Photographic Assessment of Baseline Fundus Morphologic Features in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Objective: To describe the methods used for assessment of baseline fundus characteristics from color photography and fluorescein angiography (FA) in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and to describe the relationship between these characteristics and visual acuity.

Design: Randomized, masked, multicenter trial.

Participants: This investigation included 1185 participants of the CATT study.

Methods: Baseline stereoscopic color fundus photographs and FAs of participants in the CATT study were assessed at a central fundus photograph reading center by masked readers. Replicate assessments of random samples of photographs were performed to assess intragrader and intergrader agreements. The association of the lesion characteristics with baseline visual acuity was assessed using analyses of variance and correlation coefficients.

Main Outcome Measures: Intragrader and intergrader reproducibility, visual acuity, and lesion characteristics.

Results: Intragrader and intergrader reproducibility showed agreements ranging from 75% to 100% and weighted κ values ranging from 0.48 to 1.0 for qualitative determinations. The intraclass correlation coefficients were 0.96 to 0.97 for quantitative measurements of choroidal neovascularization (CNV) area and total area of CNV lesion. The mean visual acuity varied by the type of pathologic features in the foveal center: 64.5 letters (standard error, 0.7 letters) for fluid only, 59.0 letters (standard error, 0.5 letters) for CNV, and 58.7 letters (standard error, 1.3 letters) for hemorrhage ($P<0.001$). Fibrotic or atrophic scar present in the lesion, but not under the center of the fovea, also was associated with a markedly reduced visual acuity of 48.4 letters (standard error, 2.2 letters; $P<0.0001$). Although total area of CNV lesion was correlated weakly with visual acuity when all participants were assessed (Spearman correlation coefficient, $\rho = -0.16$; $P<0.001$), the correlation was stronger within patients with predominantly classic lesions ($\rho = -0.42$; $P<0.001$).

Conclusions: These results show that the methodology used for grading CATT fundus images has good reproducibility. As expected, larger total CNV lesion area and pathologic findings such as hemorrhage, fibrosis, and atrophy at baseline are associated with decreased visual acuity.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2012;xx:xxx*

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The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) is a randomized clinical trial designed to compare the efficacy and safety of ranibizumab and bevacizumab and to investigate whether less than monthly dosing compromises long-term visual acuity.[1] All color photographs and fluorescein angiograms collected during the study were assessed at the fundus photography reading center located at the Department of Ophthalmology of the Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. The purposes of this article are: (1) to review the methodology used for grading these photographs, (2) to describe the baseline fundus morphologic and fluorescein angiographic characteristics of the CATT participants, and (3) to evaluate the association between morphologic features and visual acuity.

Patients and Materials

Study Participants

Between February 2008 and December 2009, a total of 1185 patients were enrolled through 43 clinical centers in the United

ISSN 0161-6420/12/$–see front matter
doi:10.1016/j.ophtha.2012.02.013

States. Inclusion criteria included: aged 50 years or older, presence of previously untreated active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye, and visual acuity between 20/25 and 20/320 (letter score, 23–82 on electronic visual acuity testing).[2] Both leakage on fluorescein angiography and fluid on optical coherence tomography (OCT), located either within or below the retina or below the retinal pigment epithelium, were required to establish the presence of active CNV. Choroidal neovascularization or its sequelae such as fluid, pigment epithelial detachment, or hemorrhage needed to be under the fovea. The total area of retinal fibrosis could not exceed 50% of the total lesion. Although patients with hemorrhage involving more than 50% of the total lesion area initially were excluded from the trial, this exclusion criterion later was eliminated, allowing patients with hemorrhage larger than 50% to enroll in the study. One or more drusen (>63 μm) had to be present in either eye or late AMD had to be present in the fellow eye. The study was approved by an institutional review board associated with each center. All patients provided written informed consent. The study was compliant with Health Insurance Portability and Accountability Act regulations. The CATT study was registered with ClinicalTrials.gov (NCT00593450).

