Baseline Predictors for One-Year Visual Outcomes with Ranibizumab or Bevacizumab for Neovascular Age-related Macular Degeneration

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Objective: To determine the baseline predictors of visual acuity (VA) outcomes 1 year after treatment with ranibizumab or bevacizumab for neovascular age-related macular degeneration (AMD).

Design: Cohort study within the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

Participants: A total of 1105 participants with neovascular AMD, baseline VA 20/25 to 20/320, and VA measured at 1 year.

Methods: Participants were randomly assigned to ranibizumab or bevacizumab on a monthly or as-needed schedule. Masked readers evaluated fundus morphology and features on optical coherence tomography (OCT). Visual acuity was measured using electronic VA testing. Independent predictors were identified using regression techniques.

Main Outcome Measures: The VA score, VA score change from baseline, and ≥3-line gain at 1 year.

Results: At 1 year, the mean VA score was 68 letters, mean improvement from baseline was 7 letters, and 28% of participants gained ≥3 lines. Older age, larger area of choroidal neovascularization (CNV), and elevation of retinal pigment epithelium (RPE) were associated with worse VA (all $P < 0.005$), less gain in VA (all $P < 0.02$), and a lower proportion gaining ≥3 lines (all $P < 0.04$). Better baseline VA was associated with better VA at 1 year, less gain in VA, and a lower proportion gaining ≥3 lines (all $P < 0.0001$). Predominantly or minimally classic lesions were associated with worse VA than occult lesions (66 vs. 69 letters; $P=0.0003$). Retinal angiomatous proliferans (RAP) lesions were associated with more gain in VA (10 vs. 7 letters; $P=0.03$) and a higher proportion gaining ≥3 lines (odds ratio, 1.9; 95% confidence interval, 1.2–3.1). Geographic atrophy (GA) was associated with worse VA (64 vs. 68 letters; $P=0.02$). Eyes with total foveal thickness in the second quartile (325–425 μm) had the best VA ($P=0.01$) and were most likely to gain ≥3 lines ($P=0.004$). Predictors did not vary by treatment group.

Conclusions: For all treatment groups, older age, better baseline VA, larger CNV area, predominantly or minimally classic lesion, absence of RAP lesion, presence of GA, greater total fovea thickness, and RPE elevation on optical coherence tomography were independently associated with less improvement in VA at 1 year.

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The visual acuity (VA) prognosis among patients who develop choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) has changed dramatically during the last 7 years since the introduction of highly effective treatments with anti-vascular endothelial growth factor (VEGF).[1–4] The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) recently showed that bevacizumab (Avastin; Genentech Inc., South San Francisco, CA) was equivalent to ranibizumab (Lucentis; Genentech Inc.) in improving the VA of patients with CNV when treatment was administered monthly or pro re nata (PRN).[5] At 1 year, participants treated monthly with bevacizumab or ranibizumab gained 8.0 and 8.5 letters, respectively, and those treated PRN gained 5.9 and 6.8 letters, respectively. The majority of CATT participants had the same or improved VA relative to their baseline VA. However, response to treatment varied substantially among patients. Although VA improved ≥3 lines in 25% to 34% of CATT participants in the 4 treatment arms, it worsened by ≥3 lines in 5% to 8% of participants.[5]

This report provides a comprehensive evaluation of baseline predictors for VA outcomes at 1 year, including demo-

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graphic characteristics and medical history, ocular factors, and CNV lesion features determined from fundus photographs, fluorescein angiograms, and optical coherence tomography (OCT) scans. Identification of these baseline predictors associated with VA outcomes may provide a more accurate assessment of the potential benefit from treatment with ranibizumab or bevacizumab and provide further insight into the mechanisms of action of these anti-VEGF drugs. In addition, identifying these predictors may allow refinement of inclusion criteria for clinical trials evaluating novel therapies for neovascular AMD.

Materials and Methods

Details of the study design and methods have been reported previously[5] and are available at ClinicalTrials.gov (NCT00593450). Only the major features related to the evaluation of predictors for visual outcomes are described in this article.

