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.

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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

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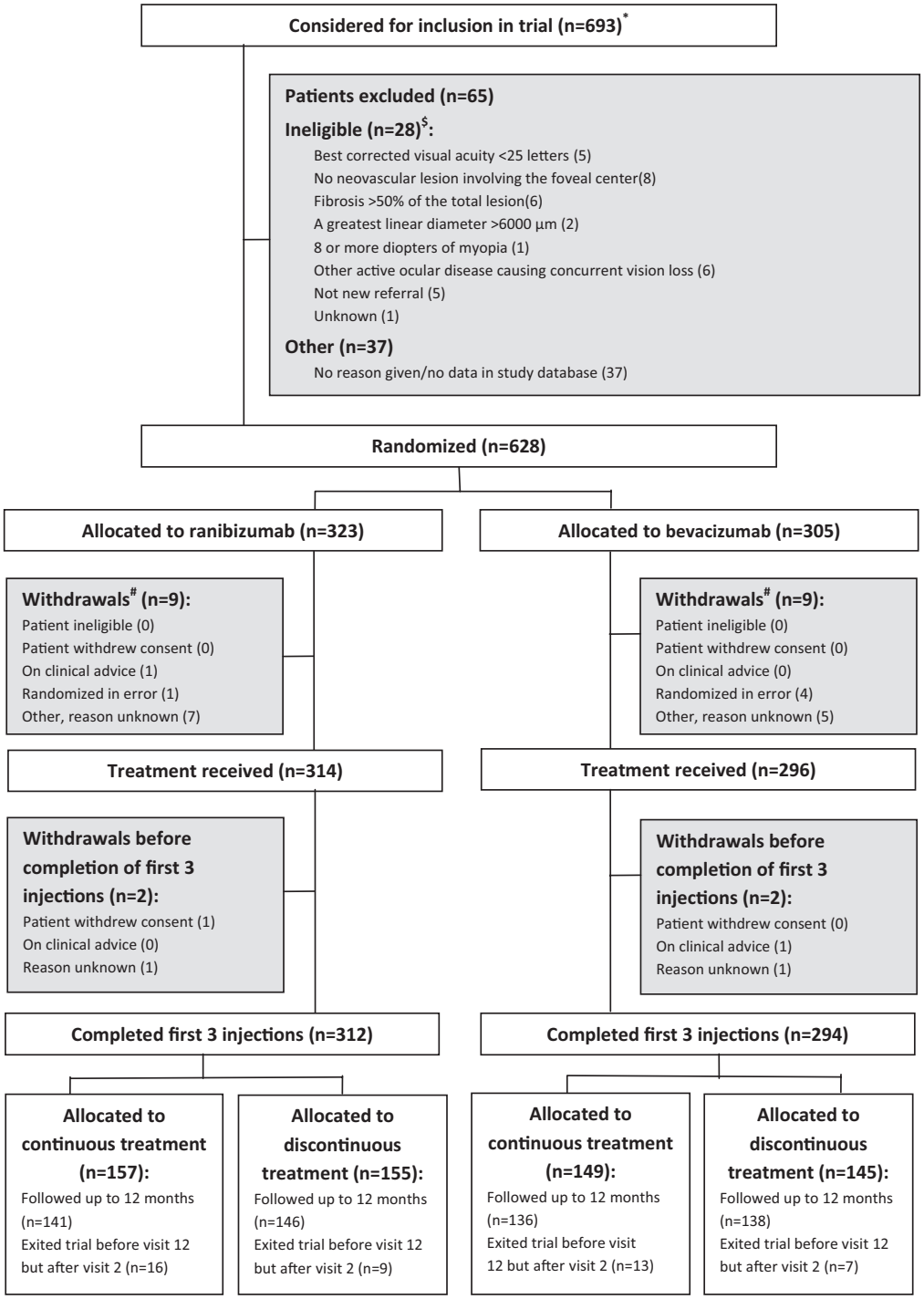

Notes: The exclusions section is incomplete as not all sites have entered full screening data.

* 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.

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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

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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,

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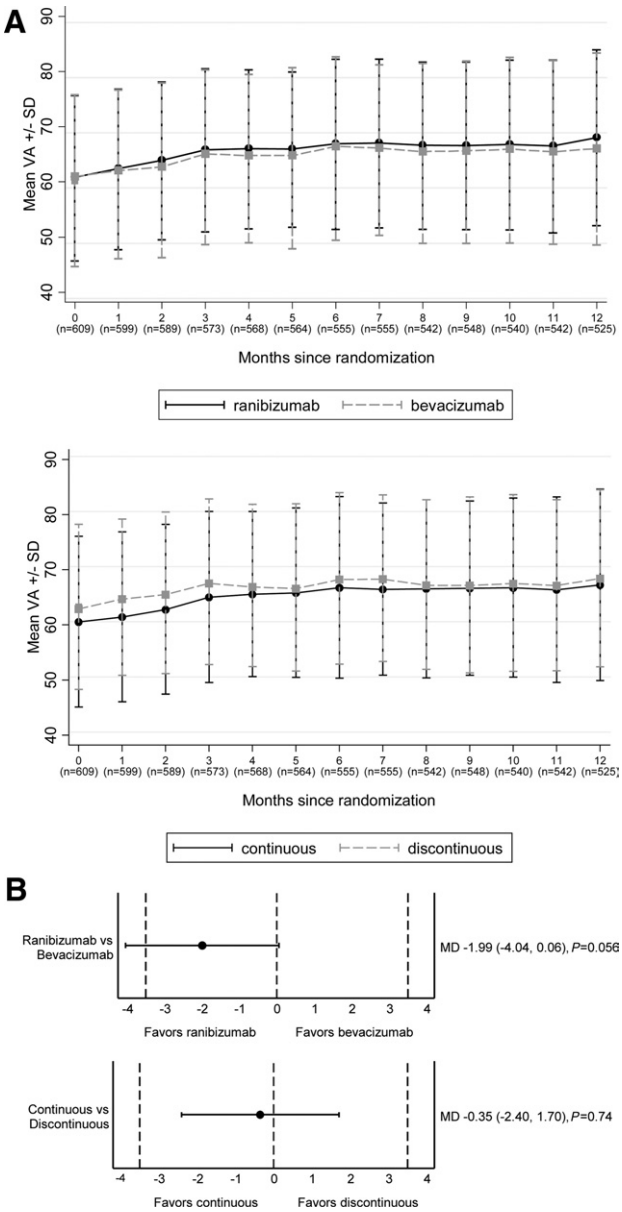