Patients with previous treatment for neovascular AMD in the study eye, patients actively receiving intravenous bevacizumab, or patients receiving treatment with any investigational drug or device likely to have ocular effects were ineligible. Ocular exclusion criteria included: fibrosis or geographic atrophy involving the center of the fovea; CNV in either eye resulting from causes other than AMD such as ocular histoplasmosis, trauma, or pathologic myopia; retinal pigment epithelial tear; any concurrent intraocular conditions that could require medical or surgical intervention during the 2 years of the study; and patients with other progressive retinal diseases likely to affect visual acuity within 2 years. Patients with pattern dystrophy with CNV and drusen determined to have definite AMD were deemed eligible.[3]

Image Acquisition, Transfer, and Viewing

Mydriatic stereoscopic color photographs and fluorescein angiograms of the macula were obtained from both eyes of each participant using standardized protocols. Stereo photographic images were acquired digitally in almost all cases. In 21 cases from 2 sites, photographic film was used for color photographs. Stereo pair color and red-free images of the disc (modified field 1) and macula (field 2) were obtained for each eye. Fluorescein angiography stereo pairs of the study eye were obtained during the early (15–45 seconds, 5–8 pairs), mid (1–3 minutes, 3 pairs), and late (1 pair at each of 5 and 10 minutes) phases and of the nonstudy eye at 2 and 10 minutes. All digital imaging systems at the clinical centers were certified by the CATT Fundus Photography Reading Center before patient enrollment was started. The Topcon IMAGENet System (Topcon Medical Systems, Inc., Oakland, NJ) Ophthalmic Imaging System (OIS) WinStation (Merge Healthcare, Sacramento, CA), Escalon System (Escalon Digital Vision, Inc, New Berlin, WI) or Zeiss Visupac System (Carl Zeiss Meditec AG, Jena, Germany) were acceptable. An alternate ophthalmic digital system was approved if all requirements for acquisition, archiving, magnification, image quality, and image accessibility by the reading center were met. The entire angiogram and color photographs were written to a compact disk using CATT custom-developed submission application software. The submission application checked for image resolution, bit depth, and other certified image parameters and had filtering capabilities that prompted for missing and incomplete entries.

The fundus digital images were viewed on dual liquid crystal display color monitors using software applications that included methods for rendering stereoscopic images, image comparison, and measurements. To achieve comparable grading results at multiple workstations, the viewing monitors were calibrated and standardized for brightness and color characteristic. Original images were not enhanced or otherwise altered. Film-based images were viewed in stereo on a light box with ×5 Donaldson stereo viewers.

All graders were masked to the treatment assignment of the patient. A multistep grading procedure was used for photographic assessment. The first step assessed eligibility and photographic quality. The eligibility assessment determined whether: (1) the fluorescein angiogram images were of sufficient quality to determine eligibility; (2) there was active leakage of fluorescein on the angiogram; (3) either CNV or sequelae of CNV, such as pigment epithelial detachment, hemorrhage, blocked fluorescence, macular edema, or fluid involving the center of the fovea, were present; (4) the area of fibrosis was less than 50% of the total lesion; (5) no fibrosis or geographic atrophy was present in the foveal center; (6) no retinal pigment tear was present; (7) the CNV was not the result of causes other than AMD; and (8) there was no progressive retinal disease that might affect vision.

After the patient was enrolled by the clinical sites, an eligibility grading was carried out independently by a grader (R.W.M., C.R.P., K.S.) and the director of the reading center (E.D.) and were recorded on baseline eligibility evaluation forms. Discrepancies on the 2 forms were adjudicated between the grader and the director of the reading center, (J.E.G.), and a final consensus eligibility form was completed. In cases where persisting discrepancies existed, the images were reviewed by the principal investigator of the reading center, and then the consensus form was completed. Only the consensus forms data were entered into the CATT reading center data base. Ineligible cases were reported back to the clinical sites. After initial grading of eligibility and photographic quality, a detailed grading of the CNV and total CNV lesion were performed following a similar adjudication and review process.

The type of CNV, retinal hemorrhages, fluid, serous pigment epithelial detachment (SPED), and atrophic or fibrotic scars were identified using previously outlined descriptions.[4] There were no limitations on the shape and size of geographic atrophy. Features commonly associated with retinal angiomatous proliferans (RAP) lesions such as hot spot (focal area of hyperfluorescence), superficial hemorrhage, lipid, SPED, fibrovascular pigment epithelial detachment, and retinal and choroidal vessel anastomosis were documented. The presence of a hotspot on fluorescein angiography was required for a lesion to be identified as RAP lesion.[5–7] Blocked fluorescence was diagnosed only if it was not related to increased pigmentation or hemorrhage. A finding was considered present or absent if the decision reflected 80% or greater certainty. Otherwise, lesion presence or absence was graded as questionable. A decision of cannot grade was made if other fundus pathologic features, photographic quality, or artifact obscured the object of interest in a way that a definitive decision could not be made with 80% certainty.

