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Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Retinal Vein Occlusion

The Bevacizumab to Ranibizumab in Retinal Vein Occlusions (BRVO) study, a Randomized Trial

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Purpose: Comparing the efficacy of intravitreal injections of bevacizumab to ranibizumab in the treatment of macular edema (ME) resulting from retinal vein occlusion (RVO).

Design: Comparative, randomized, double-masked, multicenter, noninferiority clinical trial. The noninferiority margin was 4 letters.

Participants: Patients with vision loss resulting from ME secondary to a branch or (hemi) central RVO who might benefit from anti−vascular endothelial growth factor treatment were eligible for participation.

Methods: From June 2012 through February 2018, 277 participants were randomized to receive injections of 1.25 mg bevacizumab (n = 139) or 0.5 mg ranibizumab (n = 138). The follow-up was 6 months with a monthly dosing interval.

Main Outcome Measures: The primary outcome was a change in visual acuity from baseline at 6 months. Changes in the central area thickness and safety were studied as secondary outcomes.

Results: The mean visual acuity (±standard deviation) improved, with 15.3±13.0 letters for bevacizumab and 15.5±13.3 letters for ranibizumab after 6 months of monthly treatment. The lower limit of the 2-sided 90% confidence interval was −1.724 letters, which is within the noninferiority margin of 4 letters. Even in the branch and (hemi-)central RVO subgroups, minimal differences were found in visual acuity outcomes between treatment arms. Changes in central area thickness on OCT at 6 months did not differ significantly between treatment groups, with a decrease of 287.0±231.3 μm in the bevacizumab group and 300.8±224.8 μm in the ranibizumab group. Severe adverse events (SAEs) were also distributed equally over both treatment groups: 10 participants (7.1%) in the bevacizumab group and 13 participants (9.2%) in the ranibizumab group experienced SAEs.

Conclusions: This study showed, based on the change in visual acuity, that bevacizumab is noninferior to ranibizumab for patients with ME resulting from RVO of either subtype when receiving monthly injections for a period of 6 months. In addition, anatomic and safety outcomes did not differ between treatment groups. Based on our findings, bevacizumab may be an effective alternative to ranibizumab. *Ophthalmology Retina 2020;■:1−12 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Bevacizumab is used as an off-label alternative to the registered but more expensive anti−vascular endothelial growth factor (VEGF) agents ranibizumab and aflibercept in the treatment of macular edema (ME) resulting from retinal vein occlusion (RVO), but virtually no state-of-the-art comparative clinical studies supporting this approach have

https://doi.org/10.1016/j.oret.2019.12.019
ISSN 2468-6530/20

been reported.[1] Retinal vein occlusion is the second most prevalent retinal vascular disease, affecting an estimated 16 million people worldwide. Therefore, conclusive comparisons with available anti-VEGF agents regarding efficacy, safety, and cost are needed.[2–4]

Three subtypes of RVO have been identified: branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and hemi-central retinal vein occlusion (hemi-CRVO), with hemi-CRVO seeming to be a variant of CRVO, with similar pathogenesis and risk factors.[5] The development of ME is the most important cause of visual impairment in all forms of RVO. Retinal ischemia resulting from circulatory stasis because of venous obstruction promotes the production of VEGF-A, leading to increased vascular permeability and, finally, edema.[5–7] Intravitreal injections for anti-VEGF therapy are the standard care for ME occurring after RVO,[2,8] and the 3 commonly used anti-VEGF agents are ranibizumab, a humanized high-affinity antibody fragment that targets all isoforms of VEGF-A; bevacizumab, a humanized full-length antibody; and aflibercept, a complex of VEGF receptors 1 and 2 fused to a humanized monoclonal antibody backbone.[7–12] All 3 anti-VEGF agents result in significant improvement in visual acuity and reduced ME in patients with BRVO and CRVO compared with sham injections or photocoagulation, although for bevacizumab, only a few small randomized controlled trials (RCTs) have been reported.[6,9,10,13–15] In other retinal vascular disorders, several RCTs have compared the efficacy of anti-VEGF agents directly in patients with exudative age-related macular degeneration, demonstrating similar efficacy between bevacizumab and ranibizumab.[11,12,16,17] The Diabetic Retinopathy Clinical Research Network Protocol T study compared all 3 anti-VEGF agents in patients with diabetic ME and showed that at 2 years, aflibercept resulted in an outcome superior to that of bevacizumab in a subgroup of patients with lower baseline visual acuity.[18,19]

In patients with RVO, similar state-of-the-art comparative RCTs on the efficacy and safety of anti-VEGF agents are virtually missing. However, 2 underpowered studies comparing bevacizumab with ranibizumab have been reported, the Bevacizumab versus Ranibizumab in Branch Retinal Vein Occlusion (MARVEL) study and the Bevacizumab versus Ranibizumab in Treatment of Macular Edema From Vein Occlusion (CRAVE) study, which found a similar effect on improving visual acuity after bevacizumab and ranibizumab treatment in 75 BRVO patients and 98 RVO patients, respectively.[20,21] The only state-of-the-art RCT for RVO patients with ME, the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) study, compared bevacizumab with aflibercept in 362 patients with ME resulting from CRVO or hemi-CRVO. This study confirmed the noninferiority of bevacizumab compared with aflibercept with regard to visual outcome after 6 monthly injections.[1] In the present study, we aimed to generate similar conclusive evidence of the noninferiority of 1.25-mg bevacizumab compared with 0.5-mg ranibizumab in the treatment of patients with ME secondary to RVO.

Methods

Study Design and Study Population

The BRVO study was a multicenter, randomized, double-masked, noninferiority clinical trial. This study is registered with ClinicalTrials.gov (identifier, NCT01635803) and Trialregister.nl (identifier, NTR3257). A total of 286 patients were included from June 2012 through February 2018. Patients were recruited at 8 clinical centers throughout The Netherlands. The Medical Ethical Committee of the Amsterdam University Medical Centers, location AMC, approved the BRVO study. The study adhered to the principles of the Declaration of Helsinki. Patients were given at least 1 week to read the Patient Information Form, and each participant provided written informed consent before randomization. Patients with vision loss resulting from ME secondary to RVO who might benefit from anti-VEGF treatment were eligible for participation in the study. Other inclusion criteria were age older than 18 years, central area thickness of more than 275 μm on OCT, and a best-corrected visual acuity (BCVA) of more than 24 and less than 79 letters on the standardized Early Treatment Diabetic Retinopathy Study chart. The exclusion criteria are listed in Table S1 (available at www.ophthalmologyretina.org).

