Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration

Two-Year Results

*Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group**
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Objective: To describe effects of ranibizumab and bevacizumab when administered monthly or as needed for 2 years and to describe the impact of switching to as-needed treatment after 1 year of monthly treatment.

Design: Multicenter, randomized clinical trial.

Participants: Patients (n = 1107) who were followed up during year 2 among 1185 patients with neovascular age-related macular degeneration who were enrolled in the clinical trial.

Interventions: At enrollment, patients were assigned to 4 treatment groups defined by drug (ranibizumab or bevacizumab) and dosing regimen (monthly or as needed). At 1 year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment.

Main Outcome Measures: Mean change in visual acuity.

Results: Among patients following the same regimen for 2 years, mean gain in visual acuity was similar for both drugs (bevacizumab-ranibizumab difference, −1.4 letters; 95% confidence interval [CI], −3.7 to 0.8; P = 0.21). Mean gain was greater for monthly than for as-needed treatment (difference, −2.4 letters; 95% CI, −4.8 to −0.1; P = 0.046). The proportion without fluid ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab monthly group (drug, P = 0.0003; regimen, $P < 0.0001$). Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2 (−2.2 letters; P = 0.03) and a lower proportion without fluid (−19%; $P < 0.0001$). Rates of death and arteriothrombotic events were similar for both drugs ($P > 0.60$). The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07−1.57; P = 0.009). Most of the excess events have not been associated previously with systemic therapy targeting vascular endothelial growth factor (VEGF).

Conclusions: Ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period. Treatment as needed resulted in less gain in visual acuity, whether instituted at enrollment or after 1 year of monthly treatment. There were no differences between drugs in rates of death or arteriothrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab is uncertain because of the lack of specificity to conditions associated with inhibition of VEGF.

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**Group members listed online in Appendix 1 (available at http://aaojournal.org).*

Clinical trials established ranibizumab as a highly effective treatment for neovascular age-related macular degeneration (AMD), the leading cause of legal blindness in the United States.[1,2] While awaiting approval of ranibizumab by the Food and Drug Administration, ophthalmologists began using off-label bevacizumab because the drug had target specificity similar to that of ranibizumab and was available at low cost. Bevacizumab rapidly became the most commonly used drug for the treatment of neovascular AMD, despite the absence of data from randomized clinical trials supporting its use.[3]

In May 2011, the authors reported the 1-year results of the Comparison of AMD Treatments Trials (CATT).[4] This randomized clinical trial demonstrated that bevacizumab and ranibizumab had nearly identical effects on visual acuity and that less than monthly, or as-needed, dosing did not compromise vision. Both drugs dramatically reduced retinal and subretinal fluid, but ranibizumab eliminated fluid more

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often. Although there were no differences between drugs in rates of death and arteriothrombotic events, there were more serious adverse events in patients treated with bevacizumab (risk ratio, 1.29). Because neither drug eliminates neovascularization, treatment continues indefinitely for most patients. Therefore, the longer-term effects of these drugs and dosing regimens are important.

Patients and Methods

Study Population

The design and methods for CATT have been published previously.[4] Eligible eyes had active choroidal neovascularization secondary to AMD, no previous treatment, visual acuity between 20/25 and 20/320, and neovascularization, fluid, or hemorrhage under the fovea. The study was approved by an institutional review board associated with each center. The study adhered to the tenets of the Declaration of Helsinki and was performed in compliance with the Health Insurance Portability and Accountability Act. All patients provided written informed consent. The study is registered on http://www.clinicaltrials.gov (no. NCT00593450, accessed March 26, 2012).