Study Participants

The institutional review board associated with each center approved the study protocol, and a written consent form was obtained from each participant. Participants were enrolled from 43 clinical centers in the United States between 2008 and 2009 and randomized to 1 of the 4 treatment groups: (1) ranibizumab monthly, (2) bevacizumab monthly, (3) ranibizumab PRN, and (4) bevacizumab PRN. The study enrollment criteria included an age of ≥50 years, the study eye (1 eye per patient) had untreated active CNV due to AMD, and VA between 20/25 and 20/320 on electronic VA testing.[6] The presence of active CNV, as seen on fluorescein angiography, and fluid, as seen on time-domain OCT, located either within or below the retina or below the retinal pigment epithelium (RPE), were required to establish the presence of active CNV. Neovascularization or its sequelae (i.e., pigment epithelium detachment, subretinal or sub-RPE hemorrhage, blocked fluorescence, macular edema, or intraretinal, subretinal, or sub-RPE fluid) needed to be under the fovea.

Study Procedures

During the initial visit, participants provided information about demographic characteristics and medical history. Certified photographers followed a standard protocol for field definition and image sequencing to obtain stereoscopic, color fundus photographs, and fluorescein angiograms. Photographs from all clinical centers were digital except photographs from 1 center (film-based). Optical coherence tomography was obtained with a Stratus (v. 4.0 or higher) time-domain OCT machine (Carl Zeiss Meditec, Dublin, CA). Certified OCT imagers followed a standard protocol that included fast macular thickness map and macular thickness map protocols. Each protocol included 6 radial lines of 6-mm length placed across the fovea center at 30-degree rotational increments, with 128 A-scans per line for fast macular thickness map and 512 A-scans per line for macular thickness map.

Two masked trained readers in the CATT Fundus Photograph Reading Center independently evaluated baseline fundus photographs and fluorescein angiograms. Discrepancies between 2 trained readers were adjudicated between the readers and director of the Photograph Reading Center. Qualitative evaluations of lesion characteristics included identification of the lesion location, lesion type, lesion composition, retinal angiomatous proliferans (RAP) features, hemorrhage contiguous with the lesion, serous retinal pigment epithelial detachment (SPED), atrophic or fibrotic scars, any hemorrhage associated with lesion (not necessarily contiguous), and geographic atrophy (GA) anywhere in the macula. To be considered GA, there should be an area of hypopigmentation or hyperfluorescence of at least 250 μm in its minimum linear dimension and have 2 of the 3 following characteristics: (1) circular shape, (2) sharp borders, or (3) visibility of choroidal vessels within the area of GA. Quantitative measurements of the CNV area and the total area of CNV lesion were made using Image J, a public-domain Java-based image processing program developed by the National Institutes of Health and available free from http://rsbweb.nih.gov/ij/ (accessed March 22, 2012). The total area of the CNV lesion includes CNV and 1 or more of the following in or adjacent to the location of CNV: SPED, hemorrhage, blocked fluorescence, scar, GA, non-GA, or RPE tear. Fluid was not considered to be part of the total CNV lesion. Two trained readers independently measured the lesions; discrepancies were adjudicated if the difference was >50% of the lesion area obtained by averaging the 2 measurements or >3.0 mm^2. In addition, adjudications were performed if one reader could not grade an image and the other reader made a measurement. Quantitative measurements could not be determined because of poor-quality photographs, leakage from the edge of GA, and relatively flat occult lesions with indistinct borders.

Independent trained readers at the OCT Reading Center, masked to the treatment assignment, evaluated the time-domain OCT images with respect to the presence of fluid, location of fluid (intraretinal, subretinal, sub-RPE) (Fig 1A), foveal fluid, and RPE elevation. In addition, trained readers measured the total thickness at the foveal center point, which was subdivided into 3 measurements: thickness of retina, subretinal fluid, and subretinal tissue complex (material between Bruch's membrane and outer retina or subretinal fluid, which includes pigment epithelial detachment, CNV, blood, and fibrosis) from 6 radial fast macular thickness scans (Fig 1B). When the 2 readers disagreed on a morphologic parameter, the vertical measurement differed by more than 65 μm, or the horizontal measurement differed by more than 220 μm, a third independent senior reader resolved the discrepancy, and this arbitrated value was used as the final grade.

