The Incidence of Neovascular Subtypes in Newly Diagnosed Neovascular Age-Related Macular Degeneration

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• PURPOSE: To determine the frequency of neovascularization subtypes as determined by fluorescein angiography (FA) alone vs FA and optical coherence tomography (OCT) grading in age-related macular degeneration (AMD).

• DESIGN: Retrospective cohort.

• METHODS: PARTICIPANTS: Newly diagnosed neovascular AMD patients who initiated intravitreal anti–vascular endothelial growth factor therapy by 1 physician from October 1, 2005 to December 1, 2012. INTERVENTIONS: Two independent graders classified the baseline lesions using FA alone and FA + OCT. MAIN OUTCOME MEASURES: Analysis of the frequency of lesion subtypes by FA alone or FA + OCT and agreement between both classification systems was performed.

• RESULTS: A total of 232 patients (266 eyes) fit the inclusion criteria. Mean age was 86.3 years; 67.7% of eyes (180/266) were from female patients, and 95.5% (254/266) were from white patients. The distribution using FA alone was 49.6% (132/266), 12.0% (32/266), 28.6% (76/266), and 9.8% (26/266) among occult, classic, retinal angiomatous proliferation, and mixed choroidal neovascularization, respectively. With FA + OCT, 39.9% (106/266), 9.0% (24/266), 34.2% (91/266), and 16.9% (45/266) were type 1 (sub–retinal pigment epithelium), type 2 (subretinal), type 3 (intraretinal), and mixed neovascularization (NV), respectively. The κ statistic was 0.65 (standard error ±0.37, $P < .001$) between the 2 classification systems, representing good agreement.

• CONCLUSION: With both FA-alone and FA + OCT grading, we found a higher incidence of type 3 NV in eyes with newly diagnosed neovascular AMD than that reported in prior studies. The κ statistic between the 2 classification systems showed "good" agreement. The discrepancies are likely attributable to the identification of a higher frequency of type 3 and mixed NV and a lower frequency of type 1 NV with the aid of OCT. (Am J Ophthalmol 2014;158:769–779. © 2014 by Elsevier Inc. All rights reserved.)

Accepted for publication Jul 8, 2014.

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AGE-RELATED MACULAR DEGENERATION (AMD) IS the most common cause of irreversible central vision blindness among individuals older than 50 years of age in the developed world,[1] and while neovascular AMD represents only 10%–15% of AMD eyes, it is responsible for more than 80% of cases of severe visual loss attributable to retinal exudation, hemorrhage, and disciform scarring.[2] The most commonly used classification of neovascular AMD was first developed for the Macular Photocoagulation Study (MPS) in 1991.[3] It was based on the only available imaging modality at that time, fluorescein angiography (FA). It characterized lesion subtypes as "classic" or well-defined choroidal neovascularization (CNV) and "occult" or poorly defined CNV. Subsequently, this classification scheme was important in determining treatment response in the first pivotal trials with photodynamic therapy[4,5] and, more recently, in selecting eligible patients and monitoring their response to treatment in the major anti–vascular endothelial growth factor (VEGF) trials.[6–11] The FA classification system has continued to be used for enrollment into subsequent neovascular AMD treatment trials.

High-definition spectral-domain optical coherence tomography (OCT) has been developed with an axial resolution as high as 7 μm and offers near histologic visualization of the retina.[12] Current treatment paradigms continue to use OCT imaging to monitor response to anti-VEGF therapy.[7–11,13,14] Additional subtypes of neovascular AMD, such as polypoidal choroidal vasculopathy (PCV)[15] and retinal angiomatous proliferation (RAP),[16–19] have been further detailed with the use of OCT. With the availability of these advancements in imaging, a new classification scheme of neovascularization (NV) based on anatomic

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2014.07.006

localization with multimodal imaging including FA and OCT[13] has been proposed, expanding upon Grossniklaus and Gass' original observations from histopathologic slides of neovascular AMD.[20]

The first purpose of this study was to evaluate the frequencies of newly diagnosed lesion subtypes in neovascular AMD in treatment-naïve patients presenting to 1 retinal physician (K.B.F.) over a 6-year time period using both the original FA classification system as originally defined by the MPS[21] and the anatomic classification with multimodal imaging combining both FA and OCT.[13] The second purpose of the study was to compare the 2 systems and to assess the agreement between the 2 classification systems.

METHODS

THIS RETROSPECTIVE COHORT STUDY DESIGN WAS approved by the Western Institutional Review Board (Olympia, Washington, USA). It complied with the Health Insurance Portability and Accountability Act of 1996 and followed the tenets of the Declaration of Helsinki.

• **DATA COLLECTION:** We retrospectively reviewed the charts and imaging data of 374 consecutive patients diagnosed with treatment-naïve neovascular AMD between October 1, 2005 and December 1, 2012. Treatments with ranibizumab (0.5 mg/0.05 mL; Lucentis, Genentech, San Francisco, California, USA), bevacizumab (1.25 mg/0.05 mL, Avastin; Genentech), or aflibercept (2.0 mg/0.05 mL, Eylea; Regeneron, Tarrytown, New York, USA) were administered by a single physician (K.B.F.).

Inclusion criteria were similar to the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[9] and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study groups.[10] All participants were older than 50 years with newly diagnosed treatment-naïve NV as evidenced by clinical examination and FA. Best-corrected visual acuity was 20/20–20/800 on a Snellen chart (differed from ANCHOR/MARINA, which included 20/40–20/320 on the Early Treatment Diabetic Retinopathy Study charts). Additionally, eyes in the study must have had OCT imaging (time-domain or spectral-domain) performed at the time of diagnosis.

