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Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Diabetic Macular Edema (BRDME)

The BRDME Study, a Randomized Trial

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Purpose: To generate conclusive evidence regarding the noninferiority of intravitreal bevacizumab compared with ranibizumab in patients with diabetic macular edema (DME).

Design: Comparative, randomized, double-masked, multicenter, noninferiority clinical trial.

Participants: Eligible patients were older than 18 years, diagnosed with type 1 or type 2 diabetes mellitus, with glycosylated hemoglobin of less than 12%, central area thickness of more than 325 μm, and visual impairment from DME with a best-corrected visual acuity (BCVA) between 24 letters and 78 letters.

Methods: From June 2012 through February 2018, a total of 170 participants were randomized to receive 6 monthly injections of either 1.25 mg bevacizumab (n = 86) or 0.5 mg ranibizumab (n = 84).

Main Outcome Measures: Primary outcome was change in BCVA from baseline to month 6 compared between the 2 treatment arms. The noninferiority margin was 3.5 letters.

Results: The difference in mean BCVA between treatment arms was 1.8 letters in favor of ranibizumab after 6 months of follow-up; BCVA improved by 4.9±6.7 letters in the bevacizumab group and 6.7±8.7 letters in the ranibizumab group. The lower bound of the 2-sided 90% confidence interval (CI) was −3.626 letters, exceeding the noninferiority margin of 3.5 letters. Central area thickness decreased more with ranibizumab (138.2±114.3 μm) compared with bevacizumab (64.2±104.2 μm). In a post hoc subgroup analysis, participants with a worse BCVA at baseline (≤69 letters) improved by 6.7±7.0 letters with bevacizumab and 10.4±10.0 letters with ranibizumab, and central area thickness decreased significantly more in the ranibizumab arm of this subgroup compared with the bevacizumab arm. Participants with an initially better BCVA at baseline (≥70 letters) did not demonstrate differences in BCVA or OCT outcomes between treatment arms.

Conclusions: Based on change in BCVA from baseline to month 6, the noninferiority of 1.25 mg bevacizumab to 0.5 mg ranibizumab was not confirmed. Only the subgroup of patients with a lower BCVA at baseline showed better visual acuity and anatomic outcomes with ranibizumab. Our study confirmed the potential differential efficacy of anti−vascular endothelial growth factor agents in the treatment of DME as well as the difference in response between patient groups with different baseline visual acuities. *Ophthalmology Retina 2020;4:777-788 © 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.

In the treatment of diabetic macular edema (DME), off-label bevacizumab is a low-priced alternative to the registered and more expensive ranibizumab and aflibercept. However, only 1 state-of-the-art randomized clinical trial, the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study, has compared the efficacy and safety of these anti−vascular endothelial growth factor (VEGF) agents directly in DME.[1,2]

Diabetic macular edema is the most important cause of vision loss in patients with diabetic retinopathy (DR). It is

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characterized by breakdown of the blood–retina barrier, leading to leakage of proteins and fluid from blood vessels, tissue edema, and eventually neurodegeneration and permanent visual loss.[3] Diabetic macular edema is associated with a high patient burden and high societal costs because of the growing number of patients with diabetes mellitus and has become a serious global health issue.[4–6]

The pathophysiology of DME is multifactorial, complex, and not fully understood. Vascular endothelial growth factor A is a major mediator,[7,8] according to the results of several trials that demonstrated a positive effect on visual acuity outcomes with anti-VEGF therapies compared with laser photocoagulation or sham injections.[9–12] The anti-VEGF agents commonly used for the treatment of DME are ranibizumab, a humanized monoclonal antibody fragment; bevacizumab, a humanized full-length monoclonal antibody that, like ranibizumab, neutralizes all VEGF A isoforms[7]; and aflibercept, a construct of 2 VEGF receptors fused to a humanized monoclonal antibody backbone.[13]

Only ranibizumab and aflibercept are registered as treatment for macular edema, but bevacizumab is used off-label because its cost is 20- to 40-fold lower compared with the other drugs. In the DRCR.net Protocol T study comparing the 3 agents, after 1 year, aflibercept was more effective in improving visual acuity compared with bevacizumab or 0.3-mg ranibizumab. However, these findings were not interpreted as clinically meaningful because they were driven by baseline visual acuity. In fact, aflibercept was superior to bevacizumab and 0.3-mg ranibizumab only in a subgroup of patients with a baseline visual acuity of less than 69 letters. After 2 years, aflibercept was superior only to bevacizumab in this subgroup of patients.[1,2] One other small randomized clinical trial of 63 eyes demonstrated no difference between bevacizumab and ranibizumab in effects on central area thickness and visual acuity after 1 year of monthly injections, but that study was not powered to detect small but clinically meaningful differences.[14] In the present study, we aimed to generate conclusive evidence regarding the noninferiority of 1.25 mg bevacizumab to ranibizumab at a higher dose of 0.5 mg in patients with DME in terms of visual acuity outcomes.

Methods

Study Design and Population

The study protocol has been detailed previously.[15] In summary, the Bevacizumab and Ranibizumab in Diabetic Macular Edema (BRDME) trial was a prospective, randomized, double-masked clinical trial with a noninferiority design performed in 8 clinical centers throughout The Netherlands. The Medical Ethical Committee of the Amsterdan University Medical Centers, location AMC, approved the trial protocol, and the study adhered to the principles of the Declaration of Helsinki. All participants signed written informed consent before screening. The trial is registered at ClinicalTrials.gov (identifier, NCT01635790) and at the Dutch trial register (identifier, NTR3247).

From June 2012 through February 2018, a total of 170 participants were screened for eligibility. Eligible patients were older than 18 years, diagnosed with type 1 or type 2 diabetes mellitus and with a glycosylated hemoglobin of less than 12%, central area thickness on optical coherence tomography (OCT) of more than 325 μm, and visual impairment resulting from DME with best-corrected visual acuity (BCVA) outcome of at least 24 letters and less than 79 letters on standardized Early Treatment Diabetic Retinopathy Study charts. A complete list of inclusion and exclusion criteria are found in Table S1 (available at www.ophthalmologyretina.org). At the screening visit, we verified that glycosylated hemoglobin levels were less than 12%. However, the actual values of glycosylated hemoglobin were not recorded. The diagnosis of DME and DR, together with fulfillment of eligibility criteria, was validated through spectral-domain OCT and fluorescein angiography examination and was reviewed by an independent reading center (the Belfast Reading Center, Belfast, United Kingdom, part of the Network of Ophthalmic Reading Centers of the United Kingdom).

