Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration

One-Year Findings from the IVAN Randomized Trial

*The IVAN Study Investigators**
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Purpose: To compare the efficacy and safety of ranibizumab and bevacizumab intravitreal injections to treat neovascular age-related macular degeneration (nAMD).

Design: Multicenter, noninferiority factorial trial with equal allocation to groups. The noninferiority limit was 3.5 letters. This trial is registered (ISRCTN92166560).

Participants: People >50 years of age with untreated nAMD in the study eye who read ≥25 letters on the Early Treatment Diabetic Retinopathy Study chart.

Methods: We randomized participants to 4 groups: ranibizumab or bevacizumab, given either every month (continuous) or as needed (discontinuous), with monthly review.

Main Outcome Measures: The primary outcome is at 2 years; this paper reports a prespecified interim analysis at 1 year. The primary efficacy and safety outcome measures are distance visual acuity and arteriothrombotic events or heart failure. Other outcome measures are health-related quality of life, contrast sensitivity, near visual acuity, reading index, lesion morphology, serum vascular endothelial growth factor (VEGF) levels, and costs.

Results: Between March 27, 2008 and October 15, 2010, we randomized and treated 610 participants. One year after randomization, the comparison between bevacizumab and ranibizumab was inconclusive (bevacizumab minus ranibizumab −1.99 letters, 95% confidence interval [CI], −4.04 to 0.06). Discontinuous treatment was equivalent to continuous treatment (discontinuous minus continuous −0.35 letters; 95% CI, −2.40 to 1.70). Foveal total thickness did not differ by drug, but was 9% less with continuous treatment (geometric mean ratio [GMR], 0.91; 95% CI, 0.86 to 0.97; $P = 0.005$). Fewer participants receiving bevacizumab had an arteriothrombotic event or heart failure (odds ratio [OR], 0.23; 95% CI, 0.05 to 1.07; $P = 0.03$). There was no difference between drugs in the proportion experiencing a serious systemic adverse event (OR, 1.35; 95% CI, 0.80 to 2.27; $P = 0.25$). Serum VEGF was lower with bevacizumab (GMR, 0.47; 95% CI, 0.41 to 0.54; $P<0.0001$) and higher with discontinuous treatment (GMR, 1.23; 95% CI, 1.07 to 1.42; $P = 0.004$). Continuous and discontinuous treatment costs were £9656 and £6398 per patient per year for ranibizumab and £1654 and £1509 for bevacizumab; bevacizumab was less costly for both treatment regimens ($P<0.0001$).

Conclusions: The comparison of visual acuity at 1 year between bevacizumab and ranibizumab was inconclusive. Visual acuities with continuous and discontinuous treatment were equivalent. Other outcomes are consistent with the drugs and treatment regimens having similar efficacy and safety.

