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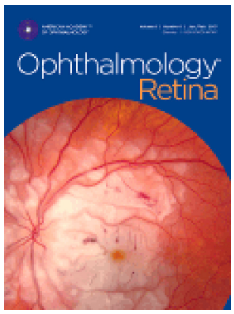

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Comparing the efficacy of bevacizumab and ranibizumab in patients with diabetic macular edema: the BRDME study, a randomized trial

Maartje J.C. Vader[1], Ann-Sofie M.E. Schauwvlieghe[1], Frank D. Verbraak[2], Greetje Dijkman[3], Johanna M.M. Hooymans[4], Leonoor I. Los[4], Aeilko H. Zwinderman[5], Tunde Peto[6], Carel B. Hoyng[7], Redmer van Leeuwen[8], Johannes R. Vingerling[9], Annette C. Moll[2], Janneke J.C. van Lith-Verhoeven[10], Marcel G.W. Dijkgraaf[5] and Reinier O. Schlingemann[1,11], for the BRDME Study Group.

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Supplemental materials

This article contains additional online-only material. The following should appear online-only: Figure S1, Tables S1, S2, S3 and Appendix S1, S2.

Meeting presentation

The data presented in this manuscript were partly presented at the annual Dutch Ophthalmology Association Meeting, Maastricht, the Netherlands, March 27 - 29, 2019; the Annual Meeting of The Association for Research in Vision and Ophthalmology, Vancouver, British Columbia, Canada, April 28 – May 2 2019; and the Annual Meeting of the European Association for the Study of Diabetes Eye Complications Study Group, Amsterdam, the Netherlands, May 16 – 18 2019.

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Conflict of interest

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No conflicting relationships exist for other authors.

Running head

Bevacizumab and Ranibizumab for Diabetic Macular Edema

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Abbreviations and Acronyms

AE = adverse event; **BCVA** = best corrected visual acuity; **CI** = confidence interval; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRCR.net** = Diabetic Retinopathy Clinical Research Network; **ETDRS** = Early Treatment of Diabetic Retinopathy Study; **GLP** = good laboratory practice; **HbA1c** = hemoglobin A1c; **IOP** = intraocular pressure; **MedDRA** = Medical Dictionary for Regulatory Activities; **NPDR** = non-proliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **PRN** = pro re nata; **SD-OCT** = spectral domain optical coherence tomography; **SAE** = severe adverse event; **SD** = standard deviation; **VEGF** = vascular endothelial growth factor.

Abstract

Purpose: To generate conclusive evidence on the non-inferiority of intravitreal bevacizumab compared to ranibizumab in patients with diabetic macular edema (DME).

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

Participants: Eligible patients were over 18 years of age, diagnosed with type 1 or type 2 diabetes mellitus, with glycosylated hemoglobin (HbA1c) <12%, central area thickness of >325 microns, and visual impairment from DME with a best corrected visual acuity (BCVA) of ≥24 letters and ≤78 letters.

Methods: From June 2012 to 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 two treatment arms. The non-inferiority 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 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 two-sided 90% confidence interval (CI) was -3.626 letters, exceeding the non-inferiority margin of 3.5 letters. Central area thickness decreased more with ranibizumab (138.2±114.3 µm) compared to 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, central area thickness decreased significantly more in the ranibizumab arm of this subgroup compared to bevacizumab. Participants with an initially better BCVA at baseline (≥70 letters) did not demonstrate differences in BCVA or OCT outcomes between treatment arms (lower bound of the two-sided 90% CI:-2.566 letters).

Conclusions: Based on change in BCVA from baseline to month 6, the non-inferiority 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 anatomical outcomes with ranibizumab. Our study confirms 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.

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 one state-of-the-art randomized clinical trial, the Diabetic Retinopathy Clinical Research Network Protocol T (DRCR.net Protocol T) study, has directly compared the efficacy and safety of these anti-vascular endothelial growth factor (VEGF) agents in DME.[1, 2]

DME is the most important cause of vision loss in patients with diabetic retinopathy (DR). It is 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] DME 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. VEGF-A is a major mediator,[7, 8] according to the results of several trials which demonstrated a positive effect on visual acuity outcomes with anti-VEGF therapies compared to 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 two 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 to the other drugs. In the DRCR.net Protocol T study comparing the three agents, after one year, aflibercept was more effective in improving visual acuity compared to 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 <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 one 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 non-inferiority of 1.25 mg bevacizumab to ranibizumab at a higher dose of 0.5 mg in patients with diabetic macular edema in terms of visual acuity outcomes.

Material and methods

Study design and population

The study protocol has been detailed previously.[15] In summary, the BRDME trial is a prospective, randomized, double-masked clinical trial with a non-inferiority design, performed in eight clinical centers throughout the Netherlands. The Institutional Review Board/Ethics Committee approved the trial protocol, and the study was regulated following the principles of the Declaration of Helsinki. All participants signed written informed consent before screening. The trial is registered at ClinicalTrials.gov (NCT01635790) and at the Dutch trial register (NTR3247).

