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

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Abstract

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

Design—Cohort study within the Comparison of AMD Treatments Trials.

Participants—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 either a monthly or as-needed schedule. Masked readers evaluated fundus morphology, and features on optical coherence tomography (OCT). VA was measured using electronic visual acuity testing. Independent predictors were identified using regression techniques.

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

Results—At one year, the mean VA score was 68 letters, mean improvement from baseline was 7 letters, and 28% of participants gained 3-line. 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).

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Geographic atrophy (GA) was associated with worse VA (64 vs. 68 letters, $p=0.02$). Eyes with total foveal thickness in the 2nd quartile (325 – 425 microns) had the best visual acuity ($p=0.01$) and were most likely to gain 3 lines ($p=0.004$). Predictors did not vary by treatment group.

Conclusion—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 OCT were independently associated with less improvement in VA at 1 year.

INTRODUCTION

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

This report provides a comprehensive evaluation of baseline predictors for VA outcomes at 1 year, including demographic characteristics and medical history, ocular factors and CNV lesion features determined from fundus photographs, fluorescein angiograms, and 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.

METHODS

Details on the study design and methods have been reported previously⁵ and on ClinicalTrials.gov (NCT00593450). Only the major features related to the evaluation of predictors for visual outcomes are described here.

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 through 2009, and randomized to one of the four treatment groups: (1) ranibizumab monthly; (2) bevacizumab monthly; (3) ranibizumab as needed (pro re nata, PRN); and (4) bevacizumab PRN. The study enrollment criteria included age of 50 or older, the study eye (one 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 were required to establish the presence of active CNV. Either neovascularization or its sequela, i.e., pigment epithelium detachment, subretinal or sub-retinal pigment

epithelium (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 on 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 one center (film-based). Optical coherence tomography (OCT) was obtained with a Stratus (version 4.0 or higher) time domain OCT machine (Carl Zeiss Meditec, Dublin, California). Certified OCT imagers followed a standard protocol that included fast macular thickness map (FMTM) and macular thickness map (MTM) 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 FMTM and 512 A-scans per line for MTM.

Two masked trained readers in the CATT Fundus Photographic Reading Center independently evaluated baseline fundus photographs and fluorescein angiograms. Discrepancies between two 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 anywhere in the macula. To be considered GA, there should be an area of hypopigmentation and/or hyperfluorescence of at least 250 μ 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 of the total area of CNV lesion were made using Image J, a public domain Java image processing program developed by the National Institute of Health and available as a free software from <http://rsbweb.nih.gov/ij/> (accessed on March 22, 2012). Total area of CNV lesion include CNV and/or one or many of the following in or adjacent to the location of CNV: SPED, hemorrhage, blocked fluorescence, scar, geographic atrophy, non-geographic atrophy 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 two measurements or >3.0 mm². 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 a GA and in relatively flat occult lesions whose borders were indistinct.

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 (intra-retinal, sub-retinal, sub-RPE) of fluid (Figure 1A), foveal fluid and RPE elevation. In addition, trained readers measured the total thickness at the foveal center point which was subdivided into three measurements: thickness of retina, subretinal fluid, and subretinal tissue complex (material between Bruch's membrane and outer retina or subretinal fluid which includes PED, CNV, blood and fibrosis) from 6 radial fast macular thickness scans (Figure 1B). When the two readers disagreed on a morphological parameter, or when the vertical measurement differed by more than 65 micrometers, or the horizontal measurement differed by more than 220 micrometers, 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 visual acuity examiners, masked to the treatment assignment, measured visual acuity after refraction in both eyes using the Electronic Visual Acuity Tester (EVA) following the protocol used in the Diabetic Retinopathy Clinical Research Network.⁶ The VA scores (the number of letters read correctly on the ETDRS chart, measured with best-corrected visual acuity) from EVA can range from 0 to 100, corresponding to Snellen equivalents of worse than 20/800 to 20/10.

Data Analysis

Hypertension was defined as systolic blood pressure (BP) of 160 mmHg or more, diastolic BP of 95 mmHg or more, 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 (such as 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 either the normal range (retinal thickness), quartiles of the distribution (total fovea thickness), or clinically relevant cut-points (baseline visual acuity).