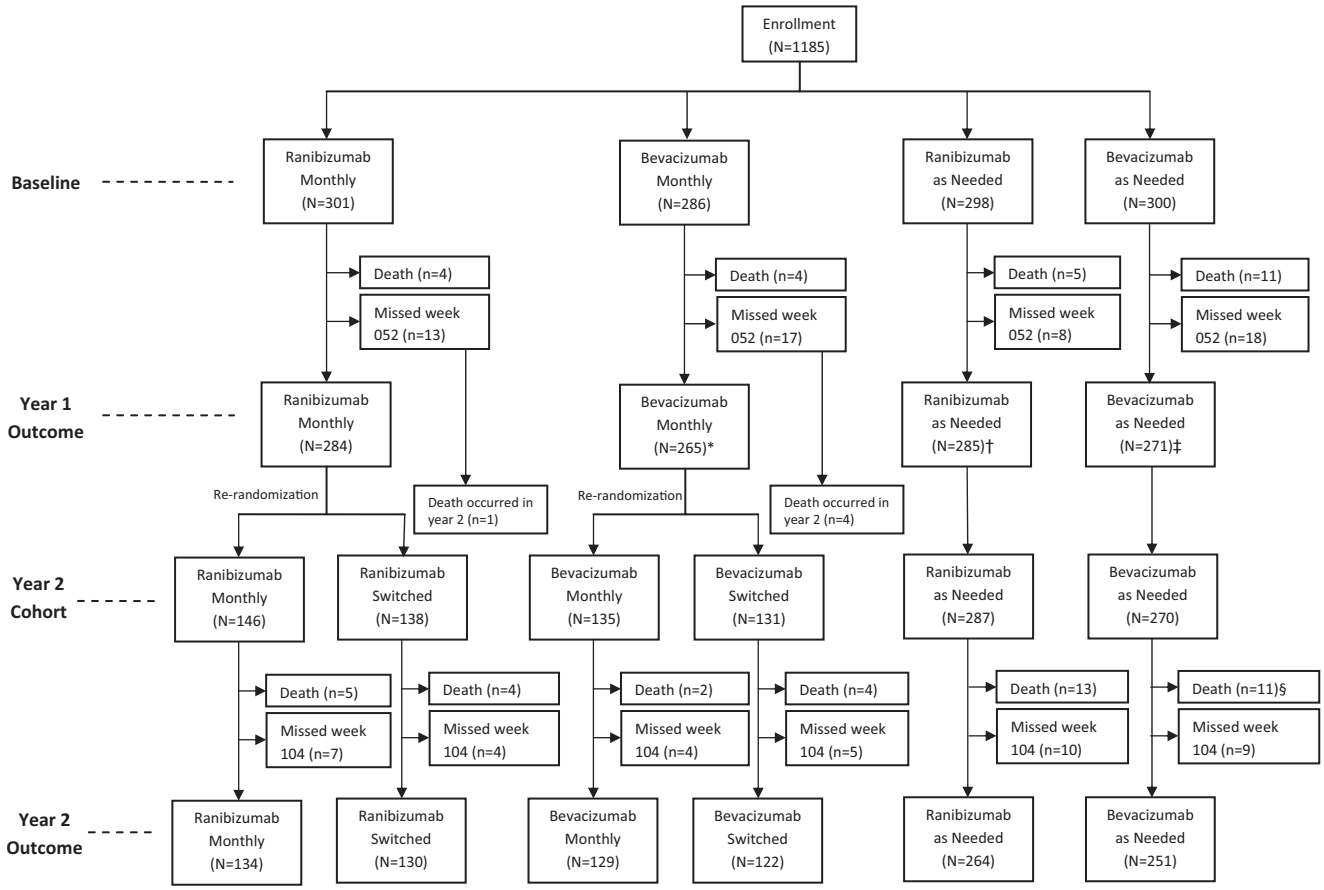
Treatment

At enrollment, patients were assigned with equal probability to 1 of 4 treatment groups defined by drug (ranibizumab or bevacizumab) and by dosing regimen (monthly or as needed). At 1 year, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly, with equal probability, to either monthly or as-needed treatment (the so-called "switched regimen" group). Patients initially assigned to as-needed treatment had no change in assignment; that is, they retained both their drug assignment and as-needed dosing regimen for year 2.

The dose per intravitreal injection was 0.50 mg ranibizumab in 0.05 ml solution or 1.25 mg bevacizumab in 0.05 ml solution. Patients receiving the monthly dosing regimen received an injection every 4 weeks. Patients receiving the as-needed dosing regimen were evaluated for treatment every 4 weeks and were treated when fluid was present on optical coherence tomography (OCT) or when new or persistent hemorrhage, decreased visual acuity relative to the previous visit, or dye leakage on fluorescein angiography was present.

Outcome Measures

The primary outcome measure was mean change in visual acuity. Prespecified secondary outcomes were the proportion of patients



*One patient did not complete the week 52 visit yet had ≥1 follow-up visits in year 2.
† Two patients did not complete the week 52 visit yet had ≥1 follow-up visits in year 2.
‡ One patient had a week 52 examination at a nonparticipating clinical center, and no further follow-up visits occurred in year 2.
§ One death occurred after the clinic visit for week 104, but within the follow-up period.

Figure 1. Flow diagram of patient participation.

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with a change in visual acuity of 15 letters or more, number of injections, drug costs (per-dose cost, approximately $2000 for ranibizumab and $50 for bevacizumab),[5] presence of fluid and change in foveal retinal thickness, change in lesion size on fluorescein angiography, and incidence of systemic and ocular adverse events. The OCT scans during year 1 were performed with time-domain OCT. Spectral-domain OCT was used for 22.6% of scans during year 2. Clinic coordinators questioned patients at each visit regarding adverse events and coded events according to the *Medical Dictionary for Regulatory Activities* (MeDRA) system; a medical monitor reviewed serious adverse events and their coding. Arteriothrombotic events (as defined by the Antiplatelet Trialists' Collaboration) were prespecified for monitoring.[6]

Masking to Treatment Assignment

Image graders, visual acuity examiners, and the medical monitor were unaware of drug and dosing regimen. Ophthalmologists were unaware of drug assignment. Clinic coordinators were aware of both drug and regimen. Patients were not informed of their drug assignment; however, insurance and billing documents specified ranibizumab but not study-supplied bevacizumab. Therefore, patients may have learned or deduced their assigned drug from these financial documents.

Statistical Analysis

The CATT was designed as a randomized noninferiority clinical trial involving 4 treatment groups, with the primary analysis at 1 year. The primary analysis was prespecified as a comparison of mean change in visual acuity from baseline among the 4 treatment groups. The sample size of approximately 300 patients in each of the treatment groups was sufficient to provide 2-sided 99.2% confidence limits that would exclude a difference of 5 letters (the noninferiority limit) if the true difference were 0 letters.

Table 1. Characteristics at Enrollment by Treatment Group

Characteristic	(n = 146)	(n = 135)	(n = 287)	(n = 270)	(n = 138)	(n = 131)
Drug	Ranibizumab	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	Bevacizumab
Year 1 Regimen	Monthly	Monthly	As Needed	As Needed	Monthly	Monthly
Year 2 Regimen	Monthly	Monthly	As Needed	As Needed	As Needed	As Needed
Age (yrs), no. (%)						
50–59	0 (0.0)	0 (0.0)	6 (2.1)	2 (0.7)	2 (1.4)	1 (0.8)
60–69	18 (12.3)	17 (12.6)	31 (10.8)	31 (11.5)	14 (10.1)	10 (7.6)
70–79	44 (30.1)	38 (28.1)	113 (39.4)	98 (36.3)	55 (39.9)	39 (29.8)
80–89	72 (49.3)	68 (50.4)	118 (41.1)	126 (46.7)	57 (41.3)	72 (55.0)
≥90	12 (8.2)	12 (8.9)	19 (6.6)	13 (4.8)	10 (7.2)	9 (6.9)
Mean (SD)	79.5 (7.4)	79.7 (7.5)	78.3 (7.8)	78.9 (7.4)	78.8 (7.5)	80.4 (7.1)
Gender, no. (%)						
Female	90 (61.6)	82 (60.7)	179 (62.4)	166 (61.5)	82 (59.4)	86 (65.6)
Male	56 (38.4)	53 (39.3)	108 (37.6)	104 (38.5)	56 (40.6)	45 (34.4)
Race, no. (%)						
White	143 (97.9)	132 (97.8)	285 (99.3)	264 (97.8)	137 (99.3)	130 (99.2)
Other	3 (2.1)	3 (2.2)	2 (0.7)	6 (2.2)	1 (0.7)	1 (0.8)
Medical history, no. (%)						
Myocardial infarction	15 (10.3)	16 (11.9)	28 (9.8)	33 (12.2)	17 (12.3)	19 (14.5)
Stroke	6 (4.1)	7 (5.2)	22 (7.7)	16 (5.9)	7 (5.1)	9 (6.9)
Transient ischemic attack	8 (5.5)	12 (8.9)	11 (3.8)	17 (6.3)	4 (2.9)	11 (8.4)
Hypertension						
Normal	29 (19.9)	35 (25.9)	60 (20.9)	59 (21.9)	34 (24.6)	34 (26.0)
Suspect	15 (10.3)	7 (5.2)	32 (11.1)	15 (5.6)	7 (5.1)	13 (9.9)
Definite	102 (69.9)	93 (68.9)	195 (67.9)	196 (72.6)	97 (70.3)	84 (64.1)
Visual acuity score (letters) and Snellen equivalent, no. (%)						
68–82, 20/25–40	47 (32.2)	42 (31.1)	113 (39.4)	92 (34.1)	61 (44.2)	44 (33.6)
53–67, 20/50–80	55 (37.7)	60 (44.4)	102 (35.5)	110 (40.7)	36 (26.1)	51 (38.9)
38–52, 20/100–160	31 (21.2)	22 (16.3)	58 (20.2)	53 (19.6)	30 (21.7)	29 (22.1)
23–37, 20/200–320	13 (8.9)	11 (8.2)	14 (4.9)	15 (5.6)	11 (8.0)	7 (5.3)
Mean (SD)	59.9 (14.2)	60.2 (13.6)	61.6 (13.1)	60.6 (13.0)	60.9 (14.3)	60.4 (12.4)
Total thickness at fovea, μm						
Mean (SD)	460 (190)	462 (205)	462 (195)	459 (173)	462 (184)	471 (185)
Retinal thickness plus subfoveal fluid thickness at fovea, μm						
Mean (SD)	254 (127)	249 (117)	248 (124)	251 (116)	251 (119)	253 (114)
Foveal center involvement, no. (%)						
Choroidal neovascularization	81 (55.5)	65 (48.1)	169 (58.9)	159 (58.9)	87 (63.0)	79 (60.3)
Fluid	45 (30.8)	42 (31.1)	76 (26.5)	67 (24.8)	34 (24.6)	31 (23.7)
Hemorrhage	10 (6.8)	12 (8.9)	23 (8.0)	24 (8.9)	8 (5.8)	11 (8.4)
Other	9 (6.2)	11 (8.1)	14 (4.9)	18 (6.7)	8 (5.8)	8 (6.1)
Not possible to grade	1 (0.7)	5 (3.7)	5 (1.7)	2 (0.7)	1 (0.7)	2 (1.5)

