Is Drusen Area Really So Important? An Assessment of Risk of Conversion to Neovascular AMD Based on Computerized Measurements of Drusen

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Purpose. To assess the relative risk of an eye's conversion to wet age-related macular degeneration (AMD) based primarily on drusen measurements obtained from analysis of digitized images.

Methods. Four hundred forty-four subjects (820 eyes) enrolled in the Age-Related Eye Disease Study (AREDS I) and 78 subjects (129 eyes) from the Prophylactic Treatment of AMD trial (PTAMD) were studied retrospectively. Drusen size, distribution, drusen area, and hyperpigmentation in two central macular regions on baseline fundus images were determined using an image analysis algorithm. The relative risk for choroidal neovascularization (CNV) based on drusen area, presence of one or five large drusen, hyperpigmentation, and fellow eye status was calculated.

Results. Odds ratios (ORs) for measured drusen area within the 1000- and 3000-μm regions were 1.644* (1.251–2.162) and 1.278 (0.927–1.762) for AREDS eyes and 0.832 (0.345–2.005) and 1.094 (0.524–2.283) for PTAMD eyes (*$P < 0.05$). In the 1000-μm region, respective ORs for the presence of a large druse, hyperpigmentation, and fellow eye affected were 2.60, 1.71, and 6.44* for AREDS eyes and 8.24, 1.37, and 17.56* for PTAMD eyes; for the 3000-μm region, ORs were 3.45*, 3.40*, and 4.59* for AREDS and nonsignificant, 6.58, and 11.62* for PTAMD eyes, respectively.

Conclusions. Total drusen area, presence of large drusen, and the presence of hyperpigmentation were not consistent risk factors for an eye's development of CNV. Risk depended on study cohort as well as location. Having an affected fellow eye was the strongest and most consistent risk factor across all models. A larger drusen area does not necessarily increase an eye's risk of conversion to CNV. (*Invest Ophthalmol Vis Sci.* 2012;53:1742–1751) DOI:10.1167/iovs.11-9338

Determining the odds that a patient with dry or a nonexudative form of age-related macular degeneration (AMD) will progress to the neovascular form is important. Prompt intervention with pharmacologic treatments can greatly improve visual outcomes in neovascular or wet AMD. High-risk patients should therefore have more frequent follow-up visits, as many patients who develop wet AMD are unaware of subtle visual changes. While systemic[1,2] and genetic[3–7] risk factors continue to be identified, the results of a fundus examination allow a clinician to approximate risk immediately.

Many studies have emphasized the importance of the presence of a large druse in the macula in estimating the risk of developing late AMD.[8–13] It has been stated that the number of large drusen is closely related to the total area of drusen and that total drusen area is an important reported risk factor for the development of late AMD.[14,15] Unfortunately, the actual measurement of the area covered by drusen in a specific region of regard is not a simple task. The drusen area in eyes of subjects enrolled in large trials has been measured using fixed circular templates, requiring that some estimates be made by the reader.[10] We carefully investigated the association between drusen size and drusen area using a computer algorithm and found that the number of intermediate drusen, as measured rigorously in a large cohort of AMD patient eyes, was more highly correlated to drusen area than was the number of large drusen.[16]

In the Age-Related Eye Disease Study (AREDS I), a severity scale for AMD was developed after the assessment of fundus images from 3212 subjects who did not have advanced AMD bilaterally.[17] Advanced AMD was defined as the presence of neovascular AMD, a history of photocoagulation for AMD, or geographic atrophy involving the central macula. Trained readers made morphological assessments of baseline photos, grading each image for drusen characteristics (size, type, and area), pigment abnormalities (increased pigment, decreased pigment, geographic atrophy), and the presence or absence of abnormalities characteristic of wet AMD such as hemorrhage, fibrosis, and fluid. Large drusen were defined as those being at least 125 microns in size, measured along the smallest dimension. Intermediate drusen were 63 to 124 microns in diameter, while small drusen were less than 62 microns. A detailed and comprehensive severity scale was subsequently derived from these image data, allowing the risk of developing end-stage or advanced AMD to be estimated from morphological criteria as assessed at baseline.[14]

A simplified severity scale using a point scoring system was subsequently developed for easier application in the clinical setting.[15] With the simplified scale, pigment abnormalities and the presence or absence of a large druse are key to the risk assessment, and if present, 1 point is given for each of these features. The points for each eye are summed then converted to a probability. If a patient has no late AMD in either eye, the scale gives the chance of that patient progressing to late AMD in either one of their two eyes. If a patient already has late AMD in one eye, the risk of progression is estimated for the remaining eye.

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While the presence of such morphological findings is important, their location has received little attention. In AREDS, according to the comprehensive severity scale,[14] large drusen located within two disc diameters from the foveola were counted (inside a 6000-micron diameter circle). Pigmentary abnormalities, however, were tallied when they were found within 1500 microns from the fovea. This disparity is not mentioned in the simplified scale descriptions,[15] and the effect that such ambiguity has on risk assessment is not clear.