Eligibility was determined during the screening visit (<14 days before baseline) and based on visual acuity, fluorescein angiography findings, OCT findings, and slit-lamp examination results. Diagnosis of BRVO, CRVO, or hemi-CRVO was confirmed by the Belfast Reading Centre, part of the Network of Ophthalmic Reading Centers in the United Kingdom. At screening and after 6 months, a more extensive examination was performed consisting of fluorescein angiography, fundus photography, measurement of intraocular pressure, OCT, and slit-lamp examination of both eyes. Monthly ophthalmic examinations during follow-up consisted of BCVA and OCT of the study eye only. In addition, blood pressure, pulse, and weight were determined monthly (Fig S1, available at www.ophthalmologyretina.org). Best-corrected visual acuity was measured by certified personnel following protocol and using the standardized Early Treatment Diabetic Retinopathy Study chart. OCT was performed with a Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany), Topcon (Topcon, Tokyo, Japan), or Cirrus Zeiss (Carl Zeiss Meditec, Dublin) device, depending on availability at the participating center. For statistical analysis, central area thickness measured by the Topcon or Cirrus Zeiss device was converted to Heidelberg Spectralis values using the conversion table of Giani et al.[22]

Interventions

Participants received the first intravitreal injection of either 1.25 mg bevacizumab (Avastin; Genentech, South San Francisco, CA/Hoffman-La Roche, Basel, Switzerland) or 0.5 mg ranibizumab (Lucentis; Genentech, South San Francisco, CA/Novartis, Inc, Basel, Switzerland) at the baseline visit. The study drug was administered monthly for a period of 6 months, with an interval between injections of 30±7 days. Both medications were reconstituted and supplied by the hospital pharmacy in masked injection syringes containing a sterile solution of 0.15 ml of 10 mg/ml ranibizumab or 0.15 ml of 25 mg/ml bevacizumab, and the injection was given within 24 hours after preparation at a volume of 0.05 ml. The syringes were labeled with only the study identification number of the patient. Therefore, the patient, treating physician, and evaluating investigator staff were blinded to treatment allocation. The randomization procedure was computer and web based using permuted blocks (minimal 2 patients, maximal 4 patients) and stratified for center, BCVA of the study

eye (52 letters or fewer vs. 53 letters or more), and RVO subtype (CRVO or BRVO).

Outcomes

The primary outcome was the change in BCVA of the study eye from baseline to 6 months, with a noninferiority margin of 4 letters. Secondary outcome measures were the proportion of participants with a loss or gain in BCVA of fewer than 15 letters from baseline to 6 months (stabilizers), the proportion of participants with a loss in BCVA of 15 letters or more from baseline to 6 months (losers), the proportion of participants with a gain in BCVA of 15 letters or more from baseline to 6 months (gainers), the change in central area thickness from baseline to 6 months, the proportion of patients who left the study prematurely, the occurrence of (severe) adverse events during the study period, and the change in intraocular pressure from baseline to 6 months.

Sample Size Calculation

At the start of the study, the sample size calculation for 80% power demonstrating noninferiority required a sample size of 296 patients (148 patients in each group), starting from a standard deviation (SD) for the change in BCVA of 14 letters from baseline to 6 months in both groups, and assuming an improvement of 9 letters in the ranibizumab group and bevacizumab group. Noninferiority was demonstrated by excluding a difference of 4 letters or more using a 1-sided t test at an α level of 0.05. The SD of 14 letters and mean change of 9 letters were based on previous clinical trials with ranibizumab in RVO patients, and the noninferiority margin chosen was equivalent to less than half this improvement.[9,10]

After checking the assumed SD for the change in BCVA in the blinded study data in February 2018, the sample size was adjusted based on the lower observed SD of 12.1 letters. Still assuming an improvement of 9 letters in both treatment groups, a sample size of 228 patients (114 in each group) was calculated to give 80% power demonstrating noninferiority. For this reason, inclusion was halted at 286 patients in March 2018.

Statistical Analysis

Intention-to-treat analysis was performed, and all randomized patients who received the allocated treatment at least once and for whom BCVA and OCT measurements were performed afterward were included in the analysis. The last available BCVA score was used as BCVA at 6 months (last observation carried forward). If patients missed an injection during follow-up, the BCVA measurement from the previous visit was used as the last available BCVA. Noninferiority was tested using a 1-sided test, and bevacizumab was considered noninferior to ranibizumab if the lower bound of the 2-sided 90% confidence interval (CI) of the difference in the change in BCVA did not exceed the noninferiority margin of 4 letters. To evaluate the influence of the last observation carried forward, a linear mixed-effects regression analysis was performed to analyze the repeatedly measured change in BCVA from baseline to 6 months. The proportion of stabilizers, losers, and gainers were compared between treatment groups using the linear-by-linear association test. The change in central area thickness as measured by OCT from baseline to 6 months was analyzed between treatment groups using covariance analysis. Anatomic outcomes are presented without carrying out the last observation carried forward method, because covariance analyses demonstrated similar OCT outcomes both with and without the last observation carried forward method. The proportion of early dropouts was compared between treatment groups using the Pearson chi-square test. Adverse events were coded according to the Medical Dictionary for Regulatory Activities system (MedDRA; version 20.0). The numbers and proportions of (serious) adverse events during the study period were compared between treatment groups using the Mann−Whitney U test and Pearson chi-square test. Patients who received at least 1 injection were included in this analysis. A significance level of 0.05 was applied for all statistical tests.

Based on the stratification criteria, a predefined subgroup analysis was performed to compare changes in visual acuity and central area thickness between treatment arms in patients with BRVO and CRVO or hemi-CRVO. Because hemi-CRVO is considered to be clinically and pathogenetically closely correlated to CRVO,[23] hemi-CRVO patients were included in the CRVO subgroup for analysis. However, because of a stratification error, some hemi-CRVO patients were randomized in the BRVO group. Despite these errors, patients with BRVO, CRVO, and hemi-CRVO were all distributed equally over both treatment arms (Table 1). Because no imbalance of RVO types over treatment groups occurred, noninferiority outcomes and secondary outcomes were not affected. Regarding stratification based on BCVA of the study eye at baseline, the distribution of patients in the 2 subgroups (BCVA, $\leq$52 letters or $\geq$53 letters at baseline) was misaligned, with 200 patients and 77 patients, respectively. Therefore, a post hoc analysis was performed on 2 subgroups derived from the median of 63 letters at baseline in both treatment arms (BCVA $\leq$62 letters, approximately <20/63 at baseline; or BCVA $\geq$63 letters, approximately $\geq$20/63 at baseline). Such an analysis based on the median was introduced by the Diabetic Retinopathy Clinical Research Network Protocol T study, which found significant differences between anti-VEGF agents in patients with lower baseline BCVA.[18,19] Primary and secondary outcomes in subgroup analyses were assessed using the same statistical tests described above.