Exclusion criteria were any of the following: previous treatments for CNV in the study eye, including photodynamic therapy (PDT), intravitreal steroids, intravitreal pegaptanib (Macugen; Valeant, Montreal, Quebec, Canada), or thermal laser and eyes with CNV lesions presenting with subfoveal fibrosis, central geographic atrophy (GA) at baseline, or retinal pigment epithelial tears, or composed of more than 50% hemorrhage. Eyes with CNV secondary to other maculopathies, including degenerative myopia, angioid streaks, presumed ocular histoplasmosis syndrome, or inflammatory maculopathies, were excluded.

Demographic information including age; sex; race; family history of AMD, smoking status (current, former, never), history of hypertension and diabetes, history of statin, aspirin, clopidogrel, and/or warfarin use, and history of glaucoma were collected for each patient.

FA images were obtained using a Topcon TRC 501x fundus camera (Topcon Imagenet, Tokyo, Japan). OCT imaging of all patients was performed with time-domain OCT (Stratus; Carl Zeiss Meditec Inc, Dublin, California, USA) or spectral-domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany; or 3-D OCT-2000; Topcon, Tokyo, Japan). OCT instrumentation was necessary for additional accurate identification of lesion subtype utilizing the anatomic classification of lesion subtype.[13] Standard methods of image acquisition were employed for all imaging modalities.

• **IMAGE GRADING:** The classification of neovascular lesions was made independently by 2 experienced retina specialists (S.M. and R.G.P.) who evaluated the presenting color photographs, FA, and OCT. First, all the color photographs and FA corresponding to the baseline diagnostic visit were analyzed. Neovascular lesions were subtyped according to the MPS criteria[21]and the Digital Angiographic Reading Center (DARC) Reader's Manual as occult or classic CNV, and RAP lesions were identified by criteria defined by Yannuzzi and associates[16] and the DARC Reader's Manual. Secondly, OCT images corresponding to the same diagnostic visit were reviewed, and each case was classified according to the guidelines provided by Freund and associates.[13] The anatomic classification, which uses OCT in combination with FA, categorizes lesions as type 1 (sub–retinal pigment epithelium [RPE]), type 2 (subretinal), type 3 (intraretinal), or mixed NV. Eyes with PCV were considered to be a form of type 1 CNV. Type 1, 2, and 3 NVs corresponded to occult, classic, and RAP angiographic lesions, respectively. Cases with multiple lesion types were identified as mixed NV and each component was also recorded. Table 1 provides further details of the criteria of CNV subtype classification based on each imaging modality. Finally, in cases with disagreement between FA and OCT findings (Figure 1), FA images were reanalyzed focusing on early frames to better recognize subtle angiographic findings, in particular those of RAP lesions. A third supervising grader (K.B.F.) evaluated the lesion type in the presence of significant discrepancies.

Readers also graded the lesion location and overall size. FA was used to measure the greatest linear diameter (mm) and the total area of CNV lesion (mm^2). Measurements were performed only on fundus camera images. The total area of CNV lesion was defined as the area of CNV leakage plus any contiguous areas of hemorrhage, blocked fluorescence, or serous PED that could be obscuring the boundaries of the CNV. The lesion location was defined as

TABLE 1. Correlation of Key Findings Between Different Imaging Modalities in the Classification of Neovascularization Subtypes in Eyes With Neovascular Age-Related Macular Degeneration

CNV	Color & Red-free Photographs	FA Early	FA Late	OCT
Type 1	RPE elevation with irregular height and shape; pigment mottling	Stippled hyperfluorescence within 1 or 2 minutes (fibrovascular PED), or lack of early hyperfluorescent signal (late leakage of undetermined source)	Mild to moderate staining and/or leakage corresponding to the RPE abnormalities	The area of staining corresponds to an elevation of the RPE line with sub-RPE material of mixed reflectivity, often with overlying subretinal fluid. Intraretinal fluid is less common.
Type 2	Grayish subretinal lesion occasionally with a surrounding ring of hyperpigmentation	Early intense, well-demarcated hyperfluorescence with a characteristic lacy pattern	Intense leakage originating from the area of early hyperfluorescence	The early lacy hyperfluorescence corresponds to a linear collection of subretinal hyperreflective material directly above the RPE line. The leakage corresponds to intraretinal edema and/or subretinal fluid.
Type 3	Focal intraretinal hemorrhages. Dilated right angle corkscrew-like vessels. May occur over a PED. Dilated compensatory retinal vessels. May have visible retinal-retinal anastomoses.	Early, but focal, leakage often seen in close proximity to retinal vessels. May have retinal-retinal anastomoses.	Focal intense leakage, often with cystoid macular edema	There is an intraretinal focal hyperreflective lesion in an area of localized outer retinal disruption. Often, there is a focal defect and variable degree of elevation of the underlying RPE. This intraretinal lesion corresponds to the early focal FA leakage and manifests surrounding intraretinal cystic changes.
Mixed variants				
Type 1 and 2	Various combinations of findings from types 1 and 2	Well-demarcated hyperfluorescent lacy ± surrounding area of stippled hyperfluorescence	Leakage and staining	Type 1 and Type 2 findings The area of stippled hyperfluorescence corresponds to the type 1 findings extending beyond the type 2 findings
Type 1 and 3	Various combinations of findings from types 1 and 3	Stippled hyperfluorescence ± hot spot	Staining or leakage, often with cystoid macular edema	Type 1 and type 3 findings. The area of angiographic staining corresponds to the type 1 lesion extending beyond the type 3 findings.
Type 2 and 3	Various combination of findings from types 2 and 3	Well-demarcated hyperfluorescence. No contrast of the hot spot.	Intense leakage, often with cystoid macular edema	Type 3 and type 2 findings