From June 2012 until February 2018, a total of 170 participants were screened for eligibility. Eligible patients were over age 18 years, diagnosed with type 1 or type 2 diabetes mellitus and with a glycosylated hemoglobin (HbA1c) of less than 12%, central area thickness on optical coherence tomography (OCT) of more than 325 µm, and visual impairment from DME with best corrected visual outcome of at least 24 letters and less than 79 letters on standardized Early Treatment Diabetic Retinopathy Study (ETDRS) charts. A complete list of inclusion and exclusion criteria are listed in Table S1, available at www.aaojournal.org. At the screening visit we verified that HbA1c levels were below 12%. However, the actual values of HbA1c were not recorded. The diagnosis of DME and DR, together with fulfillment of eligibility criteria, was validated through spectral domain OCT (SD-OCT) and fluorescein angiography examination and reviewed by an independent reading center (the Belfast Reading Center, part of the Network of Ophthalmic Reading Centers, United Kingdom).

Interventions and randomization

After giving written informed consent and completing a successful screening visit, participants were randomly assigned to receive intravitreal injections of either 1.25 mg bevacizumab (Avastin, Genentech/Hoffman-La Roche) or 0.5 mg ranibizumab (Lucentis, Genentech/Novartis). Randomization was stratified by center, the best corrected visual acuity (BCVA) of the study eye (≤52 letters versus ≥53 letters)[16, 17] and by central area thickness on SD-OCT (≤400 µm or >400 µm). Permuted blocks (block size minimum 2, 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 only with a patient identification number. Thus, all study participants, investigator staff, and treating physicians were unaware of treatment allocation. During 6 months, patients received 6 monthly injections with an interval of 30 ± 7 days between visits. BCVA of the study eye was determined at every visit together with SD-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 photos of both eyes. During each visit, concomitant medication and (severe) adverse events (AEs; SAEs) were registered. BCVA 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 or Topcon devices were converted to Heidelberg Spectralis values for analysis and reporting, using the conversion table reported by Giani et al.[18]

198

199 *Outcomes*

200 The primary outcome was the difference in BCVA change in the study eye from baseline to month 6
201 between treatment arms, with a non-inferiority margin of 3.5 letters. Prespecified secondary
202 outcomes were the proportion of participants with a BCVA loss or gain of less than 15 letters from
203 month 0 to month 6 (stabilizers), with a loss of 15 letters or more (non-responders), or with a gain of
204 15 letters or more in BCVA (gainers). Secondary outcomes included change in central area thickness
205 as measured by SD-OCT at 6 months, change in intraocular pressure (IOP) from baseline to month 6,
206 the proportion of dropouts before the final examination at 6 months, and the occurrence of SAEs and
207 AEs during the study period. All AEs were coded according the Medical Dictionary for Regulatory
208 Activities (MedDRA, version 20.0) system.

209 Participants were randomized based on their visual acuity at baseline (≤52 letters versus ≥53
210 letters). However, the number of patients between groups was misaligned so that the group with a
211 baseline BCVA ≥53 letters had 156 participants compared to 10 participants in the group with a
212 baseline BCVA ≤52 letters. To yield equally distributed groups for statistical analysis, we followed the
213 methods of the Protocol T study of the DRCR network, using the median letter score at baseline as a
214 cutoff value for subgroup analysis.[1, 2] The baseline median in our study was 70 letters in each group,
215 therefore we performed a post-hoc analysis comparing visual acuity and retinal thickness outcomes
216 of patients with a higher baseline visual acuity (≥70 letters, Snellen equivalent of approximately
217 >20/40) to patients with a lower baseline visual acuity (≤69 letters, Snellen equivalent of
218 approximately ≤20/40).

219 The Belfast Reading Center confirmed the diagnosis of DR and DME and checked adherence
220 to in- and exclusion criteria. Furthermore, they classified DR into non-proliferative DR (NPDR), stable
221 proliferative DR (stable PDR) and active PDR. The classification into NPDR included all severities of
222 non-proliferative diabetic retinopathy of the ETDRS diabetic retinopathy severity scale. Stable PDR
223 was identified by the absence of leakage due to a neovascularization on the fluorescein angiogram, in

the presence of laser scars and/or fibrous proliferations. Active PDR was classified as definite leakage on fluorescein angiogram due to a neovascularization on the disc or elsewhere and/or the presence of a preretinal hemorrhage or a vitreous hemorrhage, including retinal laser scars. 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 non-inferiority 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 non-inferiority, given a non-inferiority 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 non-inferiority 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 non-inferiority by excluding a difference of 3.5 letters or more at a one-sided alpha 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 and BCVA measurements one month after the last injection, were included. If participants did not complete the study, the last available BCVA was used as BCVA at month 6 (last observation carried forward). The latter approach was also applied when

patients missed an injection during follow-up: the BCVA measurement from the previous visit was used as last available BCVA. Non-inferiority was tested using a one-sided t-test. Bevacizumab was considered non-inferior to ranibizumab if the lower bound of the two-sided 90% confidence interval (CI) of the difference in visual acuity did not exceed the non-inferior margin of 3.5 letters. The two-sided 90% confidence interval is equivalent to the one-sided 95% confidence interval, which is used as the outcome measurement in non-inferiority 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 non-responders, stabilizers, and gainers between treatment groups, we used the linear-by-linear association test. The difference in 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 IOP 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 test and the Pearson chi-square test. For all statistical tests, a significance level of 0.05 was applied. These statistical tests were also used for primary and secondary outcomes in post-hoc analyses.

Results

Study participants

From June 2012 until 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 (Figure S1, available at www.aaojournal.org).