Financial Disclosure(s): Proprietary or commercial disclosures may be found after the references.
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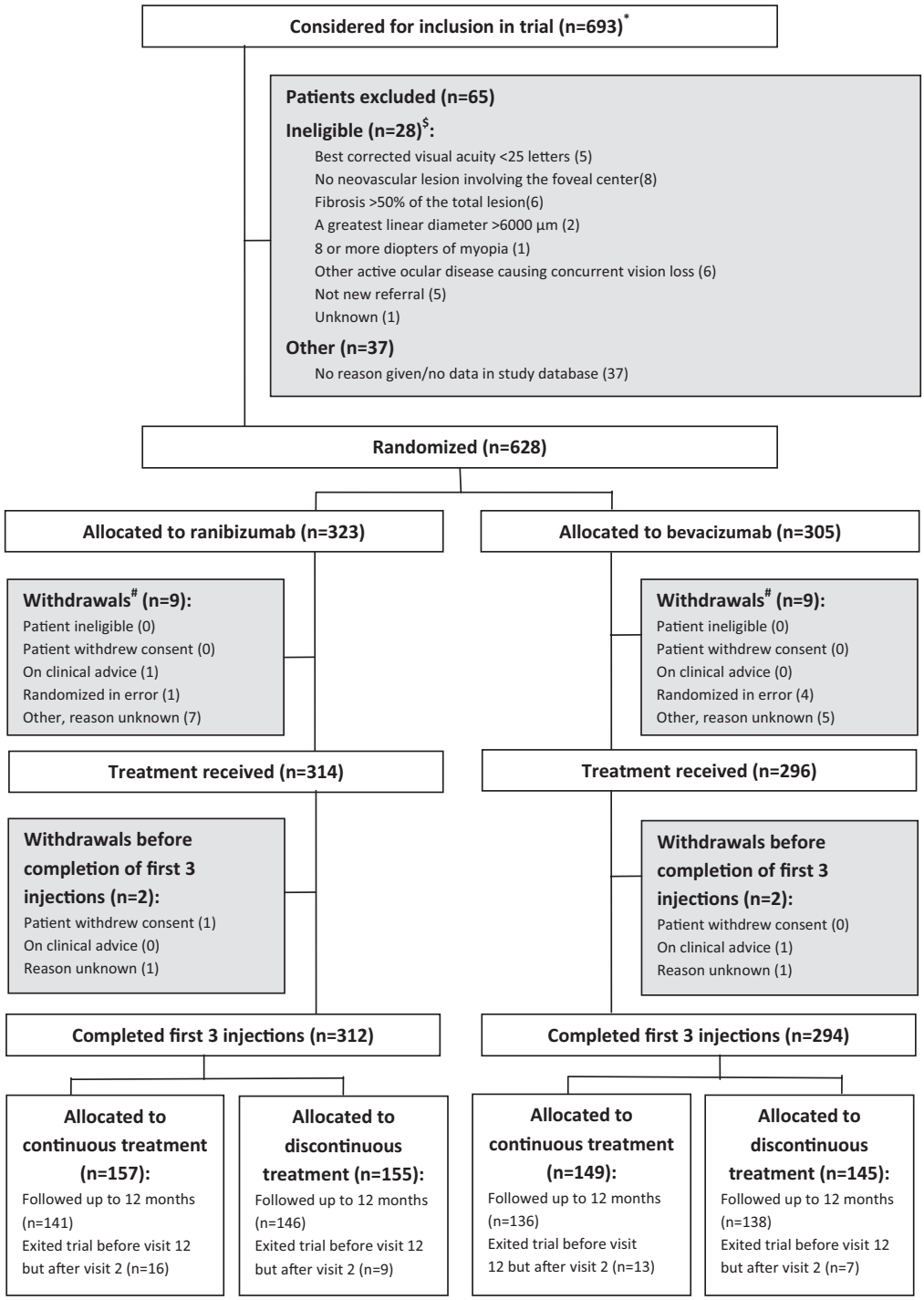
**Group members listed online in Appendix 1 (available at http://aaojournal.org).*

Neovascular age-related macular degeneration (nAMD) is a common bilateral condition that affects older adults and causes severe impairment of central vision. It is currently treated by intravitreal injection of ranibizumab or bevacizumab, an antibody fragment and antibody respectively to vascular endothelial growth factor (VEGF). These treatments maintain vision in >90% of patients, but do not cure nAMD. They are expensive because patients need monthly review and frequent retreatment for ≥2 years.

Ranibizumab has been evaluated in multiple trials,[1,2] whereas bevacizumab, originally developed to treat cancer and available earlier, has gained widespread acceptance for treating nAMD, but without marketing authorization.[3–6] The Comparison of AMD Treatment Trials (CATT)[7] studied monthly or as-needed ranibizumab or bevacizumab (4 groups). The CATT reported that distance visual acuity after 1 year was equivalent for the 2 drugs within each treatment regimen. Ranibizumab as needed and monthly were equivalent; the comparison between monthly and as-needed bevacizumab was inconclusive. The



Notes: The exclusions section is incomplete as not all sites have entered full screening data.

