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**SCORE2 Report 2**

**Study Design and Baseline Characteristics**

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**Purpose:** To describe the design and baseline characteristics of participants in the Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2) and to compare with cohorts from other retinal vein occlusion trials.

**Design:** Phase III prospective, multicenter, randomized clinical trial designed to assess whether intravitreal bevacizumab is noninferior to intravitreal aflibercept for treatment of decreased vision attributable to macular edema associated with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).

**Participants:** Total of 362 participants: 307 with CRVO and 55 with HRVO.

**Methods:** Demographic and study eye characteristics are summarized and compared between CRVO and HRVO study participants.

**Main Outcome Measures:** Baseline ophthalmic characteristics, including visual acuity and retinal thickness, and medical history characteristics, including hypertension, diabetes mellitus, and coronary artery disease.

**Results:** The mean age of participants was 69 years, 76% of participants were white, and 90% were non-Hispanic. There was a racial disparity with respect to disease type, with 38% of HRVO patients being black compared with 11% of CRVO patients (P value adjusted for multiple testing = 0.0001). This is similar to findings from the previous SCORE Study. Comorbidities included hypertension (77%), diabetes mellitus (31%), and coronary artery disease (15%). At baseline, mean visual acuity letter score was 50 (20/100) (range, 19–73 [20/400 to 20/40]), mean optical coherence tomography (OCT)—measured central subfield thickness was 678 μm (range, 300–1203 μm), and mean number of months from diagnosis of macular edema to randomization was 6 (range, 0–104 months). One hundred twenty (33%) SCORE2 participants had been treated previously with anti–vascular endothelial growth factor (anti-VEGF) therapy, with these participants having baseline visual acuity letter score and OCT-measured central subfield thickness similar to those without prior anti-VEGF treatment, but longer mean duration of macular edema before randomization (18 months vs. 1 month for those without prior anti-VEGF treatment; P < 0.0001).

**Conclusions:** The SCORE2 cohort is a heterogeneous population, including both CRVO and HRVO eyes and both treatment-naïve eyes and eyes treated previously with anti-VEGF, which will allow study results to have broad applicability to CRVO and HRVO patients receiving treatment for macular edema. Similarities of the baseline characteristics of the SCORE2 population to other CRVO trial cohorts will allow meaningful comparisons of outcome results across trials. Ophthalmology 2017;124:245-256 © 2016 by the American Academy of Ophthalmology

Retinal vein occlusion (RVO) is the most common retinal vascular disorder after diabetic retinopathy, affecting 1% to 2% of the population older than 40 years1,2 and 16 million persons worldwide.3 Macular edema is the most frequent cause of vision loss in patients with RVO.4-6 Although many treatment options have been investigated for decreased vision attributable to macular edema associated with central RVO (CRVO),7-10 the Standard Care versus CORTicosteroid for REtinal Vein Occlusion (SCORE) Study, sponsored by the National Eye Institute, was the first phase III clinical trial to demonstrate that a therapy could favorably alter the visual outcomes of CRVO-associated macular edema. The SCORE Study demonstrated that intravitreal injection(s) of triamcinolone acetonide was superior to standard care established by the Central Vein Occlusion Study’ (i.e., observation) for vision loss associated with macular edema secondary to CRVO.11 Subsequently, several industry-sponsored phase III trials demonstrated the efficacy of anti–vascular endothelial growth factor (VEGF) therapy for the treatment of decreased vision due to CRVO-associated macular edema; the Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE) trial18 Study demonstrated favorable visual outcomes associated with the use of intravitreal ranibizumab, and the VEGF Trap-Eye for macular edema secondary to CRVO (COPERNICUS)19 and VEGF Trap-Eye: Investigation of Efficacy and Safety in CRVO (GALILEO)20 studies demonstrated favorable visual outcomes associated with the use of intravitreal aflibercept. In addition, numerous case reports and small randomized clinical trials demonstrating favorable visual...
acuity outcomes following intravitreal bevacizumab in patients with decreased vision attributable to macular edema secondary to CRVO were published.\textsuperscript{15,21–30} In 2009, the Food and Drug Administration approved Ozurdex (Allergan Pharmaceuticals, Inc, Irvine, CA), an intravitreal dexamethasone implant, for treatment of macular edema associated with RVO.\textsuperscript{31} However, it is not commonly used as a first-line therapy for RVO-associated macular edema owing to the higher reported rates of ocular adverse events, such as intraocular pressure (IOP) elevation and cataract, associated with the dexamethasone implant than with anti-VEGF agents.\textsuperscript{18–20,31–33}

Ranibizumab (an antibody fragment) and bevacizumab (a full-length antibody) inhibit all VEGF-A isoforms and have demonstrated similar efficacy and safety in the treatment of age-related macular degeneration\textsuperscript{32} and diabetic macular edema.\textsuperscript{33} Afibercept, a fusion protein of key domains from both VEGF receptor 1 and VEGF receptor 2, includes inhibition of not only all VEGF-A isoforms, but also VEGF-B and placenta-derived growth factor.\textsuperscript{34} In addition to its broader mechanism of action, afibercept has been reported to have a higher binding affinity than ranibizumab.\textsuperscript{35} Bevacizumab repackaged at compounding pharmacies into syringes for treatment of CRVO is much less costly, at approximately $60 per dose,\textsuperscript{36} compared with either ranibizumab ($1950/dose) or afibercept ($1850/dose).\textsuperscript{37}

The Study of COmparative Treatments for REtinial Vein Occlusion 2 (SCORE2) study is designed to determine whether bevacizumab is noninferior to afibercept for the treatment of macular edema secondary to CRVO. In addition, SCORE2 is designed to investigate whether the frequency of intravitreal injections can be reduced in eyes that have responded well to anti-VEGF treatment (reduced injection frequency would represent a more cost-effective treatment regimen, with fewer risks to patients of injection-related adverse events and a lesser logistical treatment burden for patients and providers), and to explore the impact of alternative treatment strategies (a different anti-VEGF agent or intravitreal dexamethasone) in eyes that have not responded well to an anti-VEGF agent.