In general, ocular and demographic baseline characteristics did not differ between treatment groups (Table 1). Only a difference in sex distribution was noted (P = 0.024), with 40 female participants included in the bevacizumab group compared to 25 in the ranibizumab group. Non-Caucasian participants were evenly distributed 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 presented with the exclusion criteria 'untreated proliferative diabetic retinopathy in the study eye' (n = 4) or 'structural damage within 600 µm of the center of the macula' (n = 18). Untreated proliferative diabetic retinopathy was defined as leakage on fluorescein angiogram due to a neovascularization and/or the presence of preretinal hemorrhages or vitreous hemorrhages, without the detection of retinal laser scars. Structural damage included the presence of laser scars, retinal pigment epithelium atrophy and organized hard exudates plaques close to the macula. These 22 participants were evenly distributed over both treatment arms, (13 [15.5%] in the bevacizumab group and 9 [11.0%] in the ranibizumab group; P = 0.393). The mean baseline visual acuity of the study eye of these 22 patients was (mean ± standard deviation) 65.5±10.9 letters in the bevacizumab arm and 73.8±6.7 letters in the ranibizumab arm (P = 0.057). However, since our statistical analysis is based on the intention-to-treat principle, all randomized participants were included in the analyses.

In addition, among the 166 participants analyzed, 6 (7.1%) participants in the bevacizumab group and 2 (2.4%) participants 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 whole study protocol. Patients in the bevacizumab group received5.95±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, Figure 1.a). The lower bound of the two-sided 90% confidence interval for change in visual acuity from baseline to month 6 was -3.626 letters, exceeding the non-inferiority margin of 3.5 letters (Figure 3). These outcomes were verified with linear mixed-effects regression analysis, in which case the lower bound of the two-sided 90% confidence interval was -3.844 letters.

The proportion of stabilizers, non-responders, and gainers did not differ between treatment arms (P = 0.105), with 5 (5.8%) gainers in the bevacizumab group and 11 (13.1%) patients in the ranibizumab group. The number of stabilizers was equally distributed over the two treatment arms, and no patients lost ≥15 letters 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 (n = 79) to participants with a baseline visual acuity of ≥70 letters (n = 87; Table 3). In both subgroups, participants were equally distributed 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 two-sided 90% CI at -6.430 (Table 3, Figures 1.b and 3). Again, this result excludes the non-inferiority margin of 3.5 letters, but this subgroup was not powered to reliably reject non-inferiority. 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 two-sided CI at -2.566 letters, suggesting non-inferiority of bevacizumab to ranibizumab in this subgroup (Table 3, Figures 1.c and 3).

Additional analyses excluding the 22 patients who did not meet all eligibility criteria again demonstrated non-inferiority in the subgroup with a higher baseline BCVA only (results not shown). The 22 patients were equally distributed over the subgroups with a lower and higher baseline visual acuity. When we exclusively analyzed these 22 participants, 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, Figure 2.a). 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 presented 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, central area thickness decreased by 58.7±114.2 µm in the bevacizumab group and with 189.5±137.3 µm in the ranibizumab group ($P < 0.001$) (Table 3, Figure 2.b). 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, Figure 2.c).

When we excluded the 22 patients who did not meet all eligibility criteria, again ranibizumab decreased central area thickness significantly more compared to bevacizumab, both in the whole cohort and in the subgroup with a lower baseline BCVA.

Subgroup analysis: DR severity score

Of all patients randomized, 78 patients were diagnosed with NPDR, 29 with active PDR and 58 with stable PDR (Table S2, available at www.aaojournal.org). The Belfast Reading Center could not diagnose one patient because of missing proper imaging material. For analysis, patients with active and stable PDR were merged into one 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 ranibizumab (lower bound of the two-sided 90% CI for the difference in change in visual acuity was -5.721 letters). The non-inferiority margin of 3.5 letters was exceeded,

however, again this subgroup was not powered to reject non-inferiority. 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 two-sided 90% CI: -2.558) (Table S2, available at www.aaojournal.org), suggesting non-inferiority 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 solely detected 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 to bevacizumab, and non-inferiority of bevacizumab to ranibizumab could no longer 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). Arterio-thrombotic events were equally distributed over both study arms: one patient in the bevacizumab group had a nonfatal stroke, and one patient in the ranibizumab group had a myocardial infarction (Table 4). A difference between treatment groups was identified in the MedDRA system organ class 'Immune system disorders' ($P = 0.014$), adverse events described in this class consisted solely of allergic reactions due to fluorescein angiogram. Another difference was found in the system organ class 'Injury, poisoning and procedural complication' ($P = 0.005$) (Table S3, available at www.aaojournal.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. IOP changed minimally over the course of 6 months in both the bevacizumab and ranibizumab groups (Table 2).

Discussion

This study shows that based on the change in visual acuity from baseline to month 6, non-inferiority of 1.25 mg bevacizumab to 0.5 mg ranibizumab could not be confirmed in patients with DME, as the lower bound of the two-sided 90% CI of -3.626 exceeded the non-inferiority margin of 3.5 letters. When patients were analyzed based on baseline visual acuity, bevacizumab was non-inferior 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 whole study group. The subgroup with a lower baseline BCVA was not powered to reject non-inferiority 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, where visual acuity improved equally in both treatment arms.