Drusen size and drusen area measurements made by different readers often differ substantially. In one study using conventional template techniques applied to fundus photographs, agreement was only 66% for drusen area and 67% for drusen size measurements.[10] Computer analysis has been shown to facilitate reproducible assessment of satellite and surveillance images, and the technique is valuable in drusen detection and characterization.[18,19]

In the present study, we wished to determine an eye's risk of neovascular AMD when drusen were categorized and measured using quantitative image analysis methods.[19] We also assessed these and other features in specific regions of regard to investigate whether the location of the pathology had a substantial influence on the risk profiles. We are unaware of other reports wherein computerized methods were applied to thousands of digital images from large cohorts of subjects to study drusen.

Methods

We evaluated the morphological characteristics of the previously acquired fundus images of 522 subjects (949 eyes) at the UPMC Eye Center who were enrolled in one of two separate prospective clinical trials, AREDS I[17] and the Prophylactic Treatment of Age-Related Macular Degeneration study (PTAMD).[20,21] The images were digitized and read by masked readers. Institutional review board approval was obtained, and the Declaration of Helsinki was followed. To be eligible for AREDS, subjects had to have had good visual acuity of at least 20/32 in both eyes (categories 1–3) or in one eye with a specific AMD morphological profile in the fellow eye (category 4). The amount of AMD varied from virtually none in both eyes (category 1), mild or borderline AMD in one or both eyes (category 2), or large drusen or extensive intermediate drusen in one or both eyes (category 3), to advanced AMD in one eye and good visual acuity $\geq$20/32 in the fellow eye. We studied 376 AREDS subjects who had both eyes eligible and 68 who had only one eligible eye (total 444 AREDS subjects, 820 eyes). We also analyzed the images of 78 subjects in the PTAMD study, 51 of whom had both eyes eligible and 27 of whom had only one eye eligible.

In PTAMD, eyes of subjects had to manifest more drusen at baseline than AREDS subjects to be eligible, as the trial investigated laser effects on drusen. PTAMD eyes had to have at least 5 drusen of at least 63 microns in diameter located in the central macula and a best-corrected visual acuity of at least 20/63 at baseline. Subjects in whom both eyes were eligible had one of their eyes randomly selected to subthreshold laser treatment. Subjects having only one eye eligible had that eye randomized to either treatment or observation. In the present study, we did not include in the formal analysis any PTAMD eyes that were subsequently treated with subthreshold laser, as such treatment could have influenced the development of choroidal neovascularization (CNV). For PTAMD, our analysis was thus limited to 62 subjects and 62 eyes. We did, however, perform all the analyses on all the eligible eyes of the PTAMD subjects but do not report them specifically.

A previously described drusen analyzer[15] was used to measure the features of drusen. An advantage of the software that helps make the data more reproducible is the requirement that the measurements made on each digital image be indexed to the diameter of the optic nerve on that image. In this way, any noise in the measurements resulting from variable magnification or from the influence of the refractive status of each eye is minimized. The drusen area measurement provided by the analytical software results in the form of a continuous variable, in increments of one hundredth of a square millimeter.[19] The drusen distribution, that is, the number of drusen of various sizes, is also generated.

In addition to drusen, we also assessed the presence or absence of fundus hyperpigmentation, although we did not quantify the area of this hyperpigmentation. We did not include hypopigmentation in the assessment as such changes are typically more subtle and less apparent than hyperpigmentation. As the readers looked at every fundus image, it is unlikely that hypopigmented regions were mistaken for drusen. We did not distinguish between soft and hard drusen and lumped them together in our counts. Fluorescein angiography was not performed in AREDS at baseline, and neither optical coherence tomography (OCT) nor autofluorescence imaging had been clinically introduced when the study was launched. Thus, we did not consider reticular drusen separately. We excluded those few subjects who had end-stage central geographic atrophy in either eye at baseline. We considered the fellow eye to be affected with CNV only if there was evidence of wet AMD including previous laser or photodynamic therapy treatment by history or the presence of fibrotic scarring, subretinal fluid, hemorrhage, or hard exudates on clinical examination.

Subjects were followed from 12 to 2953 days, with an average follow-up of 1294 days or 3.5 years. One AREDS subject (category 3) was lost to follow-up after having only one postbaseline visit (12 days), and one AREDS subject (category 4) suffered an event 20 days after enrollment. All other subjects were followed for a minimum of 200 days. All morphological assessments were performed in a masked manner and in a random order. In the AREDS trial, subjects were randomized to intervention with one of four vitamin or micronutrient groups. We controlled for the possible effect of the assigned intervention as part of our analysis.