Results

Patient Characteristics

From June 2012 through February 2018, 286 participants were randomized to receive either bevacizumab (n = 144) or ranibizumab (n = 142). It took almost 6 years to enroll the necessary number of patients, because referrals from general ophthalmologists to the academic study sites decreased considerably during the study period. Eventually, 139 patients in the bevacizumab group and 138 patients in the ranibizumab group were available for analysis (Fig S2, available at www.ophthalmologyretina.org). Of all participants analyzed, 133 were diagnosed with BRVO (48%), 97 were diagnosed with CRVO (35%), and 47 were diagnosed with hemi-CRVO (17%). The mean visual acuity (±SD) at baseline was 60.3±14.8 letters in the group receiving bevacizumab and 59.0±16.7 letters in the group receiving ranibizumab (P = 0.203). The mean central area thickness was 602.3±201.2 μm in the bevacizumab group and 615.2±217.3 μm in the ranibizumab group (P = 0.607). The number of current smokers was twice as high in the bevacizumab group (14.4% vs. 7.2%), but this difference was not significant (P = 0.101). An equal number of patients in both study arms demonstrated classical risk factors for RVO developing, such as hypertension, hypercholesterolemia, and diabetes mellitus (Table 1). The mean duration between follow-up visits was 29.4±1.2 days in the bevacizumab group and 29.5±1.2 days in the ranibizumab group (P = 0.606). Patients in both groups received a mean of 5.9±0.050 injections (P = 0.373).

Table 1. Baseline Characteristics of the Study Patients

Baseline Characteristics	Bevacizumab (n = 139)	Ranibizumab (n = 138)
Age (yrs), mean (SD)	68.3 (11.84)	67.4 (11.6)
Gender, no. (%)		
Female	76 (54.7)	69 (50)
Male	63 (45.3)	69 (50)
Ethnicity, no. (%)		
Dutch	121 (87.1)	119 (86.2)
Moroccan	1 (0.7)	3 (2.2)
Surinamese	9 (6.5)	6 (4.3)
Netherlands Antilles & Aruba	2 (1.4)	1 (0.7)
Other non-Western immigrant	4 (2.9)	7 (5.1)
Other Western immigrant	2 (1.4)	2 (1.4)
Smoking behavior, no. (%)		
Smoker	20 (14.4)	10 (7.2)
Former smoker	55 (39.6)	67 (48.6)
Nonsmoker	64 (46.0)	61 (44.2)
Visual acuity of study eye (letters), mean (SD)	60.3 (14.8)	59.0 (16.7)
Central area thickness (μm), mean (SD)	602.3 (201.2)	615.2 (217.3)
Intraocular pressure (mmHg), mean (SD)	14.7 (2.8)	14.2 (3.1)
Retinal vein occlusion subtype, no. (%)		
BRVO	62 (44.6)	71 (51.4)
CRVO	51 (36.7)	46 (33.3)
Hemi-CRVO	26 (18.7)	21 (15.2)
Systolic blood pressure (mmHg), mean (SD)	146.9 (19.1)	149.3 (18.3)
Diastolic blood pressure (mmHg), mean (SD)	84.0 (11.1)	85.2 (11.6)
Presence of intraretinal cysts in study eye, no. (%)		
Absent	3 (2.2)	3 (2.2)
Definite	134 (96.4)	133 (96.4)
Questionable	1 (0.7)	2 (1.4)
Cannot grade	1 (0.7)	0 (0)
Presence of subretinal fluid in study eye, no. (%)		
Absent	44 (31.7)	47 (34.1)
Definite	77 (55.4)	73 (52.9)
Questionable	16 (11.5)	14 (10.1)
Cannot grade	2 (1.4)	4 (2.9)
Prior retinal vein occlusion of study eye, no. (%)	19 (13.7)	17 (12.3)
Prior anti-VEGF treatment of study eye, no. (%)	4 (2.9)	6 (4.3)
Prior photocoagulation treatment of study eye, no. (%)	2 (1.4)	3 (2.2)
History of hypertension, no. (%)	80 (57.6)	84 (60.9)
History of myocardial infarction, no. (%)	7 (5.0)	11 (8.0)
History of transient ischemic attack, no. (%)	4 (2.9)	6 (4.3)
History of diabetes mellitus, no. (%)	23 (16.5)	22 (15.9)
History of hypercholesterolemia, no. (%)	38 (27.3)	28 (20.3)
History of thrombosis, no. (%)	3 (2.2)	1 (0.7)
History of cerebrovascular accident, no. (%)	4 (2.9)	4 (2.9)
Body mass index (kg/m^2), mean (SD)	26.7 (4.8)	27.1 (4.0)

BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; SD = standard deviation; VEGF = vascular endothelial growth factor.

Primary Outcome

Visual acuity improved to identical levels in both treatment groups after 6 months, with a mean gain of 15.3±13.0 letters in the bevacizumab group and 15.5±13.3 letters in the ranibizumab group (Table 2; Fig 1A). The lower bound of the 2-sided 90% CI for the change in BCVA from baseline to 6 months was −1.724 letters. This is within the chosen noninferiority margin of 4 letters, demonstrating that monthly bevacizumab is noninferior to monthly ranibizumab in the treatment of ME resulting from RVO (Fig 2). To evaluate the influence of carrying forward the last available BCVA scores to month 6 in patients without a BCVA score at 6 months (n = 19), a linear mixed-effects regression analysis was performed. This gave us a lower bound of the 2-sided 90% CI of −2.819 letters, confirming noninferiority, because it also excludes the noninferiority margin of 4 letters.