Figure 2. Best-corrected visual acuity. **A**, Mean and standard deviation of the visual acuity at each visit during the first year of follow-up (by ranibizumab and bevacizumab at the top and by continuous and discontinuous treatment regimen below). The circles and squares indicate the mean and the bars 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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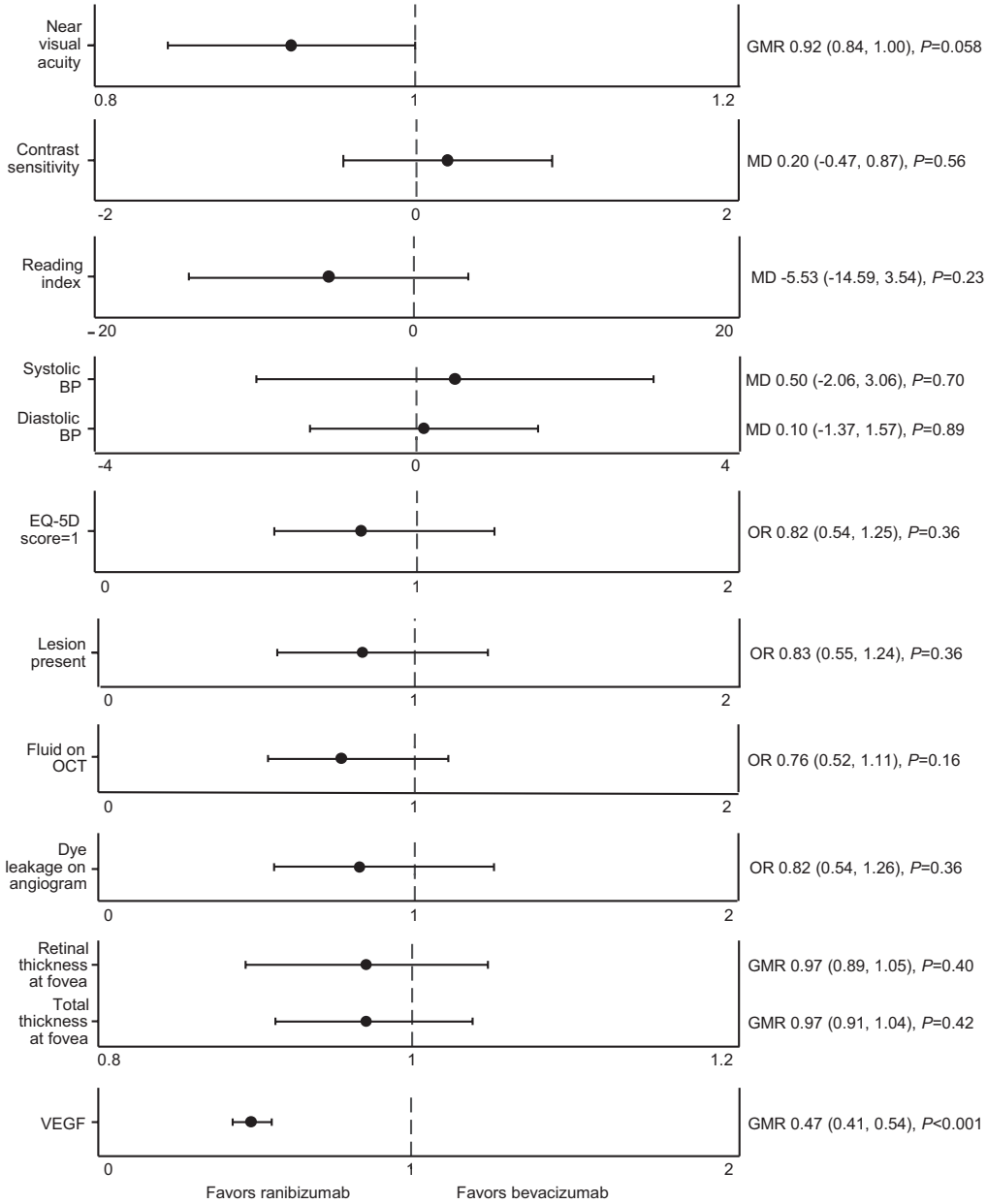

Figure 3. Secondary outcomes. Differences between ranibizumab and bevacizumab (above) and between continuous and discontinuous treatment regimen (next page) in the secondary functional outcomes at 1 year. The circles indicate the mean difference (MD), geometric mean ratio (GMR), or odds ratio (OR) and the bars 95% confidence intervals. Negative values for the MD or ratios less than 1 reflect better functional outcomes at 1 year in the ranibizumab or continuous groups. The numbers in brackets give the 95% confidence interval. BP = blood pressure; OCT = ocular coherence tomography; VEGF = vascular endothelial growth factor.