CNV = choroidal neovascularization; FA = fluorescein angiography; OCT = spectral-domain optical coherence tomography; PED = pigment epithelial detachment; RAP = retinal angiomatous proliferation; RPE: retinal pigment epithelium.

foveal (subfoveal or juxtafoveal) or extrafoveal, as determined according to the MPS terminology.[21]

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using SPSS software Version 21 (SPSS, Inc, Chicago, Illinois, USA). The numbers of neovascular AMD lesions as identified by the FA classification system and by the anatomic (FA and OCT) classification system were recorded, including the breakdown of neovascular lesion components in the mixed NVs. A subgroup analysis was also performed to identify

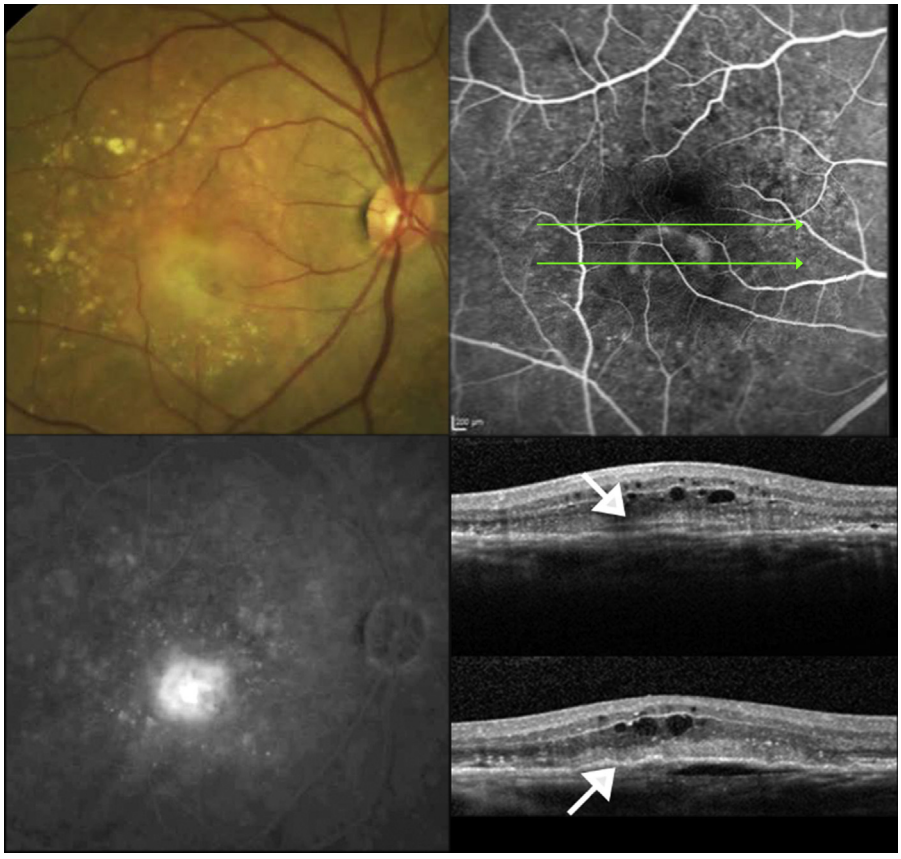

FIGURE 1. Color fundus photograph of the right eye of an 82-year-old white woman with age-related macular degeneration (Top left) showing a grayish choroidal neovascular membrane (CNV) with surrounding drusen. Fluorescein angiogram shows early well-demarcated intense hyperfluorescence (Top right) and intense late leakage (Bottom left) graded as classic CNV. The addition of spectral-domain optical coherence tomography (green arrows, Top right) shows both type 2 neovascularization (white arrow, upper image of Bottom right) and type 1 neovascularization (white arrow, lower image of Bottom right) with associated cystoid macular edema, constituting a mixed lesion.

neovascular AMD lesions based on these same classification systems in the newly diagnosed neovascular AMD eyes that had baseline spectral-domain OCT (3-D OCT 2000; Topcon, Tokyo, Japan; and Spectralis; Heidelberg Engineering, Heidelberg, Germany). The κ statistic was performed to compare the agreement between both classification systems with the entire cohort and subgroup with initial spectral-domain OCT.[22] This analysis expresses the extent to which the observed agreement exceeds that which would be expected by chance alone and is defined as follows: greater than 0.75 represents "excellent" agreement; 0.40–0.75 represents "fair" to "good" agreement; and less than 0.40 represents "poor" agreement.

The associations between FA CNV and anatomic NV classifications and each possible demographic variable were assessed individually by Fisher exact test, χ^2 test, or independent Student *t* test. Similarly, the associations between lesion characteristics such as size, greatest linear diameter, and location and each possible demographic variable were also analyzed. The demographic factors that were shown to have a significant association were incorporated into regression analyses as covariates when examining the associations between lesion characteristics and neovascular lesion subtypes. Adjusting for demographic confounders ensured that the observed associations between clinical characteristics and NV types were real and not attributable to demographic confounders.

RESULTS

A TOTAL OF 374 PATIENTS WITH TREATMENT-NAÏVE neovascular AMD in at least 1 eye treated with anti-VEGF therapy were identified. Among these 374 patients, 232 patients (266 eyes) met the eligibility criteria. The mean age was 86.3 $\pm$ 8.1 years; 67.7% of eyes (180/266) were from female patients and 95.5% (254/266) from white patients, followed by 2.6% (7/266) Hispanic, 1.5% (4/266) Asian, and 0.4% (1/266) African-American.