Quality Assurance Activities

Graders were trained for a period of 3 months to perform systematic evaluations of the color photographs and fluorescein angiograms of eyes with AMD. Training also was aimed at achieving consistent grader agreement in the identification of key features such as leakage from the CNV, hemorrhage, fibrotic scar, fluid, SPED, retinal pigment epithelium tear, geographic atrophy, and RAP. Grade–regrade reproducibility was assessed in 84 participants for qualitative gradings and in 24 participants for quantitative determinations.

Measurement of Age-Related Macular Degeneration Lesions

Measurements of CNV area were carried out using Image J, a public domain Java image processing program developed by the National Institutes of Health, which is available as free software from http://rsbweb.nih.gov/ij/ (accessed July 7, 2009). The CNV and total CNV lesion (TCNVL) area were measured. The TCNVL area included the CNV plus contiguous hemorrhage, SPED, atrophic scar, fibrotic scar, and blocked fluorescence.

Because the fundus cameras used in the study had different magnifications, the University of Wisconsin Fundus Photograph Reading Center Pragmatic Calibration method was used, which accounts for differences in photographic settings (Invest Ophthalmol Vis Sci 49 [Suppl]: 2243, 2008). For each participant's visit, an image clearly showing the optic disc center and the center of the fovea was chosen, and a line was drawn between these 2 points. The distance was assumed to be 4.5 mm, and a calibration factor was generated and applied to all the images of that eye.

Images were measured independently by 2 graders using dual monitors. One monitor displayed the fluorescein angiogram image used for measurement and the other displayed the color images, red-free images, and all the fluorescein angiogram images obtained during that visit. One high-quality fluorescein angiogram image was chosen for drawing the extent of the lesion. Typically, for classic CNV, the image obtained just before the onset of leakage was chosen. For occult CNV, a later image showing maximum staining was chosen. For mixed CNV lesions, where the full extent of the occult component was visible only in later frames of the angiogram, a later image was chosen.

Using the freehand selections tool provided by the software, the outline of the CNV was drawn. The output of the total measurement in square millimeters was recorded, and the image was saved. The procedure was repeated for measurement of the TCNVL area on the same image. The area in square millimeters was converted to disc area by dividing by 2.54. The contours of the drawing outlines were as circumferential as possible, inclusive of outcroppings of CNV larger than the diameter of the largest vein at the disc margin. In rare instances showing more than 1 discrete CNV lesion, the lesion closer to the foveal center was measured. While measuring an RAP lesion without associated larger areas of occult or classic CNV, the area of the hot spot in its widest appearance and any contiguous intraretinal hemorrhage were measured.

In some instances, measurements could not be obtained because of poor-quality photographs, because of the presence of leakage from undetermined source at the edge of GA, or in relatively flat occult lesions whose borders merged with areas of nonspecific atrophy. In cases where lesions extended beyond the image edge, the measurement included the area up to the edge of the image.

Adjudication was carried out if the difference between 2 graders was more than 50% or the absolute value of the difference in the area was more than 3.0 mm^2. In addition, adjudications also were performed if one grader could not grade an image and the other grader made a measurement. The graders had access to their original drawings and data forms during adjudication. The refraction and visual acuity testing protocol designed by the Diabetic Retinopathy Clinical Research Network (2005) was used during the study.[8]

Statistical Methods

All analyses were conducted using SAS software version 9.2 (SAS Inc., Cary, NC). Descriptive analyses were performed to summarize the baseline lesion features, CNV area, TCNVL area, and visual acuity score. Grade–regrade agreements were evaluated on 4 random samples of images chosen for regrade of lesion features (n = 84 eyes total) and on 1 random sample of images chosen for remeasure of the CNV size and lesion type (n = 24). Percentage agreement and weighted κ statistics with confidence intervals were calculated for grade–regrade agreement based on the consensus grading. Pairwise percent agreement and multigrader (2 to 3 graders) κ values with bootstrapped confidence intervals were calculated for assessing the intergrader agreement.[9] For grade–regrade and intergrader agreement for CNV area measurements, intraclass correlations with mean difference and 95% limit of agreement were calculated.

Analyses of variance were used to assess the association of baseline lesion characteristics with visual acuity score. Study eyes without CNV or that were ungradable on a particular characteristic are reported but not included in the statistical comparisons. The CNV area measurements were categorized by quartile, with gradable but unmeasureable CNV as a separate category. In addition to analyses of variance comparisons of VA score among groups categorized by quartiles, correlations between visual acuity and lesion size also were assessed by Spearman correlation coefficient ρ because of the skewed distributions of lesion size measurements.