The Protocol T study of the DRCR.network is the largest study to date to compare the efficacy and safety of all three anti-VEGF agents in patients with DME, with ranibizumab used in the 0.3 mg dose. After one year of follow-up, aflibercept was linked to a larger improvement in visual acuity than bevacizumab and 0.3 mg ranibizumab. The DRCR.network 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 to bevacizumab in this subgroup.[1, 2] As noted, our study showed that 0.5 mg ranibizumab had better outcomes compared to bevacizumab in terms of both visual acuity and anatomical outcomes. Nevertheless, when patients were divided into subgroups with a higher/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 significantly differ in visual acuity outcomes after either one or two years of treatment. This difference between the two studies may be explained by the choice of study design, because the BRDME study was conducted as a non-inferiority trial to describe visual acuity outcomes, of which the lower bound of the two-sided 90% confidence interval was given as a measure for outcome differences between anti-VEGF agents, instead of *P* values used in the Protocol T study. In addition, as the Protocol T study investigated 0.3 mg ranibizumab instead of the 0.5 mg 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 three years.[9,22] A possible explanation may therefore lie in the different treatment regimens of the two 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 shows more similarities with a pro re nata (PRN) protocol, in which patients are treated “as needed”, which led to an average monthly dose of 0.235 mg ranibizumab in the first 12 months of the Protocol T study. However, since patients may be injected more frequently in the first 6 months compared to 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 will vary between 0.235 mg and 0.3 mg. Therefore it is hard to compare the outcomes of the Protocol T study with the BRDME study.

In line with the visual acuity outcomes, central area thickness decreased significantly more in the ranibizumab arm in the whole cohort, and more patients in the bevacizumab group had 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 not confirmed by an external reading center. Nevertheless, similar findings were seen in the CATT study and the BRAMD study, which both compared the efficacy of bevacizumab to ranibizumab in patients with

exudative age related macular edema.[23, 24] In the subgroup analysis based on baseline visual acuity, again anatomical 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 anatomical outcomes in the subgroups based on baseline visual acuity may be explained in part or completely by the ceiling effect originating from the physiological 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 letter increase or per micron central area thickness decline between these subgroups. In other words, 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]

Non-inferiority 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 to patients with PDR, irrespective of the treatment arm. Although these subgroups were not powered to reject non-inferiority, the reasons for these differences between diabetic retinopathy subgroups remain unclear. That these differences may be due to 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, non-inferiority could no longer be confirmed in the PDR subgroup either.

A significant difference in sex distribution over the treatment arms was found, as more female participants were included in the bevacizumab arm compared to the ranibizumab arm. Since sex 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 can potentially 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 MedDRA classes '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.aaojournal.org) the 'good laboratory practice' (GLP) certified hospital pharmacies prepared multiple dosages 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 adverse events which 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, while patients with macular edema are generally treated for a longer period. However, previous randomized clinical trials demonstrated that improvement in visual acuity predominantly occurs during the first 3 to 6 months of anti-VEGF therapy and 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, as at the 6 month time point after initiation of anti-VEGF treatment most ophthalmologists will evaluate the need for additional deferred treatment with laser

and/or for switching drugs. 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 since our study followed the intention-to-treat principle, all patients were included in analyses. Besides, primary and secondary outcomes did not alter 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 non-inferiority between treatment arms in small subgroups. Nevertheless, the visual acuity outcomes in the subgroup with a higher visual acuity were suggestive of non-inferiority 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, non-inferiority 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, anatomical 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 network, 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 below 20/40 with aflibercept or 0.5 mg ranibizumab, rather than with 1.25 mg bevacizumab.

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Figure legends

Figure 1. Mean change in visual acuity from baseline to month 6 in patients treated with bevacizumab and ranibizumab. **a.** Whole cohort. **b.** Patients with a baseline visual acuity of ≤69 letters. **c.** Patients with a baseline visual acuity of ≥70 letters.

Figure 2. Mean change in central area thickness (µm) from baseline to month 6. **a.** Whole cohort. **b.** Patients with a baseline visual acuity of ≤69 letters. **c.** Patients with a baseline visual acuity of ≥70 letters.

Figure 3. The two-sided 90% confidence intervals with the non-inferiority margin of 3.5 letters. Non-inferiority of bevacizumab compared to ranibizumab could not be confirmed in the whole study cohort, although the lower bound of the CI just exceeded the non-inferiority margin of 3.5 letters. In patients with a lower baseline visual acuity, non-inferiority of bevacizumab could not be confirmed either, whereas the CIs for patients with a higher baseline visual suggested non-inferiority of

bevacizumab to ranibizumab. However, these subgroups were not powered to reliably demonstrate non-inferiority. BCVA = best corrected visual acuity; CI = confidence interval.

Table 1. Baseline and demographic characteristics.