* Patients had to consent before they could be considered for the trial; data characterizing patients who withheld consent could not be collected.

$. Some patients may be ineligible for more than one reason.

\# Of the patients who did not drop out, not all of them completed all 3 treatments

Figure 1. Participant flow through the trial.

Table 1. Patient Demographics and Past History

Demographics	Randomized to Ranibizumab (n = 314)		Randomized to Bevacizumab (n = 296)		Randomized to Continuous (n = 308)		Randomized to Discontinuous (n = 302)		Overall (n = 610)	
Age, yrs	77.8	7.6	77.7	7.2	77.8	8.0	77.6	6.8	77.7	7.4
Male gender (n, %)	129	41%	115	39%	126	41%	118	39%	244	40%
Blood pressure, mmHg										
Systolic	141.9	19.5	143.0	19.5	143.2	19.8	141.7	19.1	142.5	19.5
Diastolic	76.4	10.2	77.1	9.9	77.4	10.1	76.2	10.0	76.8	10.1
Nonocular past history (n, %)										
Angina	35	11%	51	17%	45	15%	41	14%	86	14%
Dyspnea*	56	18%	60	20%	56	18%	60	20%	116	19%
Myocardial infarction	24	8%	22	7%	26	8%	20	7%	46	8%
Transient ischemic attack†	20	7%	9	3%	15	5%	14	5%	29	5%
Stroke‡	7	2%	7	2%	4	1%	10	3%	14	2%
DVT/PE§	16	5%	18	6%	16	5%	18	6%	34	6%
Current or past smoker#	200	65%	185	63%	194	64%	191	64%	385	64%
Ocular details										
Best-corrected visual acuity, letters‖	61.8	15.0	61.1	15.6	60.0	15.5	62.9	15.0	61.4	15.3
Near visual acuity, logMAR**	0.66	0.34	0.67	0.33	0.70	0.34	0.63	0.32	0.66	0.33
Reading index (median, IQR)††	47.3 (18.6, 85.7)		43.8 (17.5, 90.9)		41.7 (17.0, 87.0)		51.8 (20.4, 88.9)		46.2 (18.2, 88.2)	
Contrast sensitivity, letters‡‡	26.2	6.2	26.3	5.8	26.1	6.0	26.4	5.9	26.2	6.0
Total thickness at the fovea, μm§§	468	187	465	184	474	188	459	182	466	185
Foveal retinal plus subfoveal fluid, μm§§	271	129	264	131	263	127	272	134	268	130
Foveal center involvement (n, %)										
Choroidal neovascularization##	148	56%	153	59%	161	61%	140	54%	301	58%
Fluid‖‖	154	53%	154	56%	149	51%	159	57%	308	54%
Hemorrhage‖‖	52	18%	38	14%	45	16%	45	16%	90	16%
Other‖‖	45	16%	30	11%	39	13%	36	13%	75	13%
No choroidal neovascularization or unable to grade***	7	2%	8	3%	4	1%	11	4%	15	3%
Area of lesion (median, IQR), optic disc area‖‖	3.30 (1.16, 7.86)		3.97 (1.48, 8.38)		3.64 (1.28, 7.81)		3.86 (1.39, 8.66)		3.71 (1.37, 8.10)	
Serum VEGF (median, IQR), pg/mL†††	173 (102, 289)		203 (111, 319)		193 (100, 308)		178 (118, 298)		183 (106, 304)	
Below lower limit of detection (n, %)	22	7%	22	7%	23	7%	21	7%	44	7%
Quality of life										
EQ-5D state score (median, IQR)‡‡‡	0.81 (0.73, 1.00)		0.85 (0.73, 1.00)		0.85 (0.73, 1.00)		0.85 (0.73, 1.00)		0.85 (0.73, 1.00)	