Secondary Outcomes

The proportion of stabilizers (loss or gain of <15 letters from baseline), losers (loss of ≥15 letters from baseline), and gainers (gain of ≥15 letters from baseline) did not differ between treatment groups ($P = 0.684$; Table 2). The decrease in central area thickness from baseline to 6 months was also equivalent between groups, because bevacizumab resulted in a decrease of 287.0±231.3 μm and ranibizumab resulted in a decrease of 300.8±224.8 μm ($P = 0.694$; Table 2; Fig 3A). The presence of subretinal fluid and intraretinal cysts did not differ between treatment arms at

Table 2. Primary and Secondary Outcomes after 6 Months

Outcomes	Bevacizumab (n = 139)	Ranibizumab (n = 138)	Lower Bound of the 90% Confidence Interval*	*P* Value
Primary				
Change in visual acuity of study eye (letters), mean (SD)				
Month 1	10.1 (10.5)	9.8 (10.8)	−1.048	
Month 2	12.0 (12.4)	12.9 (12.3)	−2.428	
Month 3	13.2 (12.3)	14.1 (12.5)	−2.494	
Month 4	14.8 (12.2)	15.0 (13.1)	−1.727	
Month 5	14.6 (13.2)	16.1 (13.4)	−2.989	
Month 6	15.3 (13.0)	15.5 (13.3)	−1.724	
Mean visual acuity at 6 months (letters), mean (SD)	75.6 (12.13)	74.5 (14.7)		
Secondary				
Proportion of, no (%)				0.684
Stabilizers (loss or gain <15 letters from baseline)	68 (48.9)	73 (52.9)		
Losers (loss ≥15 letters from baseline)	2 (1.4)	1 (0.7)		
gainers (gain ≥15 letters from baseline)	69 (49.6)	64 (46.4)		
Change in central area thickness (μm), mean (SD)				
Month 1	−242.5 (201.5)	−243.1 (205.4)		
Month 2	−262.0 (215.9)	−273.6 (216.9)		
Month 3	−281.7 (221.1)	−271.9 (220.5)		
Month 4	−279.2 (222.1)	−289.4 (230.2)		
Month 5	−290.9 (220.4)	−304.7 (223.1)		
Month 6	−287.0 (231.3)	−300.8 (224.8)		0.694
Mean central area thickness at 6 months (μm), mean (SD)	314.6 (115.0)	310.0 (89.5)		
Intraretinal cysts on OCT at 6 months, no (%)				**0.015**
Absent	65 (48.5)	82 (55.8)		
Definite	57 (42.5)	39 (31.5)		
Questionable	9 (6.7)	2 (1.6)		
Cannot grade	3 (2.2)	1 (0.8)		
Subretinal fluid on OCT at 6 months, no (%)				0.642
Absent	118 (88.1)	113 (91.1)		
Definite	7 (5.2)	7 (5.6)		
Questionable	4 (3.0)	2 (1.6)		
Cannot grade	5 (3.7)	2 (1.6)		
Proportion of dropouts, no (%)	4 (2.9)	8 (5.8)		0.233
Change in systolic blood pressure from baseline to 6 mos (mmHg), mean (SD)	−4.7 (21.7)	−3.4 (19.4)		0.204
Systolic blood pressure at 6 mos (mmHg), mean (SD)	142.3 (19.1)	146.0 (18.0)		
Change in diastolic blood pressure from baseline to 6 mos (mmHg), mean (SD)	−1.8 (10.9)	−1.9 (11.0)		0.768
Diastolic blood pressure at 6 mos (mmHg), mean (SD)	82.5 (9.6)	83.2 (11.7)		
Intraocular pressure (mmHg), mean (SD)	15.0 (3.2)	15.4 (3.1)		
Change in intraocular pressure from baseline to 6 mos (mmHg), mean (SD)	0.3 (3.1)	1.2 (3.6)		0.083

SD = standard deviation.
Bolding indicates significant *P* value.
*The lower bound of the 2-sided 90% confidence interval of the difference in the change in visual acuity is noted as an outcome for noninferiority. Bevacizumab is considered noninferior to ranibizumab if the noninferiority margin of 4 letters can be excluded.

baseline ($P = 0.721$; Table 2). However, after 6 months, the proportion of patients with intraretinal cysts was higher in the bevacizumab group (42.5% vs. 31.5% in the ranibizumab group; $P = 0.015$), whereas subretinal fluid was absent in most patients (88.1% and 91.1%, respectively; $P = 0.642$). Four patients (2.9%) in the bevacizumab group and 8 patients (5.8%; $P = 0.233$) in the ranibizumab group did not complete the 6-month study protocol. Reasons for early termination included a severe adverse event not related to study medication, adverse event not related to study medication, progression of ischemia for which laser treatment was indicated, and death (Table 2). After 6 months, intraocular pressure exhibited a trend of a minimal increase compared with baseline in both the bevacizumab group (0.3±3.1 mmHg) and ranibizumab group (1.2±3.6 mmHg; $P = 0.083$; Table 2).

Subgroup Analysis: Baseline Best-Corrected Visual Acuity

Post hoc analysis was performed based on the median visual acuity score at baseline, that is, in the subgroup of patients with BCVA of