Baseline characteristics	Bevacizumab (n = 84)	Ranibizumab (n = 82)
Age, years	63.9 (11.6)	64.9 (11.6)
Sex*		
Female	40 (47.6%)	25 (30.5%)
Male	44 (52.4%)	57 (69.5%)
Ethnicity		
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 & Aruba	1 (1.2%)	0
Other non-Caucasian participants	8 (9.5%)	5 (6.1%)
Other Caucasian participants	1 (1.2%)	0
Smoking behavior		
Smoker	9 (10.7%)	10 (12.2%)
Ex-smoker	39 (46.4%)	39 (47.6%)
Non-smoker	36 (42.9%)	33 (40.2%)
Visual acuity of the study eye, letters	69.0 (1.0)	68.5 (10.2)
Central area thickness, µm	450.2 (91.9)	465.9 (104.6)
Intraocular pressure, mmHg	15.0 (3.1)	15.0 (3.7)
Prior anti-VEGF treatment in study eye	14 (16.7%)	17 (20.7%)
Prior focal/grid photocoagulation treatment in the study eye	11 (12.8%)	13 (15.5%)
Prior pan-retinal photocoagulation treatment in the study eye	13 (15.1%)	14 (16.7%)
Diabetes mellitus type		
Type I	10 (11.9%)	12 (14.5%)
Type II	74 (88.1%)	71 (85.5%)
Duration of diagnosis of diabetes mellitus, years	15.40 (8.82)	17.48 (13.44)
Diabetic retinopathy severity		
NPDR	37 (44.0%)	41 (50.0%)
PDR – active	19 (22.7%)	10 (12.2%)
PDR – stable	28 (33.3%)	30 (36.6%)
Missing	0	1 (1.2%)
Systolic blood pressure, mmHg	144.5 (15.4)	143.9 (17.3)
Diastolic blood pressure, mmHg	78.8 (10.4)	80.2 (10.7)
Body mass index	28.9 (0.6)	29.1 (4.9)
Insulin use	54 (64.3%)	55 (67.1%)
Presence of intraretinal cysts in the study eye		
Absent	2 (2.4%)	0
Definite	81 (96.4%)	82 (100%)
Questionable	1 (1.2%)	0
Presence of subretinal fluid in the study eye		
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	55 (65.5%)	57 (69.5%)
History of myocardial infarction	6 (7.1%)	8 (9.8%)
History of transient ischemic attack	6 (7.1%)	4 (4.9%)
History of cerebrovascular accident	5 (6.0%)	4 (4.9%)
History of hypercholesterolemia	17 (20.2%)	19 (23.2%)
History of thrombosis	2 (2.4%)	1 (1.2%)
History of renal disease	8 (9.5%)	10 (12.2%)

Data are reported as mean (SD) or n (%).

*: A significant difference was found between treatment groups with *P*-value < 0.05.

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation; VEGF = vascular endothelial growth factor.

Table 2. Primary and secondary outcomes after 6 months.

Primary outcome	**Bevacizumab (n = 84)**	**Ranibizumab (n = 82)**	**Lower bound 90% CI[a]**
Chang in visual acuity of study eye from month 0 to month 6, 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
Visual acuity of the study eye at 6 months, letters	73.5 (9.8)	75.2 (9.0)	
Secondary outcomes	**Bevacizumab (n = 84)**	**Ranibizumab (n = 82)**	***P*-value**
Change in visual acuity			
Stabilizers (loss or gain <15 letters from baseline)	81 (94.2%)	73 (86.9%)	0.105
Non-responders (loss ≥15 letters from baseline)	0	0	
Gainers (gain ≥15 letters from baseline)	5 (5.8%)	11 (13.1%)	
Central area thickness at 6 months, µm	383.40 (102.64)	327.40 (67.23)	0.000
Change in central area thickness, µm			
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)	0.000
Intraretinal cysts on OCT at 6 months			
Absent	8 (10.7%)	12 (15.8%)	0.107
Definite	64 (85.3%)	55 (72.4%)	
Questionable	3 (4.0%)	9 (11.8%)	
Subretinal fluid on OCT at 6 months			
Absent	60 (80.0%)	68 (89.5%)	**0.028**
Definite	11 (14.7%)	2 (2.6%)	
Questionable	4 (5.3%)	6 (7.9%)	
Proportion of dropouts	6 (7.1%)	2 (2.4%)	0.157
Change in systolic blood pressure from month 0 to month 6, mmHg	2.4 (16.3)	4.9 (17.2)	0.262
Mean systolic blood pressure at 6 months, mmHg	146.2 (19.5)	149.5 (16.6)	
Change in diastolic blood pressure from month 0 to month 6, mmHg	0.03 (8.2)	-1.0 (10.2)	0.854
Mean diastolic blood pressure at 6 months, mmHg	78.0 (11.0)	79.4 (11.4)	
Change in intraocular pressure from month 0 to month 6, mmHg	0.2 (3.7)	-0.1 (2.9)	0.718
Mean intraocular pressure at 6 months, mmHg	15.0 (3.5)	15.0 (3.4)	

Data are reported as mean (SD) or n (%).

[a]: The lower bound of the two-sided 90% CI of the difference in visual acuity change is noted as an outcome for non-inferiority; bevacizumab will be considered non-inferior to ranibizumab if the non-inferiority margin of 3.5 letters can be excluded.

CI = confidence interval; OCT = optical coherence tomography; SD = standard deviation.

Table 3. Primary and secondary outcomes based on baseline visual acuity.