We analyzed predictors for three VA outcomes at 1 year including: VA score, change in VA score from baseline, and 3-lines (i.e., 15 letters) gain from baseline. The predictors for 3-lines loss were not analyzed because only 68 (6%) of patients had 3-lines loss from baseline, it didn't provide enough statistical power to assess the predictors for 3-lines 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 using logistic regression models for 3-lines 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 treatment group by predictor interaction term. The interaction term that had a p-values > 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 changed were calculated based on the final multivariate linear models, and adjusted odds ratios (OR) of 3-lines gain and their 95% confidence intervals (95% CI) were calculated based on the final multivariate logistic regression model. All data analyses were performed using SAS (v9.2, SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics of Study Participants

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

The mean baseline VA score in the study eye was 61 letters (Snellen equivalent =20/63) (SD=13), and in the fellow eye was 66 letters (Snellen equivalent =20/50) (SD=27) (Table 2, available at <http://aaojournal.org>). The median CNV area at baseline was 3.0 mm² (range: 0.03 to 28.7 mm²), and the median total area of CNV lesion was 4.3 mm² (range: 0.05 to 56.9 mm²). Based on 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 thickness of retina, subretinal fluid, and subretinal tissue complex was 218 microns (SD = 107 microns), 32 microns (SD=70 microns), and 210 microns (SD=176 microns) respectively. The mean total fovea thickness was 460 microns (SD=190 microns). The morphological fluid location was also determined. Subretinal fluid was most common (82%), followed by intraretinal fluid (75%), and sub-RPE fluid (49%). At baseline, all three types of fluid were observed in 30% of study eyes, and 82% of study eyes had fluid involving the foveal center point at baseline. RPE elevation (which could be from drusen, or PED 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 (6.8%) participants. Among these participants, 24 (2.0%) died before week 052 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 one year (data not shown) with respect to the baseline demographic, ocular and OCT characteristics, except that participants without VA score at 1 year were significantly older at baseline (mean 82 vs. 79 years, $p=0.002$).

Predictors for VA score at 1 year

The mean VA score at one 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 one year were presented in Table 1 (available at <http://aaojournal.org>) for baseline participant factors, in Table 2 (available at <http://aaojournal.org>) for the baseline ocular and fundus characteristics of the study eye, and in Table 3 (available at <http://aaojournal.org>) for the baseline OCT features.

When the baseline factors associated with $p<0.20$ in the above 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 ($p<0.001$), geographic atrophy ($p=0.02$), 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 group and any of these predictors.

Predictors for VA 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 four treatment groups ($p=0.16$). The univariate results for the predictors of the VA score change from baseline at one year were presented in Table 1 (available at <http://aaojournal.org>) for baseline participant factors, in Table 2 (available at <http://aaojournal.org>) for the baseline ocular and fundus characteristics of the study eye, and in Table 3 (available at <http://aaojournal.org>) for the baseline OCT features.

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 or better in 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 group and any of these predictors.

Predictors for ≥ 3 -line (i.e., 15 letters) gain from baseline at 1 year

At one year, 327 (29.6%) participants gained 3 lines or more in visual acuity from baseline. The univariate results for the predictors of the proportion with ≥ 3 lines gain at one year were presented in Table 1 (available at <http://aaojournal.org>) for baseline participant factor, in Table 2 (available at <http://aaojournal.org>) for the baseline ocular and fundus characteristics of the study eye, and in Table 3 (available at <http://aaojournal.org>) for the baseline OCT features.

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 odds ratio (OR) of 0.4 (95% CI: 0.3 – 0.7) for age 80–89 years as compared with 50–69 years old. In the study eye, better VA at baseline was associated with a decreased likelihood of gaining ≥ 3 lines ($p<0.001$). Compared to 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 VA 20/40 or better, 2.60 (1.80 – 3.77) for eyes with baseline VA of 20/100 to 20/160, and 1.7 (0.97 – 2.07) for 20/200–320. 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 with 20/50 or worse when compared to fellow eyes with VA 20/20 or better. 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). Presence of RAP lesion was associated with 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 2nd quartile (325–425 microns) with OR of 1.7 (95% CI: 1.1–2.7), and lowest likelihood of ≥ 3 lines gained occurred in the 4th quartile (>550 microns) (OR=0.8, 95% CI: 0.5–1.3). The presence of RPE elevation was associated with 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 two 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 to ranibizumab monthly. There were no statistically significant interactions between treatment group and any of the above 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 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 CATT, such as younger age, better baseline VA, smaller CNV area, are consistent with predictors identified from two pivotal clinical trials of ranibizumab.^{7,8,9} 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 four treatment groups of CATT.