Using the FA classification system, the distribution of neovascular subtypes was 49.6% (132/266) occult CNV, 12.0% (32/266) classic CNV, 28.6% (76/266) RAP lesions,

and 9.8% (26/266) mixed CNV. Of mixed lesions, 50.0% (13/26) were minimally classic, 30.8% (8/26) predominantly classic, 11.5% (3/26) occult and RAP, and 7.6% (2/26) classic and RAP. Based on anatomic classification using both FA and OCT, 39.9% (106/266) had type 1 (sub-RPE), 9.0% (24/266) type 2 (subretinal), 34.2% (91/266) type 3 (intraretinal), and 16.9% (45/266) mixed NVs. Of mixed lesions, 80.0% (36/45) were mixed 1 and 2, 15.5% (7/45) mixed 1 and 3, and 4.4% (2/45) mixed 2 and 3. Overall, there was good agreement between FA and anatomic classification with a κ statistic of 0.65 (standard error $\pm$0.37, $P < .001$). When looking at each subtype individually, there was a significant increase in type 3 and mixed lesions and a decrease in type 1 subtype frequencies with the anatomic classification as compared to the FA classification (Figure 2). The overall incidence of pure classic or type 2 lesions was low in both the FA and anatomic classifications.

In the subgroup that had baseline spectral-domain OCT, using the FA classification system, the distribution of neovascular subtypes was 52.9% (82/155) occult CNV, 9.0% (14/155) classic CNV, 32.3% (50/155) RAP lesions, and 5.8% (9/155) mixed CNV. Of mixed lesions, 66.7% (6/9) were minimally classic, 11.1% (1/9) predominantly classic, 11.1% (1/9) occult and RAP, and 11.1% (1/9) classic and RAP. Based on anatomic classification using both FA and spectral-domain OCT, 40.6% (63/155) had type 1, 7.1% (11/155) type 2, 40.0% (62/155) type 3, and 12.2% (19/155) mixed NVs. Of mixed lesions, 57.9% (11/19) were mixed 1 and 2, 36.8% (7/19) mixed 1 and 3, and 5.2% (1/19) mixed 2 and 3. Overall, again there was good agreement between FA and anatomic classification, with a κ statistic of 0.67 (standard error $\pm$0.05, $P < .001$).

Of the demographic factors examined, age and use of warfarin were found to be significantly associated with the anatomic classification system (Table 2). Age at first injection was significantly older for patients with type 3 NV (88.4 years) compared with type 1 (84.9 years), 2 (84.9 years), and mixed (86.4 years) NV, respectively. Use of warfarin was more common in study eyes with type 2 (14.3%, 3/21) and 3 (12%, 11/80) NV compared to type 1 (3.8%, 4/102) and mixed (2.2%, 1/44) NV. The FA classification was not found to be associated with any of the demographic factors examined.

History of smoking was significantly associated with both lesion area and lesion diameter (Table 3). Lesion area was significantly larger for current smokers (13.05 $\pm$ 7.38 mm^2) than for nonsmokers (6.40 $\pm$ 5.81 mm^2) or former smokers (5.77 $\pm$ 5.16 mm^2). Lesion diameter was significantly larger for current smokers (4.40 $\pm$ 1.78 mm) than for nonsmokers (3.13 $\pm$ 1.44 mm) or former smokers (3.00 $\pm$ 1.58 mm).

Associations between lesion characteristics (lesion location, lesion area, and lesion diameter) and neovascular lesion subtypes were analyzed with age, history of smoking, and use of warfarin as covariates (Table 4). Compared to type 1 NV, type 2, 3, and mixed NVs were less likely to

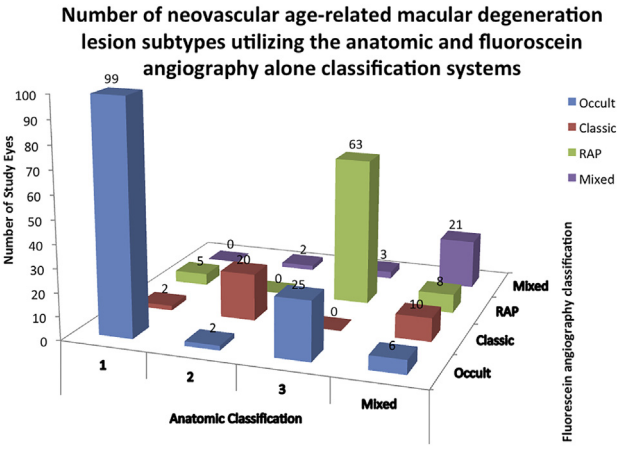

FIGURE 2. Three-dimensional graph demonstrating the correlation between the anatomic (fluorescein angiography [FA] and optical coherence tomography [OCT]) and FA-alone classification systems. X-axis is the breakdown of neovascularization (NV) lesion subtypes as identified with the anatomic classification (FA + OCT). Z-axis is the breakdown of choroidal neovascularization (CNV) as identified with the FA-alone classification. Note that there is "good" agreement with a majority of the lesion subtypes except with the anatomic identification of more type 3 (intraretinal) NV compared to FA-alone classification, identifying these as occult CNV, and anatomic identification of more mixed NV compared to FA-alone, identifying these as classic CNV.

be foveal in location. This finding was not observed with the FA classification (Table 4). Lesion area and lesion diameter were significantly associated with both anatomic and FA classification. Mixed NV had greater lesion areas and diameters compared to type 1 NV, which in turn had greater lesion areas and diameters than type 2 and 3 NV (Table 4). Similar findings were observed with the FA classification.

DISCUSSION

THE IDENTIFICATION OF NEOVASCULAR AMD LESION subtypes and their relative frequencies in newly diagnosed eyes have been assessed by FA alone with the occasional addition of indocyanine green angiography (ICG).[23–30] To our knowledge, the present study is the first to determine lesion frequencies using both an FA-based and an anatomic classification using both FA and OCT.