Interventions and Randomization

After giving written informed consent and completing a successful screening visit, participants were assigned randomly to receive intravitreal injections of either 1.25 mg bevacizumab (Avastin; Genentech, South San Francisco, CA, United States/Hoffman-La Roche, Basel, Switzerland) or 0.5 mg ranibizumab (Lucentis; Genentech, South San Francisco, CA, United States/Novartis, Inc, Basel, Switzerland). Randomization was stratified by center, the BCVA of the study eye (≤52 letters vs. ≥53 letters),[16,17] and central area thickness on spectral-domain OCT (≤400 μm or >400 μm). Permuted blocks (block size minimum, 2 patients; block size maximum, 4 patients) were used, and allocation was computer- and internet-based. Each participant received a unique patient identification number at randomization.

Within 14 days after screening, study participants received their first injection at the baseline visit. The hospital pharmacy reconstituted and supplied the study drug in injection syringes, labeled with only a patient identification number. Thus, all study participants, investigator staff, and treating physicians were unaware of treatment allocation. Over the course of 6 months, patients received 6 monthly injections with an interval of 30±7 days between visits. Best-corrected visual acuity of the study eye was determined at every visit together with spectral-domain OCT examination and basic clinical examination (pulse and blood pressure measurement). At screening and exit visits, a more extensive dilated ophthalmic examination was performed together with fluorescein angiography and color fundus photography of both eyes. During each visit, concomitant medication, adverse events (AEs), and severe AEs (SAEs) were registered. Best-corrected visual acuity was measured by trained personnel following protocol and using the standardized Early Treatment Diabetic Retinopathy Study chart. Retinal area thickness was examined with the system available at the participating center (Zeiss Cirrus, Heidelberg Spectralis, or Topcon). OCT values obtained by Zeiss Cirrus (Carl Zeiss Meditec, Dublin, Ireland) or Topcon (Topcon, Tokyo, Japan) devices were converted to Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) values for analysis and reporting, using the conversion table reported by Giani et al.[18]

Outcomes

The primary outcome was the difference in BCVA change in the study eye from baseline to month 6 between treatment arms, with a noninferiority margin of 3.5 letters. Prespecified secondary outcomes were the proportion of participants with a BCVA loss or gain of fewer than 15 letters from months 0 to 6 (stabilizers), with a BCVA loss of 15 letters or more (nonresponders), or with a BCVA gain of 15 letters or more (gainers). Secondary outcomes included change in central area thickness as measured by spectral-domain

OCT at 6 months, change in intraocular pressure from baseline to month 6, the proportion of dropouts before the final examination at 6 months, and the occurrence of SAEs and AEs during the study period. All AEs were coded according the Medical Dictionary for Regulatory Activities system version 20.0.

Participants were randomized based on their visual acuity at baseline (≤52 letters vs. ≥53 letters). However, the number of patients between groups was misaligned so that the group with a baseline BCVA of 53 letters or more had 156 participants compared with 10 participants in the group with a baseline BCVA of 52 letters or fewer. To yield equally distributed groups for statistical analysis, we followed the methods of the Protocol T study of the DRCR.net, using the median letter score at baseline as a cutoff value for subgroup analysis.[1,2] The baseline median in our study was 70 letters in each group; therefore, we performed a post hoc analysis comparing visual acuity and retinal thickness outcomes of patients with a higher baseline visual acuity (≥70 letters; Snellen equivalent, approximately >20/40) with patients with a lower baseline visual acuity (≤69 letters; Snellen equivalent, approximately ≤20/40).

The Belfast Reading Center confirmed the diagnosis of DR and DME and checked adherence to inclusion and exclusion criteria. Furthermore, they classified DR into nonproliferative DR (NPDR), stable proliferative DR (PDR), and active PDR. The classification into NPDR included all severities of NPDR of the Early Treatment Diabetic Retinopathy Study diabetic retinopathy severity scale. Stable PDR was identified by the absence of leakage resulting from a neovascularization on the fluorescein angiogram, in the presence of laser scars, fibrous proliferations, or both. Active PDR was classified as definite leakage on fluorescein angiogram resulting from a neovascularization on the disc or elsewhere, the presence of a preretinal hemorrhage or a vitreous hemorrhage, including retinal laser scars, or both. For this reason, we performed another post hoc analysis comparing primary and secondary outcomes between treatment groups in patients classified with NPDR and with stable and active PDR. Other secondary outcomes that have been described in the study protocol[15] will be presented in separate reports.

Sample Size Calculation

At the start of the study, the sample size for an 80% power of demonstrating noninferiority was based on the standard deviation (SD) of the change in a visual acuity score of 11 letters from baseline to month 6.[9] According to this calculation, 123 patients in each study arm would be needed to demonstrate noninferiority, given a noninferiority margin of 3.5 letters. A mean improvement of 7 letters reflected the average change in visual acuity observed in placebo-controlled trials with ranibizumab.[10,19–21] The noninferiority margin was set equivalent to less than half of this improvement.

In February 2018, the assumed SD of the change in BCVA was checked on the blinded study data, yielding a lower SD of 7.8 letters. Given this lower SD and still assuming an improvement of 7 letters, a sample size of 126 patients (63 in each study arm) would have an 80% power of demonstrating noninferiority by excluding a difference of 3.5 letters or more at a 1-sided α significance level of 0.05.

Statistical Analysis

Statistical analysis was based on the intention-to-treat principle. Participants who received the allocated treatment at least once, along with OCT examination and BCVA measurements 1 month after the last injection, were included. If participants did not complete the study, the last available BCVA was used as the BCVA at month 6 (last observation carried forward). The latter approach also was applied when 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 t test. Bevacizumab was considered noninferior to ranibizumab if the lower bound of the 2-sided 90% confidence interval (CI) of the difference in visual acuity did not exceed the noninferior margin of 3.5 letters. The 2-sided 90% CI is equivalent to the 1-sided 95% CI, which is used as the outcome measurement in noninferiority trials.

To evaluate the influence of using the last observation carried forward, we performed a linear mixed-effects regression analysis to analyze the repeatedly measured BCVA change from baseline to month 6. For the analysis of the proportion of nonresponders, stabilizers, and gainers between treatment groups, we used the linear-by-linear association test. The difference in the number of dropouts was analyzed with the Pearson chi-square test. Covariance analysis was completed to compare change in central area thickness and change in intraocular pressure from baseline to month 6 between treatment groups. The numbers and proportion of SAEs and AEs per study arm were compared using the Mann−Whitney U test and the Pearson chi-square test. For all statistical tests, a significance level of 0.05 was applied. These statistical tests also were used for primary and secondary outcomes in post hoc analyses.