SD = standard deviation.

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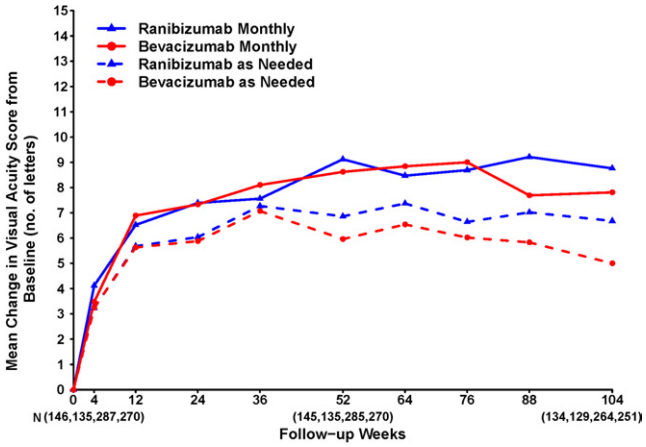

Figure 2. The mean change in visual acuity from enrollment over time in patients treated with the same dosing regimen for 2 years.

Year 2 of CATT was conducted to describe longer-term effects of the original 4 treatment groups and to describe the impact of switching from monthly to as-needed treatment after a year of monthly treatment. The rerandomization of each monthly treatment group at the end of 1 year into 2 groups created 6 treatment groups and reduced the sample size of groups originally treated monthly. The result is a higher number of possible comparisons, loss of statistical power, and increased likelihood of an inconclusive result regarding noninferiority for each comparison. The analyses presented herein describe the effects of the drugs and the effects of the regimens in year 2, rather than the effects of each drug and dosing regimen combination. This approach yields larger sample sizes, greater precision, and increased power. The approach provides an accurate description of the results when there is no interaction between drug and dosing regimen, that is, when the beneficial or harmful effect of a drug is the same for each dosing regimen and the effect of the dosing regimen is the same for each drug.

For comparisons of patients remaining with their originally assigned dosing regimen in year 2, change relative to baseline was used. For comparisons of patients randomly reassigned to a dosing regimen for year 2, change relative to the 1-year value was used. Comparisons without covariate adjustment were made with analysis of variance for continuous outcome measures and chi-square tests for categorical outcome measures, with treatment specified by drug and dosing regimen (main effects). Interaction between drug and dosing regimen was assessed with linear regression for continuous outcome measures and with logistic regression for categorical outcome measures. Unless specified otherwise, interaction terms for primary and secondary outcomes were associated with P values > 0.10 and were not included in models. Adjustment for covariates and 3 alternative approaches for handling missing data (multiple imputation using propensity scoring or regression modeling and last observation carrying forward) for the 2-year visual acuity were performed as sensitivity analyses.[7,8] Quarterly measurements of change in visual acuity were summarized by means of longitudinal analysis.[8] Time to first systemic serious adverse event was analyzed using a Cox proportional hazards model that included dosing regimen as a time-dependent covariate and a propensity score based on age, smoking status, use of dietary supplements, and status of 15 conditions associated ($P < 0.10$) with incidence of serious adverse events.[9,10] Serious adverse events were classified further as previously associated with drugs affecting the vascular endothelial growth factor pathway (arteriothrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, hypertension, vascular death).[11,12] Analyses followed the intention-to-treat principle.

This report includes data available by December 31, 2011. Only the 1107 patients with at least 1 visit completed in a CATT center between weeks 52 and 104, inclusive, are included in efficacy analyses, whereas all 1185 patients enrolled through 43 centers are included in safety analyses (Fig 1). Statistical computations were performed with SAS software version 9.2 (SAS Inc., Cary, NC).

Results

Patients and Treatment

At enrollment, there were no substantial imbalances in demographic or ocular characteristics among the 6 treatment groups (Table 1). Two years after enrollment, visual acuity scores were available for 1030 of 1107 patients (93.0%). Missed visit rates at 2 years were similar across treatment groups (3.0%−5.0%). Additional information about follow-up may be found in Appendix 2 (available at http://aaojournal.org).

Treatment decisions by ophthalmologists in year 2 were consistent with the identification of fluid on OCT scans by the reading center for 3337 of 4872 examinations (68.5%) in the

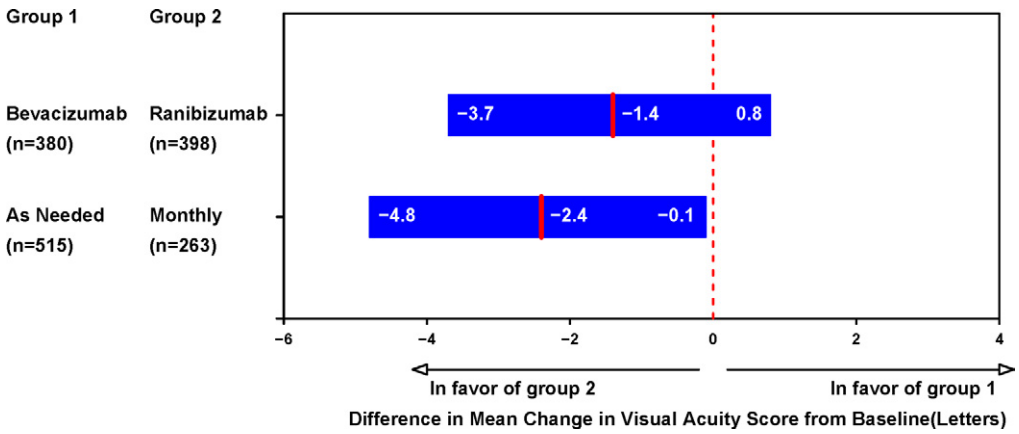

Figure 3. Differences in mean change in visual acuity at 2 years and 95% confidence intervals in patients treated with the same dosing regimen for 2 years.