Results are reported as effect estimates with 95% confidence intervals (CI). Comparisons between drugs are only reported separately for the continuous and discontinuous regimens if the interaction of drug and dosing regimen reached a prespecified level of statistical significance (5% for foveal thickness and presence of fluid on OCT, for which the CATT suggested a possible interaction,[7] or 1% otherwise).

Cost Analysis

The differences in total 1-year costs between continuous and discontinuous dosing regimens were estimated for each drug from a UK NHS perspective, using established guidelines.[17] Quantities of concomitant medications, hospitalizations, and ambulatory consultations attributable to expected adverse events were measured using questionnaires completed by participants. Detailed costing of consultations to administer VEGF and/or monitor outcomes were carried out using data from 14 of the 19 IVAN centers that recruited more than 10 patients. Resources were valued in 2010 and 2011 pounds Sterling using national sources.[18–21] Ranibizumab was costed at UK list price (£742.17/dose[18]) and bevacizumab at the price charged by the trial manufacturing facility (£49/dose). Data were analyzed using bootstrapping, allowing for withdrawals and deaths using

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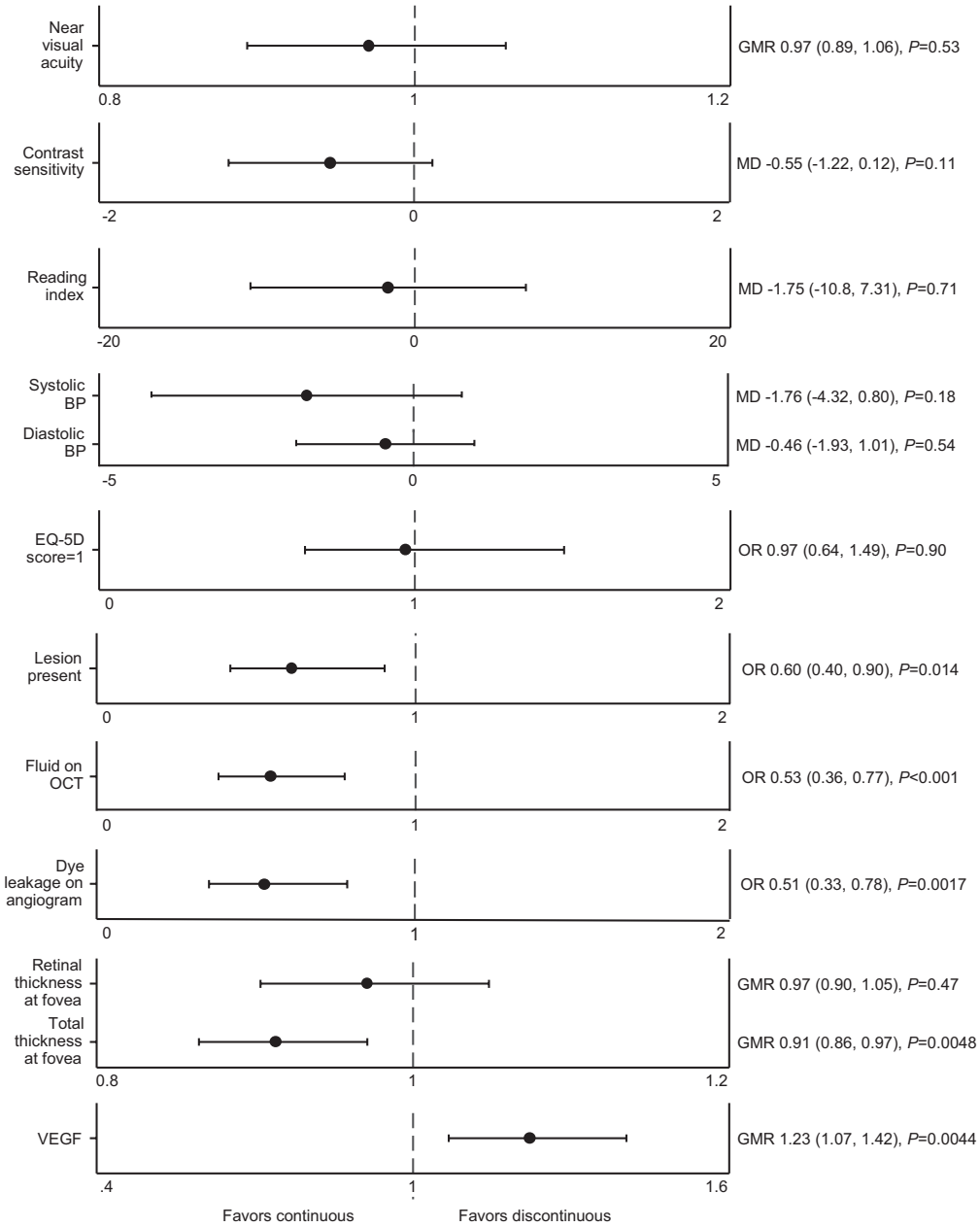

Figure 3. (Continued., see preceding page for figure legend).

Kaplan–Meier sample averaging. Analyses were performed with Stata version 12 (STATA Corp, Inc, College Station, TX) and SAS version 9.2 (SAS, Inc, Chicago, IL).

Results

Participants and Treatment

Between March 27, 2008, and October 15, 2010, we randomized 628 participants; 18 were withdrawn before receiving the first treatment, leaving 610 who were treated and included in analyses (Fig 1). Participants' characteristics at baseline were similar across the groups (Table 1). Nine participants were ineligible. One read <25 letters; 8 failed the independent graded angiographic eligibility criteria, although 2 had fluid on OCT suggesting an active lesion.