After collecting the data, we developed retrospective risk models predictive of CNV event occurrence for an eye, based on the eye's morphological features seen at baseline in both AREDS and PTAMD cohorts. In our models, we studied the following parameters: (1) the presence or absence of hyperpigmentation in the central 1000- and 3000-micron-diameter regions of the macula, (2) whether or not the fellow eye was affected by previous neovascular AMD, and (3) the total drusen area, measured as a continuous variable, within the central 1000- and 3000-micron regions.

We also included two categorical statistical models. The first was based on whether or not the total drusen area in a region reached a threshold amount, equivalent to the area of either one or five large drusen. The second categorical model was based on the presence or absence of at least one large druse. We also included best-corrected ETDRS visual acuity and age of the subjects.

To account for the clustering of eyes within subjects, we estimated logistic regression models using the method of generalized estimating equations. Two regions of interest within the macula were considered: the central 1000- and 3000-micron-diameter circles, centered at the foveola. For each region, four models were estimated: (1) the full model in which both the AREDS and PTAMD study subjects were pooled and allowing for an interaction between drusen area and the specific study in which the patient participated, (2) a model using AREDS subjects alone, (3) a model using only PTAMD subjects, and (4) a model in which both studies were simply combined without allowing for an interaction. The R statistical programming language and environment was used to perform all of the computations and to construct graphs (R Development Core Team. 2009. R: A language and environment for statistical computing. Foundation for Statistical Computing, Vienna, Austria. ISBN 3–900,051-07-0, http://www.R-project.org).

We expressed the effects of all the explanatory factors for CNV event occurrence as odds ratios (ORs). For categorical explanatory factors such as pigment occurrence (yes/no), the effect is the odds for a CNV event occurring given a "yes" response divided by the odds for

Table 1. Logistic Regressions Odds Ratio Point Estimates Using the Method of Generalized Estimating Equations (Response: CNV Event): Central 1000-Micron Region

	Odds Ratio Point Estimates (Except as Noted)				
	Model 1				
Parameter	AREDS as Reference	PTAMD as Reference	Model 2 AREDS Only	Model 3 PTAMD Only*	Model 4 AREDS + PTAMD Assumes No Influence of Study Group
No. of subjects	506	506	444	62	506
Intercept (age = 0, pigment = N, fellow eye affected = N, Drusen area = 0)	0.128	0.385	0.026	0.894	0.359
Age, y	0.975	0.975	0.994	0.955	0.963
Pigment = Y	1.836	1.836	1.634	3.050	1.850
Fellow eye affected = Y	***7.202***	***7.202***	***6.177***	***13.100***	***7.769***
Drusen area (scaled)	***1.685***	0.862	***1.644***	0.832	***1.540***
Study = AREDS	NA	0.331	NA	NA	NA
Drusen area × (study = AREDS)	NA	***1.956***	NA	NA	NA
Study = PTAMD	3.022	NA	NA	NA	NA
Drusen area × (study = PTAMD)	***0.511***	NA	NA	NA	NA

Models 2, 3, and 4 are for comparison only. Odds ratio estimates in ***bold italic*** are statistically significantly different from 1 (intercept terms are ignored).

* Estimated as a generalized linear model, generalized estimating equation not needed (only one eye for each subject).

an event given a "no" response. For continuous explanatory factors such as age, the OR is the ratio of the odds for a CNV event at age x in years divided by the odds at age $x - 1$. For these statistical models, the measured drusen area in the eyes of cohorts was transformed to have a mean of 0 and a standard deviation of 1. Thus, the OR is based on the effect of a 1-standard deviation increase of drusen area. The level of statistical significance was set at 0.05.

As neither baseline visual acuity nor the AREDS supplement group assignment achieved statistical significance in any of our models, we did not include them in our final models. Age of the subjects in years was included for descriptive purposes.

Results

Tables 1 and 2 summarize our results for each statistical model for parameters that included measured drusen area and presence of hyperpigmentation located within the central 1000- and 3000-micron-diameter regions of regard. The subject's age and whether or not the fellow eye was affected were also included. We found a statistically significant (SS) interaction effect between drusen area and the particular study in which the subject was enrolled (AREDS versus PTAMD). Because model 1 includes this interaction, the effect of drusen area was allowed to be different for PTAMD and AREDS. This interaction was statistically significant in the 1000-micron region, which indicates that the effect of drusen area is different in the two studies. Models 2, 3, and 4 provide a better understanding of the interaction term in model 1. Model 2 estimated the drusen area effect separately for AREDS and model 3 similarly for PTAMD. Model 4 does not include the interaction and essentially averages over the two different effect estimates. Detailed results for the separate models, including confidence intervals, are shown in Table 1A. For the 3000-micron region, the interaction term was not statistically significant. The results for this region are presented in Table 2, with more details in Table 2A.