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ranibizumab-as-needed groups and 3190 of 4583 examinations (69.6%) in the bevacizumab-as-needed groups. Ninety-five percent of inconsistencies were instances of missed treatments; that is, the OCT reading center detected fluid and the patient was not treated. The proportions consistent on spectral-domain OCT scans (1442 of 2058 [70.1%]) and on time-domain OCT scans (5085 of 7397 [68.7%]) were similar ($P = 0.22$). During year 2, ophthalmologists reported knowing the identity of the assigned drug in 66 of 12 645 evaluations (0.5%) for treatment (9 patients assigned to ranibizumab and 2 patients assigned to bevacizumab). During an exit interview, 252 of 525 patients (48.0%) assigned to ranibizumab and 124 of 500 patients (24.8%) assigned to bevacizumab responded that they knew which drug had been used to treat their study eye and then correctly identified the drug. Few (<3%) patients said they knew the drug and identified the incorrect drug.

Change in Visual Acuity in Patients Treated with the Same Dosing Regimen for 2 Years

Most of the change in mean visual acuity occurred during year 1, with relatively little change during year 2 (Fig 2). At 2 years, the mean increase in letters of visual acuity from baseline was 8.8 in the ranibizumab-monthly group, 7.8 in the bevacizumab-monthly group, 6.7 in the ranibizumab-as-needed group, and 5.0 in the bevacizumab-as-needed group (Table 2; drug, $P = 0.21$; regimen, $P = 0.046$). The difference in mean improvement for patients treated with bevacizumab relative to those treated with ranibizumab was −1.4 letters (95% confidence interval [CI], −3.7 to 0.8; Fig 3). The difference in mean improvement for patients treated by an as-needed regimen relative to those treated monthly was −2.4 letters (95% CI, −4.8 to −0.1). The results of the above analyses were similar after application of alternative methods for handling missing visual acuity data at 2 years. After adjusting for baseline predictors of visual acuity in a multivariate longitudinal regression model, the estimated change in visual acuity, averaged over 2 years of follow-up, was 0.7 letters better for ranibizumab (95% CI, −0.9 to 2.3; $P = 0.41$) and 1.7 letters better for patients treated monthly (95% CI, −0.1 to 3.4; $P = 0.07$).

Secondary Outcomes in Patients Treated with the Same Dosing Regimen for 2 Years

At 2 years, the proportions of patients without a decrease in vision of 15 letters or more were similar, ranging from 88.4% for the bevacizumab-as-needed group to 93.3% for the ranibizumab-monthly group (Fig 4; Table 2; $P = 0.24$). The mean visual acuity at 2 years was similar among the 4 treatment groups, with an approximate Snellen equivalent of 20/40 (drug, $P = 0.17$; regimen, $P = 0.41$). The proportions with 20/20 or better visual acuity and with 20/200 or worse visual acuity were also similar among the treatment groups (Fig 5). The mean± standard deviation number of injections through year 2 in the as-needed groups, from a maximum of 26, was 12.6±6.6 for patients treated with ranibizumab and 14.1±7.0 for those treated with bevacizumab ($P = 0.01$). The estimated 2-year drug cost per patient varied from $705 in the bevacizumab-as-needed group to $44 800 in the ranibizumab-monthly group.

At 2 years, mean retinal thickness was 29 μm less in patients treated monthly than in patients treated with an as-needed regimen (regimen, $P = 0.005$). The proportion of patients without fluid on OCT ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab-monthly group (drug, $P = 0.0003$; regimen, $P < 0.0001$). Fluorescein dye leakage was absent in a higher percentage of patients treated monthly than in patients treated as needed (regimen, $P = 0.002$). The mean change in lesion area from baseline ranged from −0.4 mm^2 for the ranibizumab-monthly group to 3.0 mm^2 for the bevacizumab-as-needed group (drug, $P = 0.006$; regimen, $P = 0.0003$). Most of the increase in mean lesion area occurred during year 2. The proportion of study eyes with geographic atrophy at 2 years among eyes without apparent geographic atrophy at enrollment, ranging from 25.8% in the ranibizumab-monthly group to 12.9% in the bevacizumab-as-needed group, was greater among patients treated monthly ($P = 0.007$).

Outcomes among Patients with Dosing Regimen Reassigned at 1 Year

The mean visual acuity among patients assigned to continue monthly treatment changed little during year 2, whereas the mean changes in the groups switched from monthly to treatment as needed were −1.8 letters in ranibizumab-treated patients and −3.6 letters in bevacizumab-treated patients (Table 3; regimen, $P = 0.03$). For both drugs, mean change in visual acuity at 2 years was similar in the as-needed groups and the groups that switched from monthly to as-needed treatment (Figs 4 and 6). Among switched patients, the mean number of injections was 5.0 for ranibizumab-treated patients and 5.8 for bevacizumab-treated patients ($P = 0.11$). The mean total retinal thickness in monthly treated patients changed little, but increased in the switched patients (ranibizumab, +31 μm; bevacizumab, +19 μm; regimen, $P = 0.0004$; Fig 7). The proportions of patients without fluid on OCT were similar in the 2 switched groups (19.2% for ranibizumab; 18.0% for bevacizumab) and were substantially higher in the bevacizumab-monthly group (30.2%) and ranibizumab-monthly group (45.5%; drug, $P = 0.03$; regimen, $P < 0.0001$).

Adverse Events

At 2 years, 32 of 599 patients (5.3%) assigned to ranibizumab and 36 of 586 (6.1%) assigned to bevacizumab had died (Table 4; $P = 0.62$). The proportion of patients with arteriothrombotic events was similar in the ranibizumab-treated patients (4.7%) and in the bevacizumab-treated patients (5.0%; $P = 0.89$). Venous thrombotic events occurred in 3 (0.5%) ranibizumab-treated patients and in 10 (1.7%) bevacizumab-treated patients ($P = 0.054$).