Regarding adequacy of masking, ophthalmologists reported not knowing which drug participants were receiving on 97.9% of visits 3, 98.7% of visits 12, and 100% of exit visits; the corresponding percentages for participants were 99.3%, 98.6%, and 100%.

There were some protocol deviations (Appendix 4, Tables A1 to A3, available at http://aaojournal.org). The wrong study drug was administered on 2 of 6699 follow-up visits. Adherence to treatment regimens was excellent (according to allocation on 6576 of 6699 visits [98.2%]). Overall, 35% of participants missed ≥1 visit, but the methods of analysis allowed most participants to be included.

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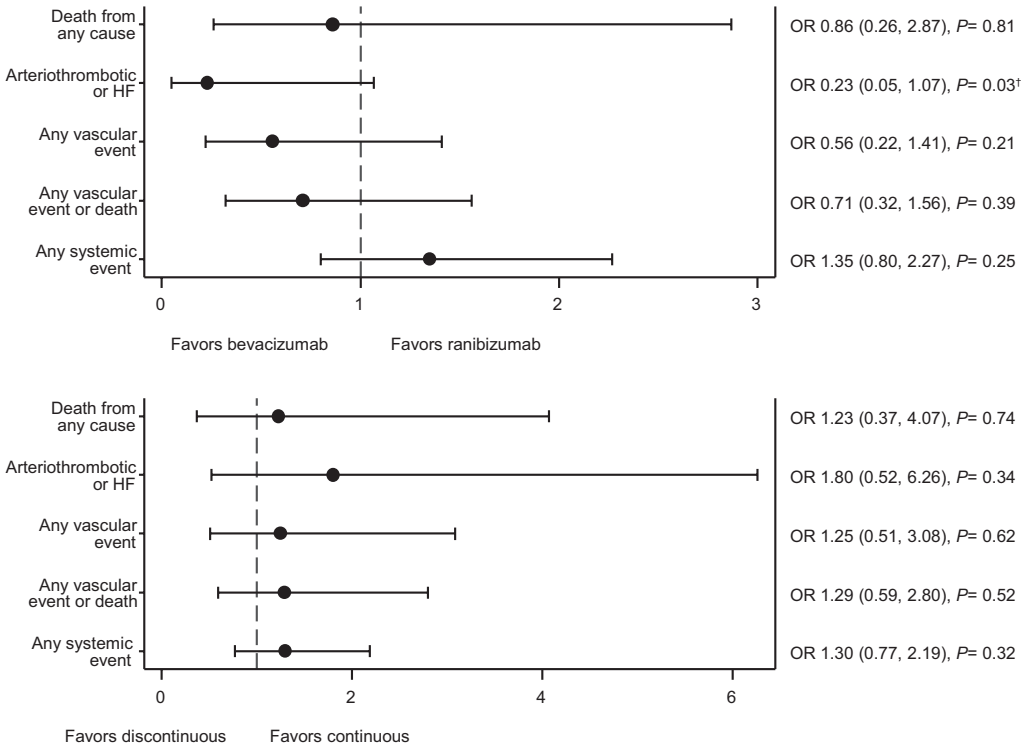

Figure 3. (Continued.) Differences between ranibizumab and bevacizumab (top) and between continuous and discontinuous treatment regimen (bottom) in the safety outcomes at 1 year. Circles indicate odds ratios and bars indicate 95% confidence intervals. Odds ratios <1 reflect fewer serious adverse events during the first year in the bevacizumab or discontinuous groups. HF = heart failure; OR = odds ratio. †*P* value from likelihood ratio test, whereas the 95% confidence interval was derived from Wald-based normal approximation.

Visual Acuity

All 610 participants were included in the analysis of visual acuity. Mean acuities at 1 year were 69.0 and 66.1 letters in the ranibizumab and bevacizumab groups, respectively, and 66.8 and 68.4 letters in the continuous and discontinuous regimens (Table 2). The difference between drugs (bevacizumab minus ranibizumab) was −1.99 letters (95% CI, −4.04 to 0.06) and between treatment regimens (discontinuous minus continuous) was −0.35 (95% CI, −2.40 to 1.70; Fig 2). The comparison by drug was inconclusive; bevacizumab was neither inferior nor equivalent to ranibizumab using the 3.5 letter limit. Discontinuous treatment was equivalent to continuous treatment.

Secondary Outcomes

Contrast sensitivity and reading index did not differ significantly between drugs or treatment regimens (Fig 3; Table 2). Near visual acuity was 8% worse in the bevacizumab group (GMR, 0.92; 95% CI, 0.84 to 1.00; $P = 0.058$), but did not differ with treatment regimen.

Mean foveal retinal thickness, which we defined as the sum of the thickness of the neurosensory retina (measured from the internal limiting membrane to its outer boundary with the retinal pigment epithelium and which on the stratus OCT output is seen as the outer high reflectivity band) and the height of the subretinal fluid (hyporeflective area between the neurosensory retina and the outer high reflectivity band), did not differ significantly between drugs but was, on average, 9% less for participants receiving continuous treatment (GMR, 0.91; 95% CI, 0.86 to 0.97; $P = 0.005$; Fig 3; Table 2). Percentages of participants with fluorescein leakage were 29% and 31% in the ranibizumab and bevacizumab groups ($P = 0.36$) and 24% and 36% in the continuous and discontinuous groups ($P = 0.002$; Fig 3). Median lesion area in the discontinuous group was larger and significantly more participants had evidence of dye leakage, but no differences by drug were found.

The median EuroQol EQ-5D state scores were identical (0.85) for all 4 groups and the proportion of participants reporting a state score of 1.0 did not differ by drug or treatment regimen ($P = 0.36$ and $P = 0.90$; Fig 3).

