVO trial.[2] However, there needs to be caution when interpreting a predictor whose baseline value is part of the calculation of the outcome, as this relationship is affected by "part-whole correlation"[14] For example, the negative correlation between baseline center point thickness and year-1 change from baseline may simply be because, to calculate year-1 change, the baseline value is subtracted from year-1 thickness. Thus, for a fixed year-1 thickness, year-1 change varies inversely with the baseline thickness. The negative association between center point thickness at baseline and subsequent change from baseline needs to be interpreted in light of this "part-whole correlation." It should also be noted that, even though those with a higher center point thickness tend to decrease, those with higher center point thickness had an increased likelihood of the ≥500 microns outcome at year 1 in both CRVO and BRVO participants, suggesting that those with high center point thickness are at greatest risk of continued retinal thickness.

The better visual acuity outcome associated with intravitreal triamcinolone treatment compared with observation in the CRVO-trial has been discussed extensively in SCORE Report 5. The effects of triamcinolone may be due to corticosteroid-induced inhibition of vascular endothelial growth factor (VEGF) bioactivity, reduction in retinal capillary permeability, or other anti-inflammatory or perhaps neuroprotective properties of corticosteroids.[2] The better visual acuity outcome associated with a lower center point thickness and smaller areas of retinal thickening, retinal hemorrhage, and fluorescein leakage at baseline in the SCORE-CRVO trial may be due, at least in part, to the possibility that patients with such features may have less severe CRVO and/or less severe anatomic changes which, in turn, may be more likely to be associated with reversible visual acuity loss.

In patients with BRVO, absence of a history of coronary artery disease, lower baseline visual acuity letter score, and shorter duration of macular edema were significant predictors of a better visual acuity outcome. A history of coronary artery disease may be a marker for more underlying systemic ischemia, which may, in turn, portend a graver visual acuity prognosis following retinal vein occlusion. History of coronary artery disease was not found to be a significant predictor in the SCORE-CRVO trial perhaps because in the latter trial, patients who were judged by the investigator to have an ischemic CRVO were excluded from the study (the SCORE-BRVO trial did not have such an exclusion criterion). In the SCORE-BRVO trial, lower baseline visual acuity letter score was associated with better visual acuity outcome possibly because of a greater opportunity for visual acuity improvement in patients who start out with poorer visual acuity, which may be in part due to the natural history of the disease. This hypothesis is supported by the fact that, in the BVOS, 37% of untreated eyes followed for 3 years gained two or more lines of vision from baseline

maintained for at least two consecutive study visits.[11] Consistent with the findings from the SCORE-BRVO trial, the DRCR.net recently reported that worse baseline visual acuity was associated with more frequent visual acuity improvement in eyes with diabetic macular edema treated with focal/grid photocoagulation.[12] However, this relationship between baseline visual acuity score and change from baseline in visual acuity score may be affected by "part-whole correlation," as noted above for center point thickness. Shorter duration of macular edema may be associated with a better visual acuity outcome in patients with BRVO but not CRVO because there may be a higher rate of spontaneous improvement in patients with BRVO, perhaps because less of the macula is involved in BRVO compared with CRVO. The smaller number of patients studied in the SCORE-CRVO trial compared with the SCORE-BRVO trial may explain, at least in part, why the SCORE-CRVO trial found no association between duration of macular edema and visual acuity outcome while the SCORE-BRVO trial did find such an association since the SCORE-BRVO trial (due to its larger sample size) had a higher power to detect such an association.

The decreased likelihood of a ≥500 micron outcome at 1 year for those with higher visual acuity letter score and smaller area of retinal hemorrhage in the grid at baseline in the SCORE-CRVO trial may be due, at least in part, to the possibility that patients with such features may have less severe CRVO and/or less severe anatomic changes which, in turn, may be more likely to be associated with reversible architectural changes in the retina.