At baseline and at follow-up weeks 4, 12, 24, 36, and 52, certified VA examiners, masked to the treatment assignment, measured VA after refraction in both eyes using the Electronic Visual Acuity Tester following the protocol used in the Diabetic Retinopathy Clinical Research Network.[6] The VA scores (the number of letters read correctly on the Early Treatment of Diabetic Retinopathy Study chart, measured with best-corrected VA) from the Electronic Visual Acuity can range from 0 to 100, corresponding to Snellen equivalents of <20/800 to 20/10.

Data Analysis

Hypertension was defined as a systolic blood pressure of ≥160 mmHg, diastolic blood pressure of ≥95 mmHg, or current use of antihypertensive medications. The thickness of retina, subretinal fluid, and subretinal tissue complex was calculated as the average of measurements from 6 macular thickness map scans, and the total thickness at the fovea center was calculated as the sum of the 3 averages.

Most of the baseline predictors were measured with respect to the presence or absence of a particular feature (e.g., lesion features, fluid). For predictors measured on a continuous scale (e.g., VA and retinal thickness), we assessed their association with visual outcomes by modeling them as continuous measures. In addition, we classified continuous measurements into categories for easier clinical interpretation. Categorizations of continuous variables were based on the normal range (retinal thickness), quartiles of the