Median serum VEGF concentrations at 1 year were lower than at baseline in all groups (Appendix 4, Table A7; available at http://aaojournal.org). Median serum VEGF concentrations at 1 year were 151 and 83 pg/mL for ranibizumab and bevacizumab, and 114 and 131 pg/mL for continuous and discontinuous regimens (Table 2). The VEGF concentrations were significantly lower at 1 year for bevacizumab than ranibizumab and higher for the discontinuous than continuous regimen (GMR, 0.47 [95% CI, 0.41 to 0.54] and GMR, 1.23 [95% CI, 1.07 to 1.42], respectively; $P<0.01$; Fig 3).

Adverse Events

One year after randomization, 6 participants (1.9%) in the ranibizumab group and 5 (1.7%) in the bevacizumab group ($P = 0.81$) had died; 5 (1.6%) had received continuous and 6 (2.0%) discontinuous treatment ($P = 0.74$; Table 3). Fewer participants treated with bevacizumab compared with ranibizumab had an arteriothrombotic event or heart failure (0.7% vs. 2.9%; odds ratio, 0.23; 95% CI, 0.05 to 1.07; $P = 0.03$; Fig 3), but no difference between treatment regimens was found ($P = 0.34$). One or more serious systemic adverse events occurred in 30 (9.6%) in the ranibizumab group and 37 (12.5%) in the bevacizumab group ($P = 0.25$; Fig 3). Similarly, 30 (9.7%) in the

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Table 3. Serious Adverse Events Within 1 Year of Recruitment

Serious Systemic Event	Randomized to Ranibizumab (n = 314)		Randomized to Bevacizumab (n = 296)		Randomized to Continuous (n = 308)		Randomized to Discontinuous (n = 302)		Overall (n = 610)	
	Events/ Patients	*%**	*Events/ Patients*	*%**	*Events/ Patients*	*%**	*Events/ Patients*	*%**	*Events/ Patients*	*%**
Death by any cause	6/6	1.9	5/5	1.7	5/5	1.6	6/6	2.0	11/11	1.8
Arteriothrombotic event	6/6	1.9	1/1	0.3	3/3	1.0	4/4	1.3	7/7	1.1
Nonfatal myocardial infarction	2/2	0.6	1/1	0.3	1/1	0.3	2/2	0.7	3/3	0.5
Nonfatal stroke	3/3	1.0	0/0	0.0	2/2	0.6	1/1	0.3	3/3	0.5
Death from vascular causes	1/1	0.3	0/0	0.0	0/0	0.0	1/1	0.3	1/1	0.2
Arteriothrombotic event or heart failure	9/9	2.9	2/2	0.7	4/4	1.3	7/7	2.3	11/11	1.8
Heart failure	3/3	1.0	1/1	0.3	1/1	0.3	3/3	1.0	4/4	0.7
Venous thrombotic event	0/0	0.0	2/2	0.7	1/1	0.3	1/1	0.3	2/2	0.3
Transient ischemic attack	1/1	0.3	1/1	0.3	0/0	0.0	2/2	0.7	2/2	0.3
Hospitalized for angina	3/3	1.0	2/2	0.7	4/4	1.3	1/1	0.3	5/5	0.8
Any of the above excluding nonvascular deaths	13/13	4.1	7/7	2.4	9/9	2.9	11/11	3.6	20/20	3.3
Any of the above including nonvascular deaths	16/16	5.1	11/11	3.7	12/12	3.9	15/15	5.0	27/27	4.4
≥1 serious systemic event†	30	9.6	37	12.5	30	9.7	37	12.3	67	11.0

*Percentage of patients.
†Includes any nonocular serious adverse event.

continuous and 37 (12.3%) in the discontinuous group had ≥1 serious systemic adverse events ($P = 0.32$). More than 10 participant-specific events occurred in 3 MedDRA categories: cardiac disorders, surgical or medical procedure, and any other class (Appendix 4, Table A8; available at http://aaojournal.org). Comparisons by drug and regimen for cardiac disorders and surgical or medical procedure showed no differences ($P \geq 0.46$). Severe uveitis developed after 1 injection; there was 1 reported traumatic cataract and 3 retinal pigment epithelial tears. Five "other" ocular events were each reported once.

Cost Analysis

Table 4 reports the results of the cost analysis, based on annual costs per patient. Including the costs of monitoring, adverse events and drugs, continuous ranibizumab treatment was the most expensive option (£9656 per patient per year) followed by discontinuous ranibizumab (difference £3258; 95% CI, £2905 to £3659; $P<0.0001$). Bevacizumab was less costly than ranibizumab for both continuous and discontinuous regimens ($P<0.0001$). Although continuous bevacizumab was more costly than discontinuous, the difference was not significant (£145; 95% CI, –£48 to £338; $P = 0.099$). The main cost driver for ranibizumab was drug cost (85% of costs), whereas for bevacizumab it was treatment administration and monitoring (64% of costs).