Referring to the central 1000-micron region (Table 1), all models showed a large positive effect for fellow eye affected, with the ORs ranging from 6.177 to 13.1. Neither age nor pigment occurrence was statistically significant (pigment increased the odds, while age slightly decreased the odds, but the ORs for age were very near 1). In model 1, the odds of a CNV event occurrence increased by a factor of approximately 1.685 (95% confidence interval [CI], 1.248–2.276) for each standard deviation increase in drusen area in eyes of the AREDS subjects; for PTAMD subjects, an increase in drusen area resulted in a decreased chance of having a CNV event occurrence, with an OR of 0.862 (95% CI, 0.494–1.502).

Model 2 estimates the drusen area OR as 1.644 (95% CI, 1.251–2.162) for eyes of AREDS subjects alone, and model 3 estimates the drusen area OR as 0.832 (95% CI, 0.334–2.005) for PTAMD subject eyes. As can be seen from the CIs in Table 1A, the former OR was significantly different from 1, but the latter was not (no effect). Note that in model 4, where any interaction between drusen area and study is ignored, the effect of fellow eye affected (OR, 7.769) seems to be somewhat overstated; the influence of drusen area (OR, 1.540) fell between the separately estimated effects. Both were statistically significant. For the central 1000-micron-diameter region, the drusen area measurements ranged from 0 to 0.35 mm^2, with a mean and standard deviation of 0.043 ± 0.060 for AREDS, 0.123 ± 0.076 for PTAMD, and 0.049 ± 0.065 for AREDS and PTAMD combined. To put these results into perspective, the area covered by 5 large drusen is 0.06136 mm^2.

When we expanded the region of regard to 3000 microns (Table 2), all four models showed a large, statistically significant effect when the fellow eye was affected. The OR for age is slightly below 1, but again, not statistically significant in any of the four models. The odds ratios for pigment in the 3000-micron region were higher compared with those for the 1000-micron region, and they were all statistically significant. For models 1, 2, and 4, the OR for pigment ranged from 4.250 to 4.591, while for model 3, the OR was 7.399.

Compared with the 1000-micron region, the ORs for drusen area as a continuous variable for the 3000-micron location were closer to 1 and not statistically significant in any of the models, including our adjusted pooled model, model 1 (Table 2A). Model 2 estimated the drusen area OR for AREDS subjects alone as 1.278 (95% CI, 0.927–1.762). Model 3 estimated the drusen area parameter OR for PTAMD subjects alone as 1.094 (95% CI, 0.524–2.283). The drusen area for the 3000-micron region ranged from 0 to 2.16 square microns with a mean ± standard deviation of 0.208 ± 0.335 for AREDS, 0.693 ± 0.458

Table 1A. Detailed Results for the Central 1000-Micron Region

Model 1: AREDS as Base				
		95% Confidence Interval		
1000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.128	0.002	9.636	
Age, y	0.975	0.924	1.029	
Pigment = Y	1.836	0.739	4.559	
Fellow eye affected = Y	7.202	3.201	16.205	*
Drusen area (scaled)	1.685	1.248	2.276	*
Study = PTAMD	3.022	1.160	7.871	
Drusen area × (study = PTAMD)	0.511	0.280	0.934	*
Model 1: PTAMD as Base				
		95% Confidence Interval		
1000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.385	0.006	25.579	
Age, y	0.975	0.924	1.029	
Pigment = Y	1.836	0.739	4.559	
Fellow eye affected = Y	7.202	3.201	16.205	*
Drusen area (scaled)	0.862	0.494	1.502	
Study = PTAMD	0.331	0.127	0.862	
Drusen area × (study = AREDS)	1.956	1.071	3.571	*
Model 2: AREDS Only				
		95% Confidence Interval		
1000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.026	0.000	23.387	
Age, y	0.994	0.914	1.082	
Pigment = Y	1.634	0.573	4.661	
Fellow eye affected = Y	6.177	2.406	15.857	*
Drusen area (scaled)	1.644	1.251	2.162	*
Model 3: PTAMD Only†				
		95% Confidence Interval		
1000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.894	0.001	704.18	
Age, y	0.955	0.886	1.029	
Pigment = Y	3.050	0.370	25.113	
Fellow eye affected = Y	13.100	1.878	91.380	*
Drusen area (scaled)	0.832	0.345	2.005	

* The parameter met statistical significance, $P < .05$.

† Estimated as a generalized linear model, generalized estimating equation not needed (only one eye for each subject).

for PTAMD, and 0.243 ± 0.366 for AREDS and PTAMD combined.