	BCVA at baseline ≥ 70 letters (n = 87)			BCVA at baseline ≤69 letters (n = 79)			*P*-value[b]
Primary outcome	**Bevacizumab (n = 43)**	**Ranibizumab (n = 44)**	**Lower bound 90% CI[a]**	**Bevacizumab (n = 41)**	**Ranibizumab (n = 38)**	**Lower bound 90% CI[a]**	
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 outcome	**Bevacizumab (n = 43)**	**Ranibizumab (n = 44)**	***P*-value**	**Bevacizumab (n = 41)**	**Ranibizumab (n = 38)**	***P*-value**	
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)	-148.70 (148.2)		
Month 4	-61.4 (84.5)	-82.1 (63.3)		-68.7 (99.9)	-162.24 (145.4)		
Month 5	-63.9 (93.5)	-90.3 (60.7)		-71.7 (102.9)	-180.48 (141.7)		
Month 6	-69.2 (95.3)	-95.1 (66.0)	0.073	-58.7 (114.2)	-189.54 (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 reported as mean (SD).

[a]: The lower bound of the two-sided 90% CI of the difference in BCVA change is noted as an outcome for non-inferiority; bevacizumab will be considered non-inferior to ranibizumab if the non-inferiority margin of 3.5 letters can be excluded.

[b]: P value for BCVA at baseline × treatment group interaction on both visual acuity outcome and central area thickness outcome.

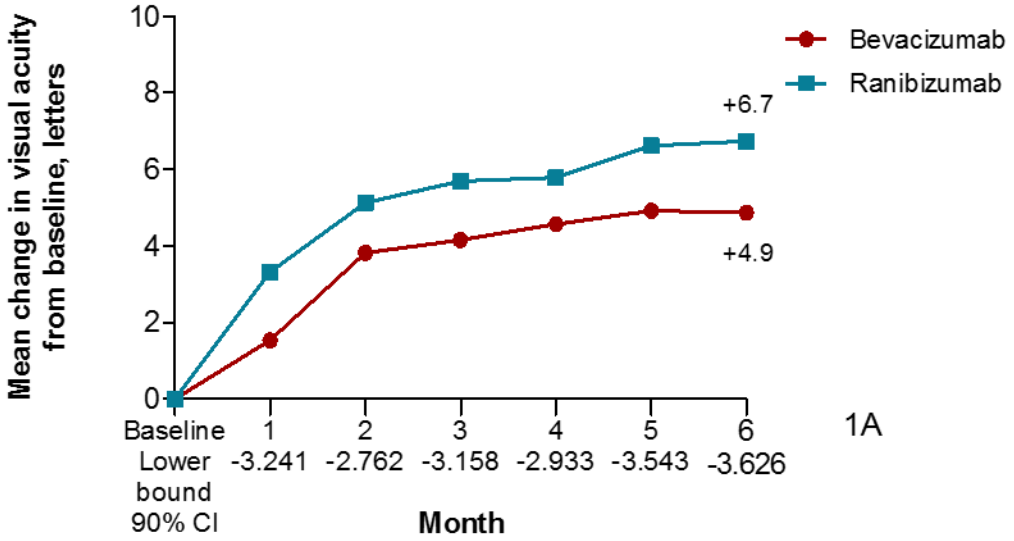
CI = confidence interval; SD = standard deviation.

Table 4. Numbers and percentages of patients with (severe) adverse events.

Event[a]	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 due to vascular problems	1 (1.2%)	2 (2.4%)	0.546
Transient ischemic attack	2 (%)	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 reported as n (%).

[a]Multiple events in the same study patient were counted only once.



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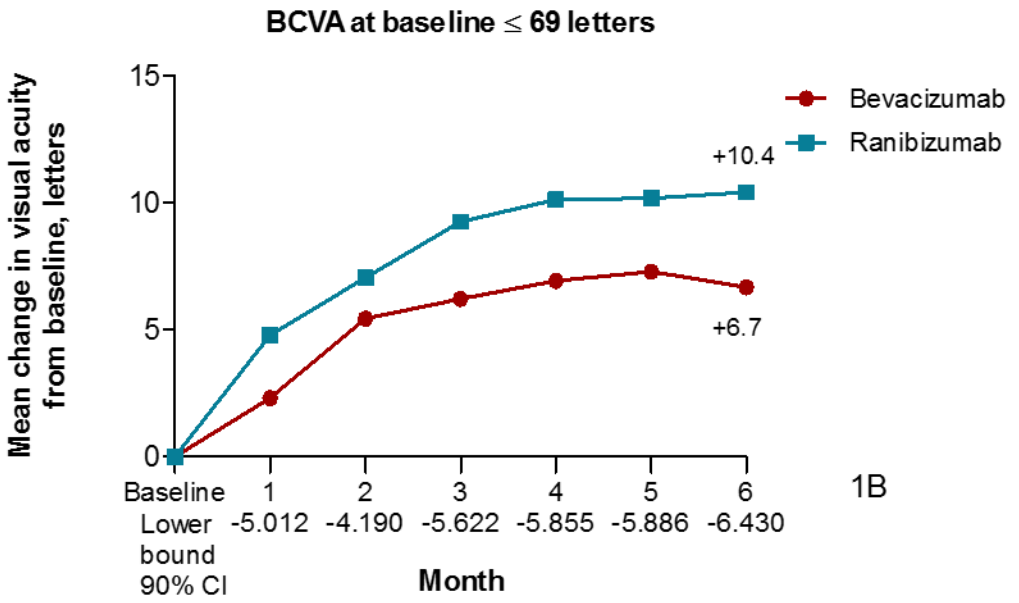