Results

Study Participants

From June 2012 through February 2018, a total of 170 participants were randomized to receive bevacizumab (n = 86) or ranibizumab (n = 84). The extensive inclusion and exclusion criteria of the study protocol and a decrease in referrals to the academic study sites caused the prolonged inclusion period. Eventually, 84 patients receiving bevacizumab and 82 patients receiving ranibizumab were included in primary and secondary analyses (Fig S1, available at www.ophthalmologyretina.org).

In general, ocular and demographic baseline characteristics did not differ between treatment groups (Table 1). Only a difference in gender distribution was noted (P = 0.024), with 40 women included in the bevacizumab group compared with 25 women in the ranibizumab group. Nonwhite participants were distributed evenly among the treatment groups (P = 0.530).

The presence of DME secondary to DR was confirmed for all patients by the Belfast Reading Center. Fulfillment of all eligibility criteria could not be confirmed in all participants because 22 patients showed the exclusion criteria of untreated PDR in the study eye (n = 4) or structural damage within 600 μm of the center of the macula (n = 18). Untreated PDR was defined as leakage on fluorescein angiogram resulting from a neovascularization, the presence of preretinal hemorrhages or vitreous hemorrhages, or both, without the detection of retinal laser scars. Structural damage included the presence of laser scars, retinal pigment epithelium atrophy, and organized hard exudate plaques close to the macula. These 22 participants were distributed evenly over both treatment arms (13 [15.5%] in the bevacizumab group and 9 [11.0%] in the ranibizumab group; P = 0.393). The mean ± SD baseline visual acuity of the study eye of these 22 patients was 65.5±10.9 letters in the bevacizumab arm and 73.8±6.7 letters in the ranibizumab arm (P = 0.057). However, because our statistical analysis is based on

Table 1. Baseline and Demographic Characteristics

Baseline Characteristics	Bevacizumab (n = 84)	Ranibizumab (n = 82)
Mean age (SD), yrs	63.9 (11.6)	64.9 (11.6)
Gender, no. (%)*		
Female	40 (47.6)	25 (30.5)
Male	44 (52.4)	57 (69.5)
Ethnicity, no. (%)		
Dutch	60 (71.4)	67 (81.7)
Moroccan	3 (3.6)	1 (1.2)
Turkish	1 (1.2)	0
Surinamese	10 (11.9)	9 (11.0)
Netherlands Antilles and Aruba	1 (1.2)	0
Other nonwhite participants	8 (9.5)	5 (6.1)
Other white participants	1 (1.2)	0
Smoking behavior, no. (%)		
Smoker	9 (10.7)	10 (12.2)
Former smoker	39 (46.4)	39 (47.6)
Nonsmoker	36 (42.9)	33 (40.2)
Mean visual acuity of the study eye (SD), letters	69.0 (1.0)	68.5 (10.2)
Mean central area thickness (SD), μm	450.2 (91.9)	465.9 (104.6)
Mean intraocular pressure (SD), mmHg	15.0 (3.1)	15.0 (3.7)
Prior anti-VEGF treatment in study eye, no. (%)	14 (16.7)	17 (20.7)
Prior focal–grid photocoagulation treatment in the study eye, no. (%)	11 (12.8)	13 (15.5)
Prior panretinal photocoagulation treatment in the study eye, no. (%)	13 (15.1)	14 (16.7)
Diabetes mellitus type, no. (%)		
Type I	10 (11.9)	12 (14.5)
Type II	74 (88.1)	71 (85.5)
Mean duration of diagnosis of diabetes mellitus (SD), yrs	15.4 (8.8)	17.5 (13.4)
Diabetic retinopathy severity, no. (%)		
NPDR	37 (44.0)	41 (50.0)
Active PDR	19 (22.7)	10 (12.2)
Stable PDR	28 (33.3)	30 (36.6)
Missing	0	1 (1.2)
Mean blood pressure (SD), mmHg		
Systolic	144.5 (15.4)	143.9 (17.3)
Diastolic	78.8 (10.4)	80.2 (10.7)
Mean body mass index (SD), m^2/kg	28.9 (0.6)	29.1 (4.9)
Insulin use, no. (%)	54 (64.3)	55 (67.1)
Presence of intraretinal cysts in the study eye, no. (%)		
Absent	2 (2.4)	0
Definite	81 (96.4)	82 (100)
Questionable	1 (1.2)	0
Presence of subretinal fluid in the study eye, no. (%)		
Absent	51 (60.7)	48 (58.5)
Definite	20 (23.8)	25 (30.5)
Questionable	12 (14.3)	9 (11.0)
Could not be graded	1 (1.2)	0
History of hypertension, no. (%)	55 (65.5)	57 (69.5)
History of myocardial infarction, no. (%)	6 (7.1)	8 (9.8)
History of transient ischemic attack, no. (%)	6 (7.1)	4 (4.9)
History of cerebrovascular accident, no. (%)	5 (6.0)	4 (4.9)
History of hypercholesterolemia, no. (%)	17 (20.2)	19 (23.2)
History of thrombosis, no. (%)	2 (2.4)	1 (1.2)
History of renal disease, no. (%)	8 (9.5)	10 (12.2)

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation; VEGF = vascular endothelial growth factor.
*A significant difference was found between treatment groups with $P < 0.05$.

the intention-to-treat principle, all randomized participants were included in the analyses.

In addition, among the 166 participants analyzed, 6 participants (7.1%) in the bevacizumab group and 2 participants (2.4%) in the ranibizumab group dropped out of the study before the final 6-month assessment ($P = 0.157$). No difference was found in the mean number of injections between treatment groups for participants who completed the entire study protocol. Patients in the