The anatomic classification of NV is accomplished by using both FA and OCT to define the location of the neovascular tissue with respect to the retinal layers.[13,31] This system builds on Gass' original histologic classification scheme with the addition of type 3 NV, also known as RAP.[13] Neovascular lesions are described as type 1 (sub-RPE), type 2 (subretinal), type 3 (intraretinal), and mixed NV. This classification

TABLE 2. Baseline Demographic Factors and Their Association With the Method Used for Classifying Neovascularization Subtypes in Neovascular Age-Related Macular Degeneration

	Anatomic Classification	FA Classification
	P (Fisher Exact, χ^2, or Independent Student *t* Test)[a]	
Age	.018[b]	.301
Sex	.383	.467
Race	.608	.922
Family history of AMD	.575	.628
History of smoking	.077	.428
History of HTN	.596	.770
History of DM	.561	.939
Statin	.618	.792
Aspirin	.684	.092
Clopidogrel	.811	.585
Warfarin	.041[b]	.198
Glaucoma	.149	.786

AMD = age-related macular degeneration; DM = diabetes mellitus; FA = fluorescein angiography; HTN = hypertension.

[a]Fisher exact and χ^2 test were used when comparing categorical variables. Fisher exact test was used if a cell value was less than 5. Independent Student *t* test was used when comparing categorical variable against continuous variable.

[b]Statistical significance of $P < .05$.

TABLE 3. Baseline Demographic Factors and Their Association With Initial Lesion Area and Diameter in Neovascularization Subtypes Attributable to Neovascular Age-Related Macular Degeneration

	Lesion Area	Lesion Diameter
	P (Univariate)	
Age	.274	.070
Sex	.679	.923
Race	.670	.064
Family history of AMD	.465	.634
History of smoking	.001[a]	.024[a]
History of HTN	.672	.583
History of DM	.566	.905
Statin	.093	.151
Aspirin	.105	.113
Clopidogrel	.103	.094
Warfarin	.176	.582
Glaucoma	.171	.090

AMD = age-related macular degeneration; DM = diabetes mellitus; HTN = hypertension.

[a]Statistical significance of $P < .05$.

refines the pre-established FA-based grading guidelines of the MPS[21] (Table 1) by using OCT to better localize the neovascular tissue according to Gass' anatomic terminology[32] with the goal of making a more objective and reproducible grading of neovascular lesions. While this approach is still imperfect, we believe that including OCT findings in lesion classification reduces some of the subjectivity of relying on FA alone. Since its inception, this anatomic classification has been used more frequently in clinical practice and in the literature.[33–37] Gass recognized that it was very difficult to determine clinically or even with FA the precise anatomic location of the CNV because of various factors, including the degree of pigmentation and scarring, disruptive effects on the RPE, and associated features of exudation and/or hemorrhage.[31,32] Accurate identification of the presence, location, and nature of CNV is facilitated by a multimodal approach correlating FA with OCT and may have advantages over using FA alone.[31] Previously, there have been 2 reports that used FA, ICG, and time-domain OCT to observe neovascular subtypes of AMD but defined them according to the MPS CNV classification system.[38,39] Hirami and associates divided their Japanese study population into typical AMD (54.9%), of which 46.4% had classic CNV and 0.8% had RAP, and PCV (45.1%), of which 15.0% had classic CNV and 0.0% had RAP.[38] Liakopoulos and associates designed their study in the United States to analyze and compare quantitatively the appearance of various angiographic subtypes of active CNV lesions on OCT, and they found that 36.3% were occult, 34.8% were minimally classic, 16.7% were predominantly classic, and 12.1% were RAP.[39] Despite the limitations of FA-based grading, all of the major PDT and anti-VEGF trials have continued to use this classification system even though it was developed for the application of thermal laser photocoagulation in studies conducted over 20 years ago.[3–11]

In our cohort, we found that the overall incidence of type 3 NV or RAP was much higher than what has been previously reported in white patients.[16,17,27,38–40] Previous reports estimated the incidence among Asian patients with AMD at 0.8%–4.5% in the Japanese population[38,41] and 4.5% in the Chinese population.[29] RAP is considered rare in African-American patients.[19] Among white patients, the reported incidence varies from 10% to 21.7%.[16,17,27,39,40] While the manifestations of AMD certainly differ between ethnicities owing to genetic and environmental factors,[42] varying techniques used to identify type 3 lesions may also help explain the wide range in reported frequency. While FA alone is useful for identifying early type 3 lesions, more advanced lesions may be obscured by intense intraretinal fluorescein leakage and staining of associated PEDs, leading to a diagnosis of occult CNV.[19] In the current study of a predominantly white population using the anatomic classification, we demonstrated a frequency of 34.2% (91/266) type 3 lesions, whereas using FA alone, only 28.6% (76/266) were identified as RAP. Analyzing eyes that had baseline spectral-domain OCT, we found an increased frequency of 40.0% (62/155) compared to the same cohort that demonstrated only 32.3% (50/155) by FA classification alone. As expected, OCT was useful in identifying the neovascular

TABLE 4. Comparison and Detailed Analysis of Baseline Topographic Distribution and Size of Each Neovascularization Subtype in Neovascular Age-Related Macular Degeneration

Lesion Location									
Anatomic NV Types	Foveal Location[a]	Adjusted OR	95% CI	*P*	FA CNV Types	Foveal Location[a]	Adjusted OR	95% CI	*P*
1	79.2% (84/106)	Reference			Occult	80.3% (106/132)	Reference		
2	70.8% (17/24)	0.180	0.039–0.823	.027[b]	Classic	81.2% (26/32)	0.173	0.021–1.395	.099
3	79.1% (72/91)	0.103	0.018–0.537	.007[b]	RAP	77.6% (59/76)	0.172	0.018–1.618	.124
Mixed	95.5% (43/45)	0.184	0.039–0.834	.028[b]	Mixed	96.1% (25/26)	0.129	0.015–1.087	.129