The correlation analyses were stratified further by lesion type. After the univariate analysis of each lesion characteristic with visual acuity, a multivariate linear regression model was performed by initially including all variables with P values less than 0.10 from the univariate analysis. The multivariate model went through backward selection, and only variables with P values less than 0.05 were kept in the final multivariate model. An interaction between CNV size by quartile and lesion type was included in the multivariate model because the correlation coefficient between lesion area and visual acuity score varied across type of lesion.

Results

Among 1185 patients enrolled in the study, 2.36% (28 patients) did not meet the photography eligibility criteria. The most common reason for ineligibility was absence of leakage on fluorescein angiography (Table 1). Other reasons included more than 50% of the lesion being composed of fibrotic scars or hemorrhage, fibrosis or geographic atrophy in the foveal center, no sequelae of CNV under the fovea, and others (Table 1). Of all baseline visit images, 96.7% were judged to be gradable.

Table 2 summarizes the intragrader and intergrader agreement for baseline features in the study eyes. Weighted κ values for the consensus grade–regrade agreement based on repeated measurements in 84 study eyes ranged from 0.48 to 1.0, and the percent agreement ranged between 75% and 100%. Intergrader agreement

Table 1. Reasons for Ineligibility as Determined by the Fundus Photograph Reading Center (n = 28 Ineligible Participants)

Reasons	Number*
No leakage on fluorescein angiograms	12
Total area of fibrosis >50% of total lesion	7
No sequelae of CNV under the fovea	7
Total area of hemorrhage or fibrosis >50% total lesion	7
Fibrosis or geographic atrophy involving the foveal center	4
Progressive disease in study eye	3
CNV in either eye resulting from causes other than AMD	1
Angiogram of insufficient quality to grade eligibility	2
Tear of the RPE involving the macula	1

AMD = age-related macular degeneration; CNV = choroidal neovascularization; RPE = retinal pigment epithelium.
*The number exceeds the total number of ineligible participants for multiple reasons in some cases.

Table 2. The Intragrader and Intergrader Agreement for the Grading of Baseline Lesion Features in the Study Eye

Baseline Lesion Features (n = 84 Study Eyes)	Consensus Grade–Regrade Agreement		Intergrader Agreement	
	% Agree	*Weighted* κ (95% Confidence Interval)	% Agree	κ (95% Confidence Interval)
Lesion components				
Hemorrhage	90	0.79 (0.66–0.93)	91	0.81 (0.69–0.91)
Blocked fluorescence	88	0.62 (0.40–0.83)	90	0.53 (0.30–0.72)
SPED	95	0.48 (0.04–0.91)	97	0.75 (0.30–1.00)
Lesion scar	100	1.00 (1.00–1.00)	99	0.82 (−0.05–1.00)
Pathologic features in foveal center	75	0.71 (0.57–0.85)	77	0.66 (0.54–0.77)
Location of lesion	79	0.59 (0.42–0.76)	80	0.59 (0.43–0.72)
Hemorrhage associated with lesion	80	0.72 (0.59–0.86)	85	0.74 (0.63–0.83)
RAP lesion	92	0.65 (0.41–0.89)	92	0.64 (0.37–0.84)
Lesion characteristic*	100	1.00 (1.00–1.00)	100	1.00 (1.00–1.00)
Geographic atrophy	100	1.00 (1.00–1.00)	96	0.76 (0.46–0.95)
		Intraclass Correlation (95% Confidence Interval)		
Lesion size (n = 23 study eyes)				
Area of CNV (DA)		0.96 (0.91–0.98)		0.97 (0.93–0.99)†
Total area of CNV lesion (DA)		0.96 (0.91–0.98)		0.97 (0.93–0.99)†
Lesion size (n = 23 study eyes)		Difference‡ (95% Confidence Interval)		
Area of CNV (DA)		0.07 (−0.90 to 1.04)		−0.14 (−1.02 to 0.74)†
Total area of CNV lesion (DA)		0.11 (−0.88 to 1.10)		−0.09 (−1.06 to 0.88)†

CNV = choroidal neovascularization; DA = disc area; RAP = retinal angiomatous proliferans; SPED = serous pigment epithelium detachment.
*n = 24 for lesion characteristic: predominantly classic, minimally classic, occult, and no lesion or cannot grade.
†One measurement pair was excluded from the intergrader agreement because 1 grader recorded an extreme value that was decided to have been erroneous.
‡The direction of differences in grade–regrade are sample minus original. The direction of differences between graders is arbitrary but consistent, with only 2 graders.

showed weighted κ values ranging from 0.53 to 1.00 and percent agreements ranging from 80% to 100%.