One or more serious systemic adverse events occurred in 190 (31.7%) of ranibizumab-treated patients and in 234 (39.9%) of bevacizumab-treated patients ($P = 0.004$). When patients were grouped according to their originally assigned drug and dosing regimen, the rates continued to diverge in year 2 (Fig 8). Considering only events occurring in year 2, 131 of 536 bevacizumab-treated patients (24.4%) and 103 of 571 ranibizumab-treated patients (18.0%) experienced a systemic serious adverse event ($P = 0.009$). After adjustment for demographic features and coexisting illnesses at baseline, the risk ratio for all systemic serious adverse events within 2 years for bevacizumab was 1.30 (95% CI, 1.07−1.57; $P = 0.009$). Patients treated as needed had higher rates than patients treated monthly (risk ratio, 1.20; 95% CI, 0.98−1.47; $P = 0.08$). When only year 2 was considered, 182 of 826 patients (22.0%) treated as needed and 52 of 281 patients (18.5%) treated monthly experienced a serious adverse event ($P = 0.21$). After excluding all events previously associated with systemic treatment with anti–vascular endothelial growth factor drugs, 170 (28.4%) of ranibizumab-treated patients and 202 (34.5%) of bevacizumab-treated patients had experienced events ($P = 0.02$). The proportion

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Table 2. Outcomes at 2 Years: Patients Treated with the Same Dosing Regimen for 2 Years

Outcome	Ranibizumab Monthly (n = 134)	Bevacizumab Monthly (n = 129)	Ranibizumab as Needed (n = 264)	Bevacizumab as Needed (n = 251)	*P* Value	
					Drug	*Regimen*
Visual acuity score, letters, Snellen equivalent, no. (%)						
83–97, 20/12–20	24 (17.9)	17 (13.2)	44 (16.7)	35 (13.9)		
68–82, 20/25–40	67 (50.0)	61 (47.3)	123 (46.6)	121 (48.2)		
53–67, 20/50–80	23 (17.2)	31 (24.0)	59 (22.3)	46 (18.3)		
38–52, 20/100–160	11 (8.2)	14 (10.9)	23 (8.7)	28 (11.2)		
≤37, ≤20/200	9 (6.7)	6 (4.7)	15 (5.7)	21 (8.4)		
Mean letters (SD)	68.5 (18.9)	68.2 (16.1)	68.5 (15.3)	66.0 (19.9)	0.17	0.41
Change in visual acuity score from baseline (letters), no. (%)						
≥15 increase	44 (32.8)	41 (31.8)	81 (30.7)	71 (28.3)		
5–14 increase	49 (36.6)	36 (27.9)	78 (29.5)	79 (31.5)		
≤4 change	22 (16.4)	31 (24.0)	62 (23.5)	49 (19.5)		
5–14 decrease	10 (7.5)	11 (8.5)	24 (9.1)	23 (9.2)		
≥15 decrease	9 (6.7)	10 (7.8)	19 (7.2)	29 (11.6)		
Mean (SD)	8.8 (15.9)	7.8 (15.5)	6.7 (14.6)	5.0 (17.9)	0.21	0.046
No. treatments, 2 yrs						
Mean (SD)	22.4 (3.9)	23.4 (2.8)	12.6 (6.6)	14.1 (7.0)	0.01*	—
Mean cost of drug/patient	$44 800	$1170	$25 200	$705		
Total thickness at fovea, μm						
Mean (SD)[†]	267 (143)	274 (137)	293 (129)	306 (134)	0.26	0.005
Mean change (SD) from baseline[‡]	−190 (172)	−180 (196)	−166 (190)	−153 (189)	0.38	0.08
Retinal thickness and subfoveal fluid thickness, μm						
Mean (SD)[†]	162 (81)	166 (79)	167 (75)	169 (83)	0.63	0.53
Mean change (SD) from baseline[‡]	−91 (152)	−84 (133)	−78 (131)	−84 (145)	0.86	0.54
Fluid on optical coherence tomography, no. (%)						
None	61 (45.5)	39 (30.2)	59 (22.3)	35 (13.9)	0.0003	<0.0001
Present	69 (51.5)	87 (67.4)	198 (75.0)	212 (84.5)		
Unknown/missing	4 (3.0)	3 (2.3)	7 (2.7)	4 (1.6)		
Dye leakage on angiogram, no. (%)						
None	102 (76.1)	97 (75.2)	183 (69.3)	161 (64.1)	0.24	0.002
Present	24 (17.9)	27 (20.9)	75 (28.4)	81 (32.3)		
Unknown/missing	8 (6.0)	5 (3.9)	6 (2.3)	9 (3.6)		
Area of lesion, mm^2						
Mean (SD)[§]	6.7 (7.8)	7.8 (8.5)	8.5 (7.4)	8.6 (8.3)	0.44	0.04
Mean Change (SD) from baseline[‖]	−0.4 (6.8)	1.6 (5.9)	1.9 (6.5)	3.0 (7.0)	0.006	0.0003
Geographic atrophy, no. (%)[¶]						
None	90 (70.3)	99 (80.5)	205 (84.0)	200 (85.8)	0.13	0.007
Nonfoveal	27 (21.1)	17 (13.8)	28 (11.5)	20 (8.6)		
Foveal	6 (4.7)	5 (4.1)	9 (3.7)	10 (4.3)		
Unknown/missing	5 (3.9)	2 (1.6)	2 (0.8)	3 (1.3)		

SD = standard deviation.

The dashes indicate that calculation of a *P*-value is not appropriate. The treatment groups are defined by dosing regimen; therefore, the role of random variation in producing a difference by regimen is not relevant because by definition they are different.

*Comparison restricted to as-needed groups.

[†]Number of unknown in each group unknown or missing: 3, 3, 3, 1.

[‡]Number in each group unknown or missing: 3, 3, 6, 2.

[§]Includes choroidal neovascularization, hemorrhage, blocked fluorescence, serous pigment epithelium detachment, scar, geographic atrophy, nongeographic atrophy or tear of the retinal pigment epithelium, adjacent to the location of choroidal neovascularization at baseline. Number in each group unknown or missing: 12, 8, 16, 18.

[‖]Number in each group unknown or missing: 16, 12, 22, 27.

[¶]Areas of hypopigmentation or hyperfluorescence of ≥250 μm diameter having ≥2 of the following characteristics: circular shape, sharp borders, visible choroidal vessels. Areas meeting this definition surrounding a scar were not considered geographic atrophy. Excluded those with geographic atrophy at enrollment: 6 (4.4%), 6 (4.7%), 20 (7.8%), 18 (7.2%).