Baseline VA in treated eyes was associated with all three 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 ≥ 3 -line improvement were greatest for the

group of eyes with baseline VA 20/100 to 20/160, and were lowest for the eyes with VA 20/40 or better. This may be explained by the fact that eyes of participants with median age of 81 years having baseline VA 20/40 or better, particularly those having 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 visual acuity 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, while eyes with 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 baseline VA of 20/25 to 20/40 improved on average only 3 letters but had 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 extremely important even in this era of highly effective treatment.

CATT evaluated the relationship of baseline OCT features with visual outcomes in response to anti-VEGF treatment. Univariate analysis showed 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 visual acuity, and other ocular features through multivariate analyses, only greater total foveal thickness and RPE elevation were independently associated with a lower proportion gaining 3 or more lines of VA.

RPE elevation anywhere in the macula was one of the OCT factors most strongly associated with vision outcomes. RPE elevation 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 were thus 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 could have consequently adversely affected visual acuity. In MARINA and ANCHOR, increased RPE abnormalities observed on color photographs was strongly associated with VA loss.⁹ Together, these findings suggest that RPE function may play an important role in the visual acuity response to anti-VEGF treatment.

Sub-foveal hemorrhage secondary to CNV in AMD, if untreated, has a poor visual acuity prognosis.¹⁰ In CATT, the presence of hemorrhage and larger size of hemorrhage at baseline were associated with worse VA at 1 year and less gain in visual acuity. 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 other studies.¹¹

It is important to note that all subgroups of participants examined in this paper, had improvement in mean visual acuity 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 CATT. The results of this paper 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 visual acuity after treatment. In addition, these predictors should not be used to justify reduced interest in

treatment since all subgroups experienced some benefit in visual acuity from treatment. Instead, the identification of these predictors allow ophthalmologists and their patients to adjust their visual acuity expectations regarding vision based on 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 visual acuity outcomes in future clinical trials for neovascular AMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Figure 1A: Location of OCT fluid (intra-retinal fluid, sub-retinal fluid, sub-RPE fluid) at baseline.

Figure 1B: OCT retinal layers and total retinal thickness at fovea center.

OCT= optical coherence tomography, SRF=Sub-retinal fluid, RPE= retinal pigment epithelium; SRHM= subretinal hyper-reflective material; RPEE= RPE elevation.

Table 1
Univariate analysis for association of baseline participant characteristics with visual outcomes at 1 year

	# of Subjects at 1 Year (N=1105)		VA score at 1 year		Change in VA score at 1 year		3-lines gain from baseline at 1 year	
Baseline Participant Characteristics	n(%)	Mean (SE)	P-value*	Mean (SE)	P-value*	n(%)	P-Value [†]	
Age (years)			<0.001		0.02		0.03	
50–69	131 (11.9%)	74.6 (1.5)		10.9 (1.3)		51 (38.9%)		
70–79	387 (35.0%)	70.3 (0.9)		7.3 (0.7)		107 (27.6%)		
80–89	512 (46.3%)	65.2 (0.8)		6.4 (0.7)		141 (27.5%)		
90	75 (6.8%)	64.0 (2.0)		7.6 (1.7)		28 (37.3%)		
As continuous (1 year increase)		−0.50 (0.07)	<0.001	−0.18 (0.06)	0.002		0.11	
Gender			0.31		0.30		0.25	
Female	684 (61.9%)	68.4 (0.7)		7.7 (0.6)		211 (30.8%)		
Male	421 (38.1%)	67.3 (0.9)		6.7 (0.7)		116 (27.6%)		
Cigarette Smoking			0.75		0.93		0.74	
Never	475 (43.0%)	68.2 (0.8)		7.4 (0.7)		140 (29.5%)		
Quit	536 (48.5%)	68.1 (0.8)		7.3 (0.6)		156 (29.1%)		
Current	94 (8.5%)	66.7 (1.8)		6.8 (1.5)		31 (33.0%)		
Hypertension			0.03		0.41		0.32	
No	346 (31.3%)	69.7 (1.0)		7.9 (0.8)		95 (27.5%)		
Yes	759 (68.7%)	67.3 (0.7)		7.1 (0.5)		232 (30.6%)		
Diabetes			0.67		0.73		0.39	
No	915 (82.8%)	68.1 (0.6)		7.4 (0.5)		276 (30.2%)		
Yes	190 (17.2%)	67.5 (1.3)		7.0 (1.1)		51 (26.8%)		
Treatment Group			0.45		0.16		0.09	
Ranibizumab Monthly	284 (25.7%)	68.8 (1.05)		8.5 (0.8)		97 (34.2%)		
Bevacizumab Monthly	265 (24.0%)	68.4 (1.09)		8.0 (1.0)		83 (31.3%)		
Ranibizumab as needed	285 (25.8%)	68.4 (1.05)		6.8 (0.8)		71 (24.9%)		
Bevacizumab as needed	271 (24.5%)	66.5 (1.08)		5.9 (1.0)		76 (28.0%)		

VA=Visual Acuity; SE = Standard Error;

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* P-value was from one-way analysis of variance (ANOVA).
† P value was from Monte-Carlo fisher exact test.
P-value in the parenthesis was calculated with category of unknown into comparison, while P-value not in the parenthesis was calculated excluding category of unknown into comparison.