Data are presented as mean values and standard deviation, unless otherwise stated.
DVT = deep venous thrombosis; IQR = interquartile range; logMAR = log(minimum angle of resolution); PE = pulmonary embolism; VEGF = vascular endothelial growth factor inhibitor.
Missing data (numbers for ranibizumab continuous, bevacizumab continuous, ranibizumab discontinuous, bevacizumab discontinuous groups, respectively): *2 patients with missing values (1, 1, 0, 0); †34 patients with missing data (9, 8, 11, 6); ‡1 patient with missing data (0, 0, 0, 1); §2 patients with missing data (0, 0, 1, 1); #6 patients with missing data (3, 0, 2, 1); ‖1 patient with missing data (0, 1, 0, 0); **7 patients with missing data (3, 2, 0, 2); ††14 patients with missing data (5, 4, 4, 1); ‡‡4 patients with missing data (3, 1, 0, 0); §§57 patients with missing data (12, 17, 15, 13); ##87 patients with missing data (24, 20, 25, 18); ‖‖43 patients with missing data (8, 10, 16, 9); ***29 patients with missing data (7, 8, 10, 4); †††54 patients with missing data (13, 16, 12, 13); ‡‡‡7 patients with missing data (3, 0, 3, 1).

CATT found no evidence of differences by drug in the frequency of serious adverse events previously associated with anti-VEGF drugs. There were slightly more serious systemic adverse events in the bevacizumab groups.

We have reported herein the 1-year findings of the "alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization" (IVAN) randomized trial, which also compares monthly or as-needed ranibizumab or bevacizumab. Although the IVAN trial was conceived and designed at the same time as the CATT, there are important differences between the 2 trials. The IVAN trial has a factorial design, an alternative as-needed regimen requiring 3 treatments if active disease was detected, measured near visual acuity, reading speed, health-related quality of life, and collected serum samples at specified times for analysis of VEGF concentrations. The IVAN also obtained information on resource use and cost for a detailed economic evaluation. Moreover, we report a meta-analysis of key outcomes from available trials.

Methods

Study Design, Participants, and Setting

The IVAN is a multicenter, factorial, noninferiority, randomized trial with equal allocation to each of 4 groups formed by all permutations of 2 drugs and 2 treatment regimens. Allocation to drug was masked. Allocation to treatment regimen was not masked. Further details are described in the protocol (Appendix 2, available at http://aaojournal.org).

Adults ≥50 years old with previously untreated nAMD in the study eye and best corrected visual acuity ≥25 letters on the Early Treatment Diabetic Retinopathy Study chart were eligible.[8,9] Diagnosis was confirmed by fluorescein angiography. Participants

Table 2. Outcomes at 1 Year*

	Randomized to Ranibizumab (n = 287)		Randomized to Bevacizumab (n = 274)		Randomized to Continuous (n = 277)		Randomized to Discontinuous (n = 284)		Overall[##] (n = 561)	
Best corrected visual acuity, letters[†]	69.0	16.0	66.1	17.4	66.8	17.4	68.4	16.1	67.6	16.7
Number of treatments (median, IQR)[¶]	10 (6, 12)		11 (7, 12)		12 (11, 12)		7 (6, 9)		10 (7, 12)	
Near visual acuity, logMAR[§,¶]	0.57	0.38	0.62	0.41	0.60	0.39	0.58	0.41	0.59	0.40
Reading index (median, IQR)[#]	73.8 (27.7, 122.0)		67.5 (13.7, 120.0)		73.8 (15.8, 117.9)		70.9 (25.5, 126.5)		71.8 (19.6, 121.6)	
Contrast sensitivity, letters[‖]	28.3	5.19	28.6	5.42	28.6	5.46	28.4	5.14	28.5	5.30
Total thickness at fovea, μm[**,‡]	322	139	325	134	311	126	335	145	323	136
Retinal thickness plus subfoveal fluid, μm**	172	78	180	92	173	82	178	88	176	85
Fluid on OCT (n, %)										
Present	126	44%	131	48%	109	39%	148	52%	257	46%
Absent	119	41%	93	34%	123	44%	89	31%	212	38%
Missing data	42	15%	50	18%	45	16%	47	17%	92	16%
Dye leakage on angiogram (n, %)										
Present	82	29%	86	31%	67	24%	101	36%	168	30%
Absent	129	45%	113	41%	135	49%	107	38%	242	43%
Missing data	76	26%	75	27%	75	27%	76	27%	151	27%
Area of lesion (median, IQR), optical disc area[††]	0.39 (0.00, 2.44)		0.51 (0.00, 3.06)		0.30 (0.00, 2.17)		0.88 (0.00, 3.41)		0.46 (0.00, 2.94)	
Serum VEGF (median, IQR), pg/mL[‡‡]	151 (100, 277)		83 (59.5, 157)		114 (71.0, 196)		131 (76.9, 263)		125 (73.8, 215)	
Below lower limit of detection (n, %)	29	10%	79	29%	60	22%	48	17%	108	19%
Blood pressure, mmHg[§§]										
Systolic	138.1	17.3	138.8	18.0	138.4	18.2	138.5	17.1	138.4	17.6
Diastolic	74.5	9.7	75.0	9.6	74.9	9.2	74.5	10.0	74.7	9.6
EQ-5D state score (median, IQR)***	0.85 (0.73, 1.00)		0.85 (0.73, 1.00)		0.85 (0.73, 1.00)		0.85 (0.73, 1.00)		0.85 (0.73, 1.00)	