Table 2. Primary and Secondary Outcomes after 6 Months

Outcomes	Bevacizumab (n = 84)	Ranibizumab (n = 82)	Lower Bound 90% Confidence Interval*	P Value
Primary				
Mean change in visual acuity of study eye from months 0 to 6 (SD), letters				
Month 1	1.5 (5.7)	3.3 (6.0)	−3.241	
Month 2	3.8 (5.2)	5.1 (6.6)	−2.762	
Month 3	4.2 (5.8)	5.7 (8.5)	−3.158	
Month 4	4.6 (6.7)	5.8 (8.8)	−2.933	
Month 5	4.9 (7.0)	6.6 (8.8)	−3.543	
Month 6	4.9 (6.7)	6.7 (8.7)	−3.626	
Mean visual acuity of the study eye at 6 months (SD), letters	73.5 (9.8)	75.2 (9.0)		
Secondary				
Change in visual acuity, no. (%)				0.105
Stabilizers (loss or gain <15 letters from baseline)	81 (94.2)	73 (86.9)		
Nonresponders (loss ≥15 letters from baseline)	0	0		
Gainers (gain ≥15 letters from baseline)	5 (5.8)	11 (13.1)		
Mean central area thickness at 6 months (SD), μm	383.40 (102.64)	327.40 (67.23)		0.000
Mean change in central area thickness (SD), μm				0.000
Month 1	−49.8 (76.6)	−86.0 (111.5)		
Month 2	−56.9 (90.4)	−108.4 (115.7)		
Month 3	−66.2 (96.7)	−107.6 (116.6)		
Month 4	−64.7 (91.3)	−119.7 (116.2)		
Month 5	−67.5 (97.4)	−132.0 (114.7)		
Month 6	−64.2 (104.2)	−138.2 (114.3)		
Intraretinal cysts on OCT at 6 mos, no. (%)				0.107
Absent	8 (10.7)	12 (15.8)		
Definite	64 (85.3)	55 (72.4)		
Questionable	3 (4.0)	9 (11.8)		
Subretinal fluid on OCT at 6 mos, no. (%)				**0.028**
Absent	60 (80.0)	68 (89.5)		
Definite	11 (14.7)	2 (2.6)		
Questionable	4 (5.3)	6 (7.9)		
Proportion of dropouts, no. (%)	6 (7.1)	2 (2.4)		0.157
Mean change in systolic blood pressure from month 0 to 6 (SD), mmHg	2.4 (16.3)	4.9 (17.2)		0.262
Mean systolic blood pressure at 6 months (SD), mmHg	146.2 (19.5)	149.5 (16.6)		
Mean change in diastolic blood pressure from month 0 to 6 (SD), mmHg	0.03 (8.2)	−1.0 (10.2)		0.854
Mean diastolic blood pressure at 6 months (SD), mmHg	78.0 (11.0)	79.4 (11.4)		
Mean change in IOP from month 0 to 6 (SD), mmHg	0.2 (3.7)	−0.1 (2.9)		0.718
Mean IOP at 6 months (SD), mmHg	15.0 (3.5)	15.0 (3.4)		

IOP = intraocular pressure; SD = standard deviation.
*The lower bound of the 2-sided 90% confidence interval of the difference in visual acuity change is noted as an outcome for noninferiority; bevacizumab is considered noninferior to ranibizumab if the noninferiority margin of 3.5 letters can be excluded.

bevacizumab group received 5.95±0.03 injections and patients in the ranibizumab group received 5.98±0.02 injections ($P = 0.391$). The mean follow-up time between visits was 29.7±1.4 days in the bevacizumab group and 29.5±1.1 days in the ranibizumab group ($P = 0.450$).

Visual Acuity Outcomes

The mean visual acuity improved from baseline to 6 months by 4.9±6.7 letters in the bevacizumab group and 6.7±8.7 letters in the ranibizumab group (Table 2; Fig 1A). The lower bound of the 2-sided 90% CI for change in visual acuity from baseline to month 6 was −3.626 letters, exceeding the noninferiority margin of 3.5 letters (Fig 2). (These outcomes were verified with linear mixed-effects regression analysis, in which case the lower bound of the 2-sided 90% CI was −3.844 letters.

The proportion of stabilizers, nonresponders, and gainers did not differ between treatment arms ($P = 0.105$), with 5 gainers (5.8%) in the bevacizumab group and 11 gainers (13.1%) in the ranibizumab group. The number of stabilizers was distributed equally over the 2 treatment arms, and no patients lost 15 letters or more from baseline.

Post hoc analysis was performed based on the median letter score at baseline, comparing participants with a baseline visual acuity of 69 letters or fewer (n = 79) with participants with a baseline visual acuity of 70 letters or more (n = 87; Table 3). In both subgroups, participants were distributed equally over the treatment arms (Table 3). Patients with an initially lower BCVA showed a mean gain of 6.7±7.0 letters when receiving bevacizumab and 10.4±10.0 letters when receiving ranibizumab, with the lower bound of the 2-sided 90% CI at −6.430 letters (Table 3; Figs 1B and 3). Again, this result excludes the noninferiority margin of 3.5 letters, but this subgroup was not