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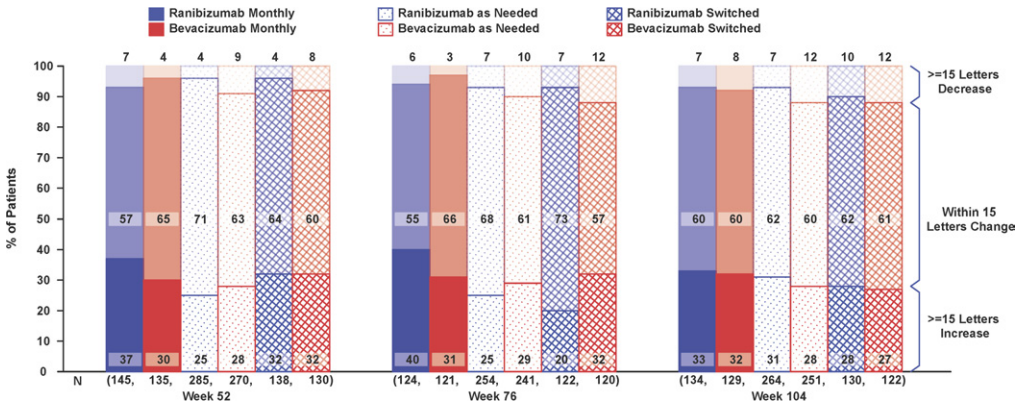

Figure 4. The 3-line change in visual acuity from enrollment by treatment group and follow-up time.

with events generally was higher among bevacizumab-treated patients for each of the *Medical Dictionary for Regulatory Activities* system organ classes displayed in Table 4, with the exception of benign and malignant neoplasms ($P = 0.56$). Gastrointestinal disorders (e.g., hemorrhage, hernia, nausea, and vomiting), occurred in 11 (1.8%) ranibizumab-treated and in 28 (4.8%) bevacizumab-treated patients ($P = 0.005$). Endophthalmitis, defined as severe inflammation that was presumed infectious and was treated with intravitreal antibiotics, developed in 4 (0.7%) ranibizumab-treated patients and in 7 (1.2%) bevacizumab-treated patients ($P = 0.38$); 10 of 11 cases occurred in monthly treated patients.

Discussion

At both 1 and 2 years, bevacizumab and ranibizumab had similar effects on visual acuity when the dosing regimen was the same (Fig 2; Tables 2 and 3). There was little difference in any visual metric evaluated, including mean gain in visual acuity, the proportion of patients who gained 3 lines, the proportion of patients who did not lose 3 lines, and the proportion of patients who achieved 20/40 or better visual acuity. Mean gains in visual acuity at 2 years were within 1.4 letters, and the difference in vision averaged over the 2-year period was 0.7 letters.

Small differences in mean gain in visual acuity emerged between dosing regimens (Table 2). At 2 years, as-needed dosing of either drug produced 2.4 letters less mean gain than monthly dosing ($P = 0.046$), with the greatest difference (3.8 letters) between ranibizumab monthly and bevacizumab as needed. This may be the result of more lesion growth, fluorescein leakage, and residual fluid on OCT in eyes in the as-needed group.

Switching to as-needed dosing after 1 year of monthly treatment, with either drug, produced a mean 2.2-letter decrease, yielding mean visual acuity nearly equal to that obtained with as-needed dosing for 2 years (Fig 6). Monthly treatment throughout year 1 did not preserve lesion stability in year 2; total retinal thickness and residual fluid was greater in the patients who switched from monthly to as-needed treatment at 2 years than in those who maintained monthly dosing (Table 3). Nonetheless, the magnitude and durability of the therapeutic effect in all 6 groups is remarkable when one considers the natural history of neovascular AMD and the modest efficacy of treatments before bevacizumab and ranibizumab. At 2 years, 60% or more of the patients in all groups had 20/40 vision or better, which was dramatically better than among patients who were untreated (<10%) or treated (<15%) with methods available before 2005.[13–16]

Both drugs substantially and immediately reduced fluid in or under the retina (Fig 7). At 1 year, more eyes had complete resolution of fluid with ranibizumab than

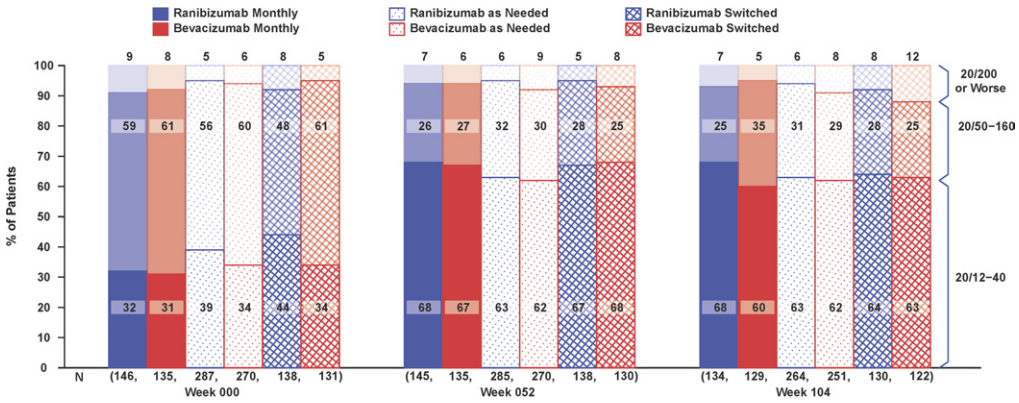

Figure 5. The visual acuity by treatment group and follow-up time.

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Table 3. Outcomes at 2 Years: Patients Whose Dosing Regimen Was Reassigned at 1 Year