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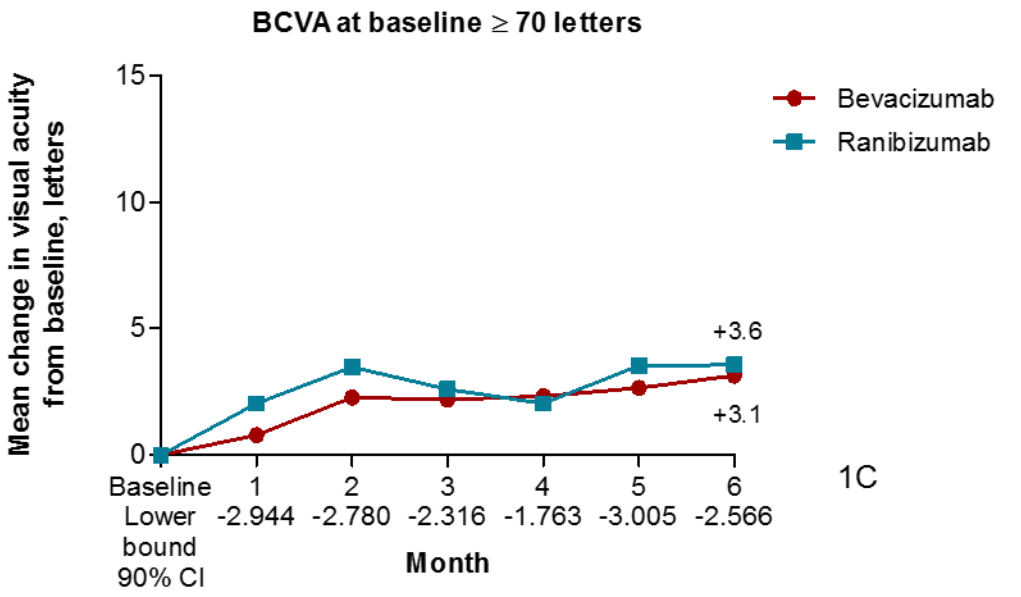
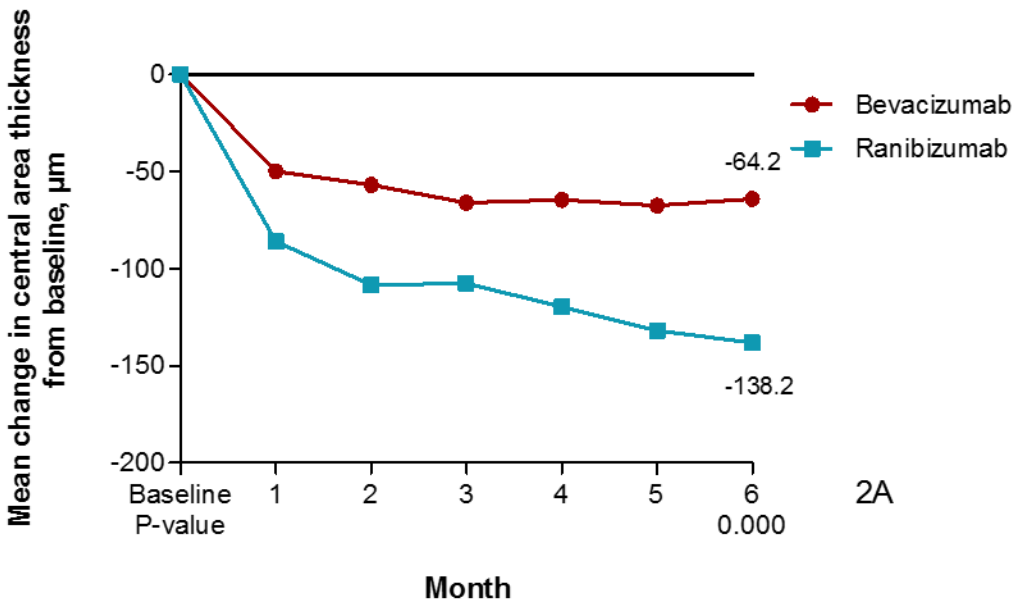
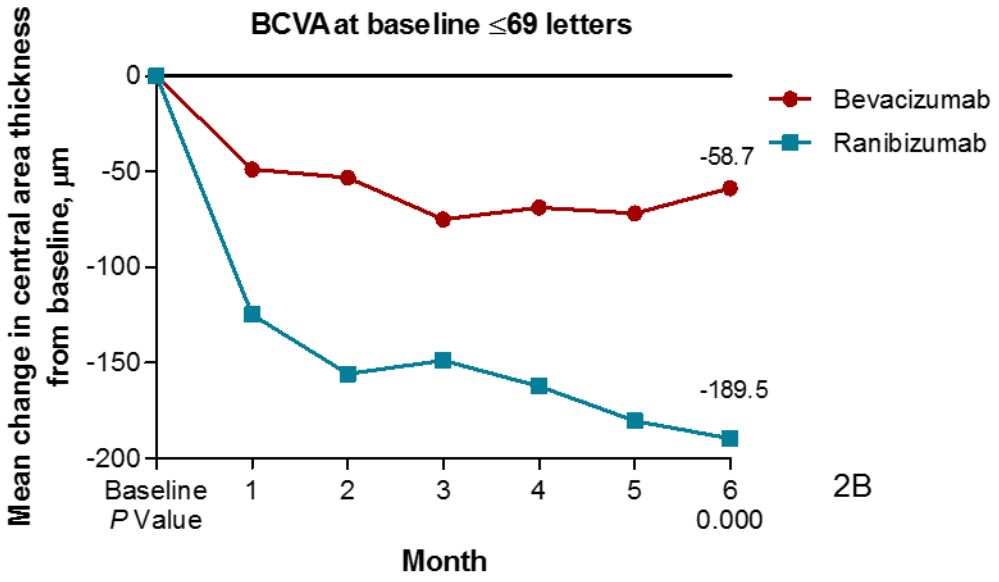