A larger area of retinal hemorrhage at baseline was associated with a significant decrease from baseline in OCT-measured center point thickness outcomes in the SCORE-BRVO, but this relation was not significant in the SCORE-CRVO trial. Although the sample size was larger in the SCORE-BRVO trial which may explain this finding, this difference may also be due, at least in part, to the fact that in the SCORE Study, the proportion of the area of retinal vein occlusion that had hemorrhage was approximately 50% in patients with BRVO (average disc areas of retinal thickening was 7.5 and average disc areas of hemorrhage was 2.9) compared with approximately 25% in patients with CRVO (average disc areas of retinal thickening was 12.3 and average disc areas of hemorrhage was 3.4). Thus, upon resolution of the retinal hemorrhage, eyes with BRVO may be more likely to experience a greater reduction in OCT-measured center point thickness because of the greater proportion of area affected by the retinal hemorrhage.

Presence of dense macular hemorrhage, presence of subretinal fluid, and larger areas of retinal thickening and hemorrhage and fluorescein leakage may be associated with mean decrease in center point thickness in patients with BRVO because of a greater opportunity for thickness reduction in patients who start out with anatomic abnormalities which may contribute to central retinal thickness, and because reduction in these anatomic abnormalities may be part of the natural course of BRVO. The latter hypothesis is supported by the fact that central retinal thickness progressively decreased over time in all treatment groups in the SCORE-BRVO[3] trial. However, because each of these anatomic abnormalities is highly correlated with center point thickness, these relationships with changes from baseline in center point thickness may also be affected by part-whole correlation.

Absence of prior grid photocoagulation may be a significant predictor of a more favorable OCT outcome in patients with BRVO because of selection bias. That is, patients treated previously with photocoagulation whose macular edema responded well to photocoagulation treatment would be less likely to have met the eligibility criteria for the SCORE-BRVO trial, and those treated with prior photocoagulation who did meet SCORE-BRVO eligibility criteria may have had macular edema more likely to be refractory to treatment and, thus, may have been less likely to achieve a favorable OCT outcome. The fact that, at year 2, treatment group (standard care over intravitreal triamcinolone) is predictive of a more

favorable OCT outcome in the SCORE-BRVO trial is consistent with the greater beneficial effect on retinal thickening in the photocoagulation group compared with the 1 mg and 4 mg triamcinolone groups observed during the second year of a randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema conducted by the Diabetic Retinopathy Clinical Research Network.[15]

It is interesting to note some of the factors which were not associated with outcome in the SCORE Study. Although hypertension is a well-reported risk factor for the occurrence of retinal vein occlusion,[16-24] a history of hypertension was not a significant predictor of outcome in the SCORE Study. This may be due, at least in part, to the fact that patients with a history of hypertension (which was assessed in the SCORE Study based on patient self-report) were aware of their diagnosis and, thus, were likely on treatment for hypertension. The association between undiagnosed, untreated, or poorly controlled hypertension and outcome in patients with retinal vein occlusion is unknown. It may be helpful in counseling patients to be aware that, although hypertension is a risk factor for the development of retinal vein occlusion, a history of hypertension may not increase the risk of poor visual outcomes once a retinal vein occlusion has occurred. It is a reasonable hypothesis that, in patients with BRVO, a dense macular hemorrhage at baseline may be associated with a higher likelihood of visual acuity improvement once the hemorrhage clears; however, this was not observed in the SCORE-BRVO trial. The lack of association may be due to the fact that while some patients may clear their hemorrhage and experience visual acuity improvement, others may have irreparable retinal and/or retinal pigment epithelial damage associated with visual acuity limitations. Lastly, the size of cystoid spaces was not associated with visual acuity outcome. As demonstrated by SCORE Study Report #1, there was no association between size of cystoid spaces at baseline and baseline visual acuity.[7]

This study demonstrates that, in patients with macular edema secondary to retinal vein occlusion, younger age is significantly associated with improved outcomes both with respect to visual acuity gain (for both CRVO and BRVO patients) and retinal thickness (for BRVO patients), and shorter duration of macular edema is significantly associated with improved retinal thickness outcomes. Systemic factors were poor predictors of outcomes except in patients with BRVO where absence of a history of coronary artery disease predicted a better chance at visual acuity gain. Just as important as the factors that were predictive of outcomes are the factors that were not predictive such as presence of cystoid spaces and, for visual acuity outcomes in patients with BRVO, presence of dense macular hemorrhage. The strengths of this study include the large number of eyes with CRVO and BRVO with standardized baseline measurements, the use of standardized treatment protocols, and prospective standardized measurements of visual acuity, fundus features and OCT.