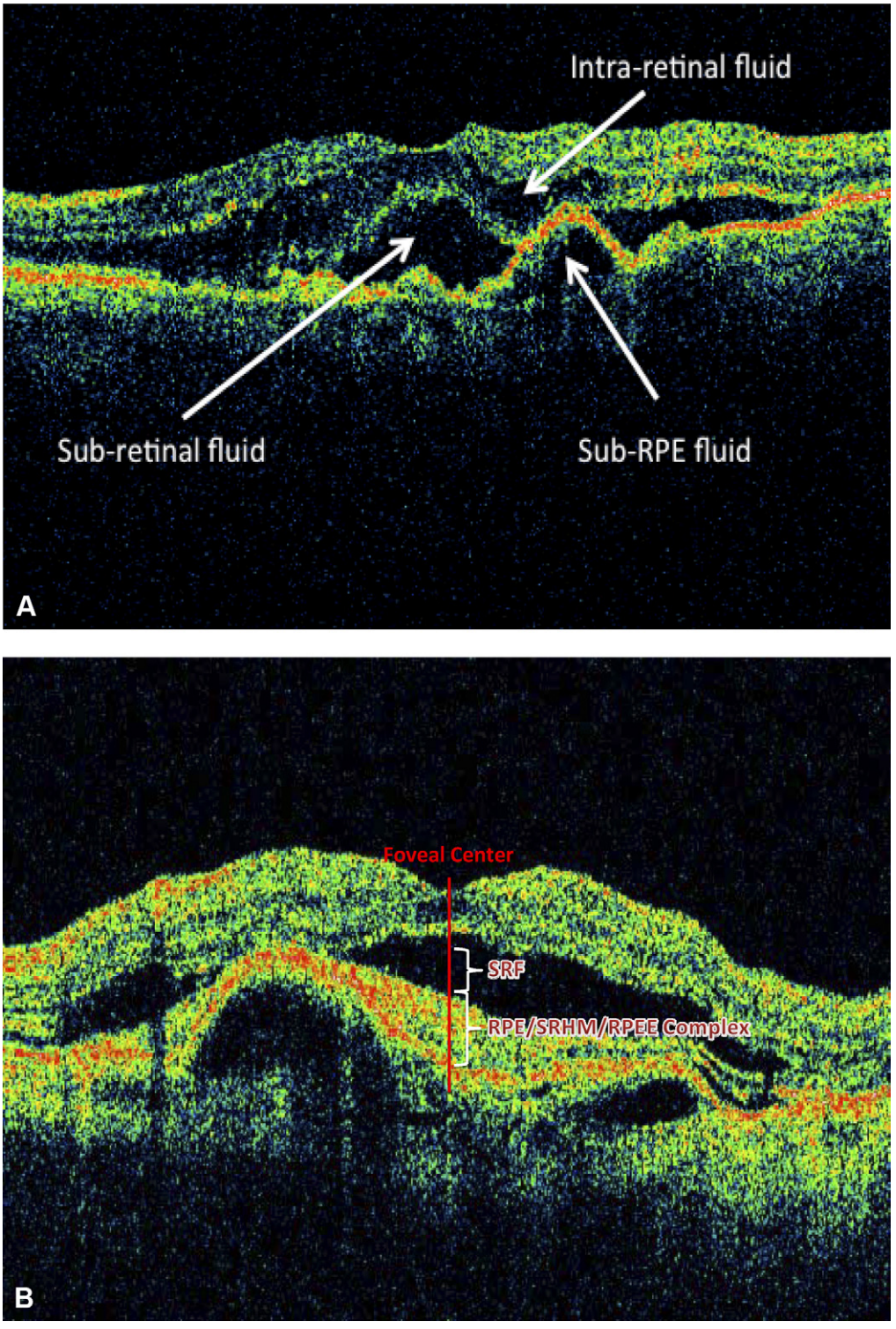

Figure 1. A, Location of optical coherence tomography (OCT) fluid (intraretinal fluid, subretinal fluid, sub-retinal pigment epithelium [RPE] fluid) at baseline. **B,** The OCT retinal layers and total retinal thickness at fovea center. RPEE = RPE elevation; SHRM = subretinal hyper-reflective material; SRF = subretinal fluid.

distribution (total fovea thickness), or clinically relevant cut-points (baseline VA).

We analyzed predictors for 3 VA outcomes at 1 year, including VA score, change in VA score from baseline, and a gain of ≥3 lines (i.e., 15 letters) from baseline. The predictors for a ≥3-line loss were not analyzed because only 68 patients (6%) had a ≥3-line loss from baseline, which did not provide enough statistical power to assess the predictors of a ≥3-line loss.

Each predictor was first evaluated by univariate analysis (without adjustment for other covariates), using generalized linear models for VA and change in VA and logistic regression models for a ≥3-line gain from baseline (yes/no). The predictors with a *P* value < 0.20 in the univariate analysis were included in a multivariate analysis so that the independent effect of each predictor could be assessed. Interaction between treatment group and each candidate predictor was first evaluated in models containing only the treatment group, the predictor, and the treatment group by predictor interaction term. The interaction term that had a *P* value ≤ 0.05 was retained for the multivariate analysis. The final multivariate model was created by applying a backward selection procedure that retained only those predictors and interaction terms with a *P* value ≤ 0.05, with the exception of treatment group, which was included in all multivariate models. Adjusted means of VA and VA change were calculated on the basis of the final multivariate linear models, and adjusted odds ratios (ORs) of a ≥3-line gain and their 95% confidence intervals (CIs) were calculated on the basis of the final multivariate logistic regression model. All data analyses were performed using SAS (version 9.2, SAS Inc., Cary, NC).

Results

Baseline Characteristics of Study Participants

The CATT enrolled 1185 participants. Among 1161 participants who survived 1 year after enrollment, VA was measured at 1 year in 1105 (95.2%), and these data were included in the analyses. The demographic characteristics of these 1105 participants are shown in the 2 left columns of Table 1 (available at http://aaojournal.org). The mean age was 79 years (standard deviation [SD], 8 years), 62% were women, 9% were current cigarette smokers, 69% had hypertension, and 17% had diabetes.

The mean baseline VA score was 61 letters (Snellen equivalent = 20/63; SD, 13) in the study eye and 66 letters (Snellen equivalent = 20/50; SD, 27) in the fellow eye (Table 2, available at http://aaojournal.org). The median CNV area at baseline was 3.0 mm^2 (range, 0.03–28.7 mm^2), and the median total area of CNV lesion was 4.3 mm^2 (range, 0.05–56.9 mm^2). On the basis of the evaluation of fundus photographs and fluorescein angiograms, 71% had a subfoveal lesion, 59% of lesions were occult only, and half of the lesions had CNV only without other lesion components (SPED, fibrosis scar, atrophy scar, hemorrhage, or blocked fluorescence).