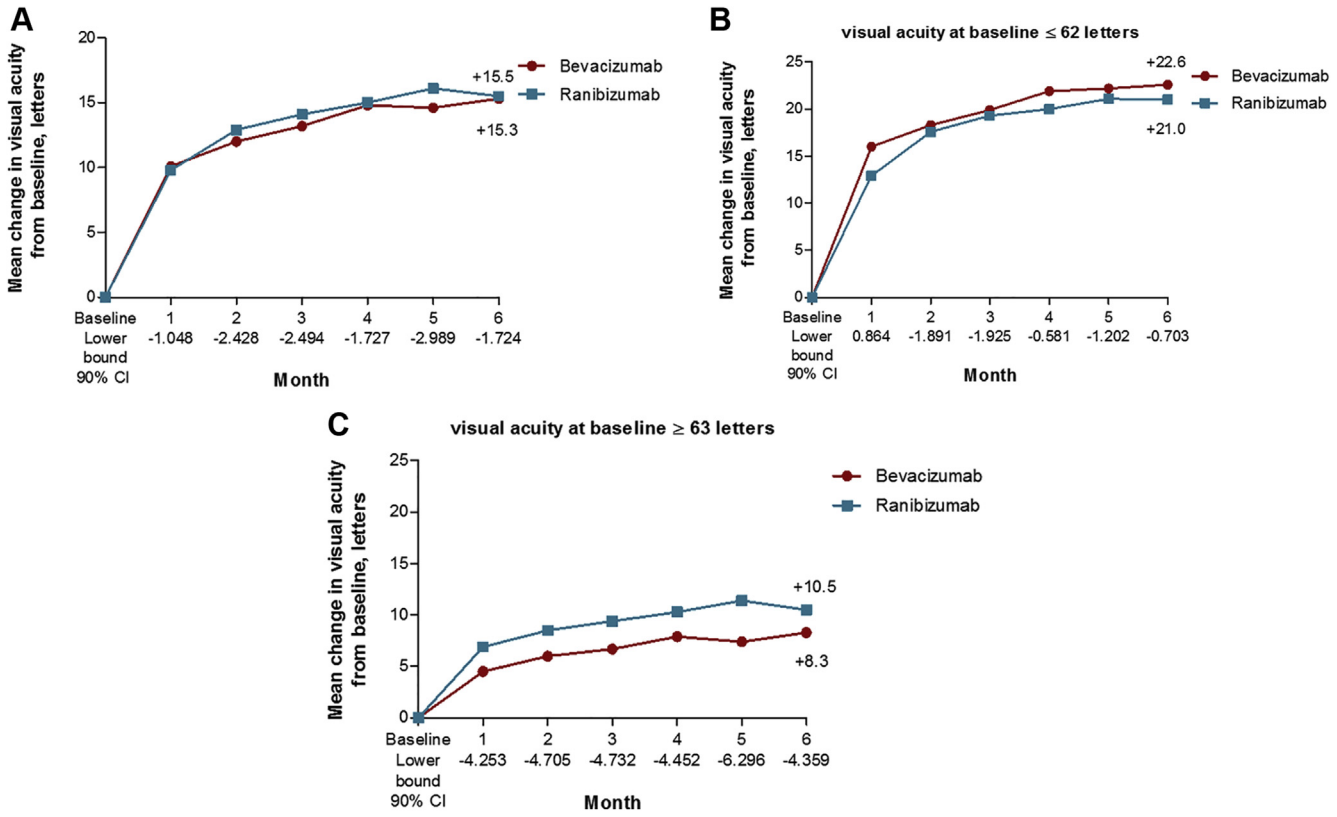

Figure 1. Graphs showing mean change in visual acuity from baseline to 6 months: (**A**) entire cohort, (**B**) patients with an initial visual acuity of 62 letters or fewer, and (**C**) patients with an initial visual acuity of 63 letters or more. CI = confidence interval.

63 letters or more (Snellen equivalent, approximately ≥20/63; n = 143) versus those with a baseline BCVA of 62 letters or fewer (Snellen equivalent, approximately <20/63; n = 134; Table 3; Fig 1B, C). Patients who started with initially higher baseline vision (≥63 letters) gained a mean of 8.3±9.5 letters in the bevacizumab group and 10.5±7.0 letters in the ranibizumab group; the lower limit of the 2-sided 90% CI was −4.359 letters, exceeding the noninferiority margin of 4 letters (Fig 3). However, these subgroups were not powered to reject noninferiority. Patients in the subgroup with a baseline BCVA of 62 letters or fewer showed an improvement of 22.6±12.1 letters with bevacizumab and 21.0±16.2 letters with ranibizumab (lower bound of the 2-sided 90% CI, −0.703 letter). Central area thickness decreased 182.2±184.0 μm in patients with a higher initial BCVA who received bevacizumab and 208.7±161.1 μm in those receiving ranibizumab (P = 0.052; Fig 2B, C). Comparing central area thickness between bevacizumab and ranibizumab in patients with an initially lower BCVA showed a decrease of 396.5±226.0 μm and 401.5±241.9 μm, respectively (P = 0.093). When we compared the differences in OCT outcomes between the bevacizumab and ranibizumab groups with low and high baseline visual acuity, we found a significant difference between the 2 subgroups, because a larger difference was seen in the decrease in central area thickness between bevacizumab and ranibizumab in the patient group with higher initial visual acuity (P = 0.012; Table 3).

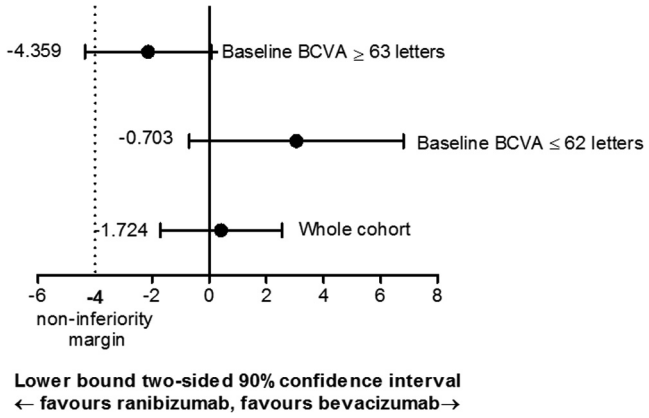

Figure 2. Graph showing the 2-sided 90% confidence intervals, with a noninferiority margin of 4 letters. Bevacizumab could be considered non-inferior in both the entire cohort and in patients with a baseline visual acuity of 62 letters or fewer. The outcomes for the group with an initially higher baseline visual acuity are inconclusive. BCVA = best corrected visual acuity.

Subgroup Analyses: Retinal Vein Occlusion Type

In patients with BRVO (n = 133), the mean gain in BCVA from baseline to 6 months was 14.2±11.2 letters in the bevacizumab group and 14.0±10.2 letters in the ranibizumab group (lower bound of the 2-sided 90% CI, −2.950 letters). The CRVO subgroup (n = 144) included patients diagnosed with CRVO (n = 97)