Outcome	Ranibizumab		Bevacizumab		P Value	
	Monthly (n = 134)	Switched (n = 130)	Monthly (n = 129)	Switched (n = 122)	Drug	Regimen
Visual acuity score, letters						
Snellen equivalent, no. (%)						
83–97, 20/12–20	24 (17.9)	22 (16.9)	17 (13.2)	23 (18.9)		
68–82, 20/25–40	67 (50.0)	61 (46.9)	61 (47.3)	54 (44.3)		
53–67, 20/50–80	23 (17.2)	23 (17.7)	31 (24.0)	19 (15.6)		
38–52, 20/100–160	11 (8.2)	13 (10.0)	14 (10.9)	11 (9.0)		
≤37, ≤20/200	9 (6.7)	11 (8.5)	6 (4.7)	15 (12.3)		
Mean letters (SD)	68.5 (18.9)	67.7 (18.5)	68.2 (16.1)	65.0 (21.8)	0.39	0.23
Change in visual acuity score, from 1 yr, letters, no. (%)*						
≥15 increase	4 (3.0)	6 (4.6)	8 (6.2)	2 (1.7)		
5−14 increase	34 (25.6)	19 (14.6)	21 (16.3)	17 (14.0)		
≤4 change	58 (43.6)	66 (50.8)	63 (48.8)	61 (50.4)		
5−14 decrease	28 (21.1)	27 (20.8)	27 (20.9)	26 (21.5)		
≥15 decrease	9 (6.8)	12 (9.2)	10 (7.8)	15 (12.4)		
Mean (SD)	−0.3 (11.1)	−1.8 (11.2)	−0.6 (10.3)	−3.6 (12.1)	0.29	0.03
No. of treatments, yr 2						
Mean (SD)	10.5 (3.1)	5.0 (3.8)	11.3 (2.3)	5.8 (4.4)	0.11†	—
Cost of drug/patient	$21 000	$10 000	$565	$290		
Total thickness at fovea, μm						
Mean (SD)‡	267 (143)	295 (135)	274 (137)	334 (190)	0.09	0.001
Mean change (SD) from1 yr§	1 (78)	31 (78)	−9 (94)	19 (114)	0.18	0.0004
Retinal thickness and subfoveal fluid thickness, μm						
Mean (SD)‡	162 (81)	162 (63)	166 (79)	189 (116)	0.04	0.14
Mean change (SD) from 1 yr§	12 (51)	10 (46)	−5 (61)	16 (92)	0.35	0.12
Fluid on optical coherence tomography						
None	61 (45.5)	25 (19.2)	39 (30.2)	22 (18.0)	0.03	<0.0001
Present	69 (51.5)	100 (76.9)	87 (67.4)	97 (79.5)		
Unknown/missing	4 (3.0)	5 (3.8)	3 (2.3)	3 (2.5)		
Dye leakage on angiogram						
None	102 (76.1)	88 (67.7)	97 (75.2)	80 (65.6)	0.59	0.01
Present	24 (17.9)	37 (28.5)	27 (20.9)	36 (29.5)		
Unknown/missing	8 (6.0)	5 (3.8)	5 (3.9)	6 (4.9)		
Area of lesion, mm^2						
Mean (SD)‖	6.7 (7.8)	9.0 (8.1)	7.8 (8.5)	8.2 (7.8)	0.80	0.06
Mean change (SD) from 1 yr¶	0.7 (4.5)	1.7 (5.3)	1.1 (4.0)	1.8 (5.7)	0.63	0.08
Geographic atrophy, no. (%)#						
None	90 (70.3)	97 (80.8)	99 (80.5)	97 (86.7)	0.05	0.02
Nonfoveal	27 (21.1)	16 (13.3)	17 (13.8)	6 (5.4)		
Foveal	6 (4.7)	4 (3.3)	5 (4.1)	6 (5.4)		
Unknown/missing	5 (3.9)	3 (2.5)	2 (1.6)	3 (2.7)		

SD = standard deviation.
The dashes indicate that calculation of a *P*-value is not appropriate. The treatment groups are defined by dosing regimen; therefore, the role of random variation in producing a difference by regimen is not relevant because by definition they are different.
*Number in each group unknown or missing: 1, 0, 0, 1.
†Comparison restricted to as-needed groups.
‡Number in each group unknown or missing: 3, 3, 3, 1.
§Number in each group unknown or missing: 5, 3, 4, 5.
‖See Table 2 for definition. Number in each group unknown or missing: 12, 8, 8, 6.
¶Number in each group unknown or missing: 22, 17, 15, 14.
#See Table 2 for definition. Excluded those with geographic atrophy at baseline: 6, 10, 6, 10.

bevacizumab. At 2 years, differences in mean retinal thickness on OCT and in the proportion of patients with residual fluid remained essentially unchanged from year 1, except in patients who switched from monthly to as-needed treatment in both drug groups. There were more eyes in the monthly treated groups with no fluid on OCT (dry OCT) at the end of year 2 than in the as-needed groups, with the highest proportion with a dry OCT found in the ranibizumab monthly treated group. However, the ranibizumab monthly treated group also had the highest proportion in which geographic atrophy developed of any of the 6 treatment groups. The development of geo-

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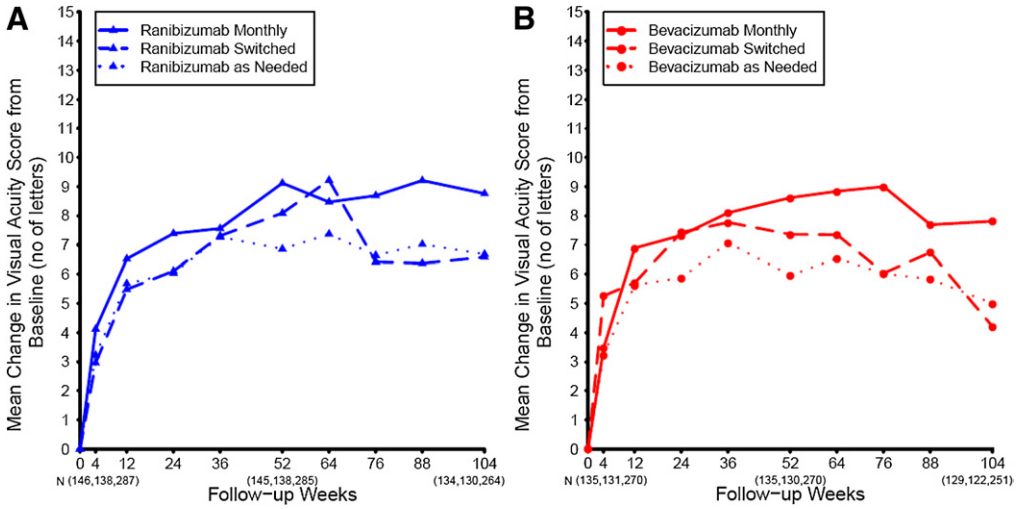

Figure 6. The mean change in visual acuity from enrollment over time by dosing regimen within drug group: (**A**) ranibizumab and (**B**) bevacizumab.

graphic atrophy was higher in both monthly treated groups than in the as-needed groups. This may be important to consider when weighing the risks and benefits of monthly versus as-needed treatment and in the selection of drug. Although most geographic atrophy in CATT was nonfoveal through the 2-year period of the study, adverse effects on visual function, such as lower reading speed and extension to the foveal center with time, are common in the natural history of geographic atrophy.

The greater prevalence of fluid in the bevacizumab-as-needed group led to an average of 0.6 more injections during the second year than in ranibizumab-as-needed patients and in an average of 1.5 injections more over a 2-year period. Despite the adoption of spectral-domain OCT in year 2, with its greater precision in assessing fluid, there was no increase in the agreement between the ophthalmologist and reading center regarding when treatment was required. For both drugs, monthly injection resulted in less growth of choroidal neovascularization than as-needed treatment (Table 2).