**Methods**

**Study Synopsis**

SCORE2 is a multicenter, prospective, randomized, phase III clinical trial designed to determine whether bevacizumab is noninferior to afibercept for the treatment of decreased vision due to macular edema associated with CRVO. The primary efficacy outcome of this study is change in Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity letter score from the randomization visit to the month 6 follow-up visit. The noninferiority margin is set at an ETDRS visual acuity letter score of 5, as measured by the electronic ETDRS (E-ETDRS) visual acuity test. Secondary efficacy outcomes are based on visual acuity testing, spectral-domain (SD) optical coherence tomography (OCT), fundus photography, ultrawide-field fluorescein angiography (FA), and quality of life as measured by the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25).\textsuperscript{38} and safety outcomes include both ocular and systemic events, as listed in Table 1. Study participants are followed for 1 year after randomization. SCORE2 is registered on http://www.clinicaltrials.gov (identifier: NCT01969708).

The target sample size was 360 patients. Study eyes were randomized in a 1:1 ratio to intravitreal bevacizumab (1.25 mg) every 4 weeks versus intravitreal afibercept (2.0 mg) every 4 weeks. The primary noninferiority comparison between the 2 groups was performed at month 6. Following assessment of the primary outcome at month 6, SCORE2 used an adaptive treatment strategy in which participants assigned at baseline to afibercept who meet the protocol-defined criteria for a good response were re-randomized to either continuing afibercept every 4 weeks or changing to a treat-and-extend (TAE) regimen. Participants assigned at baseline to bevacizumab who met the protocol-defined criteria for a good response were re-randomized to either continuing bevacizumab every 4 weeks or changing to a TAE regimen. This allowed an assessment of whether a TAE regimen can produce visual results similar to continued treatment every 4 weeks. Participants originally assigned to bevacizumab with a protocol-defined poor or marginal response at 6 months received afibercept. Participants originally assigned to afibercept with a protocol-defined poor or marginal response at month 6 received rescue therapy with a dexamethasone implant. Rescue therapy with bevacizumab for these patients was not part of the protocol because it was deemed more likely that participants who failed to respond to afibercept, with its broad mechanism of action, will more likely respond to a dexamethasone implant. An abbreviated description of the SCORE2 design and methods is given herein; a full description is provided elsewhere.\textsuperscript{39}

Participating study personnel such as physician-investigators and study coordinators were certified by the data coordinating center (The Emmes Corporation, Rockville, MD) before they could participate in this study. All physician-investigators were board-certified in ophthalmology and had completed a retina fellowship. Technicians who performed visual acuity testing and refraction had received Ophthalmic Clinical Trial Training and Certification (The Emmes Corporation, Rockville, MD). Photographers performing FA were trained and certified by Optos (Dunfermline, UK), and photographers and technicians who performed the fundus photographs and OCT images for this study were certified by the University of Wisconsin Fundus Photograph Reading Center (Reading Center) before they could participate in this study.

The SCORE2 protocol and informed consent were approved by the respective clinical centers’ institutional review boards or a centralized institutional review board. Investigators at 66 clinical centers randomized and followed SCORE2 participants in accordance with the study protocol and Manual of Policies and Procedures. Men and women at least 18 years of age could each contribute at most 1 eye to the study. Table 2 summarizes the major ocular inclusion and exclusion criteria.

**Screening and Primary Randomization**

Prospective participants first consented to screening and then were interviewed to obtain demographic information and medical history, including ocular history and current medications. The following screening examinations were required within 21 days of randomization: (1) IOP of both eyes by Goldmann applanation tonometry or a Tonopen; (2) ophthalmic examination including dilated ophthalmoscopy and slit-lamp examination (for lens assessment, modified Age-Related Eye Disease Study grading was used); (3) ultra-widefield FA at sites with an Optos ultra-widefield model 200Tx camera; (4) NEI VFQ-25\textsuperscript{35}; (5) blood pressure measurement; and (6) height and weight measurements. The following screening examinations were required within 8 days of initial randomization: measurement of visual acuity and manifest refraction, using E-ETDRS visual acuity at 3 meters by a
and stroke by prolonged antiplatelet therapy in various categories of patients.

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**Table 1. Listing of SCORE2 Secondary Outcomes**

**Efficacy: Visual acuity**
- Proportion with improvement or worsening by 15 or more in visual acuity letter score
- Proportion meeting ETDRS visual acuity letter score of 70 (approximate Snellen equivalent of 20/40) or better
- Absolute and change from baseline to each monthly visit in visual acuity letter score and within subgroups of (1) baseline visual acuity strata; (2) history and no history of anti-VEGF treatment prior to baseline; and (3) CRVO and HRVO disease status

- Spectral-domain optical coherence tomography
  - Absolute and change from baseline in central subfield thickness, center point thickness, and macular volume
  - Presence of intraretinal cystoid spaces and subretinal fluid
  - Photoreceptor length

**Color fundus photography**
- Area of retinal thickness and hemorrhage
- Ultra-widefield fluorescein angiography
  - Area of peripheral retinal nonperfusion (defined as the absence of retinal arterioles and/or capillaries and detected by characteristics such as a “pruned” appearance of adjacent arterioles and a darker appearance of area of fluorescein leakage

**National Eye Institute Visual Function Questionnaire-25**
- Absolute and change from baseline in total score and subscale scores

**Safety: Ocular events**
- Increased IOP and surgery to lower IOP
- Infectious and culture-negative endophthalmitis
- Retinal detachment
- Vitreous hemorrhage
- New-onset retinal arterial occlusion
- Neovascular events

**Systemic**
- Arterial thromboembolic events as defined by the Antiplatelet Trialist’s Collaboration*

CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; HRVO = hemiretinal vein occlusion; IOP = intraocular pressure; VEGF = vascular endothelial growth factor.


SCORE2 certified technician; (2) modified 3-field stereoscopic color fundus photographs; (3) SD OCT; and (4) for women of childbearing potential (i.e., those who are pre-menopausal and not surgically sterilized) a urine pregnancy test. All imaging tests (color fundus photographs, FA, and SD OCT) were sent to the Reading Center. For SD OCT, the Reading Center accepted scans from equipment from both the Heidelberg and Zeiss manufacturers.

Once all eligibility criteria were met, and following informed consent for randomization, the eligible eye of each participant was randomized, via a secure, Internet-based central system maintained at the Data Coordinating Center, to 1 of 2 equally sized treatment arms: (1) intravitreal bevacizumab (1.25 mg) every 4 weeks or (2) intravitreal aflibercept (2.0 mg) every 4 weeks. Randomization was stratified according to the following baseline screening visual acuity groups: good visual acuity (73–59 letters: 20/40 to 20/63), moderate visual acuity (58–49 letters: 20/80 to 20/100), and poor visual acuity (48–19 letters: 20/125 to 20/400). In participants with both eyes eligible, the eye randomized into SCORE2 was chosen by the physician and patient.