Intraclass correlations for lesion size measurements repeated in 23 study eyes were 0.96 for the consensus grade–regrade agreement and 0.97 for the intergrader agreement (Table 2). There was an error during regrading of 1 additional image in which 1 grader measured 9.0 disc areas, whereas the other measured 0.7 disc areas, for both CNV area and TCNVL area, and during consensus grading it was decided that 0.7 was correct. When all 24 participants were assessed together, the agreement was 0.63 for the consensus grade–regrade agreement and 0.65 for the intergrader agreement.

Of the 1185 study eyes, more than half had CNV under the center of the fovea, and a quarter of them had fluid only in the fovea (Table 3). Approximately one-third of the eyes had contiguous hemorrhage as part of the lesion. Other components noted were blocked fluorescence in 172 (14.5%) eyes, SPED in 63 (5.3%) eyes, and fibrotic or atrophic scar that was not subfoveal in 46 (3.9%) eyes. Retinal angiomatous proliferans lesions were present in 128 (10.8%) eyes and geographic atrophy that was not subfoveal was observed in 82 (6.9%) study eyes. More than half of the cases of CNV were occult-only lesions, followed by predominantly classic CNV (22.5%) and minimally classic CNV (16.6%).

There was a strong association between the presence of several lesion components and mean visual acuity. Patients with hemorrhage had significantly worse visual acuity than those without hemorrhage (58.2 vs. 61.7; $P < 0.001$; Table 3). Larger areas of hemorrhage were associated with worse visual acuity ($P < 0.001$). Eyes with blocked fluorescence had a significantly worse visual acuity than those without it (57.7 vs. 60.9; $P = 0.004$). Lesions that included fibrotic or atrophic scar components also were associated with a markedly reduced visual acuity (48.4 vs. 60.9; $P < 0.0001$). Although SPED was associated with mildly better visual acuity, the difference was not statistically significant.

Presence of pathologic features and the type of pathologic features in the foveal center were associated, as expected, with a significantly worse visual acuity ($P < 0.001$). For example, eyes with only fluid in the fovea had mean acuity of 64.5 letters (standard error [SE], 0.7 letters), eyes with CNV under the fovea had average acuity of 59 letters (SE, 0.5 letters), and those with hemorrhage had average acuity of 58.7 letters (SE, 1.3 letters). Presence of other lesion components under the fovea was associated with average acuity of 53.7 letters (SE, 2.3 letters), whereas eyes with SPED had a very similar acuity to those with fluid only.

The type of lesion was associated with statistically significant different average visual acuity ($P<0.001$; Table 3). Predominantly classic lesions, observed in 267 eyes (22.5%), had a mean visual acuity of 55.8 letters; minimally classic lesions, observed in 197 eyes (16.6%), had a mean visual acuity of 57.2 letters; and occult-only lesions, observed in 696 eyes (63.1%), had a mean visual acuity of 63.1 letters. Retinal angiomatous proliferans lesions present in 128 eyes (10.8%) were not associated with a significant difference in vision from other types of AMD lesions. Finally, presence of geographic atrophy (not under the foveal center) was associated with worse visual acuity, although the difference was of borderline significance ($P = 0.07$).

Larger area of both CNV and TCNVL were associated with lower average visual acuity ($P = 0.03$ and $P < 0.0001$, respectively; Table 3), with Spearman correlation coefficients of $\rho = -0.08$ and $\rho = -0.16$, respectively (Table 4). A larger area of CNV was associated significantly with worse average visual acuity for predominantly classic lesions ($\rho = -0.42$; $P < 0.001$) and occult-only lesions ($\rho = -0.11$; $P<0.01$), but not for minimally classic lesions ($\rho = -0.10$; $P = 0.20$; Table 3). Larger area of TCNVL was associated with worse acuity for predominantly classic lesions ($P<0.001$), minimally classic lesions ($P = 0.001$), and occult lesions ($P < 0.001$; Table 4).