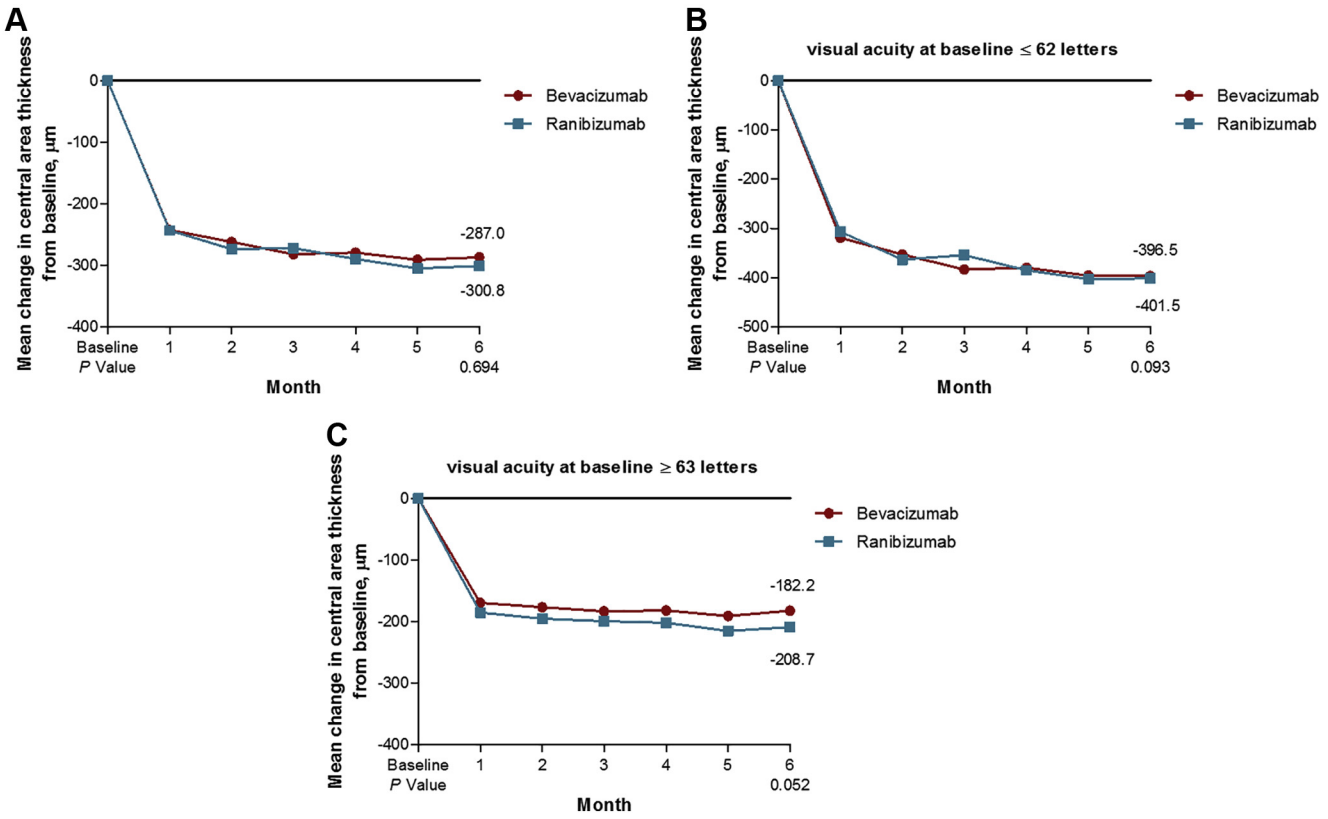

Figure 3. Graphs showing mean change in central area thickness from baseline to 6 months: (**A**) entire cohort, (**B**) patients with an initial visual acuity of 62 letters or fewer, and (**C**) patients with an initial visual acuity of 63 letters or more.

and hemi-CRVO (n = 47). Patients in this group gained 16.1±14.3 letters with bevacizumab and 17.1±15.8 letters with ranibizumab (lower bound of the 2-sided 90% CI, −1.741 letters). The noninferiority of bevacizumab to ranibizumab could be demonstrated in both RVO subgroups (Table S2, available at www.ophthalmologyretina.org). The central area thickness decreased in all RVO types from baseline to 6 months, at equal levels in the bevacizumab and ranibizumab groups. The mean change in central area thickness was 232.0±199.9 µm in BRVO patients receiving bevacizumab and 214.3±176.5 µm in BRVO patients receiving ranibizumab ($P = 0.513$). Among CRVO and hemi-CRVO patients, the bevacizumab group exhibited a decrease in central area thickness of 332.5±246.5 µm and the ranibizumab group showed a decrease of 398.3±234.4 µm ($P = 0.976$; Table S2).

Adverse Events

All patients who received at least 1 injection were included in the safety analysis (Table 4). No difference was found in the number of patients with adverse events between the bevacizumab and ranibizumab groups ($P = 0.505$). Severe adverse events were distributed equally across both treatment arms ($P = 0.509$). Three arteriothrombotic events occurred in the bevacizumab group and 1 occurred in the ranibizumab group, but this difference was not significant. All arteriothrombotic events were classified by the local investigator as being unrelated to the study medication. The frequency of adverse events in the MedDRA system organ classes was significantly different between bevacizumab and ranibizumab only for General Disorders and Administration Site Conditions ($P = 0.030$; Table S3, available at www.ophthalmologyretina.org). Adverse events appointed to this MedDRA class included reports of fever, a sore throat, or the flu in between study visits and pain after injection, burning sensations after the injection, or a hyposphagma after injection. Again, all adverse events in this class were graded as being unrelated to the study medication.

Discussion

This study showed that, based on changes in BCVA from baseline to 6 months, monthly administration of 1.25 mg bevacizumab is noninferior to monthly administration of 0.5 mg ranibizumab in the treatment of patients with macular edema resulting from RVO. Furthermore, no significant differences were seen in anatomic or safety outcomes. In both treatment groups, the mean BCVA improved substantially from baseline to 6 months, which is consistent with the visual acuity outcomes found in other studies, such as the BRAVO study, which compared 0.5-mg ranibizumab to sham injections and observed a mean gain of 18.3 letters after 6 months in patients with BRVO.[9] Similarly, the Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE) study demonstrated an