The injection protocol for intravitreal bevacizumab and intravitreal aflibercept administration is described in detail elsewhere17 and is described briefly below. The 40 mg/ml aflibercept study drug (Eylea) was provided in single-dose vials by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) for 0.05-ml intravitreal injections. The bevacizumab study drug was repackaged from the original commercial product (Avastin) made by Genentech, Inc. (South San Francisco, CA) into smaller sterile 2-ml vials by the University of Pennsylvania Investigational Drug Service. The vials contained 0.1 ml (0.05 ml minimum withdrawable volume) of 25 mg/ml bevacizumab. For dexamethasone, the commercially available intravitreal implant product (Ozurdex) 0.7 mg was supplied by Allergan Pharmaceuticals, Inc. in a foil pouch in its original box, with a single-use applicator.

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**Participant Visit Schedule and Secondary Randomization**

Once randomized, all participants were expected to be followed for 1 year. Study visits were scheduled every 4 weeks for 6 months following randomization (Table 3). At month 6, the primary outcome was assessed, after which study eyes were categorized into 1 of 2 groups (1: poor or marginal response; 2: good response) based on response to treatment. Poor or marginal response was defined as (1) visual acuity letter score less than 58 letters (less than 20/80) or a visual acuity letter score improvement of 5 or less from baseline with at least some of the visual acuity deficit attributed by the investigator to macular edema secondary to CRVO; and (2) OCT had 1 or more of the following: retinal thickness (defined as a central subfield thickness ≥300 μm, or ≥320 μm if the OCT measurement is taken using a Heidelberg Spectralis machine), presence of intraretinal cystoid spaces, subretinal fluid. All eyes that did not meet the criteria for poor or marginal response were considered to have a good response. (Note that response type is not the same as primary outcome.) For the study eyes with a good response, a secondary 1:1 randomization occurred, with assignment to either (1) 6 injections (every 4 weeks, from month 6 to month 11) with the original treatment assignment (either bevacizumab or aflibercept) or (2) TAE regimen with the originally assigned treatment (either bevacizumab or aflibercept), with each subsequent interval between visits increased by 2 weeks if the patient does well. Intervals between visits could be extended to a maximum of 10 weeks. Eyes with retinal thickness (as defined above), intraretinal cystoid spaces, or subretinal fluid on OCT were to be re-treated and brought back in 4 weeks. Study eyes with a poor or marginal response were to receive rescue therapy. Eyes in the bevacizumab arm were to receive aflibercept at
Inclusion criteria
- Best-corrected electronic ETDRS visual acuity letter score of ≥19 letters (approximately 20/400) and ≤73 letters (approximately 20/40) based on the ETDRS visual acuity protocol. The investigator must believe that a study eye with visual acuity letter score between 19 and 33 is perfused.
- Center-involved macular edema associated with CRVO or HRVO present on clinical examination. Note: Enrollment limited to no more that 25% of the planned sample size with HRVO eyes.
- Retinal thickness as measured by SD OCT, defined as central subfield thickness ≥300 μm. If the SD OCT measurement is taken using a Heidelberg Spectralis machine, the central subfield thickness must be ≥320 μm.
- Media clarity, pupilary dilation, and participant cooperation sufficient for adequate fundus photographs.

Exclusion criteria
- Examination evidence of vitreoretinal interface disease (e.g., vitreomacular traction, epiretinal membrane), either on clinical examination or OCT, thought to be contributing to macular edema.
- Presence of an ocular condition such that visual acuity would not improve from resolution of the edema (e.g., foveal atrophy).
- Presence of an ocular condition that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study.
- Substantial cataract estimated to have reduced visual acuity by ≥3 lines.
- History of laser photocoagulation for macular edema within 3 months before randomization.
- History of intravitreal corticosteroid within 4 months of randomization.
- Intravitreal anti-VEGF injection within 2 months of randomization.
- History of peribulbar or retrobulbar corticosteroid use for any reason within 2 months before randomization.
- History of periarteritis nodosa pericentral retinal vein occlusion or sector laser photocoagulation within 3 months before randomization or anticipated within the next 3 months following randomization.
- History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within 4 months before randomization or anticipated within the next 6 months following randomization.
- History of YAG capsulotomy performed within 2 months before randomization.
- Aphakia.
- Presence of an anterior chamber intraocular lens.
- Examination evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis.
- History of macular detachment.
- Examination evidence of any diabetic retinopathy.

CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; HRVO = hemiretinal vein occlusion; SD OCT = spectral-domain optical coherence tomography; VEGF = vascular endothelial growth factor; YAG = yttrium-aluminum-garnet.

Table 2. SCORE2 Study Eye Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of laser photocoagulation for macular edema within 3 months before randomization.</td>
</tr>
<tr>
<td>History of intravitreal corticosteroid within 4 months of randomization.</td>
</tr>
<tr>
<td>Intravitreal anti-VEGF injection within 2 months of randomization.</td>
</tr>
<tr>
<td>History of peribulbar or retrobulbar corticosteroid use for any reason within 2 months before randomization.</td>
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<tr>
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<tr>
<td>History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within 4 months before randomization or anticipated within the next 6 months following randomization.</td>
</tr>
<tr>
<td>History of YAG capsulotomy performed within 2 months before randomization.</td>
</tr>
<tr>
<td>Aphakia.</td>
</tr>
<tr>
<td>Presence of an anterior chamber intraocular lens.</td>
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<tr>
<td>Examination evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis.</td>
</tr>
<tr>
<td>History of macular detachment.</td>
</tr>
<tr>
<td>Examination evidence of any diabetic retinopathy.</td>
</tr>
</tbody>
</table>

months 6, 7, and 8 and then be put on a TAE regimen. Eyes in the aflibercept arm were to receive intravitreal dexamethasone implant at month 6 and then pro re nata at month 9, 10, or 11. Secondary outcomes were assessed at month 12.

Testing Procedures at Follow-up Visits
At each study follow-up visit, participants had E-ETDRS testing in each eye, IOP measurement in each eye, slit-lamp and dilated funduscopic examinations on each eye, and OCT imaging of the study eye. At month 6 and month 12, the visual acuity examiner and OCT technician were required to be masked to treatment assignment. Before each study injection, a urine pregnancy test was performed for all women of childbearing potential. Modified 3-field stereoscopic color fundus photographs of the study eye, lens assessment for cataract (using modified Age-Related Eye Disease Study standard lens photographs) in the study eye, blood pressure measurement, NEI VFQ-25, and ultra-widefield FA (at selected sites) of both eyes were performed at month 6 and month 12.