Lesion Area					
Anatomic NV Types	Mean (mm^2)	SE	FA CNV Types	Mean (mm^2)	SE
	$P = .022$[b]			$P = .016$[b]	
1	7.354	1.094	Occult	7.525	1.011
2	3.805	1.454	Classic	4.616	1.403
3	4.196	1.058	RAP	4.601	1.150
Mixed	10.106	1.337	Mixed	9.491	1.485

Lesion Greatest Linear Diameter					
Anatomic NV Types	Mean (mm)	SE	FA CNV Types	Mean (mm)	SE
	$P = .018$[b]			$P = .008$[b]	
1	3.310	0.272	Occult	3.399	0.249
2	2.308	0.361	Classic	2.554	0.346
3	2.672	0.263	RAP	2.691	0.284
Mixed	3.850	0.332	Mixed	3.651	0.366

CI = confidence interval; CNV = choroidal neovascularisation; FA = fluorescein angiography; NV = neovascularisation; OR = odds ratio; RAP = retinal angiomatous proliferation; SE = standard error.

[a]Lesion location is classified as foveal (subfoveal and juxtafoveal) and nonfoveal (extrafoveal). Ages, history of smoking, and use of warfarin were taken into account as covariates.

[b]Statistical significance of $P < .05$.

vessels and cystic spaces within the retina but was less helpful in assessing changes beneath the pigment epithelium.[18,19] The combination of FA and OCT allowed our readers to make a more precise identification of the frequency of type 3 lesions. Our finding of such a high incidence of type 3 NV among white AMD patients suggests that clinicians should maintain a high index of suspicion for this neovascular subtype and carefully review both angiographic and OCT findings to detect its presence.[41,42] Early detection of type 3 NV before its maturation enables earlier treatment with anti-VEGF therapy, which can then lead to more significant lesion regression and prevention of substantial photoreceptor loss.[13,18,19]

Interestingly, the current study found the incidence of type 2 (subretinal) NV to be 9.0% (24/266) and 12.0% (32/266) classic CNV with FA alone. In the subgroup with initial spectral-domain OCT, 9.0% (14/155) had classic CNV and 7.1% (11/155) had type 2. These percentages are lower than those seen in previous studies that used FA alone, with incidences ranging from 11.5% (15/130)[27] to 20% (32/157).[30] Given the difficulty of identifying well-defined classic CNV proliferating above the RPE with FA alone, our findings emphasize that in neovascular AMD, pure classic CNV or type 2 NV are infrequent, especially when combining FA with OCT. This finding is relevant for ongoing clinical trials, including the phase 3 safety and efficacy study of Fovista (E10030), which requires that some component of the CNV lesion be classic.[43]

Additionally, the anatomic classification identified more mixed lesions than the FA classification. With FA grading, mixed CNV subtypes are classified as predominantly classic or minimally classic,[26,30] but RAP lesions are typically categorized as a separate entity.[28] In one study of 184 fluorescein angiograms of newly diagnosed neovascular AMD eyes, George and associates noted that fewer than half of the angiograms evaluated would have met the angiographic eligibility criteria of either the ANCHOR or MARINA studies.[27] The most common reason for ineligibility was the presence of RAP, which accounted for one third of lesions classified as minimally classic or occult on presentation.[27] In the current study, classification by FA alone identified 9.8% (26/266) as mixed CNV, whereas with the addition of OCT, 16.9% (45/266) were identified as mixed NV. Similar to George and associates' study, when using the anatomic classification system, 22.2% (10/45) were mixed 1 and 3 or mixed 2 and 3, with some component of a type 3 lesion. The results from the subgroup analysis with baseline spectral-domain OCT also showed similar

results, with an even higher incidence of mixed lesions, 42.1% (8/19), that had a type 3 component, again emphasizing the increased accuracy with OCT.

It has long been recognized that, under the traditional MPS classification scheme, eyes with well-defined or classic CNV, poorly defined or occult CNV, and RAP may have different natural courses and respond differently to treatment. Large randomized clinical trials have selected distinct lesion types for inclusion criteria because they were believed to respond differently to treatment.[9,10,44] It is also well known that some patients with type 1 neovascular AMD may experience little or no vision loss.[45] Based on histopathologic data, Grossniklaus and associates suggested that the RPE and photoreceptors may be nutritionally supported by the NV tissue underneath the RPE in type 1 neovascular AMD.[46] Interestingly, in the MARINA study, these patients did not gain as many letters of vision when compared to the classic lesions in the ANCHOR study,[9,10] a finding that may imply that type 1 lesions are a more mature form of NV, providing nutrients and oxygen to an ischemic outer retina, and represent a compensatory form of neovascular AMD.[46] As treatment endpoints of all of the anti-VEGF therapy clinical trials include visual acuity and anatomic improvement on OCT, it seems logical to use OCT imaging to assist in the initial identification of neovascular AMD lesion subtypes.