Table 2

Univariate analysis for association of baseline ocular and fundus characteristics with visual outcomes at 1 year

Baseline Ocular Characteristics	# of Subjects at 1 year (N=1105) n (%)	VA score at 1 year		Change in VA score at 1 year		3-lines gain from baseline at 1 year	
		Mean (SE)	P-value*	Mean (SE)	P-value*	n (%)	P-Value [†]
Baseline VA in study eye							
68–82 letters, 20/25 - 20/40	397 (35.9%)	77.7 (0.7)	<0.001	3.7 (0.7)	<0.001	28 (7.1%)	<0.001
53–67 letters, 20/50 - 20/80	414 (37.5%)	69.2 (0.7)		8.5 (0.7)		150 (36.2%)	
38–52 letters, 20/100-20/160	223 (20.2%)	57.8 (1.0)		11.4 (1.0)		119 (53.4%)	
23–37 letters, 20/200-20/320	71 (6.4%)	39.3 (1.7)		7.8 (1.7)		30 (42.3%)	
As continuous (1 letter increase)		0.79 (0.03)	<0.001	−0.22 (0.03)	<0.001		<0.001
Baseline VA in fellow eye			0.003		0.03		0.02
83–100 letters, 20/20 or better	331 (30.0%)	70.7 (1.0)		8.9 (0.8)		110 (33.2%)	
68–82 letters, 20/25-20/40	433 (39.2%)	67.5 (0.9)		7.2 (0.7)		135 (31.2%)	
0–67 letters, 20/50 or worse	341 (30.9%)	66.1 (1.0)		5.9 (0.8)		82 (24.0%)	
As continuous (1 letter increase)		0.04 (0.02)	0.051	0.04 (0.02)	0.04		0.005
Baseline CNV area (mm²)			<0.001		0.007		0.27
2.54	443 (40.1%)	70.9(0.8)	(<0.001)	8.8 (0.7)	(0.007)	145 (32.7%)	(0.11)
>2.54 to 5.08	219 (19.8%)	68.4(1.2)		7.7 (1.0)		63 (28.8%)	
>5.08 to 10.2	207 (18.7%)	66.9(1.2)		6.6 (1.0)		65 (31.4%)	
>10.2	103 (9.3%)	63.4(1.8)		3.4 (1.4)		24 (23.3%)	
Unknown	133 (12.0%)	63.2(1.5)		5.8 (1.3)		30 (22.6%)	
As continuous (every 2.54 mm ² increase)		−1.25 (0.33)	<0.001	−0.60 (0.24)	0.01		0.02
Baseline total area of CNV lesion (mm²)			<0.001		0.04		0.13
2.54	355 (32.1%)	71.3 (0.9)	(<0.001)	8.1(0.8)	(0.04)	107(30.1%)	(0.045)
>2.54 to 5.08	240 (21.7%)	69.6 (1.2)		8.7(1.0)		76(31.7%)	
>5.08 to 10.2	265 (24.0%)	66.3 (1.1)		7.3(0.9)		89(33.6%)	
>10.2	202 (18.3%)	62.7 (1.3)		5.0(1.0)		48(23.8%)	
Unknown	43 (3.9%)	68.0 (2.7)		4.3(2.2)		7 (16.3%)	
As continuous (every 2.54 mm ² increase)		−1.39 (0.21)	<0.001	−0.58 (0.18)	0.001		0.02