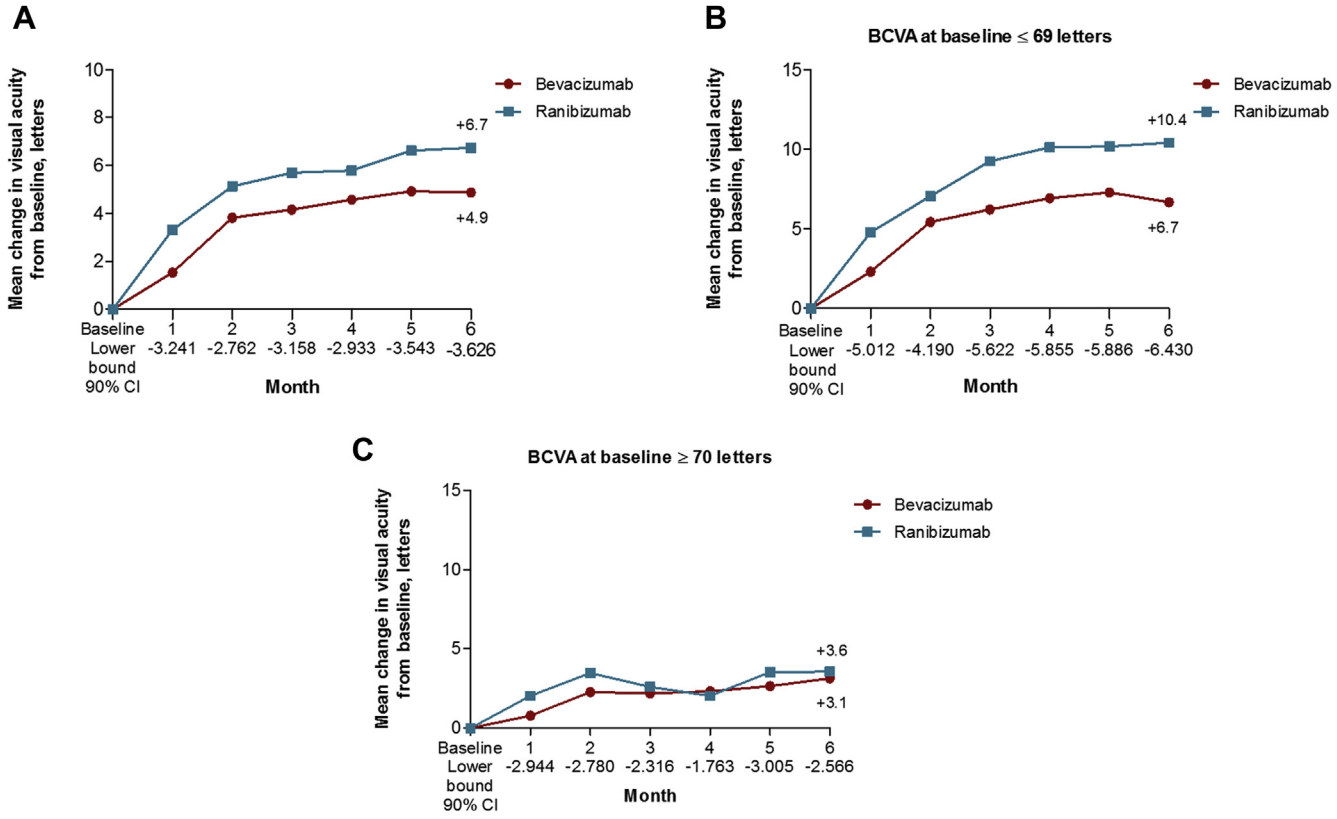

Figure 1. Graphs showing mean change in visual acuity from baseline to month 6 in patients treated with bevacizumab and ranibizumab: (**A**) entire cohort, (**B**) patients with a baseline visual acuity of 69 letters or fewer, and (**C**) patients with a baseline visual acuity of 70 letters or more. BCVA = best corrected visual acuity; CI = confidence interval.

powered to reject noninferiority reliably. Patients with an initially higher BCVA improved by 3.1±5.9 letters in the bevacizumab group and 3.6±5.7 letters in the ranibizumab group, with a lower bound of the 2-sided 90% CI at −2.566 letters, suggesting noninferiority of bevacizumab to ranibizumab in this subgroup (Table 3; Figs 1C and 3).

Additional analyses excluding the 22 patients who did not meet all eligibility criteria again demonstrated noninferiority in the subgroup with a higher baseline BCVA only (results not shown). The 22 patients were distributed equally over the subgroups with a lower and higher baseline visual acuity. When we analyzed these 22 participants exclusively, the mean visual acuity improved with 8.3±5.7 letters in the bevacizumab arm and with 1.6±3.7 letters in the ranibizumab arm from baseline to 6 months.

Central Area Thickness Outcomes

After 6 months, central area thickness decreased in the bevacizumab arm by a mean of 64.2±104.2 μm and in the ranibizumab arm by a mean of 138.2±114.3 μm ($P < 0.001$; Table 2; Fig 3A). The presence of intraretinal cysts and subretinal fluid did not differ between treatment arms at baseline visit (Table 2). However, after 6 months, more patients demonstrated subretinal fluid in the bevacizumab group (11 patients [14.7%]) than in the ranibizumab group (2 patients [2.6%]; $P = 0.028$). In the subgroup of participants with a baseline visual acuity of 69 letters or fewer, central area thickness decreased by 58.7±114.2 μm in the bevacizumab group and by 189.5±137.3 μm in the ranibizumab group ($P < 0.001$; Table 3; Fig 3B). Those with an initially better visual acuity (≥70 letters) showed a decrease in central area thickness of 69.2±95.3 μm in the bevacizumab group and 95.1±66.0 μm in the ranibizumab group ($P = 0.073$; Table 3; Fig 3C). When we excluded the 22 patients who did not meet all eligibility criteria, again ranibizumab decreased central area thickness significantly more compared with bevacizumab, both in the entire cohort and in the subgroup with a lower baseline BCVA.

Subgroup Analysis: Diabetic Retinopathy Severity Score

Of all patients randomized, 78 patients were diagnosed with NPDR, 29 patients were diagnosed with active PDR, and 58 patients were diagnosed with stable PDR (Table S2, available at www.ophthalmologyretina.org). The Belfast Reading Center could not diagnose 1 patient because of missing proper imaging material. For analysis, patients with active and stable PDR were merged into 1 PDR subgroup. In the NPDR group, the mean gain in visual acuity after 6 months was 5.5±6.3 letters in those randomized to receive bevacizumab and 8.7±10.7 letters in those randomized to receive ranibizumab (lower bound of the 2-sided 90% CI for the difference in change in visual acuity was −5.721

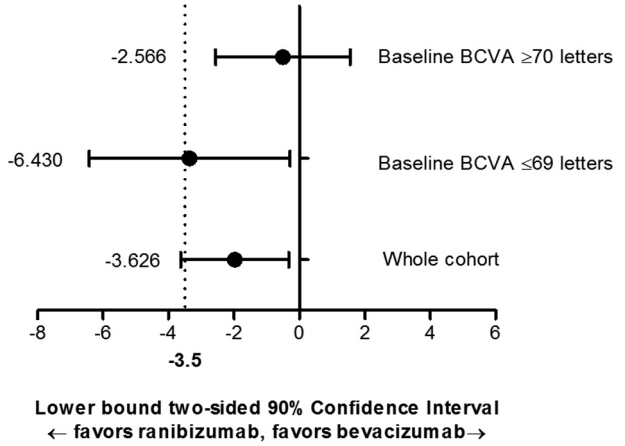

Figure 2. Graph showing the 2-sided 90% confidence intervals (CIs) with the noninferiority margin of 3.5 letters. Noninferiority of bevacizumab compared with ranibizumab could not be confirmed in the entire study cohort, although the lower bound of the CI just exceeded the noninferiority margin of 3.5 letters. In patients with a lower baseline visual acuity, noninferiority of bevacizumab could not be confirmed either, whereas the CIs for patients with a higher baseline visual acuity suggested noninferiority of bevacizumab to ranibizumab. However, these subgroups were not powered to demonstrate noninferiority reliably. BCVA = best corrected visual acuity.

letters). The noninferiority margin of 3.5 letters was exceeded; however, again, this subgroup was not powered to reject noninferiority. In patients diagnosed with PDR, the mean gain in visual acuity was almost equal in both treatment groups, with a gain of 4.4±7.0 letters in the bevacizumab group and 4.7±5.6 letters in the ranibizumab group (lower bound of the 2-sided 90% CI, −2.558 letters; Table S2), suggesting noninferiority of bevacizumab to ranibizumab in this subgroup.

A significant difference between bevacizumab and ranibizumab in the change of central area thickness after 6 months of treatment was detected solely in the subgroup with patients diagnosed with PDR ($P = 0.001$). However, when we excluded the 22 patients who did not meet all eligibility criteria, patients in the PDR subgroup who were treated with ranibizumab demonstrated a larger gain in visual acuity compared with those who were treated with bevacizumab, and noninferiority of bevacizumab to ranibizumab no longer could be confirmed. This additional analysis did not alter visual acuity outcomes in the NPDR subgroup. Besides, secondary outcomes regarding the change in central area thickness did not differ when these 22 patients were excluded from analyses in both subgroups.