When we used the presence or absence of at least one large druse as a potential risk factor for the 1000- or 3000-micron region of regard (in lieu of measured drusen area), our results were somewhat different (Table 3). A greater proportion of PTAMD subjects had a large druse (more than 50%) compared with the AREDS subjects (a large druse defined here as one having a normalized diameter of at least 125 microns using our analyzer).[19] The estimated ORs for the presence of a large druse were not consistent across study and region, and they differed from the results generated when drusen area was treated as a continuous variable (as in Tables 1 and 2). This could very well be due to confounding effects often seen when quantitative variables are artificially categorized, and especially when they are dichotomized. For the central 3000-micron region in the AREDS model, the following risk factors were statistically significant: the presence or absence of pigment, the presence or absence of a large druse, and whether or not the fellow eye was affected (Table 3A).

When we instead categorized eyes as either having or not having a threshold drusen area of at least 0.01227 mm^2 (the area of one large druse) or at least 0.06136 mm^2 (the area of five large drusen), respectively, our results again changed (Table 4). In the central 1000-micron region and using the threshold drusen area as >0.06136 mm^2, the OR for AREDS subjects was 3.299 and significant. In the 3000-micron region of regard, only pigment and fellow eye affected were

Table 2. Logistic Regressions Odds Ratio Point Estimates Using the Method of Generalized Estimating Equations (Response: CNV Event): Central 3000-Micron Region

	Odds Ratio Point Estimates (except as noted)				
	Model 1				
Parameter	AREDS as Reference	PTAMD as Reference	Model 2 AREDS Only	Model 3 PTAMD Only*	Model 4 AREDS + PTAMD Assumes No Influence of Study Group
No. of subjects	506	506	444	62	506
Intercept (age = 0, pigment = N, Fellow eye affected = N, drusen area = 0)	0.094	0.169	0.043	0.128	0.173
Age, y	0.976	0.976	0.986	0.970	0.969
Pigment = Y	***4.542***	***4.542***	***4.250***	***7.399***	***4.591***
Fellow eye affected = 1	***5.925***	***5.925***	***5.070***	***12.718***	***6.217***
Drusen area (scaled)	1.296	1.029	1.278	1.094	1.273
Study = AREDS	NA	0.559	NA	NA	NA
Drusen area × (study = AREDS)	NA	1.260	NA	NA	NA
Study = PTAMD	1.790	NA	NA	NA	NA
Drusen area × (study = PTAMD)	0.794	NA	NA	NA	NA

Models 2, 3, and 4 are for comparison only. Odds ratio estimates in ***bold italic*** are statistically significantly different from 1 (intercept terms are ignored).

* Estimated as a generalized linear model, GEE not needed (only one eye for each subject)

significant risk factors when the drusen area threshold was $\geq$0.01227 microns^2 (one large druse–equivalent area). At a threshold drusen area equivalent to at least five large drusen, all factors were significant (pigment present, fellow eye affected, and drusen area >0.06136). Note that there were no PTAMD observations in the lowest one druse area grouping for either the 1000- or 3000-micron regions of regard because the eligibility requirements for the PTAMD study required the presence of multiple macular drusen centrally. A side-by-side comparison of the data in Table 4 is made in Tables 4A and 4B, which summarize the results for the 1000 and 3000 micron regions, respectively.

In an attempt to visualize the influence of fellow eye affected and drusen area on the risk of an eye's conversion to CNV, we plotted the occurrence (1) and nonoccurrence (0) of CNV events against the measured drusen area for our AREDS subjects in Figure 1. The data points are slightly "jittered" vertically to better identify overlapping points, and a smoothing spline was drawn. This spline is similar to a moving average, showing the proportion of CNV events that occurred across all of the drusen area observations. These results are not adjusted for the other factors but agree well with the modeling results shown in Tables 1 and 2. Since involvement of the fellow eye is such a strong risk factor for CNV, we separately