IQR = interquartile range; OCT = optical coherence tomography; logMAR = log(minimum angle of resolution); VEGF = vascular endothelial growth factor inhibitor.

*Data are presented as mean values and standard deviation, unless otherwise stated.

[‡]The total thickness at the fovea includes the retina, subretinal fluid, choroidal neovascularization, and retinal pigment epithelial elevation.

Missing data (numbers for ranibizumab continuous, bevacizumab continuous, ranibizumab discontinuous, bevacizumab discontinuous groups, respectively): [†]36 patients with missing data (5, 11, 9, 11); [§]55 patients with missing data (10, 16, 12, 17); [#]67 patients with missing data (12, 18, 16, 21); [‖]50 patients with missing data (7, 16, 13, 14); **82 patients with missing data (16, 20, 23, 23); [††]148 patients with missing data (37, 35, 37, 39); [‡‡]21 patients with missing data (6, 6, 5, 4); [§§]38 patients with missing data (5, 12, 10, 11); ***63 patients with missing data (12, 17, 17, 17). [##]49 patients withdrew or died before 1 year.

[¶]Includes all 610 patients.

without a subfoveal (within 200 μm) neovascular component were eligible if subretinal fluid or serous pigment epithelial detachment was subfoveal. To avoid including inactive or advanced disease, lesions comprising >50% fibrosis or blood were excluded. Only 1 eye from each participant was studied.

We recruited participants from 23 teaching and general hospitals in the United Kingdom (UK) (Appendix 1, available at http://aaojournal.org). A UK National Health Service (NHS) Research Ethics Committee gave approval (reference 07/NIR03/37). This trial is registered (ISRCTN92166560).

Interventions

After informed written consent, participants were allocated to 1 of 4 combinations of the 2 treatment factors: intravitreal injections with ranibizumab or bevacizumab and continuous or discontinuous regimens.

Drug doses were ranibizumab 0.5 mg,[1,2] bevacizumab 1.25 mg.[7,10,11] Ranibizumab and bevacizumab were procured commercially. Bevacizumab was repackaged in prefilled syringes in an aseptic manufacturing facility.

The protocol required all participants to attend monthly (window, 28–35 days) for clinical examination, optical coherence tomography (OCT), and fundus photography. All participants were treated at visits 0, 1, and 2. Participants randomized to the continuous regimen were treated monthly thereafter. Participants randomized to the discontinuous regimen were not retreated after visit 2 unless prespecified clinical and OCT criteria for active disease were met. If retreatment was needed, a further cycle of 3 doses delivered monthly was required.