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References

1. Ip MS, Oden NL, Scott IU, et al. SCORE Study Investigator Group. SCORE Study report 3: study design and baseline characteristics. Ophthalmology 2009;116:1770–7. [PubMed: 19619896]
2. SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 5. Arch Ophthalmol 2009;127:1101–14. [PubMed: 19752419]

3. SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 6. Arch Ophthalmol 2009;127:1115–28. [PubMed: 19752420]
4. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the Early Treatment of Diabetic Retinopathy Study testing protocol. Am J Ophthalmol 2003;135:194–205. [PubMed: 12566024]
5. Blodi BA, Domalpally A, Scott IU, et al. SCORE Study Investigator Group. SCORE Study Report 9: Standard Care vs COrticosteroid for REtinal Vein Occlusion (SCORE) Study System for Evaluation of Stereoscopic Color Fundus Photographs and Fluorescein Angiograms. Arch Ophthalmol. In press.
6. Domalpally A, Blodi BA, Scott IU, et al. SCORE Study Investigator Group. The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study System for Evaluation of Optical Coherence Tomograms: SCORE Study Report 4. Arch Ophthalmol 2009;127(11):1461–1467. [PubMed: 19901211]
7. Scott IU, VanVeldhuisen PC, Oden NL, et al. SCORE Study Investigator Group. SCORE Study report 1: baseline associations between central retinal thickness and visual acuity in patients with retinal vein occlusion. Ophthalmology 2009;116:504–12. [PubMed: 19167078]
8. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289–300.
9. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. Ann Stat 2001;29:1165–88.
10. Benjamini Y, Drai D, Elmer G, et al. Controlling the false discovery rate in behavior genetics research. Behav Brain Res 2001;125:279–84. [PubMed: 11682119]
11. Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol 1984;98:271–82. [PubMed: 6383055]
12. Aiello LP, Edwards AR, Beck RW, et al. Diabetic Retinopathy Clinical Research Network. Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema. Ophthalmology. In press.
13. Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion: the Central Vein Occlusion Study Group M report. Ophthalmology 1995;102:1425–33. [PubMed: 9097788]
14. Sokal, RR.; Rohlf, FJ. Biometry: the Principles and Practice of Statistics in Biological Research. 3rd. New York: W.H. Freeman; 1995. p. 570-1.
15. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115:1447–59. [PubMed: 18662829]
16. Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion. Arch Ophthalmol 1996;114:545–54. [PubMed: 8619763]
17. Eye Disease Case-Control Study Group. Risk factors for branch retinal vein occlusion. Am J Ophthalmol 1993;116:286–96. [PubMed: 8357052]
18. Sperduto RD, Hiller R, Chew E, et al. Risk factors for hemiretinal vein occlusion: comparison with risk factors for central and branch retinal vein occlusion. Ophthalmology 1998;105:765–71. [PubMed: 9593373]
19. Elman MJ, Bhatt AK, Quinlan PM, Enger C. The risk for systemic vascular diseases and mortality in patients with central retinal vein occlusion. Ophthalmology 1990;97:1543–8. [PubMed: 2255527]
20. Appiah AP, Trempe CL. Risk factors associated with branch vs. central retinal vein occlusion. Ann Ophthalmol 1989;21:153–5. 157. [PubMed: 2729819]
21. Appiah AP, Greenidge KC. Factors associated with retinal-vein occlusion in Hispanics. Ann Ophthalmol 1987;19:307–9. 312. [PubMed: 3662315]
22. Rath EZ, Frank RN, Shin DH, Kim C. Risk factors for retinal vein occlusions: a case-control study. Ophthalmology 1992;99:509–14. [PubMed: 1584567]