Safety Outcomes

The number of patients who experienced AEs and SAEs during the study period did not differ between the bevacizumab and ranibizumab groups ($P = 0.704$ and $P = 0.711$, respectively). Arteriothrombotic events were distributed equally over both study arms: 1 patient in the bevacizumab group experienced a nonfatal stroke, and 1 patient in the ranibizumab group experienced a myocardial infarction (Table 4). A difference between treatment groups was identified in the Medical Dictionary for Regulatory Activities system organ class of immune system disorders ($P = 0.014$); AEs described in this class consisted solely of allergic reactions resulting from fluorescein angiography. Another difference was found in the system organ class of injury, poisoning and procedural complication ($P = 0.005$; Table S3, available at www.ophthalmologyretina.org), which included the occurrence of physical injuries and the presence of floaters after injection. Nevertheless, the AEs described in these system organ classes are not likely to be of clinical significance and were not considered to be caused by the anti-VEGF agent itself. Intraocular pressure changed minimally over the course of 6 months in both the bevacizumab and ranibizumab groups (Table 2).

Discussion

This study showed that based on the change in visual acuity from baseline to month 6, noninferiority of 1.25-mg bevacizumab to 0.5-mg ranibizumab could not be confirmed in patients with DME, because the lower bound of the 2-sided 90% CI of −3.626 letters exceeded the noninferiority margin of 3.5 letters. When patients were analyzed based on baseline visual acuity, bevacizumab was noninferior to ranibizumab in patients with an initially higher visual acuity (≥70 letters). Because ranibizumab showed a much better outcome in patients with an initially lower BCVA (≤69 letters), it is plausible that participants with a lower baseline visual acuity drove the visual acuity outcome of the entire study group. The subgroup with a lower baseline BCVA was not powered to reject noninferiority of bevacizumab to ranibizumab, but we considered the substantial difference of 3.7 letters in favor of ranibizumab to be clinically relevant. In addition, ranibizumab showed better visual acuity outcomes in participants diagnosed with NPDR, in contrast to results in PDR patients, in whom visual acuity improved equally in both treatment arms.

The Protocol T study of the DRCR.net is the largest study to date to compare the efficacy and safety of all 3 anti-VEGF agents in patients with DME, with ranibizumab used in the 0.3-mg dose. After 1 year of follow-up, aflibercept was linked to a larger improvement in visual acuity than bevacizumab and 0.3-mg ranibizumab. The DRCR.net stated that these outcomes were not clinically meaningful to all patients, because a subgroup analysis showed significant outcomes in favor of aflibercept over both bevacizumab and ranibizumab in only those patients with an initially lower visual acuity. The 2-year results demonstrated that aflibercept continued to be significantly more effective compared with bevacizumab in this subgroup.[1,2] As noted, our study showed that 0.5-mg ranibizumab had better outcomes compared with bevacizumab in terms of both visual acuity and anatomic outcomes. Nevertheless, when patients were divided into subgroups with a higher or lower baseline visual acuity, these results persisted only in the group with an initially lower BCVA and were absent in patients with an initially higher BCVA, similar to the observations in the protocol T study.

In contrast to our findings, in the Protocol T study, bevacizumab and ranibizumab did not differ significantly in visual acuity outcomes after either 1 or 2 years of treatment. This difference between the 2 studies may be explained by the

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

Outcomes	Best-Corrected Visual Acuity at Baseline of ≥70 Letters (n = 87)				Best-Corrected Visual Acuity at Baseline ≤69 Letters (n = 79)				
	Bevacizumab (n = 43)	*Ranibizumab (n = 44)*	*Lower Bound 90% Confidence Interval*[†]	P *Value*	*Bevacizumab (n = 41)*	*Ranibizumab (n = 38)*	*Lower Bound 90% Confidence Interval*[†]	P *Value*	**P Value***
Primary									
Visual acuity at baseline, letters	74.7 (3.2)	75.0 (3.6)			62.1 (8.5)	60.8 (10.2)			
Change in visual acuity of study eye, letters									
Month 1	0.8 (4.3)	2.0 (4.9)	−2.944		2.3 (6.8)	4.8 (6.9)	−5.012		
Month 2	2.3 (4.5)	3.5 (4.2)	−2.780		5.4 (5.4)	7.1 (8.3)	−4.190		
Month 3	2.2 (4.8)	2.6 (5.5)	−2.316		6.2 (6.1)	9.3 (10.0)	−5.622		
Month 4	2.3 (5.8)	2.1 (5.3)	−1.763		6.9 (6.9)	10.1 (10.1)	−5.855		
Month 5	2.7 (6.0)	3.6 (5.6)	−3.005		7.3 (7.4)	10.2 (10.4)	−5.886		
Month 6	3.1 (5.9)	3.6 (5.7)	−2.566		6.7 (7.0)	10.4 (10.0)	−6.430		
Visual acuity at 6 months, letters	77.9 (6.5)	78.59 (5.97)			68.80 (10.53)	71.25 (10.35)			
Secondary									
Central area thickness at baseline, μm	435.16 (83.65)	431.64 (67.61)			456.96 (98.32)	505.46 (125.03)			
Change in central area thickness, μm									
Month 1	−50.8 (61.5)	−50.9 (63.6)			−48.8 (90.6)	−124.8 (138.3)			
Month 2	−60.4 (82.4)	−68.7 (62.8)			−53.1 (99.9)	−155.7 (144.2)			
Month 3	−58.2 (77.1)	−73.1 (65.2)			−75.0 (115.1)	−148.7 (148.2)			
Month 4	−61.4 (84.5)	−82.1 (63.3)			−68.7 (99.9)	−162.2 (145.4)			
Month 5	−63.9 (93.5)	−90.3 (60.7)			−71.7 (102.9)	−180.5 (141.7)			
Month 6	−69.2 (95.3)	−95.1 (66.0)		0.073	−58.7 (114.2)	−189.5 (137.3)		0.000	0.004
Central area thickness at 6 months, μm	362.5 (71.8)	336.6 (69.6)			406.5 (125.5)	316.5 (63.5)			

Data are mean (standard deviation).

*P value for best-corrected visual acuity at baseline × treatment group interaction on both visual acuity outcome and central area thickness outcome.