Baseline Ocular Characteristics	# of Subjects at 1 year (N=1105)	VA score at 1 year		Change in VA score at 1 year		3-lines gain from baseline at 1 year	
		Mean (SE)	P-value *	Mean (SE)	P-value *	n (%)	P-Value †
Location of lesion							
Not Subfoveal	299 (27.1%)	71.7 (1.0)	<0.001	7.3(0.9)	0.90	77(25.8%)	0.08
Subfoveal	788 (71.3%)	66.5 (0.6)		7.4(0.5)	(0.48)	248(31.5%)	(0.04)
Unknown	18 (1.6%)	72.1 (4.2)		3.2(3.5)		2 (11.1%)	
Lesion type							
Predominantly or Minimally classic	431 (39.0%)	64.2 (0.9)	<0.001	7.4(0.7)	0.94		<0.001
Occult only	650 (58.8%)	70.4 (0.7)		7.3(0.6)	(0.83)	156(36.2%)	(0.001)
Unknown	24 (2.2%)	71.6 (3.6)		5.5(3.0)		167(25.7%)	
Lesion Composition							
CNV only	560 (50.7%)	69.0 (0.8)	0.19	6.9(0.6)	0.09	4(16.7%)	0.003
CNV and hemorrhage	286 (25.9%)	66.9 (1.1)		7.4(0.9)	(0.08)	152(27.1%)	(0.001)
CNV and blocked fluorescence	76 (6.9%)	67.1 (2.1)		6.5(1.7)		92(32.2%)	
CNV and SPED	47 (4.3%)	70.2 (2.6)		5.9(2.2)		22(28.9%)	
CNV and others	121 (11.0%)	65.4 (1.6)		10.8(1.3)		8(17.0%)	
Unknown	15 (1.4%)	71.2 (4.6)		2.4(3.8)		52(43.0%)	
RAP lesion							
No	966 (87.4%)	67.6 (0.6)	0.13	7.0(0.5)	0.02	1(6.7%)	0.008
Yes	118 (10.7%)	70.3 (1.7)	(0.15)	10.3(1.4)	(0.06)	276(28.6%)	(0.009)
Unknown	21 (1.9%)	72.7 (3.9)		5.7(3.2)		48(40.7%)	
Hemorrhage contiguous with lesion							
No	699 (63.3%)	68.7 (0.7)	0.07	6.9(0.6)	0.11	3(14.3%)	0.007
Yes	388 (35.1%)	66.7 (0.9)		8.4(0.8)		190(27.2%)	(0.002)
Unknown	18 (1.6%)	70.1 (4.2)		2.3(3.5)		136(35.1%)	
Blocked fluorescence lesion							
No	935 (84.6%)	68.2 (0.6)	0.38	7.1(0.5)	0.08	1 (5.6%)	0.003
Yes	157 (14.2%)	66.8 (1.4)	(0.47)	9.2(1.2)	(0.13)	263 (28.1%)	(0.002)
Unknown	13 (1.2%)	72.2 (4.9)		3.1(4.1)		63 (40.1%)	
SPED (proportion of total lesion)			0.81		0.77	1 (7.7%)	0.33

	# of Subjects at 1 year (N=1105)	VA score at 1 year		Change in VA score at 1 year		3-lines gain from baseline at 1 year	
		Mean (SE)	P-value*	Mean (SE)	P-value*	n (%)	P-Value†
Baseline Ocular Characteristics							
None	1027 (92.9%)	67.9 (0.6)	(0.84)	7.5 (0.5)	(0.47)	313 (30.5%)	(0.07)
<50%	21 (1.9%)	68.2 (3.9)		7.2 (3.2)		5 (23.8%)	
>=50%	40 (3.6%)	69.8 (2.8)		5.8 (2.3)		8 (20.0%)	
Unknown	17 (1.5%)	70.7 (4.3)		2.3 (3.6)		1 (5.9%)	
Fibrotic or atrophic scar			<0.001		0.29		0.17
No	1049 (94.9%)	68.4 (0.6)	(0.001)	7.3 (0.5)	(0.33)	309 (29.5%)	(0.08)
Yes	43 (3.9%)	58.6 (2.7)		9.7 (2.3)		17 (39.5%)	
Unknown	13 (1.2%)	72.2 (4.9)		3.1 (4.1)		1 (7.7%)	
Hemorrhage (associated with the lesion)			0.001		0.009		0.001
None	420 (38.0%)	69.3 (0.9)	(0.002)	5.7 (0.7)	(0.01)	99 (23.6%)	(<0.001)
1 DA	561 (50.8%)	68.1 (0.8)		8.8 (0.6)		198 (35.3%)	
>1 to 2 DA	55 (5.0%)	64.1 (2.4)		7.9 (2.0)		17 (30.9%)	
>2 DA	50 (4.5%)	59.4 (2.5)		4.9 (2.1)		11 (22.0%)	
Unknown	19 (1.7%)	70.4 (4.1)		3.8 (3.4)		2 (10.5%)	
Geographic atrophy			0.008		0.049		0.44
None/questionable	1027 (92.9%)	68.4 (0.6)	(0.02)	7.6 (0.5)	(0.14)	308 (30.0%)	
Present	76 (6.9%)	62.8 (2.0)		4.1 (1.7)		19 (25.0%)	
Unknown	2 (0.2%)	53.0 (13)		6.0 (10)		0 (0%)	
Glaucoma			0.15		0.97		0.53
No	981 (88.8%)	68.3 (0.6)		7.3 (0.5)		287 (29.3%)	
Yes	124 (11.2%)	65.8 (1.6)		7.3 (1.3)		40 (32.3%)	
Unknown	19 (1.7%)	70.4 (4.1)		3.8 (3.4)		2 (10.5%)	
CNV in fellow eye			0.30		0.67		0.04
None/questionable	746 (67.5%)	67.7(0.7)	(0.56)	7.4 (0.5)	(0.50)	235 (31.5%)	(0.09)
Present	334 (30.2%)	68.9(1.0)		7.0 (0.8)		84 (25.1%)	
Unknown	25 (2.3%)	67.0 (3.6)		10.5 (2.9)		8 (32.0%)	