23. Johnston RL, Brucker AJ, Steinmann W, et al. Risk factors of branch retinal vein occlusion. Arch Ophthalmol 1985;103:1831–2. [PubMed: 4074173]

24. McGrath MA, Wechsler F, Hunyor AB, Penny R. Systemic factors contributory to retinal vein occlusion. Arch Intern Med 1978;138:216–20. [PubMed: 626551]

Table 1

Summary Statistics for Visual Acuity Letter Score and OCT-Measured Center Point Thickness Outcomes

	CRVO Participants		BRVO Participants	
Outcome measure	**1 year**	**2 year**	**1 year**	**2 year**
Visual acuity letter score				
N	238	151	367	238
Gain of 15 (%)	48 (20%)	34 (23%)	100 (27%)	83 (35%)
Loss of 15 (%)	74 (31%)	52 (34%)	47 (13%)	28 (12%)
Mean change from baseline (SD)	-4.5 (23.5)	-5.7 (24.6)	4.6 (17.0)	7.3 (18.0)
OCT-measured center point thickness				
N	216	135	345	219
≤ 250 microns (%)	81 (38%)	63 (47%)	160 (46%)	125 (57%)
≥ 500 microns (%)	78 (36%)	34 (25%)	73 (21%)	28 (13%)
Mean change from baseline (SD)	-233 (270)	-273 (265)	-203 (225)	-249 (223)

OCT = optical coherence tomography; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; SD = standard deviation.

Table 2

Regression Models for Visual Acuity and Center Point Thickness Outcomes in CRVO Participants†

Baseline predictor	Change from Baseline in Visual Acuity Letter Score††						Center Point Thickness (um) †††					
	Year 1			Year 2			Year 1			Year 2		
	Gain of ≥15#	Loss of ≥15#	Change from baseline**	Gain of ≥15*	Loss of ≥15#	Change from baseline**	≤250#	≥500#	Change from baseline**	≤250#	≥500#	Change from baseline**
1 mg triamcinolone vs observation	**4.90**+	0.43	**10.93**+	4.70	0.49	6.38	1.25	1.19	28.12	1.64	1.08	15.87
4 mg triamcinolone vs observation	**4.68**+	0.44	**10.94**+	3.69	0.38	8.30	2.06	0.59	-30.70	1.06	0.86	46.70
Age (years)	**0.96**--	1.03	-0.31	0.97	**1.05**--	-0.41	0.99	1.01	3.73	0.97	1.02	4.32
Visual acuity letter score	0.98	1.00	-0.15	0.99	0.99	-0.07	1.02	**0.97**+	-0.11	1.01	0.97	0.72
Duration of macular edema (months)	0.91	0.97	-0.02	1.01	0.98	-0.05	0.91	1.08	**15.76**--	0.90	1.05	14.10
Center point thickness (per 100 microns)	0.86	**1.23**--	**-2.29**--	0.88	1.17	-1.89	**0.71**--	**1.42**--	**-53.49**+	0.79	**1.45**--	**-46.19**+
Center point thickness after subtracting out subretinal fluid height at center point (per 100 microns)	0.87	1.15	-1.70	0.91	1.13	-1.38	**0.73**--	**1.31**--	**-56.71**+	0.81	**1.32**--	**-46.71**+
Cystoid spaces***	0.70	1.28	-3.11	0.72	1.24	-4.12	0.72	1.33	**-65.87**+	0.75	1.59	-48.72
Area of retinal thickening within the grid (disc areas)	0.98	**1.12**--	**-1.12**--	1.02	1.09	-0.52	0.96	1.08	-5.10	1.03	1.06	-6.65
Area of retinal hemorrhage within the grid (disc areas)	0.96	**1.15**--	**-1.66**--	0.97	**1.23**--	**-1.69**--	0.89	**1.15**--	-10.27	0.90	1.11	-6.20
Area of fluorescein leakage within the grid (disc areas)	0.99	**1.09**--	-0.63	1.00	1.05	-0.26	0.97	1.05	**-10.89**+	1.01	1.06	-8.22

CRVO = central retinal vein occlusion; FDR = False Discovery Rate

† Effects with FDR < 0.05 are noted in bold. Variables for which FDR ≥ 0.05 in all 12 outcomes have been deleted from this table. Plus (+) superscript on estimates indicates beneficial effect on vision. Minus (--) indicates detrimental effect on vision.