The baseline OCT features are shown in Table 3 (available at http://aaojournal.org). The mean thicknesses of retina, subretinal fluid, and subretinal tissue complex were 218 μm (SD, 107 μm), 32 μm (SD, 70 μm), and 210 μm (SD, 176 μm), respectively. The mean total fovea thickness was 460 μm (SD, 190 μm). The morphologic fluid location also was determined. Subretinal fluid was most common (82%), followed by intraretinal fluid (75%) and sub-RPE fluid (49%). At baseline, all 3 types of fluid were observed in 30% of study eyes, and 82% of study eyes had fluid involving the foveal center point at baseline. An elevation in RPE (which could be from drusen or pigment epithelial detachment with fluid or reflective material beneath the elevation) was present in 85% of study eyes.

The VA score at 1 year was not available for 80 participants (6.8%). Among these participants, 24 (2.0%) died before week 52 and the remainder (4.8%) missed the 1-year measurement. The participants with missing VA at 1 year were generally comparable to participants with available VA at 1 year (data not shown) with respect to the baseline demographic, ocular, and OCT characteristics, except that participants without a VA score at 1 year were significantly older at baseline (mean 82 vs. 79 years; $P=0.002$).

Predictors for Visual Acuity Score at 1 Year

The mean VA score at 1 year after treatment was 68 letters (Snellen equivalent = 20/40) and did not differ among treatment groups ($P=0.45$). The univariate results for the predictors of the VA score at 1 year are shown in Table 1 (available at http://aaojournal.org) for baseline participant factors, the baseline ocular and fundus characteristics of the study eye are shown in Table 2 (available at http://aaojournal.org), and the baseline OCT features are shown in Table 3 (available at http://aaojournal.org).

When the baseline factors associated with $P < 0.20$ in the these univariate analyses were considered simultaneously in the multivariate analysis (Table 4), the significant predictors of worse VA score at 1 year were older age ($P=0.0006$), worse baseline VA score ($P < 0.0001$), larger CNV area ($P=0.001$), predominantly or minimally classic lesion ($P < 0.001$), GA ($P=0.02$), thicker total thickness at the fovea ($P=0.01$), and presence of RPE elevation on OCT ($P=0.005$). There were no statistically significant interactions between treatment groups and any of these predictors.

Predictors for Visual Acuity Score Change from Baseline at 1 Year

One year after treatment, the mean VA score improved 7 letters from baseline and did not differ among the 4 treatment groups ($P=0.16$). The univariate results for the predictors of the VA score change from baseline at 1 year are shown in Table 1 (available at http://aaojournal.org) for baseline participant factors, the baseline ocular and fundus characteristics of the study eye are shown in Table 2 (available at http://aaojournal.org), and the baseline OCT features are shown in Table 3 (available at http://aaojournal.org).

When baseline factors were considered simultaneously in the multivariate analysis (Table 4), the predictors of less gain in VA score at 1 year were older age ($P=0.003$), baseline VA ≥20/40 in the study eye ($P < 0.0001$), larger CNV area ($P=0.02$), absence of a RAP lesion ($P=0.03$), and presence of RPE elevation ($P=0.004$). There were no statistically significant interactions between treatment groups and any of these predictors.

Predictors for ≥3-Line (i.e., 15-Letter) Gain from Baseline at 1 Year

At 1 year, 327 participants (29.6%) gained ≥3 lines in VA from baseline. The univariate results for the predictors of the proportion with a gain of ≥3 lines at 1 year are shown in Table 1 (available at http://aaojournal.org) for baseline participant factor, the baseline ocular and fundus characteristics of the study eye are shown in Table 2 (available at http://aaojournal.org), and the baseline OCT features are shown in Table 3 (available at http://aaojournal.org).

When baseline factors were considered simultaneously in the multivariate logistic regression (Table 5), older age was associated with a lower likelihood of ≥3 lines gained ($P=0.008$), with an OR of 0.4 (95% CI, 0.3–0.7) for age 80–89 years compared with age 50–69 years. In the study eye, better VA at baseline was associated with a decreased likelihood of gaining ≥3 lines ($P < 0.001$). Compared with the study eyes with VA 20/50 to 20/80, the OR (95% CI) for gaining ≥3 lines was 0.11 (0.07–0.18) for eyes with a VA of ≥20/40, 2.60 (1.80–3.77) for eyes with a baseline VA of 20/100 to 20/160, and 1.7 (0.97–2.07) for eyes with a VA of 20/200 to 320. However, worse VA in the fellow eye was associated with a decreased likelihood of gaining ≥3 lines in the study eye ($P=0.005$). The OR was 0.5 (95% CI, 0.4–0.8) for fellow eyes