Retreatment criteria were any subretinal fluid, increasing intraretinal fluid, or fresh blood. If there was uncertainty about these criteria and visual acuity had dropped by ≥10 letters, retreatment could be initiated. In the absence of fluid on OCT or visual acuity deterioration, fluorescein leakage >25% of the lesion circumference or expansion of choroidal neovascularization was required to initiate retreatment.

Decisions about eligibility and retreatment were made on the basis of ophthalmologists' interpretation of OCTs, fluorescein angiograms, and fundus photography.

Outcome Measures

The primary endpoint is at 2 years (follow-up is ongoing), but the protocol specified an interim analysis at 1 year. The primary outcome measure is best-corrected distance visual acuity measured as Early Treatment Diabetic Retinopathy Study letters. Secondary outcome measures include (1) adverse effects; (2) EQ-5D (generic health-related quality of life assessment);[12] (3) cumulative resource use and costs; (4) contrast sensitivity,[13] near visual acuity,[14] and reading index;[15] (5) lesion morphology and metrics from angiograms and OCTs; and (6) serum VEGF levels (sandwich enzyme-linked immunosorbent assay, R & D systems, Abingdon,

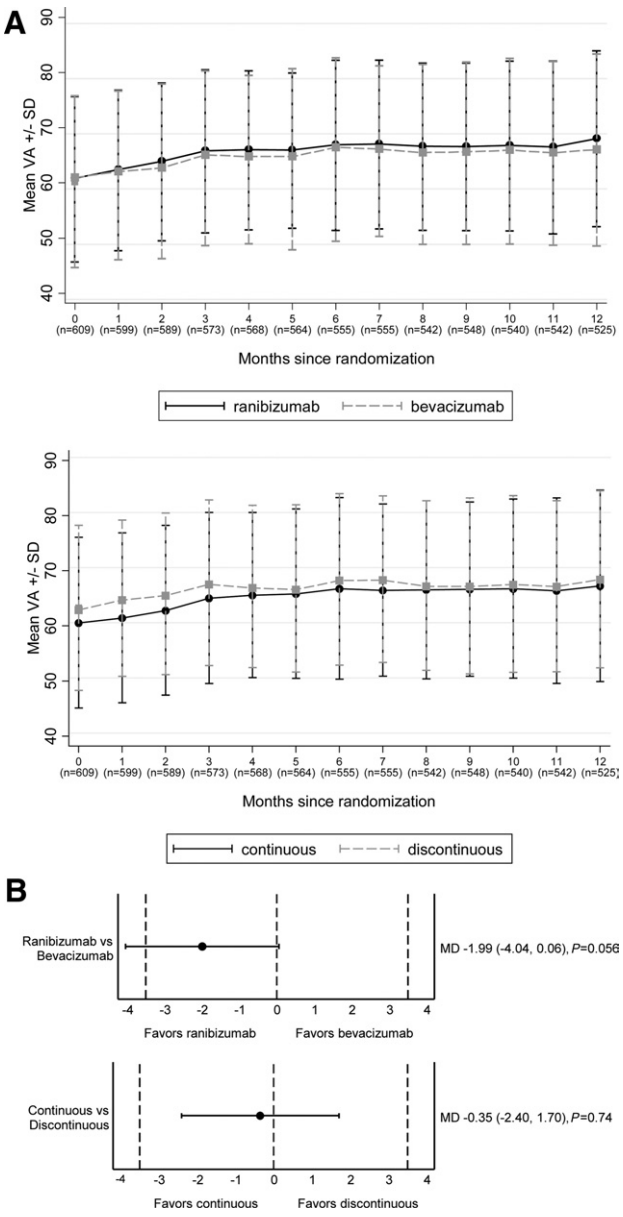


Figure 2. Best-corrected visual acuity. **A**, Mean and standard deviation of the visual acuity at each visit during the first year of follow-up (by ranibizumab and bevacizumab at the top and by continuous and discontinuous treatment regimen below). The circles and squares indicate the mean and the bars 1 standard deviation either side of the mean. The numbers in parentheses are the number of observations. **B**, Differences between ranibizumab and bevacizumab (top) and between continuous and discontinuous treatment regimen (bottom) in mean visual acuity at 1 year (estimated using data from visits 0, 3, 6, and 12, adjusted for center size). The circles indicate the mean difference and the bars 95% confidence intervals. Negative values reflect a greater mean visual acuity at 1 year in the ranibizumab or continuous groups. Confidence intervals within −3.5 and +3.5 letters (dashed vertical lines) indicate that the 2 groups are equivalent (continuous vs discontinuous treatment regimen). Confidence intervals extending beyond the noninferiority limit of −3.5 letters indicate that the comparison of the 2 groups is inconclusive (ranibizumab vs bevacizumab). MD = mean difference; SD = standard deviation; VA = visual acuity. The numbers in brackets give the 95% confidence interval.

UK) with detection limits of 2000 to 32 pg/mL. All outcomes except EQ-5D and serum VEGF were measured at baseline and visits 3, 6, and 12. The EQ-5D was measured at baseline, visits 3 and 12 and serum VEGF at baseline, visits 1, 11, and 12 (Appendix 3, available at http://aaojournal.org).

Adverse events were recorded at each visit. The primary safety outcome measure was the occurrence of an arteriothrombotic event or heart failure. Events were reviewed and classified using the *Medical Dictionary for Regulatory Activities* [MedDRA] version 14.1. All serious adverse events were reviewed by senior clinicians (U.C., S.P.H., S.M.D., A.J.L.) masked to treatment allocation.