Intravitreal Injection Procedure
On the day of injection, topical antibiotic drops could be administered to the study eye at the investigator’s discretion. A drop of topical anesthesia was applied to the study eye. Additional anesthesia was at the discretion of the investigator. Aspiration was achieved by either application of 2 to 3 drops of 5% povidone—iodine in the lower fornix and use of a cotton-tipped applicator soaked in 5% povidone—iodine applied to the conjunctiva over the intended injection site and allowed to dry for 30 to 60 seconds, or use of either a cotton-tipped applicator soaked in 5% povidone—iodine or a 10% povidone—iodine Swabstick applied to the intended injection site (scrubbing the upper and lower eyelid margins and eyelashes was optional). A sterile eyelid speculum was used to separate the eyelids.

Following the preparation procedure, either 1.25 mg aflibercept, or an intravitreal dexamethasone implant was injected into the vitreous cavity via the pars plana 3 to 4 mm posterior to the limbus. The eyelid speculum was removed and indirect ophthalmoscopy was performed to confirm the intravitreal location of the dexamethasone implant (if applicable) and to confirm that the central retinal artery was perfused. A topical antibiotic could be administered after injection at the investigator’s discretion.

Statistical Methods
The primary efficacy outcome of this study is change in visual acuity letter score from the randomization visit to the 6-month follow-up visit. A noninferiority test was carried out by modeling baseline and 6-month visual acuity data for each patient in the primary analysis as a 2-step time series in which each 6-month outcome is correlated with its corresponding baseline measure, which is modeled as being the same in both groups. The noninferiority test involves testing the null hypothesis of $I_5 \leq -M$ versus the alternative of $I_5 > -M$, where $M = 5$ is the noninferiority margin and $I_5$ the treatment effect, estimates the visual acuity change from baseline in the treated group minus the visual acuity change from baseline in the control group. Interim testing was carried out using the Lan-DeMets interim monitoring boundary with a 1-tailed level 0.025 O’Brien-Fleming-type spending function, adapted for noninferiority testing. Sample size was reestimated (before any interim monitoring) after about half
the total expected number of participants attained their 6-month outcome. This was carried out using the perturbed unblinding method,\textsuperscript{11} under which the variance structure of the data is revealed, while the treatment effect is obscured.

In Tables 4 and 5, demographic and study eye characteristics are summarized and compared between treatment arms to assess the success of the randomization process in creating comparable groups, as well as to compare the characteristics of study eyes and participants with respect to disease type, CRVO and hemiretinal vein occlusion (HRVO), and whether the participant received anti-VEGF treatment before randomization. Chi-square tests were used for categorical variables and t tests for continuous variables. No formal multiplicity adjustment to compare randomized treatment groups was performed because the aim is to indict the randomization procedure if there is even moderately convincing evidence that it performed incorrectly. However, family-wide error was controlled in the multiple-testing setting of Tables 4 and 5 when comparing disease types (CRVO vs. HRVO) and prior versus no prior anti-VEGF groups. This was accomplished by adjusting P values using Hochberg’s sequentially rejective method\textsuperscript{12} for the disease-type and prior-type P values, combined across Tables 4 and 5. To identify significant results, P values less than 0.05, either before adjustment (comparing treatment groups) or after adjustment (comparing CRVO vs. HRVO or prior vs. no prior anti-VEGF therapy), are highlighted in Tables 4 and 5.

### Results

Between September 2014 and November 2015, 362 subjects were enrolled in SCORE2. The mean age of participants in SCORE2 was 69 years; 43% were women; 76% of participants were white, 15% black, and 10% Hispanic. The mean visual acuity letter score was 50 (20/100), and participants had macular edema for an average of 6 months before randomization. The mean SD OCT—measured central subfield thickness was 678 μm, 33% had received prior anti-VEGF treatment, and 15% of the population had a HRVO as diagnosed by the investigator at the SCORE2 clinical center and defined as an eye that has retinal hemorrhage or other biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed and/or dilated venous system or previously dilated venous system) in 5 or more clock hours but fewer than all 4 quadrants. Approximately 27% of the study eyes had a cataract extraction at randomization and only 17% had no history of a cataract. Comorbid conditions included diabetes (31%; type 2 in all but 1 patient), hypertension (77%), and coronary artery disease (15%). The mean baseline NEI VFQ-25 overall composite score was 77. When comparing the treatment groups, only 1 test was significant (t test for duration of macular edema before study enrollment, aflibercept = 8 months, bevacizumab = 5 months, unadjusted P = 0.03). No other demographic, study eye, or clinical characteristic differed significantly between the treatment arms. Considering that 29 tests went into the construction of the treatment group comparisons, this is roughly the number of significant outcomes we might expect by chance even if there are no differences between groups. Also, the chi-square test for duration of macular edema before study enrollment was not significant. We ascribe this nominally significant outcome to type I error and conclude that this pattern of P values is consistent with the treatment groups being similar. In contrast to the treatment group comparisons, there are 2 significant baseline disease-type comparisons and 2
Table 4. Baseline Characteristics of Study of Comparative Treatments for Retinal Vein Occlusion 2 Participants*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomized Treatment Assignment</th>
<th>Disease Type</th>
<th>Anti-VEGF Treatment Prior to SCORE2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afibercept</td>
<td>Bevacizumab</td>
<td>CRVO</td>
</tr>
<tr>
<td>No. of participants</td>
<td>180</td>
<td>182</td>
<td>307</td>
</tr>
<tr>
<td>No</td>
<td>241</td>
<td>121</td>
<td>362</td>
</tr>
</tbody>
</table>

**Demographic characteristics**

- **Age (yrs), mean (SD)**
  - 69 (11) vs 69 (13)
  - 69 (12) vs 70 (13)
  - 68 (12) vs 71 (11)
  - 69 (12)

- **<50**
  - 7 (3.9) vs 15 (8.2)
  - 18 (5.9) vs 4 (7.3)
  - 18 (7.5) vs 4 (3.3)
  - 22 (6.1)

- **50–<60**
  - 28 (15.6) vs 26 (14.3)
  - 48 (15.6) vs 6 (10.9)
  - 35 (15.8) vs 16 (13.2)
  - 54 (14.9)

- **60–<70**
  - 59 (32.8) vs 48 (26.4)
  - 95 (30.9) vs 12 (21.8)
  - 74 (30.7) vs 33 (27.3)
  - 107 (29.6)