Discussion

One year after randomization in the IVAN trial, the visual acuity comparison by drug was inconclusive. The mean difference between the drugs was 2 letters in favor of ranibizumab, a small difference from a clinical perspective. The difference in visual acuity between continuous and

Table 4. Results of the IVAN Costing Analysis Over a 1-Year Time Horizon

Cost component	Continuous ranibizumab mean (SE)	Discontinuous ranibizumab mean (SE)	Continuous bevacizumab mean (SE)	Discontinuous bevacizumab mean (SE)	Ranibizumab vs. bevacizumab mean (SE)	Continuous vs. discontinuous mean (SE)
VEGF medication	8494 (59)	5212 (160)	546 (9)	380 (13)	Continuous, 7948 (2626)*; discontinuous, 4832 (160)*	Ranibizumab, 3282 (1945)*; bevacizumab, 166 (16)*
Drug administration and monitoring	1047 (12)	993 (14)	1043 (14)	986 (16)	3 (14)	53 (14)*
Hospitalizations, consultations, and medications for expected (serious) adverse events	115 (20)	193 (95)	66 (95)	143 (31)	50 (95)	−77 (95)
Total cost	9656 (68)	6398 (184)	1654 (96)	1509 (39)	Continuous, 8001 (113)*; discontinuous, 4889 (184)*	Ranibizumab, 3258 (193)*; bevacizumab, 145 (97)

IVAN = Inhibit VEGF in Age-related choroidal Neovascularisation; SE = standard error (calculated using bootstrapping); VEGF = vascular endothelial growth factor inhibitor.
All costs are per patient and are in 2010/11 pounds Sterling. Drug administration costs and costs attributable to expected adverse events were analyzed at the margins (assuming no interaction) because interactions were nonsignificant and did not change conclusions about total costs. Results are based on 10 000 bootstrap replicates.
*$P<0.05$.

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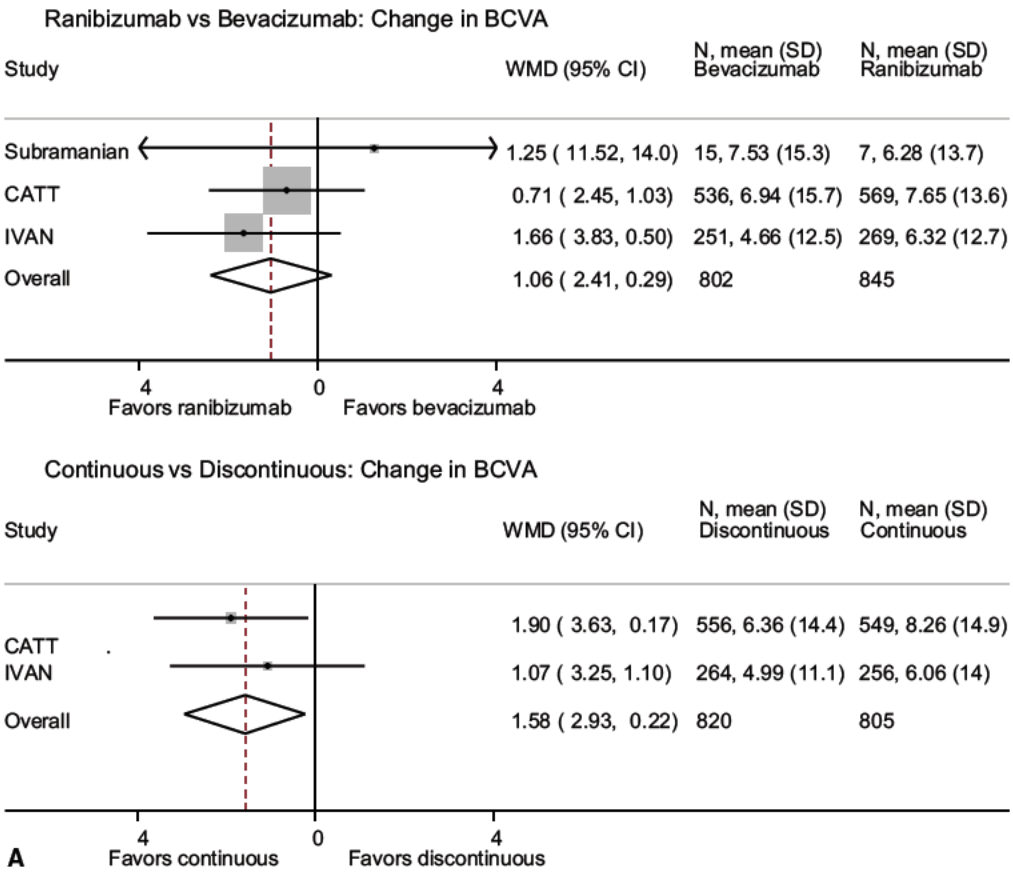

Figure 4. Meta-analysis of 1-year outcomes. **A**, Differences between ranibizumab and bevacizumab (top) and between continuous and discontinuous treatment regimen (bottom) in the change in best-corrected visual acuity from baseline (1 year minus baseline). BCVA = best-corrected visual acuity; CATT = Comparison of AMD Treatment Trials; IVAN = Alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation trial; SD = standard deviation; WMD = weighted mean difference.

discontinuous regimens was negligible, showing that the treatment regimens were equivalent.

There were no significant differences between drugs or regimens for secondary measures of visual function or generic quality of life. Although the GMR for near visual acuity seemed to favor ranibizumab, it was only 8% better; this difference is small (corresponding to about half of one logarithm of the minimum angle of resolution line) and, as for distance acuity, is unlikely to be clinically meaningful.

Angiographic and tomographic metrics favored continuous treatment, but there were no differences between the drugs. These findings contrast somewhat with the difference in visual acuity, which was greater between drugs than between treatment regimens. The CATT found differences in morphologic outcomes across their 4 groups but these were not reported by drug and dosing regimen.[7]

Serum VEGF measurements implied that an intravitreal drug can egress into the circulation. At 1 year, levels were significantly lower for bevacizumab and the continuous treatment cohorts. Binding of bevacizumab, which is a full-length humanized antibody to VEGF, may account for the lower serum VEGF concentration observed among patients receiving this drug compared with those receiving ranibizumab, which by contrast is an antibody fragment. These findings are consistent with previous case series,[22,23] but their clinical importance is difficult to judge given that other outcomes were similar for the 2 drugs and regimens. It is possible that consequences of differential suppression of circulating VEGF will only become apparent after longer follow-up.