Table 4. Multivariate Analysis for Visual Acuity and its Change from Baseline at 1 Year

Baseline Characteristics	N	VA Score (Letters) at 1 Yr*		VA Score Change (Letters) from Baseline at 1 Yr†	
		Adjusted Mean (SE)	P *Value*	*Adjusted Mean (SE)*	P *Value*
Age (yrs)					
50–69	131	72.1 (1.3)	0.0006	10.8 (1.3)	0.003
70–79	387	68.8 (0.7)		8.2 (0.8)	
80–89	512	66.4 (0.6)		5.8 (0.6)	
≥90	75	67.2 (1.7)		6.2 (1.7)	
Baseline VA in study eye					
68–82 letters, 20/25–20/40	397	76.4 (0.8)	<0.0001	3.3 (0.7)	<0.0001
53–67 letters, 20/50–20/80	414	69.1 (0.7)		8.4 (0.7)	
38–52 letters, 20/100–20/160	223	59.0 (1.0)		11.9 (1.0)	
23–37 letters, 20/200–20/320	71	41.7 (1.8)		7.9 (1.7)	
Baseline area of CNV (mm^2)					
≤2.54	443	69.9 (0.7)	0.001	8.7 (0.7)	0.02
>2.54 to ≤5.08	219	68.0 (1.0)		7.5 (1.0)	
>5.08 to ≤10.2	207	67.0 (1.0)		6.7 (1.0)	
>10.2	103	64.5 (1.4)		4.2 (1.4)	
Cannot measure	133	64.9 (1.4)		4.8 (1.4)	
Lesion type					
Predominantly or minimally classic	431	65.8 (0.7)	0.0003	—	
Occult only	650	69.3 (0.6)		—	
RAP lesion					
No	966	—		6.9 (0.5)	0.03
Yes	118	—		10.1 (1.3)	
GA					
None/questionable	1027	68.2 (0.5)	0.02	—	
Present	76	63.9 (1.7)		—	
Total foveal thickness (μm)					
First quartile (≤325)	277	68.0 (0.9)	0.01	—	
Second quartile (>325 to ≤425)	285	69.7 (0.9)		—	
Third quartile (>425 to ≤550)	253	68.7 (0.9)		—	
Fourth quartile (>550)	285	65.5 (0.9)		—	
RPE elevation					
No	145	71.2 (1.2)	0.005	10.5 (1.2)	0.004
Yes	944	67.5 (0.5)		6.8 (0.5)	
Treatment Group					
Ranibizumab monthly	284	69.4 (0.9)	0.045	8.6 (0.9)	0.07
Bevacizumab monthly	265	68.6 (0.9)		7.9 (0.9)	
Ranibizumab PRN	285	67.5 (0.9)		6.9 (0.9)	
Bevacizumab PRN	271	66.2 (0.9)		5.5 (0.9)	

CNV = choroidal neovascularization; GA = geographic atrophy; RAP = retinal angiomatous proliferans; RPE = retinal pigment epithelium; SE = standard error; VA = visual acuity.
*A total of 1061 participants were included in the final multivariate model, and 44 patients were excluded because of missing value for ≥1 predictors.
†A total of 1068 participants were included in the final multivariate model, and 37 patients were excluded because of missing value for ≥1 predictors.
—Predictor was not included in the final multivariate model because it was not statistically significant.

with a VA of ≤20/50 when compared with fellow eyes with VA ≥20/20. Larger area of CNV was associated a lower likelihood of 3 lines gained (P=0.04), and the eyes in which the area of CNV could not be measured were least likely to gain ≥3 lines (OR, 0.5; 95% CI, 0.3–0.8). The presence of a RAP lesion was associated with an increased likelihood of 3 lines gained (OR, 1.9; 95% CI, 1.2–3.1). Total thickness at the fovea was associated with ≥3 lines gained (P=0.004). However, the relationship was not monotonic. The highest likelihood of ≥3 lines gained occurred when total foveal thickness was in the second quartile (325–425 μm), with an OR of 1.7 (95% CI, 1.1–2.7), and the lowest likelihood of ≥3 lines gained occurred in the fourth quartile (>550 μm) (OR, 0.8; 95% CI, 0.5–1.3). The presence of RPE elevation was associated with a decreased likelihood of 3 lines gained (P=0.002). The proportion with 3 lines gained among the 4 treatment groups was statistically significant in the multivariate analysis (P=0.04). The 2 groups with as-needed treatment had a decreased likelihood of ≥3 lines gained with an OR of 0.6 (95% CI, 0.4–0.9) when compared with ranibizumab monthly. There were no statistically significant interactions between treatment group and any of the described factors for gaining ≥3 lines of VA.