Randomization and Masking

Randomized allocations were computer generated by a third party in blocks and stratified by center. Research teams at sites recruited participants, and accessed a password-protected website to randomize participants. Allocations were concealed until participants' eligibility and identities were confirmed.

We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments. To assess the adequacy of masking, ophthalmologists and participants stated at visits 3 and 12 (and at exit visits if participants withdrew early), whether they knew the allocated drug (don't know/Lucentis/Avastin).

Lesion morphology was assessed by independent graders, masked to drug and treatment regimen, in the UK Network of Ophthalmic Reading Centers. Serum VEGF analyses were also masked to drug and treatment regimen. Because independent assessment of lesions could not be done immediately, some randomized participants were subsequently found to be ineligible.

Statistical Analysis

We specified a noninferiority limit of 3.5 letters, assuming there would be no interaction between drug and treatment regimen, visual acuity would be analyzed by a mixed model and at least 2 postrandomization visual acuity measures would be analyzed. We set a target sample size of 600, giving 90% power to detect noninferiority (significance 2.5%, 1 sided).

Intention-to-treat analyses were performed. Drugs and dosing regimens were compared using logistic regression (binary variables) and linear mixed model regression (continuous variables), except where otherwise noted. Centers were classified into 7 strata with respect to the numbers of participants recruited. Analyses adjusted for these strata, combining adjacent strata if necessary to allow models to be fitted. For continuous variables measured at baseline, values were modeled jointly to avoid having to exclude or impute cases with missing baseline measures. Interactions with follow-up time were fitted and differences between groups are described at 1 year. Model validity was checked using standard methods.[16] If a model fitted poorly, transformations were explored. Outcomes analyzed on a logarithmic scale were transformed back to the original scale after analysis and results presented as geometric mean ratios (GMR). For Euroqol EQ-5D and lesion area at 1 year, no suitable transformation could be found; data were dichotomized, (EQ-5D score, 1 vs <1; lesion present vs absent) and analyses adjusted for the baseline value. For serum VEGF concentrations below the detection limit for the assay (32 pg/mL), values in the range of 16 to 32 pg/mL were imputed. Numbers of serious adverse events were compared by drug and treatment regimen when >10 participants experienced the event (Appendix 3, available at http://aaojournal.org). Likelihood ratio tests were used to determine statistical significance.

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