- **70–<80**
  - 58 (32.2) vs 52 (28.6)
  - 92 (30.0) vs 18 (32.7)
  - 65 (27.0) vs 45 (37.2)
  - 110 (30.4)

- **≥80**
  - 28 (15.6) vs 41 (22.5)
  - 54 (17.6) vs 15 (27.3)
  - 46 (19.1) vs 23 (19.0)
  - 69 (19.1)

- **Women**
  - 82 (45.6) vs 75 (41.2)
  - 136 (44.3) vs 21 (38.2)
  - 96 (39.8) vs 61 (50.4)
  - 157 (43.4)

- **White**
  - 131 (72.8) vs 145 (79.7)
  - 246 (80.1) vs 30 (54.5)
  - 186 (77.2) vs 90 (74.4)
  - 276 (76.2)

- **Black**
  - 28 (15.6) vs 26 (14.3)
  - 28 (9.1) vs 4 (7.3)
  - 20 (8.3) vs 12 (9.9)
  - 32 (8.8)

- **Not Hispanic or Latino**
  - 164 (91.1) vs 160 (87.9)
  - 274 (89.3) vs 50 (90.9)
  - 214 (88.8) vs 110 (90.9)
  - 324 (89.5)

**Study eye characteristics**

- **E-ETDRS visual acuity**
  - 77 (15) vs 77 (17)
  - 8 (3.3) vs 21 (17.4)
  - 29 (8.0)

- **Duration of macular edema**
  - 8 (17) vs 5 (10)
  - 7 (14) vs 3 (10)
  - 1 (3) vs 18 (19)
  - 6 (14)

- **OCT central retinal thickness**
  - 665 (220) vs 690 (238)
  - 691 (230) vs 606 (213)
  - 689 (229) vs 655 (231)
  - 678 (230)

- **Prior anti-VEGF treatment**
  - 65 (36.1) vs 56 (30.8)
  - 108 (35.2) vs 13 (23.6)
  - 42 (17.4) vs 13 (10.7)
  - 59 (15.2)

- **Lens status**
  - 123 (40.7) vs 123 (40.7)
  - 77 (20.3) vs 77 (20.3)
  - 90 (27.3) vs 90 (27.3)
  - 107 (32.1)

- **Natural lens, no history of cataract**
  - 108 (60.0) vs 95 (52.2)
  - 170 (55.4) vs 33 (60.0)
  - 137 (56.8) vs 66 (54.5)
  - 203 (56.1)

- **Diabetes mellitus**
  - 1 (0.5) vs 1 (0.5)
  - 0 (0.0) vs 0 (0.0)
  - 0 (0.0) vs 0 (0.0)
  - 0 (0.0)

- **Hypertension**
  - 114 (63.3) vs 129 (70.9)
  - 199 (64.8) vs 44 (80.0)
  - 230 (95.4) vs 13 (10.7)
  - 243 (67.1)

- **Coronary artery disease**
  - 18 (10.0) vs 11 (6.0)
  - 25 (8.1) vs 4 (7.3)
  - 8 (3.3) vs 21 (17.4)
  - 29 (8.0)

- **NEI-VFQ-25 overall score, mean (SD)**
  - 77 (15) vs 77 (17)
  - 77 (16) vs 78 (16)
  - 76 (16) vs 78 (16)
  - 77 (16)

CRVO = central retinal vein occlusion; E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study; HRVO = hemiretinal vein occlusion; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; OCT = optical coherence tomography; SD = standard deviation; VEGF = vascular endothelial growth factor.

*p values that are < 0.05, either before adjustment (comparing treatment groups) or after adjustment (comparing CRVO vs. HRVO, or prior vs. no prior anti-VEGF) appear in boldface.

1Data are n (%) unless otherwise noted.

Significant baseline prior versus no prior anti-VEGF treatment comparisons, even after P value adjustment by Hochberg’s method; these comparisons are described below.