Discussion

Our evaluation of the predictors for visual outcomes in response to treatment with ranibizumab or bevacizumab is

Table 5. Analysis for ≥3-Line Gain from Baseline at 1 Year

Baseline Characteristics	N	≥3-Line Gain, n (%)	Adjusted OR (95% CI)*	*P* Value
Age (yrs)				
50–69	131	51 (38.9)	1.00	0.008
70–79	387	107 (27.6)	0.62 (0.37–1.02)	
80–89	512	141 (27.5)	0.44 (0.27–0.73)	
≥90	75	28 (37.3)	0.67 (0.32–1.41)	
Baseline VA in study eye				
68–82 letters, 20/25–20/40	397	28 (7.1)	0.11 (0.07–0.18)	<0.0001
53–67 letters, 20/50–20/80	414	150 (36.2)	1.00	
38–52 letters, 20/100– 20/160	223	119 (53.4)	2.60 (1.80–3.77)	
23–37 letters, 20/200–20/320	71	30 (42.3)	1.73 (0.97–2.07)	
Baseline VA in fellow eye				
83–100 letters, ≥20/20	331	110 (33.2)	1.00	0.005
68–82 letters, 20/25–20/40	433	135 (31.2)	0.90 (0.63–1.30)	
0–67 letters, ≤20/50	341	82 (24.0)	0.53 (0.35–0.80)	
Baseline area of CNV (mm^2)				
≤2.54	443	145 (32.7)	1.00	0.04
>2.54 to ≤5.08	219	63 (28.8)	0.71 (0.47–1.07)	
>5.08 to ≤10.2	207	65 (31.4)	0.91 (0.60–1.37)	
>10.2	103	24 (23.3)	0.67 (0.38–1.18)	
Cannot measure	133	30 (22.6)	0.44 (0.25–0.76)	
RAP lesion				
No	966	276 (28.6)	1.00	0.006
Yes	118	48 (40.7)	1.94 (1.21–3.10)	
Total foveal thickness (μm)				
First quartile (≤325)	277	59 (21.3)	1.00	0.004
Second quartile (>325 to ≤425)	285	95 (33.3)	1.74 (1.11–2.72)	
Third quartile (>425 to ≤550)	253	83 (32.8)	1.15 (0.73–1.82)	
Fourth quartile (>550)	285	89 (31.2)	0.80 (0.50–1.27)	
RPE elevation				
No	145	61 (42.1)	1.00	0.002
Yes	944	258 (27.3)	0.52 (0.34–0.79)	
Treatment group				
Ranibizumab monthly	284	97 (34.2)	1.00	0.04
Bevacizumab monthly	265	83 (31.3)	0.80 (0.53–1.22)	
Ranibizumab PRN	285	71 (24.9)	0.56 (0.37–0.86)	
Bevacizumab PRN	271	76 (28.0)	0.63 (0.41–0.96)	

CI = confidence interval; CNV = choroidal neovascularization; OR = odds ratio; RAP = retinal angiomatous proliferans; RPE = retinal pigment epithelium; VA = visual acuity.
*A total of 1066 participants were included in the final multivariate model, and 39 patients were excluded because of missing value for ≥1 predictors.

based on prospectively collected clinical data and central grading of images performed in a multicenter randomized clinical trial with a large sample size and broad eligibility criteria. Some predictors of VA improvement identified in the CATT, such as younger age, better baseline VA, and smaller CNV area, are consistent with predictors identified from 2 pivotal clinical trials of ranbizumab.[7–9] In addition, we have identified several new predictors of vision outcomes, including total foveal thickness and RPE elevation on OCT. These identified predictors were the same across all 4 treatment groups of the CATT.