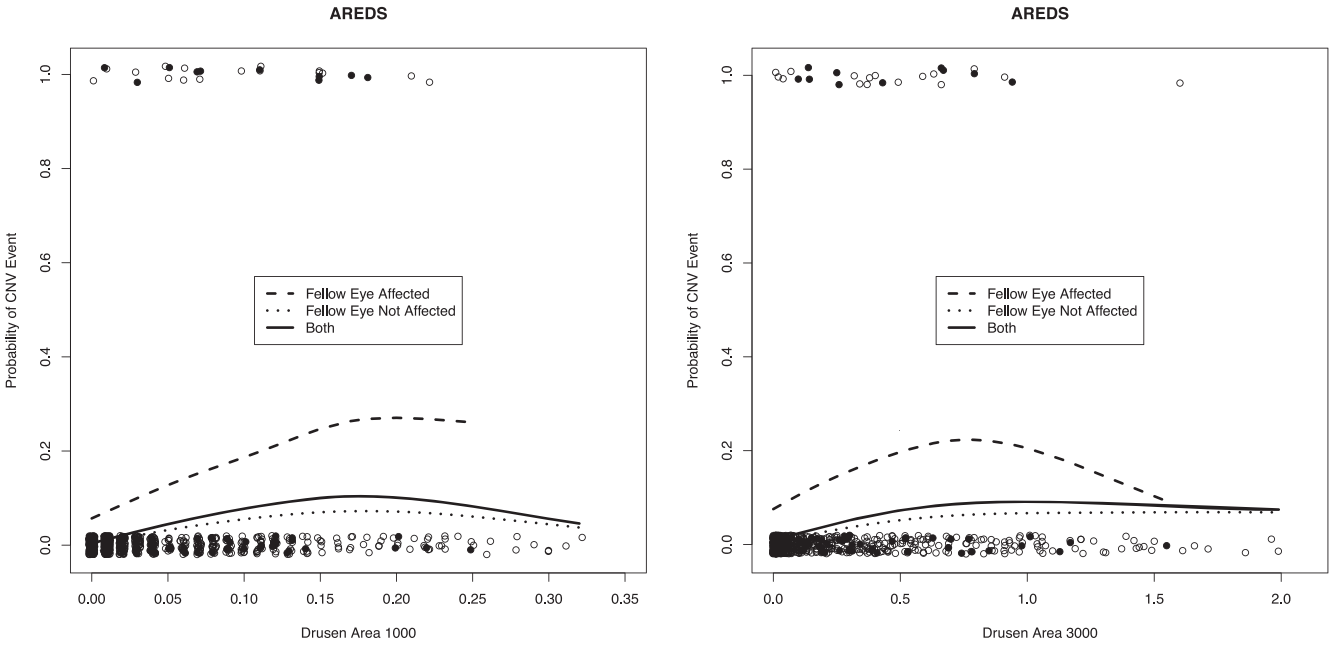

Figure 1. Crude estimates of the probability of a CNV event for AREDS subjects as a function of drusen area (in mm^2) for the central 1000- and 3000-micron-diameter macular regions based on a smoothing spline. A solid circle depicts an eye whose fellow eye was affected by CNV at baseline; open circles depict eyes with unaffected fellow eyes at baseline. Observations are vertically jittered to better show density, and the plots are vertically exaggerated to better show small probabilities. Solid lines depict the probability plots of for all AREDS subject eyes. For those eyes with a fellow eye already affected by CNV at baseline, dashed lines are used. Dotted lines plot the event probability for those eyes with an unaffected fellow eye.

Table 2A. Detailed Results for the Central 3000-Micron Region

Model 1: AREDS as Base				
		95% Confidence Interval		
3000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.094	0.001	8.542	
Age, y	0.976	0.923	1.031	
Pigment = Y	4.542	1.718	12.006	*
Fellow eye affected = Y	5.925	2.424	14.483	*
Drusen area (scaled)	1.296	0.916	1.833	
Study = PTAMD	1.790	0.594	5.396	
Drusen area × (study = PTAMD)	0.794	0.471	1.338	
Model 1: PTAMD as Base				
		95% Confidence Interval		
3000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.169	0.002	13.755	
Age, y	0.976	0.923	1.031	
Pigment = Y	4.542	1.718	12.006	*
Fellow eye affected = Y	5.925	2.424	14.483	*
Drusen area (scaled)	1.029	0.646	1.637	
Study = AREDS	0.559	0.185	1.683	
Drusen area × (study = AREDS)	1.260	0.748	2.124	
Model 2: AREDS Only				
		95% Confidence Interval		
3000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.043	0.000	30.22	
Age, y	0.986	0.909	1.069	
Pigment = Y	4.250	1.412	12.791	*
Fellow eye affected = Y	5.070	1.804	14.253	*
Drusen area (scaled)	1.278	0.927	1.762	
Model 3: PTAMD Only†				
		95% Confidence Interval		
3000	Point Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.128	0.000	222.994	
Age, y	0.970	0.881	1.068	
Pigment = Y	7.399	1.507	36.332	*
Fellow eye affected = Y	12.718	1.567	103.197	*
Drusen area (scaled)	1.094	0.524	2.283	

* The parameter met statistical significance, $P < .05$.

† Estimated as a generalized linear model, generalized estimating equations not needed (only one eye for each subject).

plotted two additional curves. One represents eyes whose fellow eye was already affected by CNV at baseline, and this has a much steeper slope initially. The other curve plots eyes of subjects whose fellow eye was not affected.

Discussion

Categorization of a patient's eye into either a high- or low-risk category for the development of a neovascular event has several implications. In addition to needing more careful monitoring, high-risk patients should themselves perform more detailed Amsler grid testing or other functional assessments at home if they are capable of doing so. Furthermore, as prophylactic strategies are introduced in an effort to prevent dry AMD from converting to the wet form, clinical trials to establish efficacy are best conducted by selecting those patients at high risk for event occurrence. This has the practical value of decreasing the number of subjects needed for such a trial while also decreasing its cost and duration.