Comparison of Hemiretinal Vein Occlusion and Central Retinal Vein Occlusion Eyes. The racial distribution differed between HRVO and CRVO patients, with 38% of participants with HRVO being black compared with 11% of CRVO participants (adjusted chi-square P = 0.0001; Table 4). Area of intraretinal and/ or subretinal hemorrhage within the grid based on fundus photography is larger in CRVO than HRVO eyes (total area of blood >50% of grid in 21% of CRVO eyes compared with 7% of HRVO eyes; adjusted chi-square P = 0.04; Table 5). One participant in SCORE2 was mistakenly randomized as a CRVO participant but actually had branch retinal vein occlusion (BRVO). This participant remains in the study and, for purposes of analyses, was included in the CRVO group. There was 98% agreement between investigators and the SCORE2 Reading Center on the diagnosis of CRVO, and 70% agreement on the diagnosis of HRVO (Table 5).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomized Treatment Assignment</th>
<th>Disease Type</th>
<th>Anti-VEGF Treatment Before SCORE2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afibercept</td>
<td>Bevacizumab</td>
<td>CRVO</td>
<td>HRVO</td>
</tr>
<tr>
<td>OCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of images evaluated for center point</td>
<td>156</td>
<td>164</td>
<td>270</td>
<td>50</td>
</tr>
<tr>
<td>Retinal thickness: center point (μm) – mean (SD)</td>
<td>687 (244)</td>
<td>709 (264)</td>
<td>714 (254)</td>
<td>613 (243)</td>
</tr>
<tr>
<td>No. of images evaluated for total volume</td>
<td>43</td>
<td>42</td>
<td>72</td>
<td>13</td>
</tr>
<tr>
<td>Retinal thickness: Total volume (mm³) – mean (SD)</td>
<td>9.95 (2.73)</td>
<td>10.1 (1.62)</td>
<td>10.0 (2.25)</td>
<td>9.77 (2.28)</td>
</tr>
<tr>
<td>No. of images assessed</td>
<td>162</td>
<td>167</td>
<td>277</td>
<td>52</td>
</tr>
<tr>
<td>Presence of subretinal fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>41 (25.3)</td>
<td>31 (18.6)</td>
<td>61 (22.0)</td>
<td>11 (21.2)</td>
</tr>
<tr>
<td>Questionable</td>
<td>6 (3.7)</td>
<td>13 (7.8)</td>
<td>16 (5.8)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Definite, central subfield involved</td>
<td>86 (53.1)</td>
<td>86 (51.5)</td>
<td>139 (50.2)</td>
<td>33 (63.5)</td>
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<tr>
<td>Definite, outside central subfield</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cannot grade</td>
<td>28 (17.3)</td>
<td>37 (22.2)</td>
<td>60 (21.7)</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Cystoid spaces</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Questionable</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Definite, central subfield involved</td>
<td>158 (97.5)</td>
<td>165 (98.8)</td>
<td>272 (98.2)</td>
<td>51 (98.1)</td>
</tr>
<tr>
<td>Definite, outside central subfield</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
<td>3 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Intraretinal fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Questionable</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Definite, central subfield involved</td>
<td>160 (98.8)</td>
<td>165 (98.8)</td>
<td>274 (98.9)</td>
<td>51 (98.1)</td>
</tr>
<tr>
<td>Definite, outside central subfield</td>
<td>2 (1.2)</td>
<td>2 (0.0)</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Posterior vitreous detachment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Absent</td>
<td>83 (51.2)</td>
<td>90 (53.9)</td>
<td>147 (53.1)</td>
<td>25 (50.0)</td>
</tr>
<tr>
<td>Questionable</td>
<td>10 (6.2)</td>
<td>7 (4.2)</td>
<td>13 (4.7)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Definite, nonadherent</td>
<td>4 (2.5)</td>
<td>5 (3.0)</td>
<td>7 (2.5)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Definite, questionable adherence</td>
<td>6 (3.7)</td>
<td>7 (4.2)</td>
<td>12 (4.3)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Definite, partially adherent</td>
<td>58 (35.8)</td>
<td>56 (33.5)</td>
<td>96 (34.7)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
<td>2 (0.7)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Epiretinal membrane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>55 (34.0)</td>
<td>57 (34.1)</td>
<td>91 (32.9)</td>
<td>21 (40.4)</td>
</tr>
<tr>
<td>Questionable</td>
<td>35 (21.6)</td>
<td>44 (26.3)</td>
<td>65 (23.5)</td>
<td>14 (26.9)</td>
</tr>
<tr>
<td>Definite, central subfield involved</td>
<td>9 (5.6)</td>
<td>11 (6.6)</td>
<td>19 (6.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Definite, outside central subfield</td>
<td>62 (38.3)</td>
<td>54 (32.3)</td>
<td>101 (36.5)</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.4)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Retinal traction and distortion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>59 (36.4)</td>
<td>61 (36.5)</td>
<td>97 (35.0)</td>
<td>23 (44.2)</td>
</tr>
<tr>
<td>Questionable</td>
<td>30 (18.5)</td>
<td>42 (25.1)</td>
<td>60 (21.7)</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>Definite, central subfield involved</td>
<td>9 (5.6)</td>
<td>11 (6.6)</td>
<td>19 (6.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Definite, outside central subfield</td>
<td>63 (38.9)</td>
<td>52 (31.1)</td>
<td>100 (36.1)</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.4)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Macular hole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>158 (97.5)</td>
<td>165 (98.8)</td>
<td>274 (98.9)</td>
<td>49 (94.2)</td>
</tr>
<tr>
<td>Questionable</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>2 (3.8)</td>
</tr>
</tbody>
</table>

(Continued)

Scott et al. SCORE2: Design and Baseline Characteristics
Table 5. (Continued.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomized Treatment Assignment</th>
<th>Disease Type</th>
<th>Anti-VEGF Treatment Before SCORE2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afiblercept</td>
<td>Bevacizumab</td>
<td>CRVO</td>
</tr>
<tr>
<td>Pseudohole or lamellar hole</td>
<td>2 (1.2)</td>
<td>0 (1.0)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Cannot grade</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Status of IS-OS within central subfield</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Questionably abnormal</td>
<td>7 (4.3)</td>
<td>7 (4.2)</td>
<td>14 (5.1)</td>
</tr>
<tr>
<td>Definitely abnormal, absent</td>
<td>14 (8.6)</td>
<td>14 (8.4)</td>
<td>23 (8.3)</td>
</tr>
<tr>
<td>Definitely abnormal, patchy</td>
<td>22 (13.6)</td>
<td>16 (9.6)</td>
<td>28 (10.1)</td>
</tr>
<tr>
<td>Cannot grade</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Color fundus photograph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of images evaluated</td>
<td>173 (87.9)</td>
<td>152 (86.4)</td>
<td>289 (98.0)</td>
</tr>
<tr>
<td>Type of vein occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>152 (87.9)</td>
<td>152 (86.4)</td>
<td>289 (98.0)</td>
</tr>
<tr>
<td>Hemicentral</td>
<td>20 (11.6)</td>
<td>23 (13.1)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Branch</td>
<td>0 (0.0)</td>
<td>3 (1.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cannot grade</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Area of intraretinal and/or subretinal hemorrhage within grid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total area of blood 1% to &lt;25% of grid</td>
<td>92 (53.2)</td>
<td>83 (47.2)</td>
<td>153 (51.9)</td>
</tr>
<tr>
<td>Total area of blood 25% to 50% of grid</td>
<td>49 (28.3)</td>
<td>45 (25.6)</td>
<td>67 (22.7)</td>
</tr>
<tr>
<td>Total area of blood &gt;50% of grid</td>
<td>25 (14.5)</td>
<td>42 (23.9)</td>
<td>63 (21.4)</td>
</tr>
<tr>
<td>Cannot grade</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>7 (4.0)</td>
<td>5 (2.8)</td>
<td>11 (3.7)</td>
</tr>
</tbody>
</table>

CRVO = central retinal vein occlusion; HRVO = hemiretinal vein occlusion; IS-OS = inner segment-outer segment; OCT = optical coherence tomography; VEGF = vascular endothelial growth factor.

*P values that are <0.05, either before adjustment (comparing treatment groups) or after adjustment (comparing CRVO vs. HRVO, or prior vs. no prior anti-VEGF) appear in boldface.

Data are n (%) unless otherwise noted.
Comparison of Study Eyes with and without Prior Anti–Vascular Endothelial Growth Factor Treatment. Eyes with prior anti-VEGF treatment had a longer duration of macular edema at baseline (mean, 18 months) compared with those without prior anti-VEGF treatment (1 month; adjusted \( t \) test, \( P < 0.0001 \), Table 4). The ability to grade presence of subretinal fluid by SD OCT differed between these 2 groups, with 6% of eyes with prior anti-VEGF treatment having “cannot grade” and 27% of eyes with no prior anti-VEGF having “cannot grade” (adjusted chi-square, \( P = 0.0101 \); Table 5). Area of intraretinal and/or subretinal hemorrhage within the grid based on fundus photography is larger in eyes with no prior anti-VEGF (total area of blood >50% of ETDRS grid = 26%) than in the prior anti-VEGF group (6%; adjusted chi-square, \( P < 0.0001 \); Table 5).