VA = Visual Acuity; SE = Standard Error; VA = Visual Acuity; CNV = choroidal neovascularization; DA = Disc Area; SPED = serous retinal pigment epithelial detachment; RAP = Retinal Angiomatous Proliferans; RPE = Retinal Pigment Epithelium.

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* P-value was from one-way analysis of variance (ANOVA).

[#] P value was from Monte-Carlo fisher exact test.

P-value in the parenthesis was calculated including the unknown category, while P-value not in parenthesis was calculated excluding the unknown category.

Table 3

Univariate analysis for association of baseline OCT features with visual outcomes at 1 year

	# of Subjects at 1 year (N=1105)	VA score at 1 year		Change in VA score at 1 year		3-lines gain from baseline at 1 year	
		Mean (SE)	P-value*	Mean (SE)	P-value*	n (%)	P-Value [†]
Baseline OCT features	n (%)						
Retinal thickness (microns)							0.002
<120	112 (10.1%)	68.8 (1.7)	<0.001	6.4(1.4)	(0.66)	30(26.8%)	(0.005)
120 to 212	581 (52.3%)	70.0 (0.7)		7.0(0.6)		150(25.8%)	
>212	407 (36.8%)	64.9 (0.9)		8.0(0.7)		146(35.9%)	
Unknown	5 (0.5%)	73.6 (7.9)		9.0(6.6)		1 (20.0%)	
As continuous (every 10 microns increase)		-0.31 (0.05)	<0.001	0.03(0.04)	0.49		0.009
Sub-retinal fluid thickness (microns)							0.002
0	735 (66.5%)	67.3 (0.7)	(0.21)	7.9(0.5)	(0.24)	242(32.9%)	(0.005)
>0 to 25	92 (8.3%)	70.1 (1.9)		7.4(1.5)		24(26.1%)	
>25	273 (24.7%)	69.3 (1.1)		5.8(0.9)		60(22.0%)	
Unknown	5 (0.5%)	73.6 (8.0)		9.0(6.6)		1 (20.0%)	
As continuous (every 10 microns increase)		-0.06 (0.08)	0.44	-0.17 (0.06)	0.006		0.02
Subretinal tissue complex thickness (microns) by quartile							<0.001
1 st (>0 to 75)	272 (24.6%)	72.2 (1.1)	<0.001	5.5(0.9)	(0.07)	53(19.5%)	<0.001
2 nd (>75 to 160)	263 (23.8%)	67.9 (1.1)		7.3(0.9)		85(32.3%)	
3 rd (>160 to 275)	282 (25.5%)	67.3 (1.1)		9.2(0.9)		101(35.8%)	
4 th (>275)	283 (25.6%)	64.8 (1.1)		7.2(0.9)		87(30.7%)	
As continuous (every 10 microns increase)		-0.13 (0.03)	<0.001	-0.00(0.03)	0.96		0.55
Retinal + sub-retinal fluid thickness (microns) by quartiles							0.17
1 st (160)	274 (24.8%)	69.8 (1.1)	<0.001	6.6(0.9)	(0.64)	72(26.3%)	(0.26)
2 nd (>160 to 225)	273 (24.7%)	69.8 (1.1)		8.4(0.9)		91(33.3%)	
3 rd (>225 to 320)	279 (25.3%)	68.6 (1.1)		6.9(0.9)		75(26.9%)	
4 th (>320)	274 (24.8%)	63.7 (1.1)		7.4(0.9)		88(32.1%)	
As continuous (every 10 microns increase)		-0.26 (0.04)	<0.001	-0.04 (0.04)	0.31		0.30
Total foveal thickness (microns) by quartile					0.08		0.004