Over 2 years, the rates of death, myocardial infarction, and stroke did not differ between drugs. The higher rate of serious adverse events for bevacizumab-treated patients reported in year 1 remained in year 2, with a similar cumulative risk ratio of 1.30. Also as reported for year 1, the risk of serious adverse events was not higher with monthly treatment relative to as-needed treatment. Among all organ systems, the greatest imbalance was in gastrointestinal disorders. Although the number of events is small, this has been an area of concern in previous studies of systemic bevacizumab. When all known vascular endothelial growth factor–related serious adverse events are excluded, most of the imbalance remains, leaving it uncertain whether this difference was the result of chance, imbalances at baseline not captured in multivariate modeling, or truly higher risk. Results from on-

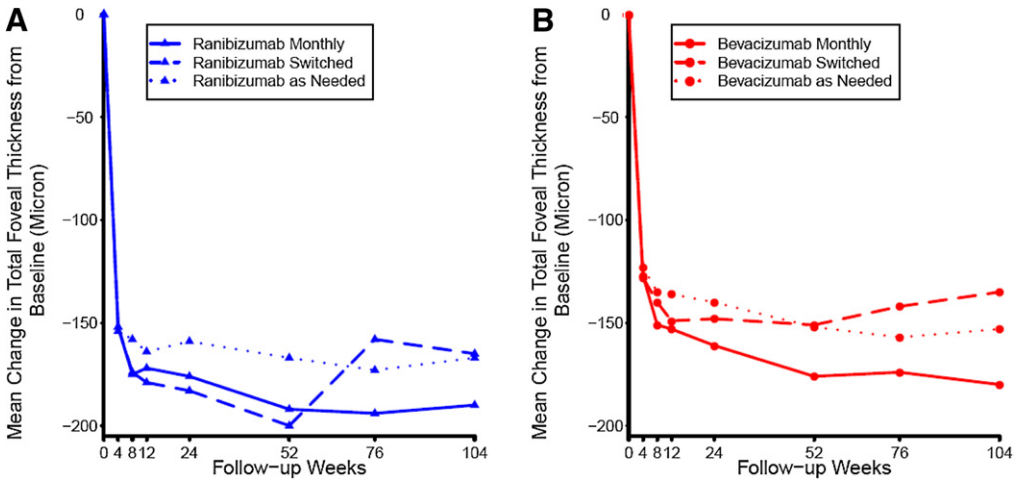

Figure 7. The mean change in total foveal thickness from enrollment over time by dosing regimen within drug group: (**A**) ranibizumab and (**B**) bevacizumab.

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Table 4. Adverse Events within 2 Years of Enrollment

Adverse Event Type	Ranibizumab (n = 599), n (%)	Bevacizumab (n = 586), n (%)	P Value*
Systemic serious			
Death, all causes	32 (5.3)	36 (6.1)	0.62
Arteriothrombotic events	28[†](4.7)	29 (5.0)	0.89
Nonfatal stroke	8 (1.3)	8 (1.4)	1.00
Nonfatal myocardial infarction	9 (1.5)	7 (1.2)	0.80
Vascular death	12 (2.0)	14 (2.4)	0.70
Venous thrombotic events	3 (0.5)	10 (1.7)	0.054
Hypertension	3 (0.5)	4 (0.7)	0.72
One or more serious adverse events	190 (31.7)	234 (39.9)	0.004
Previously associated with anti-VEGF treatment[‡]			
Yes	45 (7.5)	62 (10.6)	0.07
No	170 (28.4)	202 (34.5)	0.02
MedDRA system organ class[§]			
Cardiac disorders	47 (7.8)	62 (10.6)	0.11
Infections	41 (6.8)	54 (9.2)	0.14
Nervous system disorders	34 (5.7)	36 (6.1)	0.81
Injury and procedural complications	23 (3.8)	35 (6.0)	0.11
Neoplasms benign and malignant	27 (4.5)	22 (3.8)	0.56
Gastrointestinal disorders	11 (1.8)	28 (4.8)	0.005
Any other system organ class	81 (13.5)	104 (17.8)	0.046
Ocular, study eye			
Endophthalmitis	4 (0.7)	7 (1.2)	0.38
Pseudo-endophthalmitis	1 (0.2)	1 (0.2)	1.00

MedDRA = *Medical Dictionary for Regulatory Activities*; VEGF = vascular endothelial growth factor.
*Fisher exact test.
[†]One patient had both a nonfatal stroke and a nonfatal myocardial infarction.
[‡]Arteriothrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, hypertension, and vascular death.[12,13]
[§]Data are listed only for system organ classes with 35 or more events.

going randomized clinical trials worldwide may provide additional, independent information about the risk of treatment with bevacizumab relative to ranibizumab.

In 2010, ranibizumab accounted for nearly 10% of the entire Medicare Part B drug budget, its single largest expenditure.[17] As treatment of patients continues indefinitely, the cumulative financial burden to third-party payors and patients will only increase. The choice of drug and dosing regimen for patients must balance the comparable effects on vision, the possibility of true differences in adverse events, and the 40-fold difference in cost per dose between ranibizumab and bevacizumab.

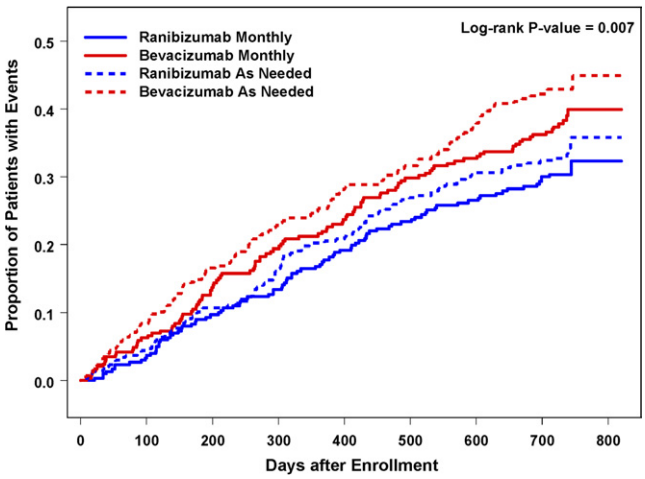

Figure 8. The cumulative proportion of patients with 1 or more systemic serious adverse events by originally assigned dosing regimen and drug.

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Footnotes and Financial Disclosures

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The members of the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group are listed in Appendix 1 (available at http://aaojournal.org).

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