**Discussion**

At present, there are no randomized controlled clinical trial data comparing the safety and efficacy of different anti-VEGF agents for the treatment of decreased vision attributable to macular edema associated with RVO. SCORE2 was designed to determine whether bevacizumab is non-inferior to aflibercept for the treatment of decreased vision attributable to macular edema secondary to CRVO, to investigate whether the frequency of intravitreal injections can be reduced in eyes that have responded well to anti-VEGF treatment, and to assess the impact of alternative treatment strategies (a different anti-VEGF agent or intravitreal dexamethasone) in eyes that have not responded well to an anti-VEGF agent.

To investigate the comparability of the SCORE2 population to those of prior clinical trials, we compared the baseline characteristics of the SCORE2 participants with baseline characteristics from other clinical studies that have evaluated patients with CRVO. The comparison described herein and summarized in Table 6 includes participants from the SCORE-CRVO trial, \(^{17} \) CRUISE trial, \(^{18} \) COPERNICUS trial, \(^{19} \) GALILEO Study, \(^{20} \) CVOS (group M study), \(^{7} \) Geneva trial, \(^{31} \) CVOS (group M study), \(^{7} \) and the Eye Disease Case-Control Study (EDCCS). \(^{43} \) Across these studies, the mean patient age was in the 60s (range of the means, 62–69 years), the proportion of women participating ranged from 41% to 47%, the mean baseline E-ETDRS visual acuity letter score was close to 50 (range, 48–54; letters were not reported for group M of the CVOS but the mean Snellen equivalent, 20/125, was comparable to that of the other studies), and the mean OCT-measured central subfield thickness ranged from 552 to 685 \( \mu \)m. At baseline, the study population of the Geneva Study had the best mean visual acuity letter score (54) and the lowest OCT-measured central subfield thickness (552 \( \mu \)m); this is likely because the Geneva Study included patients with branch RVO as well as patients with CRVO. \(^{31} \) The reported duration of disease is longer in SCORE2 compared with previous CRVO trials (Table 6), but because estimation of disease duration is generally based on patients’ recollection of symptom duration, it is unknown whether the disease duration differs meaningfully among the CRVO trials.

**Table 6. Comparison of Study Eyes with and without Prior Anti–Vascular Endothelial Growth Factor Treatment**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>BRVO (includes 55 HRVO eyes)</th>
<th>SCORE-CRVO</th>
<th>CRUISE</th>
<th>COPERNICUS</th>
<th>GALILEO Study</th>
<th>CVOS (group M study)</th>
<th>Geneva</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>362</td>
<td>271</td>
<td>187</td>
<td>155</td>
<td>177</td>
<td>126</td>
<td>353</td>
</tr>
<tr>
<td>Ages, yrs (mean)</td>
<td>69.4</td>
<td>68.3</td>
<td>68.0</td>
<td>68.4</td>
<td>62.0</td>
<td>45.0</td>
<td>67.2</td>
</tr>
<tr>
<td>Women (%)</td>
<td>43</td>
<td>45</td>
<td>43</td>
<td>43</td>
<td>44</td>
<td>47</td>
<td>41</td>
</tr>
<tr>
<td>White (%)</td>
<td>76</td>
<td>91</td>
<td>84</td>
<td>79</td>
<td>72</td>
<td>75</td>
<td>94</td>
</tr>
</tbody>
</table>
| Eyes with prior VEGF treatment having OCT differed between these 2 groups, with 6% of eyes with prior anti-VEGF treatment having “cannot grade” and 27% of eyes with no prior anti-VEGF having “cannot grade” (adjusted chi-square, \( P = 0.0101 \); Table 5). Area of intraretinal and/or subretinal hemorrhage within the grid based on fundus photography is larger in eyes with no prior anti-VEGF (total area of blood >50% of ETDRS grid = 26%) than in the prior anti-VEGF group (6%; adjusted chi-square, \( P < 0.0001 \); Table 5).

**Discussion**

At present, there are no randomized controlled clinical trial data comparing the safety and efficacy of different anti-VEGF agents for the treatment of decreased vision attributable to macular edema associated with RVO. SCORE2 was designed to determine whether bevacizumab is non-inferior to aflibercept for the treatment of decreased vision attributable to macular edema secondary to CRVO, to investigate whether the frequency of intravitreal injections can be reduced in eyes that have responded well to anti-VEGF treatment, and to assess the impact of alternative treatment strategies (a different anti-VEGF agent or intravitreal dexamethasone) in eyes that have not responded well to an anti-VEGF agent.

To investigate the comparability of the SCORE2 population to those of prior clinical trials, we compared the baseline characteristics of the SCORE2 participants with baseline characteristics from other clinical studies that have evaluated patients with CRVO. The comparison described herein and summarized in Table 6 includes participants from the SCORE-CRVO trial, CRUISE trial, COPERNICUS trial, GALILEO Study, CVOS (group M study), Geneva trial, CVOS (group M study), and the Eye Disease Case-Control Study (EDCCS). Across these studies, the mean patient age was in the 60s (range of the means, 62–69 years), the proportion of women participating ranged from 41% to 47%, the mean baseline E-ETDRS visual acuity letter score was close to 50 (range, 48–54; letters were not reported for group M of the CVOS but the mean Snellen equivalent, 20/125, was comparable to that of the other studies), and the mean OCT-measured central subfield thickness ranged from 552 to 685 \( \mu \)m. At baseline, the study population of the Geneva Study had the best mean visual acuity letter score (54) and the lowest OCT-measured central subfield thickness (552 \( \mu \)m); this is likely because the Geneva Study included patients with branch RVO as well as patients with CRVO. The reported duration of disease is longer in SCORE2 compared with previous CRVO trials (Table 6), but because estimation of disease duration is generally based on patients’ recollection of symptom duration, it is unknown whether the disease duration differs meaningfully among the CRVO trials.