Table 3. Univariate Analysis for the Association between Baseline Lesion Features and Baseline Visual Acuity in the Study Eye

Baseline Lesion Features (n = 1185 Study Eyes)	No. (%)	Mean Visual Acuity Score in Letters (Standard Error)	*P* Value*
Lesion components			
Hemorrhage			
No	750 (63.3%)	61.7 (0.5)	<0.001
Yes	421 (35.5%)	58.2 (0.7)	
No CNV or cannot grade	14 (1.2%)		
Blocked fluorescence			
No	999 (84.3%)	60.9 (0.4)	0.004
Yes	172 (14.5%)	57.7 (1.1)	
No CNV or cannot grade	14 (1.2%)		
SPED			
No	1108 (93.5%)	60.3 (0.4)	0.09
Yes	63 (5.3%)	63.3 (1.4)	
No CNV or cannot grade	14 (1.2%)		
Fibrotic or atrophic scar			
No	1125 (94.9%)	60.9 (0.4)	<0.001
Yes	46 (3.9%)	48.4 (2.2)	
No CNV or can not grade	14 (1.2%)		
Pathologic features in foveal center			
CNV	688 (58.1%)	59.0 (0.5)	<0.001
Fluid only	315 (26.6%)	64.5 (0.7)	
Hemorrhage	93 (7.9%)	58.7 (1.3)	
SPED	28 (2.4%)	64.4 (2.0)	
Other†	43 (3.6%)	53.7 (2.3)	
No CNV or cannot grade	17 (1.4%)		
Hemorrhage associated with lesion‡			
None	441 (37.2%)	63.2 (0.6)	<0.001
≤1 DA	611 (51.6%)	59.4 (0.5)	
≤2 DA	59 (5.0%)	55.3 (1.7)	
>2 DA	54 (4.6%)	54.5 (2.0)	
No CNV or cannot grade	19 (1.6%)		
RAP lesion			
None/questionable	1035 (87.4%)	60.5 (0.4)	0.60
Yes	128 (10.8%)	59.8 (1.1)	
No CNV or cannot grade	21 (1.8%)		
Lesion characteristic			
Predominantly classic	267 (22.5%)	55.8 (0.9)	<0.001
Minimally classic	197 (16.6%)	57.2 (1.0)	
Occult only	696 (58.7%)	63.1 (0.5)	
No lesion or cannot grade	25 (2.1%)		
Geographic atrophy			
None/questionable	1101 (92.9%)	60.8 (0.4)	0.07
Present	82 (6.9%)	58.0 (1.6)	
Cannot grade	2 (0.2%)		
Area of CNV (DA)			
First quartile (<0.48)	260 (21.9%)	62.8 (0.8)	<0.001 (0.03†)
Second quartile (<1.20)	261 (22.0%)	61.2 (0.8)	
Third quartile (<2.53)	261 (22.0%)	59.4 (0.8)	
Fourth quartile (≥2.53)	261 (22.0%)	60.4 (0.9)	
Cannot measure	128 (10.8%)	56.1 (1.2)	
No CNV or cannot grade	14 (1.2%)		
Total area of CNV lesion (DA)			
First quartile (<0.73)	283 (23.9%)	63.6 (0.8)	<0.001 (<0.001§)
Second quartile (<1.71)	284 (24.0%)	61.4 (0.7)	
Third quartile (<3.39)	285 (24.1%)	58.9 (0.8)	
Fourth quartile (≥3.39)	285 (24.1%)	57.8 (0.8)	
Cannot measure	34 (2.9%)	61.1 (1.9)	
No CNV or cannot grade	14 (1.2%)		

CNV = choroidal neovascularization; DA = disc area; RAP = retinal angiomatous proliferans; SPED = serous pigment epithelium detachment.
*Visual acuity of no CNV/lesion or cannot grade not included in *P* value.
†Other category includes fibrotic or atrophic scar, geographic atrophy, no pathologic features, blocked fluorescence, and could not grade or determine.
‡Includes hemorrhages contiguous and noncontiguous to the lesion.
§The cannot measure category was not included in the *P* value calculation.

The multivariate analysis showed that worse VA is associated with fibrotic or atrophic scar, presence of CNV in the fovea center, larger hemorrhage size, and presence of geographic atrophy (Table 5). A statistically significant interaction was detected between lesion type and area of CNV ($P < 0.0001$). The association between larger area of CNV and worse VA was statistically significant for predominantly classic CNV ($P < 0.001$) and was not statistically significant for minimally classic CNV ($P = 0.10$) or occult CNV ($P = 0.15$).

Study eyes in which CNV area and TCNVL area could not be determined tended to have worse visual acuity. Approximately 90% of eyes in which CNV area could not be determined had photographs of good or fair quality, suggesting that the decreased vision in these eyes was most likely the result of the complexity of the lesion and not only to decreased media clarity.