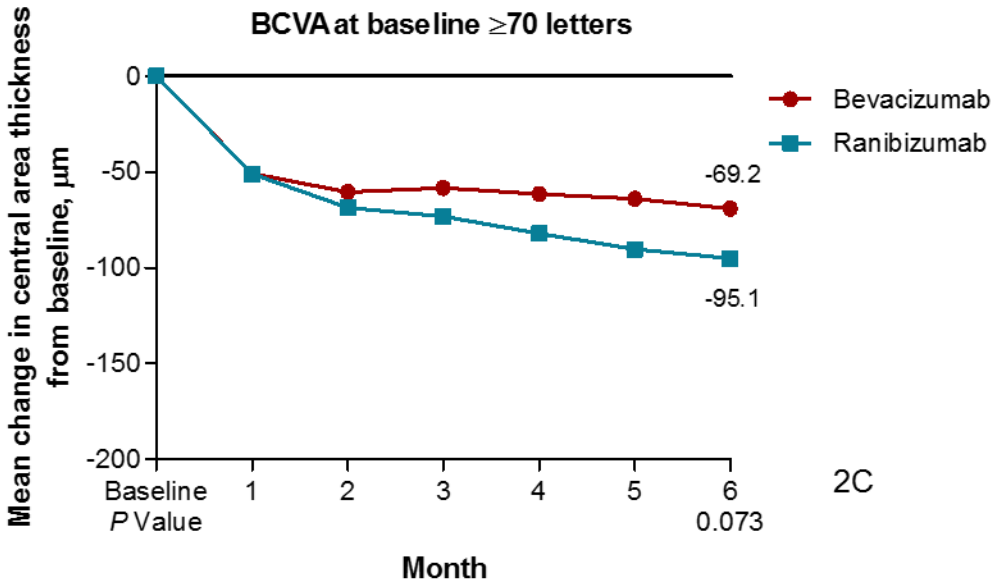
1C



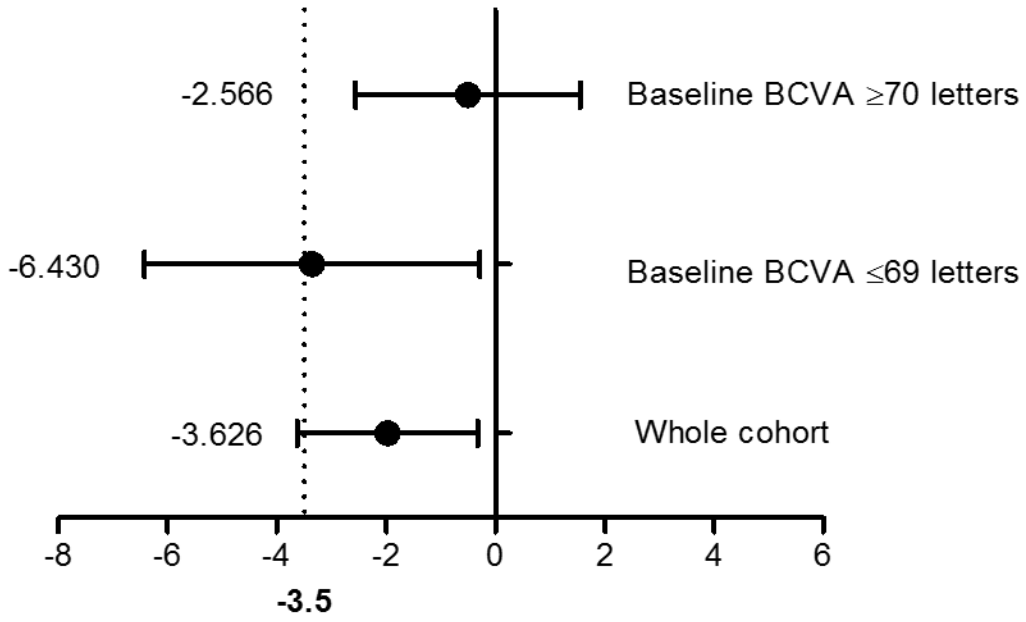
2A



2B



2C


-2.566
Baseline BCVA ≥70 letters
-6.430
Baseline BCVA ≤69 letters
-3.626
Whole cohort
-8
-6
-4
-2
0
2
4
6
-3.5
Lower bound two-sided 90% Confidence Interval
← favors ranibizumab, favors bevacizumab→

Précis

The BRDME study did not demonstrate the non-inferiority of 1.25 mg bevacizumab to 0.5 mg ranibizumab in patients with diabetic macular edema, but found better visual acuity outcomes with ranibizumab than with bevacizumab.