†† For change from baseline in visual acuity letter score, an effect on vision is considered beneficial if it increases the odds of gain, decreases the odds of loss or increases the positive change from baseline.

††† For macular thickness, an effect on vision is considered beneficial if it increases odds of a thin macula, decreases odds of a thick macula, or decreases the positive change from baseline.

* estimates are odds ratios

** estimates are beta coefficients

*** no cystoid space, ≤ 200 microns, 201-≤400 microns, and > 400 microns

Table 3

Multiple Regression Stepwise models for Visual Acuity and Center Point Thickness Outcomes in CRVO participants†

	Change from Baseline in Visual Acuity Letter Score††						Center Point Thickness (um) †††					
	Year 1			Year 2			Year 1			Year 2		
Baseline predictor	**Gain of ≥15***	**Loss of ≥15***	**Change from baseline****	**Gain of ≥15***	**Loss of ≥15***	**Change from baseline****	**≤250***	**≥500***	**Change from baseline****	**≤250***	**≥500***	**Change from baseline****
Age (years)	**0.96--**				**1.04--**							
Visual acuity letter score								**0.97+**				
Duration of macular edema (months)									**11.32--**			
Center point thickness (per 100 microns)							**0.71--**	**1.37--**	**-53.08+**		**1.45--**	**-46.19+**
Area of retinal thickening within the grid (disc areas)		**1.09--**	**-0.73--**									
Area of retinal hemorrhage within the grid (disc areas)		**1.12--**	**-1.16--**		**1.22--**	**-1.69--**						

† Plus (+) superscript on estimates indicates beneficial effect on vision. Minus (--) indicates detrimental effect on vision.

†† For change from baseline in visual acuity letter score, an effect on vision is considered beneficial if it increases the odds of gain, decreases the odds of loss or increases the positive change from baseline.

††† For macular thickness, an effect on vision is considered beneficial if it increases odds of a thin macula, decreases odds of a thick macula, or decreases the positive change from baseline.

* estimates are odds ratios

** estimates are beta coefficients

CRVO = central retinal vein occlusion

Table 4

Regression Models for Visual Acuity and Center Point Thickness Outcomes in BRVO Participants†

	Change from Baseline in Visual Acuity Letter Score††						Center Point Thickness (um) †††					
	Year 1			Year 2			Year 1			Year 2		
Baseline predictor	Gain of ≥15*	Loss of ≥15*	Change from baseline**	Gain of ≥15*	Loss of ≥15*	Change from baseline**	≤250*	≥500*	Change from baseline**	≤250*	≥500*	Change from baseline**
1 mg triamcinolone vs standard care	0.85	0.75	1.49	0.91	3.25	-5.02	0.50	1.75	82.37	0.57	3.08	**103.28**--
4 mg triamcinolone vs standard care	0.92	0.78	-0.22	0.72	3.90	-7.26	0.76	1.61	68.96	0.46	4.97	**115.00**--
Age (years)	**0.97**--	**1.05**--	**-0.42**--	**0.96**--	1.05	**-0.42**--	0.98	1.01	**3.46**--	0.97	1.04	**5.76**--
Coronary artery disease (yes: no)	0.56	2.31	**-7.77**--	0.51	**3.47**--	**-9.39**--	0.48	1.57	58.47	0.82	1.21	39.19
Visual acuity letter score	**0.95**--	1.03	**-0.34**--	**0.94**--	1.00	**-0.41**--	1.01	0.98	**3.21**--	1.00	0.96	3.30
Duration of macular edema (months)	0.92	1.02	**-0.70**--	0.90	0.99	-0.66	0.96	0.99	**9.72**--	0.94	0.95	**14.02**--
Presence of dense macular hemorrhage (yes: no)	1.44	1.22	2.12	1.60	1.08	3.27	1.34	1.19	**-104.2**+	1.21	1.27	**-103.9**+
Prior grid photocoagulation (yes: no)	0.49	1.01	-4.16	1.01	1.36	-1.79	0.49	1.21	**144.59**--	0.65	0.90	114.09
Center point thickness (per 100 microns)	0.99	1.14	-0.83	1.08	1.05	0.40	0.85	**1.29**--	**-80.11**+	0.87	1.20	**-88.43**+
Subretinal fluid (present versus absent)	0.56	1.76	-4.54	0.97	1.71	-2.62	0.85	1.54	**-76.42**+	1.21	0.55	**-121.7**+
Center point thickness after subtracting out subretinal fluid height at center point (per 100 microns)	1.05	1.12	-0.45	1.02	1.04	0.03	**0.80**--	**1.24**--	**-62.49**+	0.79	1.36	**-62.04**+
Area of retinal thickening within the grid (disc areas)	1.04	1.07	0.02	1.01	1.01	0.07	1.04	0.97	**-31.27**+	0.96	1.14	**-21.55**+
Area of retinal hemorrhage within the grid (disc areas)	1.08	1.07	0.28	1.08	0.87	1.08	1.09	1.00	**-31.63**+	1.02	1.04	**-31.09**+
Area of fluorescein leakage within the grid (disc areas)	0.98	1.06	-0.28	0.96	1.06	-0.31	1.10	0.92	**-31.95**+	0.96	1.07	**-22.71**+