FA has been instrumental in the identification of neovascular AMD lesion types but has been based on somewhat subjective interpretation of FA. The DARC Reader's Manual has provided strict guidelines for reading centers to identify neovascular lesion subtypes, but not all treating clinicians in the community are well versed in the identification of subtypes based on FA alone. Previous studies have evaluated the inter-observer reliability of retina specialists using the statistical value κ (value of $\kappa = 1$ is perfect agreement, whereas $\kappa = 0$ is no agreement). Studies using this FA classification system ranged from κ values of 0.63 to 0.64, which demonstrated "good" or "intermediate" agreement.[30,47,48] Similarly, in our study, the FA-alone classification system had "good" agreement with the anatomic classification based on a κ value of 0.65 and in the subgroup analysis, a κ value of 0.67. Although there was "good" agreement between the 2 classification systems, the differences were mainly evident in the observation that FA and OCT clearly defined more type 3 NV and mixed lesions and fewer type 1 lesions (Figure 2). This observation was expected, especially given the difficulty of diagnosing type 3 and mixed lesions based on FA alone (Figure 1). In cases of occult-like lesions on FA, the additional resolution of OCT allowed for more accurate localization of NV involvement. Especially with the improvements in spectral-domain OCT, this form of imaging in addition to FA offers clinicians a more reliable approach to identify the initial lesion subtype and monitor response to individualized treatment.

The demographic data from our patient population demonstrated a significantly older population among type 3 lesions, which has been previously reported.[16,18] The overall mean age of our entire cohort was 86.4 years, and those with newly diagnosed type 3 lesions were older than those with the other subtypes (Table 2). Interestingly, the FA-alone classification system did not find the same association and may be explained by the fact that anatomic NV classification uses multimodal imaging with both FA and OCT, allowing for a more accurate phenotyping of NV and thus a more accurate correlation of subtypes with the corresponding demographic characteristics.

In addition, the use of warfarin was also significantly associated with type 2 and 3 NVs compared to the other lesions (Table 2). As stated previously, the incidence of pure type 2 lesions was small, and therefore it is difficult to truly interpret their association. Type 3 NV is typically found in the older population, who may be at higher risk for cardiovascular disease. In a subgroup analysis of the nonneovascular eye of 83 treatment-naïve unilateral neovascular AMD patients from the same cohort, type 3 NV had an increased likelihood of reticular pseudodrusen (RPD), thinner subfoveal choroidal thickness (SFCT), and central GA. Within this same population, warfarin use was also significantly associated with a thin SFCT, and the use of statin, clopidogrel, and warfarin also approached statistically significant association with the presence of RPD and thin SFCT (Boddu S, et al. Correlation between NV lesion type and the clinical characteristics of nonneovascular fellow eyes in patients with unilateral neovascular age-related macular degeneration, unpublished data). These medications are frequently used in patients with cardiovascular disease, and their correlation to thinner SFCT, RPD, and noncentral GA may reflect that these ocular findings may be associated with significant vascular alterations and ischemia.[49] Spaide recently described that outer retinal atrophy can also develop after the regression of RPD and thinning of the underlying choroid.[50] Although RPD might not be directly associated with the onset of type 3 NV owing to their differing localization within the macula, they may be a marker of outer retinal and choroidal ischemia[42] that leads to the development of type 3 NV with anastomoses from the deep inner retinal capillary plexus to the RPE.

Initial lesion characteristics including area and diameter were both significantly larger in mixed NV lesions compared to type 1 NVs, which in turn were greater in size than type 2 and 3 NVs (Table 4) in both the FA-alone and anatomic classification systems. Correlating these lesion characteristics with the demographic variables tested, a history of smoking was significantly associated with both lesion area and diameter (Table 3). Lesion area and diameter were both significantly larger in current smokers compared to nonsmokers or former smokers. Smoking status has been strongly associated with neovascular AMD, specifically high-risk genetic haplotypes including the CFH[51–53] and LOC387715/HTRA1 haplotypes,[51] and confers a higher incidence

and risk of progression of geographic atrophy.[54] Environmental factors such as active smoking may affect lesion size and predispose patients who are genetically susceptible to developing an overall larger, mixed neovascular AMD lesion complex and could influence treatment strategies based on this original lesion subtype.

Incorporating an anatomic classification for neovascular AMD that evaluates both FA and OCT findings could potentially allow for a more individualized therapy and influence clinical trial design to target specific lesion subtypes with different treatment strategies. As noted in the 2-year outcomes from the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), ranibizumab monthly–treated groups had the highest proportion in which geographic atrophy developed and it was higher in both anti-VEGF monthly-treated groups compared to the as-needed groups.[55] Type 1 NV lesions rarely have significant regression and are likely resistant to both GA and anti-VEGF therapy,[13] whereas type 2 and 3 NV, early in their evolution prior to maturation with retinal and choroidal anastomoses, typically show exquisite sensitivity to anti-VEGF therapy,[13,56] but may also show an increased rate of GA (Xu L, et al. IOVS 2013; 54:ARVO E-Abstract 6269). Response to treatment and vision have been associated to initial lesion subtype, and a cohort study of the CATT trial demonstrated that predominantly or minimally classic lesions were associated with worse visual acuity than occult lesions.[57] Grunwald and associates also recently reported from the CATT research group that baseline risk factors for GA development included initial RAP lesion type, baseline GA in the fellow eye, ranibizumab compared to bevacizumab use, and monthly dosing compared to pro re nata dosing.[58] Accurate identification of each initial neovascular AMD lesion subtypes with the anatomic classification system would allow clinicians to tailor treatment accordingly and predict those individuals who may respond well with a monthly, treat-and-extend, or as-needed therapy and avoid long-term treatment complications such as GA.