**Table 6. Comparison of SCORE2 Baseline Characteristics and Other Studies in Central Retinal Vein Occlusion**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Genoa (includes EDCCS (Includes 55 HRVO Eyes))</th>
<th>SCORE-CRVO</th>
<th>CRUISE</th>
<th>COPERNICUS</th>
<th>GALILEO Study</th>
<th>CVOS (group M study)</th>
<th>Geneva</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>362</td>
<td>271</td>
<td>187</td>
<td>155</td>
<td>177</td>
<td>126</td>
<td>353</td>
</tr>
<tr>
<td>Ages, yrs (mean)</td>
<td>69.4</td>
<td>68.3</td>
<td>68.0</td>
<td>68.4</td>
<td>62.0</td>
<td>45.0</td>
<td>67.2</td>
</tr>
<tr>
<td>Women (%)</td>
<td>43</td>
<td>45</td>
<td>43</td>
<td>43</td>
<td>44</td>
<td>47</td>
<td>41</td>
</tr>
<tr>
<td>White (%)</td>
<td>76</td>
<td>91</td>
<td>84</td>
<td>79</td>
<td>72</td>
<td>75</td>
<td>94</td>
</tr>
</tbody>
</table>
| Eyes with prior VEGF treatment having OCT differed between these 2 groups, with 6% of eyes with prior anti-VEGF treatment having “cannot grade” and 27% of eyes with no prior anti-VEGF having “cannot grade” (adjusted chi-square, \( P = 0.0101 \); Table 5). Area of intraretinal and/or subretinal hemorrhage within the grid based on fundus photography is larger in eyes with no prior anti-VEGF (total area of blood >50% of ETDRS grid = 26%) than in the prior anti-VEGF group (6%; adjusted chi-square, \( P < 0.0001 \); Table 5).
In SCORE2, 77% of participants had a self-reported history of hypertension. In the SCORE-CRVO trial, Geneva Trial, and EDCCS, the proportion of patients with a history of hypertension was 73%, 63%, and 56%, respectively. In the CVOS, 57% of participants were reported to be taking medication for hypertension or had elevated blood pressure at baseline. In SCORE2, 31% of participants had a history of diabetes mellitus. In the SCORE-CRVO trial, Geneva Trial, CVOS, and EDCCS, the proportion of patients with a history of diabetes mellitus was 23%, 15%, 7%, and 9%, respectively. The literature supports that the incidence and prevalence of diabetes mellitus and hypertension have increased in the last few decades in the United States; the increasing prevalence of these 2 conditions in the general population over time.

The CRVO and HRVO patients enrolled into SCORE2 are similar in many respects. Demographic characteristics such as gender, ethnicity, age, history of coronary artery disease, hypertension, and history of cancer were similar between both groups and were balanced within the cohort with respect to the treatment groups. The racial disparity (38% of HRVO patients were black, while only 11% of CRVO patient were) echoes findings from the earlier SCORE Study, in which 17% of HRVO patients were black, while only 4% of CRVO patients were. Coupled with the small adjusted P value, the 2 studies provide very strong evidence that the association is real, although the causality remains obscure. At baseline, the area of intraretinal and/or subretinal hemorrhage within the grid based on fundus photography was significantly larger in CRVO than HRVO eyes; this makes sense given that the clinical distinction between CRVO and HRVO is made based on the area of retina affected by the RVO. There was high agreement (98%) between investigators and the SCORE2 Reading Center on the diagnosis of CRVO and lower agreement (70%) on the diagnosis of HRVO. In 15 of the 54 eyes that the clinical site investigator determined had an HRVO (28%), the Reading Center graded the RVO as a CRVO. We speculate that investigators determined presence of HRVO when there was a clear predominance of retinal hemorrhages in 2 retinal quadrants (superior or inferior), whereas the Reading Center graded CRVO if any biomarkers for RVO (such as dilated and tortuous veins or intraretinal hemorrhage) were present in each of the remaining 2 quadrants. In 1 eye (2%) identified as having an HRVO by the clinical site investigator, the Reading Center identified a BRVO because the retinal hemorrhages occupied fewer than 2 quadrants of the retina.

Comparison of fundus photographs in study eyes with and without prior anti-VEGF treatment demonstrated a significantly larger area of intraretinal and/or subretinal hemorrhage within the grid in eyes with no prior anti-VEGF therapy. This is likely because eyes treated previously with anti-VEGF had a significantly longer duration of macular edema compared with eyes not treated previously with anti-VEGF, which would have permitted more time for intraretinal and/or subretinal hemorrhage to resolve in the former compared with the latter eyes. In addition, perhaps anti-VEGF therapy speeds up resolution of intraretinal/subretinal hemorrhage. In turn, the larger area of intraretinal and/or subretinal hemorrhage in the eyes without prior anti-VEGF therapy likely explains the higher proportion of eyes in this group having “cannot grade” for the presence of subretinal fluid on SD OCT, because large areas of blood may block the visibility of subretinal fluid.

The SCORE2 cohort is a heterogeneous population, including both CRVO and HRVO eyes and both treatment-naïve eyes and eyes treated previously with anti-VEGF, which will allow study results to have broad applicability to CRVO and HRVO patients receiving treatment for macular edema. Similarities of the baseline characteristics of the SCORE2 population to other CRVO trial cohorts will allow meaningful comparisons of outcome results across trials.

References


Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; anti-VEGF = anti-vascular endothelial growth factor; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; EDCCS = Eye Disease Case-Control Study; E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study (visual acuity test); ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; HRVO = hemiretinal vein occlusion; IOP = intraocular pressure; IS-OS = inner segment-outer segment; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; OCT = optical coherence tomography; RVO = retinal vein occlusion; SCORE = Standard Care versus Corticosteroid for RETinal Vein Occlusion Study; SCORE2 = Study of COMparative Treatments for RETinal Vein Occlusion 2; SD OCT = spectral-domain optical coherence tomography; TAE = treat and extend; VEGF = vascular endothelial growth factor.

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Pictures & Perspectives

Melkersson-Rosenthal Syndrome Presenting as Isolated Eyelid Edema

A 75-year-old man underwent a right-upper blepharoplasty for recurrent, painless, nonpruritic, right-sided eyelid edema (Fig 1) recalcitrant to oral prednisone and topical antimicrobials. Histopathology (H&E) revealed dermal edema with non-caseating granulomatous inflammation around hair follicles (Fig 2A, black arrow), and granulomas within lymphatic channels (Fig 2B, black arrows) consistent with Melkersson-Rosenthal syndrome (MRS). Special stains for fungi and acid fast bacilli were negative, no foreign bodies were seen with polarization, and systemic work-up was negative for sarcoidosis, rosacea, Crohn’s disease, or granulomatosis with polyangiitis. Clinical suspicion of MRS should remain high in patients with eyelid edema of unknown etiology.

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