The safety profiles of the drugs were reassuring. Arteriothrombotic event or heart failure, the primary safety outcome in the IVAN, occurred in <2%, but more often with ranibizumab than bevacizumab ($P = 0.03$). There was no difference between treatment regimens. There were no differences at 1 year between drugs or treatment regimens in mortality, the odds of a serious systemic adverse event, or the 2 MedDRA-specific system organ classes with >10 participant-specific events.

As expected, continuous ranibizumab is the most expensive treatment. There was no reduction in costs of monitoring or managing expected adverse events to offset increased drug cost. The difference between continuous and discontinuous treatment was not significant for bevacizumab. Extrapolating the results for discontinuous treatment suggests that switching from ranibizumab to bevacizumab could save the NHS £84.5 million based on 17 295 eyes being treated in England annually.[24]

The IVAN trial has strengths and limitations. It was carried in out in the UK NHS usual care setting and the

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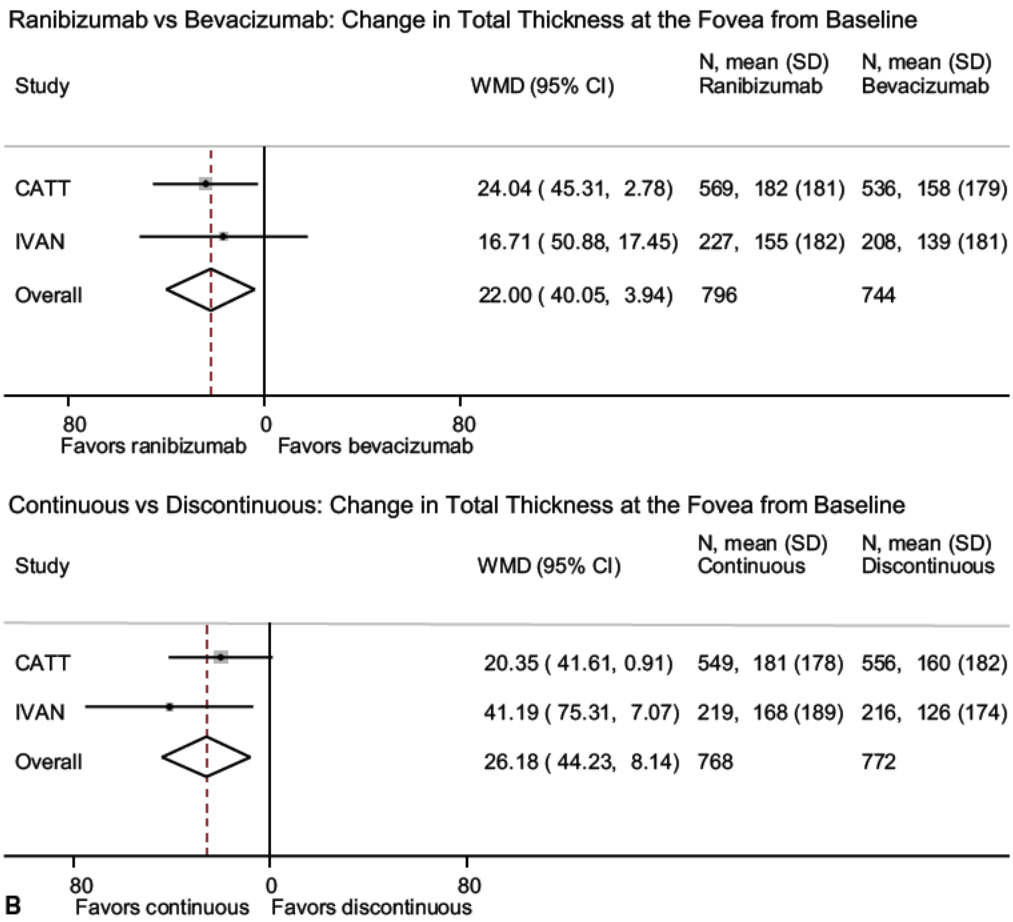

Figure 4. (Continued.) B, Differences between ranibizumab and bevacizumab (top) and between continuous and discontinuous treatment regimen (bottom) in the change in total thickness at fovea from baseline (1 year minus baseline). CATT = Comparison of AMD Treatment Trials; IVAN = Alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation trial; SD = standard deviation; WMD = weighted mean difference.

findings are applicable to this and similar settings. The factorial design and analyses provided high statistical power, despite having only half as many participants as the CATT. We studied a range of secondary functional outcomes, which are reassuringly consistent with the visual acuity findings. We undertook a cost analysis and confirmed the similarity of the monitoring and administration costs for the 2 drugs. Clinicians were effectively masked to drug allocation; unlike the CATT, participants did not receive any billing information and were also effectively masked to allocation. There was good retention given the elderly trial population.

Although this paper reports interim findings, the analyses were prespecified both in the protocol and a detailed analysis plan. The requirement for monthly attendance in this older age group meant some visits were missed; however, the numbers did not differ by group. Although VEGF measurements in serum are suboptimal, preparation of plasma was not feasible in this pragmatic trial. The release of sequestered VEGF from platelets could have confounded our findings.

Findings in Relation to Other Literature

We combined findings for changes in visual acuity at 1 year from baseline for the Subramanian et al,[25] the CATT,[7] and IVAN trials. We also combined the fluid and safety outcomes for the CATT and the IVAN (Appendix 4, section 5). The weighted mean difference in visual acuity (1.06 letters in favor of ranibizumab; 95% CI, −0.29 to 2.41 letters; Fig 4A) reinforces the conclusion of the equivalence of the 2 drugs. Visual acuity improved less with discontinuous (as needed) than continuous treatment but the difference was within the IVAN noninferiority margin (1.58 letters in favor of continuous treatment; 95% CI, 0.22 to 2.93 letters). The pooled findings for different treatment regimens should be interpreted cautiously because different as-needed regimens were used. The mean number of as-needed treatments were similar in the 2 trials, but our discontinuous regimen seems to have achieved better outcomes.