[†]The lower bound of the 2-sided 90% confidence interval of the difference in best-corrected visual acuity change is noted as an outcome for noninferiority; bevacizumab is considered noninferior to ranibizumab if the noninferiority margin of 3.5 letters can be excluded.

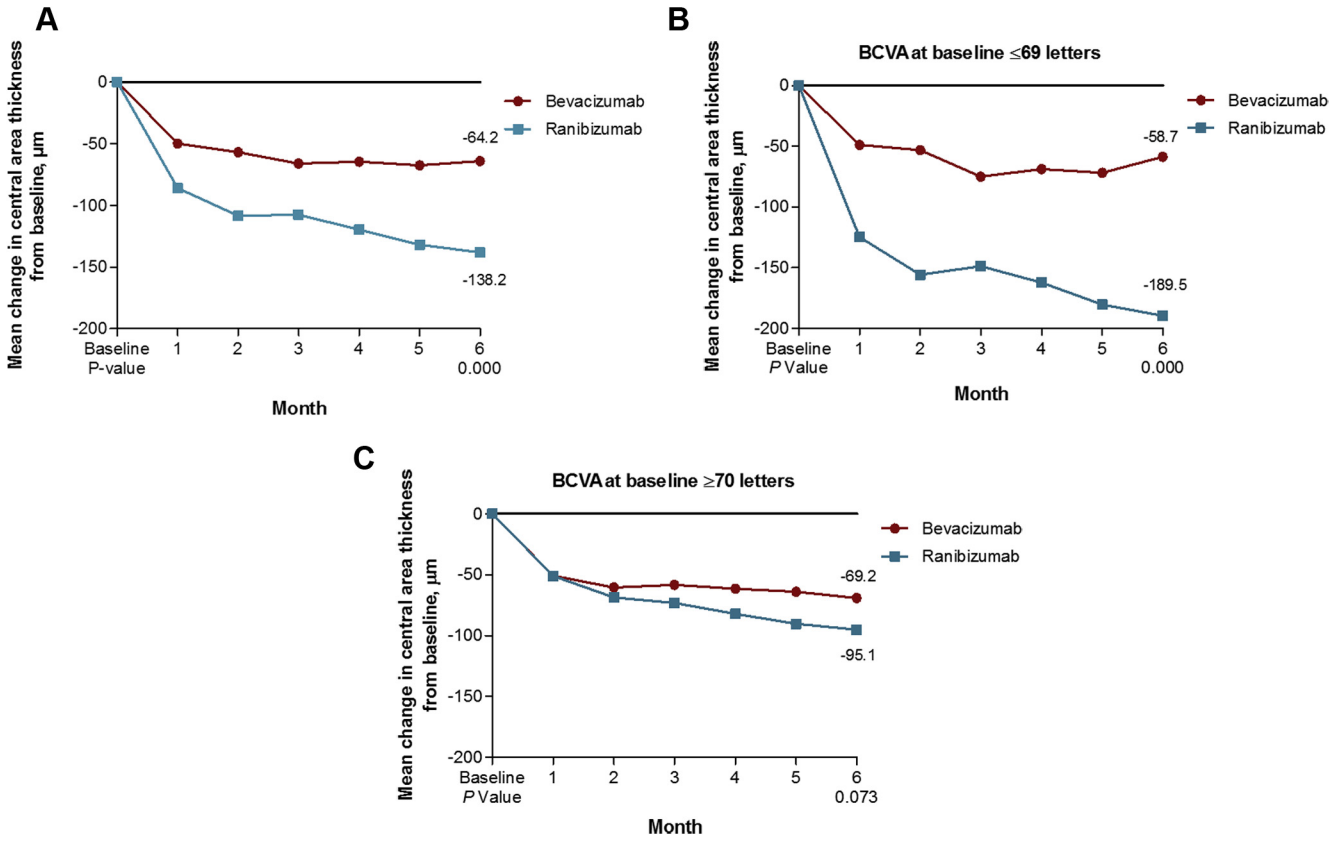

Figure 3. Graphs showing mean change in central area thickness (in micrometers) from baseline to month 6: (**A**) entire cohort, (**B**) patients with a baseline visual acuity of 69 letters or fewer, and (**C**) patients with a baseline visual acuity of 70 letters or more.

choice of study design, because the BRDME Study was conducted as a noninferiority trial to describe visual acuity outcomes, of which the lower bound of the 2-sided 90% CI was given as a measure for outcome differences between anti-VEGF agents, instead of *P* values as used in the Protocol T study. In addition, because the Protocol T study investigated 0.3-mg ranibizumab instead of the 0.5-mg dose in the BRDME Study, a dose-response effect may explain the different outcomes of these studies. However, the RISE and RIDE studies found no difference in visual acuity outcomes between patients treated with 0.3-mg ranibizumab or 0.5-mg ranibizumab when administered monthly for 3 years.[9,22] A possible explanation therefore may lie in the different treatment regimens of the 2 studies, which may have led to underdosing in the protocol T study. In contrast to the monthly dosing in the BRDME Study, the protocol T study showed more similarities with a pro re nata protocol, in which patients are treated as needed, which led to an average monthly dose of 0.235 mg of ranibizumab in the first 12 months of the protocol T study. However, because patients might be injected more frequently in the first 6 months compared with the second 6 months of the protocol T study, the average monthly dose of ranibizumab in the first 6 months of the protocol T study varies between 0.235 mg and 0.3 mg. Therefore, it is difficult to compare the outcomes of the protocol T study with those of the BRDME Study.

Table 4. Numbers and Percentages of Patients with Adverse Events or Severe Adverse Events

Event*	Bevacizumab (n = 85)	Ranibizumab (n = 83)	*P* Value
Adverse events			
Any adverse event	55 (64.7)	58 (69.9)	0.704
Elevated intraocular pressure	1 (1.2)	1 (1.2)	0.986
Anterior uveitis	1 (1.2)	3 (3.6)	0.300
Retinal tear	0	1 (1.2)	0.310
Hypertension	9 (10.6)	15 (18.1)	0.166
>1 Adverse event	29 (34.1)	28 (33.7)	0.958
Severe adverse events			
Any severe adverse event	11 (13)	9 (10.8)	0.711
Death from any cause	2 (2.4)	0	0.160
Arteriothrombotic event			
Nonfatal myocardial infarction	0	1 (1.2)	0.310
Nonfatal stroke	1 (1.2)	0	0.322
Wound resulting from vascular problems	1 (1.2)	2 (2.4)	0.546
Transient ischemic attack	2 (2.4)	0	0.160
>1 Severe adverse event	2 (2.4)	3 (3.6)	0.630
Pneumonia	1 (1.2)	1 (1.2)	0.986
Urosepsis	2 (2.4)	1 (1.2)	0.574

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

In line with the visual acuity outcomes, central area thickness decreased significantly more in the ranibizumab arm in the entire cohort, and more patients in the bevacizumab group showed subretinal fluid on OCT after 6 months of treatment ($P = 0.028$). However, it should be kept in mind that the presence or absence of subretinal fluid was scored by local investigators and was not confirmed by an external reading center. Nevertheless, similar findings were seen in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Bevacizumab to Ranibizumab in exudative Age-Related Macular Degeneration (BRAMD) study, both of which compared the efficacy of bevacizumab with that of ranibizumab in patients with exudative age-related macular edema.[23,24] In the subgroup analysis based on baseline visual acuity, again, anatomic outcomes matched visual acuity outcomes, where ranibizumab decreased the central area thickness significantly more among patients with an initially lower baseline visual acuity.