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	# of Subjects at 1 year (N=1105)	VA score at 1 year		Change in VA score at 1 year		3-lines gain from baseline at 1 year	
		Mean (SE)	P-value *	Mean (SE)	P-value *	n (%)	P-Value [†]
Baseline OCT features							
1 st (325)	277 (25.1%)	71.6 (1.0)	(<0.001)	5.8 (0.9)	(0.14)	59 (21.3%)	(0.008)
2 nd (>325 to 425)	285 (25.8%)	72.2 (1.0)		8.5 (0.9)		95 (33.3%)	
3 rd (>425 to 550)	253 (22.9%)	67.9 (1.1)		8.4 (0.9)		83 (32.8%)	
4 th (>550)	285 (25.8%)	60.4 (1.0)		6.6 (0.9)		89 (31.2%)	
Unknown	5 (0.5%)	73.6 (7.7)		9.0 (6.6)		1 (20.0%)	
As continuous (every 10 microns increase)		-0.22 (0.03)	<0.001	-0.02 (0.02)	0.49		0.23
Intra-retinal fluid			<0.001		0.40		0.007
No Fluid	264 (23.9%)	72.8 (1.1)	(<0.001)	6.9 (0.9)	(0.58)	61 (23.1%)	(0.02)
Fluid but not in foveal center point	298 (27.0%)	68.7 (1.0)		6.6 (0.9)		84 (28.2%)	
Fluid in foveal center point	525 (47.5%)	65.4 (0.8)		8.0 (0.6)		177 (33.7%)	
Unknown	18 (1.6%)	64.0 (4.1)		6.1 (3.5)		5 (27.8%)	
Sub-retinal fluid			0.045		0.19		0.01
No Fluid	189 (17.1%)	65.7 (1.3)	(0.10)	6.4 (1.1)	(0.20)	62 (32.8%)	(0.02)
Fluid but not in foveal center point	523 (47.3%)	67.7 (0.8)		8.1 (0.6)		169 (32.3%)	
Fluid in foveal center point	384 (34.8%)	69.6 (0.9)		6.5 (0.8)		92 (24.0%)	
Unknown	9 (0.8%)	65.9 (5.9)		12.9 (4.9)		4 (44.4%)	
Sub-RPE fluid			0.77		0.76		0.01
No Fluid	483 (43.7%)	68.7 (0.8)	(0.41)	7.5 (0.7)	(0.37)	163 (33.7%)	(0.02)
Fluid but not in foveal center point	194 (17.6%)	68.1 (1.3)		6.9 (1.1)		50 (25.8%)	
Fluid in foveal center point	344 (31.1%)	67.8 (1.0)		6.7 (0.8)		86 (25.0%)	
Unknown	84 (7.6%)	65.2 (1.9)		9.8 (1.6)		28 (33.3%)	
Any fluid in foveal center			0.03		0.26		0.050
No Fluid in foveal center point	201 (18.2%)	70.5 (1.3)	(0.09)	8.1 (1.0)	(0.59)	71 (35.3%)	(0.10)
Fluid in foveal center point	901 (81.5%)	67.5 (0.6)		7.1 (0.5)		255 (28.3%)	
Unknown	3 (0.3%)	70.7 (10)		12.7 (8.5)		1(33.3%)	
RPE elevation			0.009		<0.001		<0.001
No	145 (13.1%)	71.6 (1.5)	(0.03)	11.2 (1.2)	(<0.001)	61 (42.1%)	(<0.001)