Baseline VA in treated eyes was associated with all 3 visual outcomes, but in different ways. Eyes with worse baseline VA had lower mean VA scores at 1 year. However, the mean increase in VA and the proportion with a ≥3-line improvement were greatest for the eyes with a baseline VA of 20/100 to 20/160 and lowest for the eyes with a VA of ≥20/40. This may be explained by the fact that eyes of participants with a median age of 81 years and a baseline VA of ≥20/40, particularly those with a VA of 20/25 or 20/32, are unlikely to improve beyond 20/20 (1 or 2 lines of VA improvement) even if all visual loss imposed by CNV is eradicated. Although eyes with worse baseline VA had greater improvement by 1 year, the average improvement was not sufficient to restore VA at 1 year to the same level for all participants. For example, although eyes with a baseline VA of 20/100 to 20/160 improved on average 12 letters, their average VA at 1 year was only 59 letters (20/63), whereas eyes with a baseline VA of 20/25 to 20/40 improved on average only 3 letters but had an average VA at 1 year approximately 3 lines better (76 letters or 20/32). The detection of CNV before there is a large loss in vision remains important even in this era of highly effective treatment.

The CATT evaluated the relationship of baseline OCT features with visual outcomes in response to anti-VEGF treatment. Univariate analysis showed that several OCT features were associated with visual outcomes, including the presence of fluid and thickness of different layers of the retina, subretinal

space, and sub-RPE space. However, after adjusting for demographic characteristics, baseline VA, and other ocular features through multivariate analyses, only greater total foveal thickness and RPE elevation were independently associated with a lower proportion gaining ≥3 lines of VA.

An elevation in RPE anywhere in the macula was one of the OCT factors most strongly associated with vision outcomes. Elevation in RPE was common (85%) and independently associated with worse VA, lower mean increase in VA score, and a lower proportion with ≥3 lines gained in VA. This finding is unexpected. Perhaps the eyes without RPE elevation at baseline had unimpaired RPE function and thus were more likely to have VA improvement than the majority of eyes with RPE elevation. Eyes with RPE elevation include those with sub-RPE hemorrhage, neovascularization or fibrosis, or drusen alone, features that could signal abnormal RPE functional activity and may have consequently adversely affected VA. In the MARINA and ANCHOR studies, increased RPE abnormalities observed on color photographs were strongly associated with VA loss.[9] Together, these findings suggest that RPE function may play an important role in the VA response to anti-VEGF treatment.

Subfoveal hemorrhage secondary to CNV in AMD has a poor VA prognosis if untreated.[10] In the CATT, the presence of hemorrhage and larger size of hemorrhage at baseline were associated with worse VA at 1 year and less gain in VA. However, this association was statistically significant only in the univariate analysis and not after adjustment for other baseline predictors, including baseline VA. Eyes with hemorrhage may be expected to improve, consistent with findings from another study.[11]

It is important to note that all subgroups of participants examined in this study had improvement in mean VA after treatment with either drug or either regimen. Even the oldest patients or those with larger lesions experienced some improvement in vision, and it is just as important to treat these patients despite potentially reduced expectations.

In conclusion, the predictors of visual outcomes did not differ between ranibizumab and bevacizumab or between dosing regimens in the CATT. The results of this study confirmed the predictors (age, baseline VA, lesion size) of VA improvement established from the previous clinical trials involving ranibizumab. This comprehensive evaluation of predictors in CATT also identified total foveal thickness and RPE elevation as independently associated with VA outcomes. Early detection of CNV remains important for maximizing VA after treatment. In addition, these predictors should not be used to justify reduced interest in treatment because all subgroups experienced some benefit in VA from treatment. Instead, the identification of these predictors allows ophthalmologists and their patients to adjust their VA expectations regarding vision on the basis of the patient's characteristics at the time of initial treatment. Finally, these predictors may help define eligibility criteria most likely to produce favorable or adverse VA outcomes in future clinical trials for neovascular AMD.

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Footnotes and Financial Disclosures

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*A listing of the CATT Research Group is available at http://aaojournal.org.

This article contains online-only material. The following should appear online only: Tables 1–3 and the CATT Research Group.

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