Table 3. Primary and Secondary Outcomes Based on Visual Acuity at Baseline

Outcomes	Visual Acuity at Baseline ≥63 Letters (n = 143)			Visual Acuity at Baseline ≤62 Letters (n = 134)			P Value[†]
	Bevacizumab (n = 71)	*Ranibizumab (n = 72)*	*Lower Bound 90% Confidence Interval**	*Bevacizumab (n = 68)*	*Ranibizumab (n = 66)*	*Lower Bound 90% Confidence Interval**	
Primary outcomes							
Visual acuity at baseline	71.7 (5.2)	71.5 (5.08)		48.32 (11.82)	45.26 (13.96)		
Change in visual acuity of study eye (letters)							
Month 1	4.5 (7.2)	6.9 (7.0)	−4.253	16.0 (10.2)	12.9 (13.2)	0.864	
Month 2	6.0 (9.1)	8.5 (7.9)	−4.705	18.3 (12.3)	17.6 (14.4)	−1.891	
Month 3	6.7 (8.0)	9.4 (7.7)	−4.732	19.9 (12.6)	19.3 (14.6)	−1.925	
Month 4	7.9 (8.3)	10.3 (7.0)	−4.452	21.9 (11.5)	20.0 (16.1)	−0.581	
Month 5	7.4 (9.6)	11.4 (7.4)	−6.296	22.2 (12.1)	21.1 (16.5)	−1.202	
Month 6	8.3 (9.5)	10.5 (7.0)	−4.359	22.6 (12.1)	21.0 (16.2)	−0.703	
Visual acuity at 6 months	80.0 (9.4)	82.0 (7.3)		70.9 (13.0)	66.2 (16.3)		
Secondary outcomes			*P* Value			*P* Value	
Central area thickness at baseline (μm)	517.4 (156.8)	509.3 (158.8)		690.8 (205.3)	730.8 (214.4)		
Change in central area thickness (μm)							
Month 1	−169.4 (164.1)	−185.1 (155.0)		−319.0 (209.5)	−306.4 (234.2)		
Month 2	−176.4 (169.9)	−195.3 (160.1)		−352.9 (223.4)	−363.1 (238.8)		
Month 3	−183.3 (168.4)	−199.2 (169.4)		−383.1 (224.2)	−354.0 (243.1)		
Month 4	−181.7 (168.5)	−202.0 (153.0)		−379.6 (226.8)	−384.9 (261.7)		
Month 5	−190.9 (164.5)	−215.3 (160.3)		−395.6 (223.8)	−402.9 (241.5)		
Month 6	−182.2 (184.0)	−208.7 (161.1)	0.052	−396.5 (226.0)	−401.5 (241.9)	0.093	0.012
Central area thickness at 6 mos (μm)	332.8 (139.9)	296.8 (56.0)		295.6 (78.0)	324.4 (114.3)		

Data are mean (standard deviation) unless otherwise indicated.
*The lower bound of the 2-sided 90% confidence interval of the difference in the change in visual acuity is noted as an outcome for noninferiority. Bevacizumab is considered noninferior to ranibizumab if the noninferiority margin of 4 letters can be excluded.
[†]*P* value for visual acuity at baseline × treatment group interaction on central area thickness outcome.

Table 4. Adverse Events and Severe Adverse Events during the Study Period

Event*	Bevacizumab (n = 140)	Ranibizumab (n = 140)	*P* Value
Adverse events			
Any adverse event	97 (69.3)	92 (67.5)	0.505
Elevated intraocular pressure	2 (1.4)	2 (1.4)	1.000
Uveitis	1 (0.7)	1 (0.7)	1.000
Venous thrombotic event	1 (0.7)	0	0.316
Hypertension	25 (17.9)	23 (16.4)	0.751
≥1 Adverse event	60 (42.9)	55 (39.3)	0.544
Severe adverse events			
Any severe adverse event	10 (7.1)	13 (9.2)	0.509
Death from any cause	0	2 (1.4)	0.156
Arteriothrombotic event			
Nonfatal myocardial infarction	2 (1.4)	0	0.156
Nonfatal stroke	1 (0.7)	0	0.316
Angina pectoris	0	1 (0.7)	0.316
Transient ischemic attack	2 (1.4)	1 (0.7)	0.562
≥1 Severe adverse event	2 (1.4)	3 (2.1)	0.652
Acute glaucoma	1 (0.7)	0	0.316
Macular hole	0	1 (0.7)	0.316
Severe anterior uveitis	0	1 (0.7)	0.316

Data are no. (%).
*Multiple events in the same study patient were counted only once.

improvement of 14.9 letters in the BCVA of CRVO patients treated with 0.5-mg ranibizumab after 6 months.[10] For bevacizumab, Epstein et al[6] demonstrated an improvement of 14.1 letters after 6 months in CRVO patients. Focusing on visual acuity outcomes in RVO subgroups, our study demonstrated greater improvement in visual acuity in CRVO and hemi-CRVO patients than BRVO patients. In contrast, previous studies found greater improvement of visual acuity in BRVO patients than other studies that included patients with CRVO.[6,9,10]

In our study, the percentage of patients who gained 15 letters or more after 6 months was 49.6% in the bevacizumab group and 46.4% in the ranibizumab group, which is slightly lower than the proportions reported in the BRAnch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) study (61.1%) and the study by Epstein et al[6] (60%) but comparable with the CRUISE study (47.7%). Central area thickness outcomes on OCT were of a similar magnitude in our study as the studies listed above.[1,9,10]

The SCORE2 trial compared bevacizumab with aflibercept in patients with CRVO and hemi-CRVO, demonstrating a mean increase in visual acuity of 18.6 letters and 18.9 letters, respectively.[1] The proportion of gainers (improvement of ≥15 letters after 6 months) was 61.3% in the bevacizumab arm and 65.1% in the aflibercept arm. The SCORE2 trial included patients with lower baseline visual acuity (BCVA of 19−73 letters) and higher central subfield thickness limit (≥300 μm) than our trial, which could explain the slightly better visual outcome after 6 months.

As in the entire cohort, noninferiority of bevacizumab to ranibizumab could be demonstrated in the subgroup of patients with an initially lower BCVA (≤62 letters), but noninferiority in the subgroup with an initially higher BCVA (≥63 letters) was inconclusive because of the low sample size and because the CI of the difference between study arms in visual acuity from baseline to 6 months included both 0 and the noninferiority margin (Fig 3).[24] Interestingly, the subgroup with a higher baseline VA showed an unexpectedly better outcome for ranibizumab in visual acuity outcome than bevacizumab, with a mean difference of 2.2 letters between treatment arms. This is a smaller difference than the 4-letter noninferiority margin used in our study, but because of the ceiling effect that is associated with a low maximal gain in BCVA and OCT in this subgroup, even this small difference may point at a true and clinically meaningful advantage of ranibizumab in patients with a higher baseline BCVA. Our findings seem to be in contrast with the SCORE2 study, which did not find differences in treatment effect of aflibercept and bevacizumab between subgroups with a worse (20/50−20/320) or better (20/32−20/40) baseline BCVA. However, because they used the same cutoff value as the Diabetic Retinopathy Clinical Research Network Protocol T study to determine subgroups based on baseline BCVA, 2 unbalanced cohorts were compared with only 38 of 362 patients assigned to the subgroup with a higher baseline BCVA.[1] In diabetic macular edema, the protocol T study compared the efficacy of 1.25-mg bevacizumab, 0.3-mg ranibizumab, and 2.0-mg aflibercept. In a similar analysis, subgroups of patients with an initially lower or higher BCVA, based on the median visual acuity, were compared. Patients with an initial worse BCVA (<69 letters [≤20/50]) demonstrated significantly better visual acuity and OCT outcomes with aflibercept compared with both bevacizumab and ranibizumab after 1 year of treatment. This difference, which was exactly the reverse of our findings in RVO patients, was maintained for 2 years in the comparison between bevacizumab and aflibercept only.[18,19] We do not have a direct explanation of this difference between RVO and diabetic ME patients in response to different anti-VEGF agents. One might hypothesize that better outcomes with ranibizumab in patients with a higher baseline visual acuity in RVO may be explained by the specific pathogenesis of RVOs, in which hydrostatic capillary pressure and retinal ischemia may play different roles in the development of macular edema and irreversible and functional retinal damage, than in diabetic ME, in which longstanding capillary loss and chronic parainflammation may be more important.[25,26]