Our study is among the first to explore the risk of developing neovascular AMD using careful quantification of drusen and drusen area on digital images obtained over several years' time. We found that total drusen area and the presence of pigment were significant risk factors in only some of our models and that the results depended on the region of regard (Tables 1 and 2). In the central 3000 microns, total drusen area was not a significant risk factor in any model, but hyperpigmentation was. In the central 1000-micron-diameter region,

Table 3. CNV Event Occurrence as a Function of the Presence of a Large Druse: Comparison of Models (Odds Ratios)

1000		Confidence Intervals		
AREDS	**Point Estimate**	**Lower Bound**	**Upper Bound**	**SS Slope**
Intercept	0.032	0.000	35.273	
Age	0.990	0.908	1.079	
Pigment = Y	1.709	0.548	5.327	
Fellow eye affected = Y	6.437	2.496	16.595	*
At least one large druse	2.596	0.955	7.059	
1000		**Confidence Intervals**		
PTAMD†	**Point Estimate**	**Lower Bound**	**Upper Bound**	**SS Slope**
Intercept	3.654	0.002	5917.327	
Age	0.920	0.825	1.027	
Pigment = Y	1.365	0.153	12.186	
Fellow eye affected = Y	17.558	2.136	144.362	*
At least one large druse	8.235	0.308	220.073	
3000		**Confidence Intervals**		
AREDS	**Point Estimate**	**Lower Bound**	**Upper Bound**	**SS Slope**
Intercept	0.025	0.000	11.157	
Age	0.986	0.916	1.062	
Pigment = Y	3.398	1.183	9.76	*
Fellow eye affected = Y	4.586	1.689	12.454	*
At least one large druse	3.452	1.113	10.713	*
3000		**Confidence Intervals**		
PTAMD†	**Point Estimate**	**Lower Bound**	**Upper Bound**	**SS Slope**
Intercept	0.000	0.000	Infinite	
Age	0.978	0.890	1.075	
Pigment = Y	6.579	0.606	71.389	
Fellow eye affected = Y	11.624	1.542	87.646	*
At least one large druse	Infinite	0.000	Infinite	

* The parameter met statistical significance, $P < .05$.

† Estimated as a generalized linear model, generalized estimating equations not needed (only one eye for each subject)

total drusen area was significant. It is noteworthy that models using continuous parameters such as total drusen area are generally more robust than those using categorical data. Looking at previous descriptions of risk and drusen area as found in the AREDS risk scale, the depiction of measured drusen area was actually categorical in nature.[14,15] This may be one reason why our results differ from those described in previous reports. In our cohort of AREDS participants, we did find that the presence of a single large druse located within the central 3000-micron region of regard was a significant risk factor, but when the druse was found within the central 1000-micron zone alone, it was not (Table 3A).

The strongest and most consistent risk factor for the development of CNV in every model that we investigated was involvement of the fellow eye ("fellow eye affected"). Our statistical method calculated the risk for each eye alone and did not require us to express risk on a per-subject basis, as is done in other risk assessment strategies.[15] In this way, the relative importance of each risk factor for an eye can be seen more clearly.

When drusen area was treated as a threshold parameter (Table 4), its significance as a risk factor for the development of CNV was inconsistent. In the central 3000-micron-diameter region of the macula, the presence of hyperpigmentation (OR, 3.176), an affected fellow eye (OR, 4.048), or a drusen area equivalent to that of five large drusen or more (OR, 4.904) each reached significance in the AREDS cohort. Operationally, ORs for each of the significant parameters are multiplied together when more than one feature is present in a given eye, yielding the total odds for event occurrence for that eye. For example, in the AREDS subject described, the odds of a CNV event occurring in the remaining eye is $3.176 \times 4.048 \times 4.904$, or 63 times, higher than if these same features were absent.

Table 3A. Comparison of Models by Parameter (Odds Ratios)

	AREDS		PTAMD*	
Parameter	**1000**	**3000**	**1000**	**3000**
Intercept	0.032	0.025	3.654	0.000
Age	0.990	0.986	0.920	0.978
Pigment = Y	1.709	***3.398***	1.365	6.579
Fellow eye affected = Y	***6.437***	***4.586***	***17.558***	***11.624***
At least one large druse	2.596	***3.452***	8.235	Infinite

Odds ratio estimates in ***bold italic*** are statistically significantly different from 1 (intercepts ignored).

* Estimated as a generalized linear model, generalized estimating equations not needed (only one eye for each subject).