Limitations of this study include its retrospective nature and grading based on 2 independent observers who were not masked to the original diagnosis of neovascular AMD. Both observers were highly trained retina specialists, and their experience with both grading systems could have affected the results. Despite its limitations, this is the first study that utilizes OCT to help identify initial lesion subtype based on an expanded version of Gass' original anatomic classification system in treatment-naïve neovascular AMD eyes. There was "good" agreement between the FA-alone classification and anatomic classification system, but, as this study demonstrated, there remains a need to incorporate OCT imaging to accurately categorize neovascular AMD subtypes. The anatomic classification system offers a more reliable method for identifying important baseline information that should allow for a better understanding of pathogenesis and risk factors for the development of specific neovascular lesions. We believe that future studies would benefit by incorporating OCT into the classification of neovascular AMD subtypes as a more clinically relevant classification system. This would allow for more individualized therapy and would identify those eyes more susceptible to certain complications, including geographic atrophy.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and the following were indicated: K.B.F.: consultant to Regeneron, Genentech, Bayer HealthCare, and Heidelberg Engineering (honorarium for each); R.G.P.: consultant to Carl Zeiss Meditec, Bayer HealthCare, and Novartis (honorarium for each); research support from Bayer Healthcare, Novartis, Heidelberg Engineering, Thea, Sensimed; D.T. (biostatistical consultant): consultant to Regeneron. This work was supported by a research grant from the LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Hospital, New York, NY, and The Macula Foundation Inc., New York, NY. The funding organizations had no role in the design or conduct of this research. Contributions of authors: design of the study (J.J.J., S.M., R.G.P., K.B.F.), conduct of the study (J.J.J., C.Y.C., S.M., R.G.P., L.X., M.M., S.B., K.B.F.), collection of the data (J.J.J., S.M., R.G.P., L.X., M.M., S.B.), management of the data (J.J.J., C.Y.C., S.M., S.G.P., L.X., M.M., S.B., K.B.F.), analysis of the data (J.J.J., C.Y.C., S.M., L.X., K.B.F.), interpretation of the data (J.J.J., C.Y.C., S.M., R.G.P., L.X., M.M., K.B.F.), preparation of the manuscript (J.J.J., C.Y.C.), review of the manuscript (J.J.J., C.Y.C., S.M., R.G.P., L.X., M.M., S.B., K.B.F.), and approval of the manuscript (J.J.J., C.Y.C., S.M., R.G.P., L.X., M.M., S.B., K.B.F.).

The authors thank Uma Mudaliar, MD, MPH (Emory University School of Medicine, Atlanta, Georgia, USA) and Desmond Thompson, PhD (Biostatistical Consultant, New Hope, Pennsylvania, USA) for their assistance with the preliminary statistical analysis.

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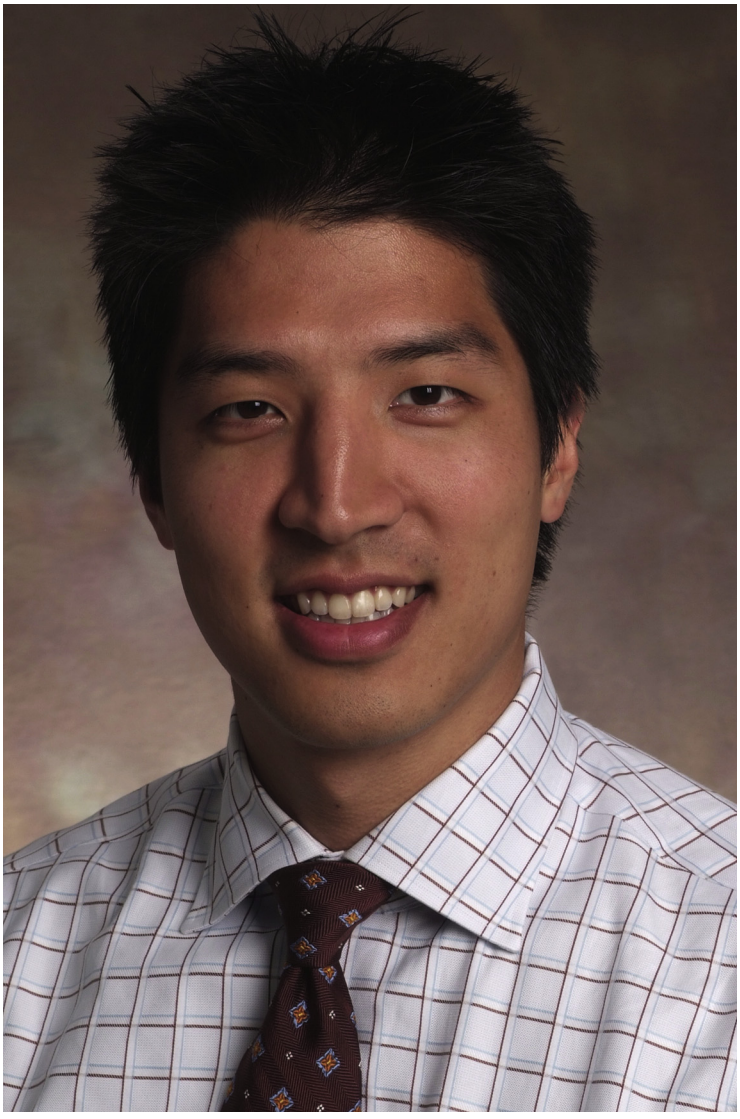

Biosketch

Jesse J. Jung received his BA in biology and psychology at Washington University in St. Louis and his MD at Emory University School of Medicine. After completing a transitional year internship at Emory University School of Medicine, he completed his Ophthalmology residency and was Chief Resident during his final year of residency at New York University School of Medicine/Manhattan Eye, Ear, and Throat Hospital. He is currently a second year vitreoretinal fellow at the Edward S. Harkness Eye Institute, Columbia University College of Physicians and Surgeons/ Vitreous Retina Macula Consultants of New York/Manhattan Eye, Ear, and Throat Hospital under the mentorship of Drs. Stanley Chang and Lawrence Yannuzzi.

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