	# of Subjects at 1 year (N=1105)	V/A score at 1 year		Change in VA score at 1 year		3-lines gain from baseline at 1 year	
Baseline OCT features	n (%)	Mean (SE)	P-value*	Mean (SE)	P-value*	n (%)	P-Value [†]
Yes	944 (85.4%)	67.5 (0.6)		6.6 (0.5)		258 (27.3%)	
Unknown	16 (1.5%)	68.3 (4.4)		14.1 (3.7)		8 (50.0%)	
RPEE maximum height (mm) by quartiles							
1 st (< 3.0)	317 (28.7%)	68.6 (1.00)	0.937	7.6 (0.83)	0.631	112 (35.3%)	0.046
2 nd (>3.0 to 5.0)	212 (19.2%)	68.9 (1.22)	(0.027)	8.3 (1.01)	(0.684)	63 (29.7%)	(0.086)
3 rd (>5.0 to 11.5)	267 (24.2%)	68.1 (1.09)		7.1 (0.90)		74 (27.7%)	
4 th (>11.5)	268 (24.3%)	68.0 (1.08)		6.7 (0.90)		67 (25.0%)	
Unknown	41 (3.7%)	59.2 (2.77)		5.6 (2.30)		11 (26.8%)	
As continuous (1 mm increase)		−0.05 (0.06)	0.45	−0.08 (0.05)	0.12		0.002
RPEE maximum width (mm) by quartiles							
1 st (< 12.0)	260 (23.5%)	69.9 (1.10)	0.094	8.3 (0.91)	0.069	92 (35.4%)	0.02
2 nd (>12 to 31.5)	250 (22.6%)	68.5 (1.12)	(0.013)	6.8 (0.93)	(0.100)	71 (28.4%)	(0.023)
3 rd (>31.5 to 55.0)	258 (23.4%)	69.0 (1.10)		8.9 (0.91)		84 (32.6%)	
4 th (>55.0)	257 (23.3%)	66.2 (1.11)		5.8 (0.91)		60 (23.3%)	
Unknown	80 (7.2%)	63.2 (1.98)		6.0 (1.64)		20 (25.0%)	
As continuous (1 mm increase)		−0.03 (0.02)	0.06	−0.02 (0.02)	0.12		0.02

OCT= Optical coherence tomography; VA = Visual Acuity; SE = Standard Error; RPE=Retinal Pigment Epithelium; RPEE=RPE elevation.

* P-value was from one-way analysis of variance (ANOVA).

[†] P-value was from Monte-Carlo fisher exact test.

P-value in the parenthesis was calculated including the unknown category, while P-value not in parenthesis was calculated excluding the unknown category.

Table 4

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

Baseline Characteristics	N	VA score (letters) at 1 Year [*]		VA score change (letters) from baseline at 1 Year [†]	
		Adjusted Mean (SE)	P-value	Adjusted Mean (SE)	P-value
Age (years)					
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 (mm²)					
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)	
Can't 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)	
Geographic atrophy					
None/questionable	1027	68.2 (0.5)	0.02	--	
Present	76	63.9 (1.7)		--	
Total foveal thickness (μ)					
1 st quartile (32.5)	277	68.0 (0.9)	0.01	--	

Baseline Characteristics	N	VA score (letters) at 1 Year [*]		VA score change (letters) from baseline at 1 Year [†]	
		Adjusted Mean (SE)	P-value	Adjusted Mean (SE)	P-value
2 nd quartile (>325 to 425)	285	69.7 (0.9)		--	
3 rd quartile (>425 to 550)	253	68.7 (0.9)		--	
4 th 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					
Ramibizumab 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)	
Ramibizumab as needed	285	67.5 (0.9)		6.9 (0.9)	
Bevacizumab as needed	271	66.2 (0.9)		5.5 (0.9)	

SE = Standard Error; VA = Visual Acuity; CNV = choroidal neovascularization; RAP = Retinal Angiomatous Proliferans; RPE = Retinal Pigment Epithelium.

^{*} A total of 1061 participants were included in the final multivariate model, and 44 patients were excluded due to missing value in one or more predictors.

[†] A total of 1068 participants were included in the final multivariate model, and 37 patients were excluded due to missing value in one or more predictors.

--: predictor was not included in the final multivariate model, because it was not statistically significant.

Table 5

Analysis for 3-line gain from baseline at 1 Year

Baseline Characteristics	N	3-line gain (%)	Adjusted OR (95% CI) §	P-value
Age (years)				
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 or better	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 or worse	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)	
Can't 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 (μ)				
1 st quartile (≤ 325)	277	59(21.3%)	1.00	0.004
2 nd quartile (>325 to ≤ 425)	285	95(33.3%)	1.74 (1.11, 2.72)	
3 rd quartile (>425 to ≤ 550)	253	83(32.8%)	1.15 (0.73, 1.82)	
4 th 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 as needed	285	71 (24.9%)	0.56 (0.37, 0.86)	
Bevacizumab as needed	271	76 (28.0%)	0.63 (0.41, 0.96)	

OR = Odds Ratio; CI = Confidence Interval; VA= Visual Acuity; CNV= choroidal neovascularization; RAP=Retinal Angiomatous Proliferans; RPE=Retinal Pigment Epithelium.

[§]A total of 1066 participants were included in the final multivariate model, and 39 patients were excluded due to missing value in one or more predictors.