Pooled analysis of total thickness at the fovea shows a significant difference of 22 μm favoring ranibizumab (95% CI, 3.94 to 40.1) and a significant difference of 26.2 μm favoring continuous treatment (95% CI, 8.14 to 44.2; Fig 4B). Differences were not related to visual function at 1 year, but may become so after longer follow-up.

With respect to safety, the pooled analyses showed that mortality was lower with ranibizumab and there were fewer arteriothrombotic events with bevacizumab, but neither out-

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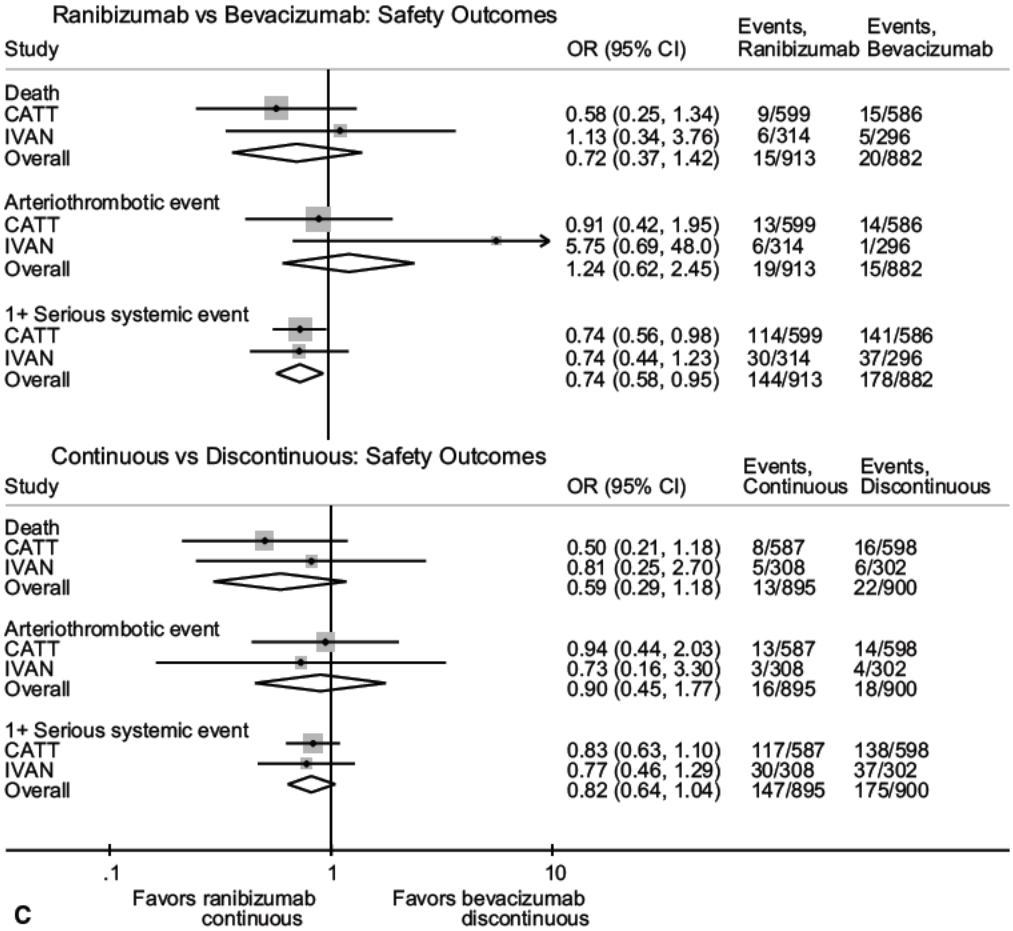

Figure 4. (Continued.) **C**, Differences between ranibizumab and bevacizumab (top) and between continuous and discontinuous treatment regimen (bottom) in the safety outcomes at 1 year. The squares indicate the weighted mean difference (WMD; **A**, **B**) or the odds ratio (OR; **C**) for each trial and the bars 95% confidence intervals (CIs). The size of the square reflects the study size. The diamond shows the pooled estimate for the trials. Negative values for the mean difference reflect better outcomes at 1 year in the ranibizumab or continuous groups. Odds ratios <1 reflect fewer serious adverse events during the first year in the bevacizumab or discontinuous groups. CATT = Comparison of AMD Treatment Trials; IVAN = Alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization trial; N = number of participants; OR = odds ratio; SD = standard deviation.

come differed between drugs ($P = 0.34$ and $P = 0.55$; Fig 4C). The increased odds of experiencing a serious adverse event with bevacizumab observed in the CATT persisted in the meta-analysis ($P = 0.016$). Both studies reported more deaths and more systemic serious adverse events with discontinuous treatment, but the pooled odds ratios were not significant ($P \geq 0.10$).

Considering all of the evidence now available, we conclude that ranibizumab and bevacizumab confer equivalent visual function benefits, but that bevacizumab is substantially less expensive. Ranibizumab, and continuous treatment, result in significantly better morphologic outcomes, but there was no similar difference in visual function. The safety profiles of the 2 drugs are similar and do not support an increased risk of arteriothrombotic events with bevacizumab.[26] Both the CATT and the IVAN reported slightly more systemic serious adverse events with bevacizumab. Further data from these and other trials will inform optimal treatment regimens.

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