Another significant difference between treatment groups was the number of participants who still demonstrated intraretinal cysts on OCT after 6 months. Notably, this was graded by the local investigators, without confirmation by an external reading center. This observation was consistent with the findings of the Comparison of Age-Related Macular Degeneration Treatments Trials and the Bevacizumab to Ranibizumab in exudative Age-related Macular Degeneration (BRAMD) trial in exudative age-related macular degeneration, in which fluid was seen on OCT in significantly more patients in the bevacizumab arm than the ranibizumab arm after 1 year.[11,12] Similarly, in the SCORE2 trial, the number of study eyes with no subretinal fluid, no intraretinal fluid, and no

cystoid spaces in CRVO patients after 6 months was significantly higher in the aflibercept group than the bevacizumab group.[1] Although these 3 studies demonstrated differences in visible fluid on OCT after anti-VEGF treatment, as in our present study, no corresponding differences in visual outcome were noted, suggesting that these differences in visible fluid do not influence visual acuity outcome.

Overall, the rates of adverse events and severe adverse events in our study were similar in both treatment groups, which is consistent with safety outcomes in other comparative trials of anti-VEGF agents.[1,11,16,18,19,27] Significantly more patients treated with bevacizumab experienced an adverse event in the MedDRA system organ class General Disorders and Administration Site Conditions. However, it is plausible that this difference is the result of chance, because the administration protocol was the same for both drugs. In addition, we do not have a reason to believe that either one of the anti-VEGF treatments influences the risk of general disorders such as fever or a sore throat, nor the risk of administration site conditions such as a painful eye or burning sensations after injection.

Intravenous treatment of cancer patients with bevacizumab is associated with an increased risk of hypertension, impaired wound healing, hemorrhages, venous thrombosis, and arteriothrombotic events.[28,29] We did not find significant differences between bevacizumab and ranibizumab in the occurrence of these adverse events, but our sample size was not calculated to give conclusive evidence regarding safety differences between bevacizumab and ranibizumab.

Our study has additional limitations. First, the study lacked a comparison with the third commonly used anti-VEGF agent, aflibercept. At the time this study started, aflibercept was not yet available in The Netherlands. Second, the follow-up was limited to 6 months, when most improvement, if any, occurs. However, it is plausible that our outcomes have predictive value for more long-term outcomes. Third, our study included patients with a central area thickness of 275 μm or more, whereas most comparative anti-VEGF trials use a cutoff value of 300 μm, and this could potentially alter primary and secondary outcomes.[1,18,19] Nevertheless, only 4 patients demonstrated a central area thickness of less than 300 μm at baseline, and in general, our BCVA and OCT outcomes were comparable with those of previous studies. Fourth, secondary and post hoc analyses based on RVO subtype and baseline visual acuity were performed but should be regarded as exploratory because of insufficient power to exclude noninferiority or detect small but potentially clinically relevant differences between treatment arms in these subgroups.

Three different spectral-domain OCT devices were used for central area examination. Each device has its own formula to convert pixel volume to micrometers, which makes OCT measurements from different devices incomparable.[30] Therefore, all OCT measurements were converted to Heidelberg Spectralis outcomes using the conversion table by Giani et al.[22] However, the software used by the devices in this study differed from the software on which Giani et al based their conversion table. However, minimal changes were expected from software updates.

In conclusion, based on visual acuity outcomes after 6 months treatment, our results demonstrate the noninferiority of 1.25 mg bevacizumab to 0.5 mg ranibizumab in the treatment of patients with macular edema resulting from RVO. Visual acuity gain, anatomic outcomes, and safety were remarkably equivalent at 6 months in both treatment arms, independent of RVO subtype. In our study, patients were treated monthly for 6 months, which is more frequent than most common regimens in daily practice. In addition, we cannot predict long-term outcomes based on our findings. However, because we conducted a representative randomized clinical trial with an extensive scope of eligibility criteria, and because patients were included in both academic and nonacademic centers throughout The Netherlands, our results are likely generalizable to a broad group of patients and indicate that bevacizumab may be an effective alternative to ranibizumab in the treatment of RVO.

Acknowledgments. This study was published with the help of the Edmond en Marianne Blaauw Fonds voor Oogheelkunde.

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Footnotes and Financial Disclosures

Originally received: August 20, 2019.
Final revision: December 6, 2019.
Accepted: December 30, 2019.
Available online: ■■■. Manuscript no. 2019-121.

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Presented in part at: Dutch Ophthalmology Association Annual Meeting, March 2019, Maastricht, The Netherlands; EURETINA 9th Winter Meeting, March 2019, Prague, Czech Republic; and EURETINA 2019 Congress, September 2019, Paris, France.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): T.P.: Consultant — Novartis, OPTOS, Heidelberg.

Y.d.J.-H.: Lecturer — Novartis.

J.J. C.v.L.-V.: Advisory board — Novartis.

R.O.S.: Consultant — Oxurion, IDx; Financial support — Novartis, Bayer, Optos.

Supported by ZonMw, The Netherlands Organization for Health Research and Development, The Hague, the Netherlands (grant no.: 171202018). The sponsor or funding organization had no role in the design or conduct of this research.

HUMAN SUBJECTS: Human subjects were included in this study. The Medical Ethical Committee of the Amsterdam University Medical Centers, location AMC, approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **BRVO** = branch retinal vein occlusion; **CI** = confidence interval; **CRVO** = central retinal vein occlusion; **hemi-CRVO** = hemi-central retinal vein occlusion; **ME** = macular edema; **MedDRA** = Medical Dictionary for Regulatory Activities; **RCT** = randomized controlled trial; **RVO** = retinal vein occlusion; **SAE** = severe adverse event; **SCORE2** = Study of Comparative Treatments for Retinal Vein Occlusion 2; **SD** = standard deviation; **VEGF** = vascular endothelial growth factor.

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