Discussion

These results show that lesion components, location of the CNV lesion, lesion characteristics, presence and extent of hemorrhage, and area of CNV and TCNVL have a strong effect on baseline visual acuity. Not surprisingly, patients with CNV, hemorrhage, or blocked fluorescence under the foveal center had significantly worse visual acuity than those who had only fluid under the fovea. Larger area of CNV and TCNVL also were associated with decreased visual acuity.

Eyes with predominantly classic CNV had worse baseline visual acuity than those with occult CNV and minimally classic CNV, a result that is consistent with the findings of the Treatment of AMD with Photodynamic Therapy investigation, in which untreated patients with predominantly classic lesions had a lower mean visual acuity letter score (51; approximate Snellen equivalent, 20/100) than untreated patients with minimally classic lesions (54; approximate Snellen equivalent, 20/80).[10]

A possible explanation for this difference may be that classic CNV develops closer to the outer receptor layer than occult CNV, and therefore may have a more deleterious effect on vision. In addition, both postmortem and surgically excised tissues have shown classic CNV to have much

Table 4. Correlation of Lesion Size with Baseline Visual Acuity by Lesion Location and Type

Feature	No.*	Median (Minimum–Maximum)	Spearman Correlation	P Value
Area of CNV (DA)				
All	1043	1.20 (0.01–11.25)	−0.08	0.009
Type				
Predominantly classic	252	0.55 (0.02–6.19)	−0.42	<0.001
Minimally classic	171	1.62 (0.02–11.25)	−0.10	0.20
Occult only	616	1.50 (0.01–10.39)	−0.11	0.006
Total area of CNV lesion (DA)				
All	1137	1.71 (0.02–22.41)	−0.16	<0.001
Type				
Predominantly classic	263	0.86 (0.02–10.45)	−0.42	<0.001
Minimally classic	192	2.23 (0.03–22.41)	−0.24	<0.001
Occult only	675	1.97 (0.06–20.29)	−0.15	<0.001

CNV = choroidal neovascularization; DA = disc area.
*Eyes without area measurements were excluded.

larger-caliber vessels,[11,12] a factor that may lead to a larger disruption in the metabolism of the photoreceptors.

Although the replacement of laser, surgical, and photodynamic therapies with the newer intravitreal anti-VEGF therapy has placed a lesser emphasis on the type of CNV defined by the Macular Photocoagulation Study,[13] it is important to identify CNV characteristics at baseline to evaluate potential differences in risk factors and treatment efficacy. The Macular Photocoagulation Study reported, for example, that classic CNV presented as smaller lesions than other types of CNV, but had the worst visual acuity at enrollment,[14,15] a result that is in agreement with the current finding showing that predominantly classic lesions have the worst visual acuity at baseline.

Different components of the CNV lesion had varied effects on visual acuity in this study. Eligibility criteria for enrollment into the CATT study required that fibrotic scars or atrophic scars had to be less than 50% of the total CNV lesion and could not be located under the foveal center. Less than 5% of the study eyes had scars associated with the lesion, and these eyes showed the largest reduction in average visual acuity when compared with study eyes with other lesion components, corroborating results from other, smaller studies.[16,17]

Eyes with geographic atrophy (which by eligibility criteria could not be under the fovea) had mildly decreased visual acuity that was not statistically significantly different from those of eyes without this feature. Finally, eyes with RAP lesions or SPED did not have a significantly different visual acuity from those of eyes without these characteristics.

The morphologic baseline characteristics in the CATT cohort differ from those of participants of earlier anti-VEGF studies targeting AMD, such as MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranimizumab in the Treatment of Neovascular AMD)[18] and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD).[19] Although ANCHOR and MARINA required that the CNV should be present under the center of the fovea, one-fourth of the current study eyes had only fluid in the center of the fovea. The MARINA[18] cohort study included minimally classic or occult CNV lesions, and the ANCHOR[19] cohort included predominantly classic CNV lesions. The CATT cohort, however, had patients of both categories, with three-fourths of patients having occult or minimally classic lesions and the other quarter made up of predominantly classic CNV. In addition, 7% of patients had hemorrhage larger than 50% of the CNV lesion and 11% of patients had RAP lesions, both features that were not included in previous trials. Therefore, the CATT cohort baseline retinal images consisted of a diversity of morphologic features that more closely represents the findings seen in a population of newly diagnosed wet AMD patients.