BRVO = branch retinal vein occlusion; FDR = False Discovery Rate

†Effects with FDR < 0.05 are noted in bold. Variables for which FDR ≥ 0.05 in all 12 outcomes have been deleted from this table. Plus (+) superscript on estimates indicates beneficial effect on vision. Minus (--) indicates detrimental effect on vision.

††For change from baseline in visual acuity letter score, an effect on vision is considered beneficial if it increases the odds of gain, decreases the odds of loss or increases the positive change from baseline.

†††For macular thickness, an effect on vision is considered beneficial if it increases odds of a thin macula, decreases odds of a thick macula, or decreases the positive change from baseline.

*estimates are odds ratios

** estimates are beta coefficients

Table 5

Multiple Regression Stepwise models for Visual Acuity and Center Point Thickness Outcomes in BRVO participants†

	Change from Baseline in Visual Acuity Letter Score††						Center Point Thickness (um) †††					
	Year 1			Year 2			Year 1			Year 2		
Baseline predictor	**Gain of ≥15***	**Loss of ≥15***	**Change from baseline****	**Gain of ≥15***	**Loss of ≥15***	**Change from baseline****	**≤250***	**≥500***	**Change from baseline****	**≤250***	**≥500***	**Change from baseline****
1 mg triamcinolone vs standard care												**57.48**--
4 mg triamcinolone vs standard care												**80.66**--
Age (years)	**0.96**--	**1.05**--	**-0.41**--	**0.95**--		**-0.39**--			**1.99**--			**3.20**--
Coronary artery disease (yes: no)			**-6.63**--		**3.47**--	**-8.19**--						
Visual acuity letter score	**0.95**--		**-0.39**--	**0.94**--		**-0.45**--						
Duration of macular edema (months)			**-0.52**--									
Center point thickness (per 100 microns)								**1.29**--	**-72.21**+			**-98.39**+
Center point thickness after subtracting out subretinal fluid height at center point (per 100 microns)							**0.80**--					**28.16**+
Area of retinal hemorrhage within the grid (disc areas)												**-9.95**+
Area of fluorescein leakage within the grid (disc areas)									**-13.28**+			

BRVO = branch retinal vein occlusion

† Plus (+) superscript on estimates indicates beneficial effect on vision. Minus (--) indicates detrimental effect on vision.

†† For change from baseline in visual acuity letter score, an effect on vision is considered beneficial if it increases the odds of gain, decreases the odds of loss or increases the positive change from baseline.

††† For macular thickness, an effect on vision is considered beneficial if it increases odds of a thin macula, decreases odds of a thick macula, or decreases the positive change from baseline.

* estimates are odds ratios

** estimates are beta coefficients