It is important to note that the observed different functional and anatomic outcomes in the subgroups based on baseline visual acuity may be explained in part or completely by the ceiling effect originating from the physiologic limits of both BCVA and OCT measurement outcomes. The closer these parameters at baseline lie to the ceiling of normal BCVA or retinal thickness, the less there is to gain from a given treatment. In addition, it is unknown whether the true gains of functional visual outcome or quality of life differ per 1-letter increase or per 1-μm central area thickness decline between these subgroups. That is, for example, a gain of 3.7 letters may have a different functional significance in the subgroup with a lower baseline visual acuity than in the subgroup with a higher baseline visual acuity.[25,26]

Noninferiority of bevacizumab to ranibizumab could be confirmed in the PDR subgroup, which included patients with active and stable PDR, but not in the subgroup of patients with NPDR. Besides, patients in the latter subgroup demonstrated a better gain in visual acuity compared with patients with PDR, regardless of the treatment arm. Although these subgroups were not powered to reject noninferiority, the reasons for these differences between DR subgroups remain unclear. That these differences may be the result of chance or confounding is supported by our finding that the 22 patients who did not meet all eligibility criteria were overrepresented in the PDR group, and when we excluded these patients from analysis, noninferiority no longer could be confirmed in the PDR subgroup, either.

A significant difference in gender distribution over the treatment arms was found, because more women were included in the bevacizumab arm compared with the ranibizumab arm. Because gender is not considered as one of the risk factors for the development of DME or its response to anti-VEGF therapy, this unbalance in patient groups is unlikely to influence study outcomes.

The safety of intravitreal injections with anti-VEGF agents remains incompletely understood. Treatment with intravitreal anti-VEGF agents suppresses systemic VEGF, which potentially can result in cardiovascular and arteriothrombotic events, wound healing complications, and hypertension.[27,28] In our study, we found no differences between bevacizumab and ranibizumab groups in cardiovascular and arteriothrombotic events or hypertension, although our study was not powered to detect small but clinically significant safety differences between bevacizumab and ranibizumab. Differences were found in Medical Dictionary for Regulatory Activities classes of immune system disorders and injury, poisoning and procedural complications. However, these AEs were not caused directly by the anti-VEGF treatment itself.

According to the pharmacy manual of the study (Appendix S1, available at www.ophthalmologyretina.org), the good laboratory practice–certified hospital pharmacies prepared multiple doses of study medication from single vials, under aseptic conditions. In the literature, this procedure has been associated with contamination with silicone droplets.[29] Nevertheless, no AEs that could be attributed to this procedure were reported. In addition, no silicone oil droplets were reported by the local investigators during slit-lamp examination after 6 months of treatment. Several patients did report the presence of transient floaters, but whether these were caused by silicone oil droplets remains unknown.

As in other clinical trials, the BRDME Study had its limitations. First, it was missing a comparison with aflibercept, which unfortunately was not yet available in The Netherlands at study start. The follow-up time was limited to 6 months, whereas patients with macular edema generally are treated for a longer period. However, previous randomized clinical trials demonstrated that improvement in visual acuity occurs predominantly during the first 3 to 6 months of anti-VEGF therapy and that only limited visual acuity gain is observed after this period.[9,20,30,31] In addition, 6 initial monthly treatments can be regarded as standard care for DME, and outcomes at 6 months are relevant for clinical management, because at the 6-month time point after initiation of anti-VEGF treatment, most ophthalmologists will evaluate the need for additional deferred treatment with laser, for switching drugs, or both. Not all participants were treatment naïve; 16.7% in the bevacizumab group and 20.7% in the ranibizumab group received prior anti-VEGF treatment. However, none of these patients had received anti-VEGF therapy for at least 3 months, and all had a clear indication for anti-VEGF therapy based on the inclusion criteria. A total of 22 patients did not meet all eligibility criteria, but because our study followed the intention-to-treat principle, all patients were included in analyses. Besides, primary and secondary outcomes were not altered when these 22 participants were excluded from analysis. Patients were divided into subgroups based on visual acuity outcome at baseline and based on DR severity; however, our study was not powered to reject noninferiority between treatment arms in small subgroups. Nevertheless, the visual acuity outcomes in the subgroup with a higher visual acuity were suggestive of noninferiority in this subgroup alone. Finally, different OCT devices were used for central area thickness examination. To compare these outcomes, all measurements were converted to Heidelberg Spectralis outcomes using the conversion table by Giani et al.[18] That said, the software version of the devices used in this study differed from the software versions on which Giani et al based their

conversion table. Nevertheless, we expected minimal changes to result from these software updates.

In conclusion, based on the difference in visual acuity outcome, noninferiority of 1.25-mg bevacizumab to 0.5-mg ranibizumab could not be confirmed in the treatment of DME when patients received monthly injections for a period of 6 months. In addition, anatomic outcomes on OCT also differed markedly between treatment groups. Patients with a lower baseline visual acuity showed an even better outcome with 0.5-mg ranibizumab. After the Protocol T study of the DRCR.net, our study is the first comparative trial to confirm differences in efficacy between anti-VEGF agents, especially in the subgroup of patients with a lower baseline visual acuity. When taking the results of these studies together, clinicians may be advised to treat patients with DME and a visual acuity of worse than 20/40 with aflibercept or 0.5-mg ranibizumab, rather than with 1.25-mg bevacizumab.

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Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **BRAMD** = Bevacizumab to Ranibizumab in exudative Age-related Macular Degeneration; **BRDME** = Bevacizumab and Ranibizumab in Diabetic Macular Edema; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CI** = confidence interval; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRCR.net** = Diabetic Retinopathy Clinical Research Network; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **SAE** = severe adverse event; **SD** = standard deviation; **VEGF** = vascular endothelial growth factor.

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