Grading of the fundus morphologic features on the color photographs and fluorescein angiograms in this study was carried out at the University of Pennsylvania Fundus Photography Reading Center, whereas concurrent grading of the OCT scans was performed at the Duke Reading Center. Study entry eligibility criteria established for the CATT study required the presence of leakage on fluorescein angiography as well as evidence of fluid on OCT. There was no transfer of participant information between the 2 centers while determining eligibility or detailed grading of baseline CNV. This enabled an unbiased masked grading in both reading centers that should be of help in correlative studies of morphometric features observed in angiography and OCT.

The masked replicate gradings that were reassessed by the graders yielded good reproducibility results. The results of quality assurance measures of contemporaneous variability were good and in agreement with those of previous reports.[20,21] The least agreement was observed for assessments requiring clear identification of the foveal center, a task that was difficult in eyes in which the lesion or its components were present partially within the foveal avascular zone.

The grading protocol used in this study, in which every eye was assessed by 2 graders and a consensus grading was obtained for both qualitative and quantitative measurements, yielded reproducible results with excellent intragrader and intergrader agreements.

Table 5. Multivariate Analysis for the Association between Baseline Lesion Features and Baseline Visual Acuity

Baseline Lesion Features (n = 1151 Study Eyes)*	No.*	Adjusted Mean Visual Acuity Score in Letters (Standard Error)	*P* Value
Lesion component: fibrotic or atrophic scar			
No	1107	60.7 (0.4)	<0.001
Yes	44	52.6 (2.1)	
Pathologic features in foveal center			
CNV	682	59.0 (0.5)	<0.001
Fluid only	310	63.5 (0.8)	
Hemorrhage	91	61.5 (1.5)	
SPED	28	61.4 (2.4)	
Other†	40	56.9 (2.0)	
Hemorrhage associated with lesion			
None	436	62.4 (0.6)	<0.001
≤1 DA	605	59.7 (0.5)	
≤2 DA	59	57.8 (1.7)	
>2 DA	51	54.5 (1.9)	
Geographic atrophy in study eye			
None/questionable	1074	60.7 (0.4)	0.003
Present	77	56.2 (1.4)	
Predominantly classic‡			
Area of CNV: lowest quartile	115	60.0 (1.2)	<0.001
Area of CNV: second quartile	80	53.4 (1.4)	
Area of CNV: third quartile	41	49.6 (2.0)	
Area of CNV: highest quartile	16	51.6 (3.1)	
Area of CNV: cannot measure	14	55.8 (3.5)	
Minimally classic‡			
Area of CNV: lowest quartile	31	56.5 (2.3)	0.1
Area of CNV: second quartile	35	62.9 (2.1)	
Area of CNV: third quartile	48	58.8 (1.8)	
Area of CNV: highest quartile	57	56.1 (1.7)	
Area of CNV: cannot measure	25	56.4 (2.6)	
Occult only‡			
Area of CNV: lowest quartile	112	63.8 (1.2)	0.15
Area of CNV: second quartile	141	63.8 (1.1)	
Area of CNV: third quartile	171	61.9 (1.0)	
Area of CNV: highest quartile	188	63.6 (0.9)	
Area of CNV: cannot measure	77	59.9 (1.5)	

CNV = choroidal neovascularization; DA = disk area; SPED = serous pigment epithelium detachment.
*Patients with a missing value for any variable were excluded from the model.
†Other category includes fibrotic or atrophic scar, geographic atrophy, no pathologic features, blocked fluorescence, and could not grade or determine.
‡*P* value for interaction between lesion characteristic and area of CNV is 0.001.

In summary, this study shows very good reproducibility of the qualitative and quantitative assessments used in the analysis of the morphometric characteristics of AMD lesions present in participants in the CATT study. As expected, there is a strong association between baseline AMD lesion characteristics and baseline visual acuity.

Acknowledgments. The authors thank the following individuals for their contributions: Stuart L. Fine, MD, for extensive guidance and knowledge, and Robert A. Mittra, MD, for his insightful review of the scientific content of this manuscript.

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Footnotes and Financial Disclosures

Originally received: January 12, 2012.
Final revision: February 7, 2012.
Accepted: February 7, 2012.
Available online: ●●●. Manuscript no. 2012-50.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by the National Eye Institute, National Institutes of Health, Bethesda, Maryland (grant nos.: U10 EY017823, U10 EY017825, U10 EY017826, and U10 EY017828).

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