Table 4. Odds Ratios for CNV Event Occurrence as a Function of Meeting Drusen Area Thresholds

AREDS One Druse Equivalent Area (EA)				
		95% Confidence Interval		
1000	Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.012	0.000	8.816	
Age, y	0.992	0.917	1.075	
Pigment = Y	1.533	0.598	3.928	
Fellow eye affected = Y	5.142	1.996	13.25	*
At least one1 large druse EA†	5.360	1.482	19.389	*
AREDS Five Drusen Equivalent Area (EA)				
		95% Confidence Interval		
1000	Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.016	0	16.168	
Age, y	0.997	0.916	1.086	
Pigment = Yes	1.484	0.548	4.022	
Fellow eye affected = Y	5.765	2.241	14.831	*
At least 5 large drusen EA†	3.299	1.347	8.08	*
PTAMD One Druse Equivalent Area (EA)				
		95% Confidence Interval		
1000	Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.000	0.000	Infinite	
Age, y	0.952	0.870	1.043	
Pigment = Y	2.821	0.404	19.688	
Fellow eye affected = Y	13.056	1.869	91.190	*
At least one large druse EA†	Infinite	0.000	Infinite	
PTAMD Five Drusen Equivalent Area (EA)				
		95% Confidence Interval		
1000	Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	1.577	0.001	2218.004	
Age, y	0.951	0.868	1.043	
Pigment = Y	2.920	0.394	21.619	
Fellow eye affected = Y	12.62	1.731	92.012	*
At least five large drusen EA†	0.728	0.080	6.632	
AREDS One Druse Equivalent Area (EA)				
		95% Confidence Interval		
3000	Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.009	0	7.781	
Age, y	0.993	0.919	1.072	
Pigment = Y	4.690	1.819	12.097	*
Fellow eye affected = Y	4.772	1.745	13.05	*
At least one large druse EA†	3.296	0.427	25.464	
AREDS One Druse Equivalent Area (EA)				
		95% Confidence Interval		
3000	Estimate	Lower Bound	Upper Bound	SS Slope
Intercept	0.018	0.000	8.35	
Age, y	0.986	0.916	1.061	
Pigment = Y	3.176	1.179	8.558	*
Fellow eye affected = Y	4.048	1.584	10.346	*
At least five large drusen EA†	4.904	1.247	19.282	*

† Estimated as a generalized linear model, generalized estimating equations not needed (only one eye for each subject).

Table 4A. Comparison of Odds Ratio Estimates by Study and Drusen Area Equivalent for the Central 1000-Micron Region

	AREDS		PTAMD*	
	One Druse	Five Drusen	One Druse	Five Drusen
Intercept	0.012	0.016	0.000	1.577
Age	0.992	0.997	0.952	0.951
Pigment = Y	1.533	1.484	2.821	2.920
Fellow eye affected = Y	***5.142***	***5.765***	***13.056***	***12.620***
At least one (or five) large drusen EA	***5.360***	***3.299***	Infinite	0.728

Odds ratio estimates in ***bold italic*** are statistically significantly different from 1.

* Estimated as a generalized linear model, generalized estimating equations not needed (only one eye for each subject).

Table 4B. Comparison of Odds Ratio Estimates for AREDS by Drusen Area Equivalent for the Central 3000-Micron Region*

	AREDS	
	One Druse	Five Drusen
Intercept	0.009	0.018
Age	0.993	***0.986***
Pigment = Y	***4.690***	***3.176***
Fellow eye affected = Y	***4.772***	***4.048***
At least one (or five) large drusen EA	3.296	***4.904***

Odds ratio estimates in ***bold italic*** are statistically significantly different from 1.

* All PTAMD eyes had 1 and 5 large druse EA in this region.

Significance for these same parameters was not met in the PTAMD cohort, except for hyperpigmentation. When the drusen area threshold was lowered to an equivalent area of just a single large druse located within in the central 3000-micron region, this risk parameter was no longer significant for predicting CNV.

We are aware of research conducted at several centers where drusen volume is determined using OCT.[22,23] The OCT provides a geometric profile of larger drusen, allowing the volume to be calculated from the cross-sectional, z-axis information. Germane to these calculations, however, is the necessity that accurate measurements of drusen area in the x-y plane must be made. Since we found that drusen area, when measured as a continuous variable, was not a consistent and compelling risk factor for the development of CNV, we are skeptical that drusen volume itself will be particularly relevant. Furthermore, as part of a recent report, we longitudinally assessed morphological features in thousands of images from hundreds of subjects with AMD followed over several years.[24] In that study, measurements of drusen were conducted at baseline and at each annual visit up to 8.1 years thereafter (median, 3.8 years). We found that sequential changes in drusen area over time did not signal an increased risk of conversion to neovascular AMD. We did find, however, that ETDRS protocol–measured visual acuity decreased in subjects well before the neovascular event occurred, and this reduction in acuity appeared to signal the eventual conversion of dry AMD to the wet form of the disease.[24]

We did not control for systemic risk factors, such as hypertension, cardiovascular disease, smoking history, family history, or dietary habits.[1,2,25] We did control for vitamin and mineral assignment in the AREDS cohort. In PTAMD, vitamin usage was not documented. Failure to control for these parameters is an admitted weakness in our investigation, but we doubt that adjusted ORs for our drusen parameters would be substantially different.

As the number of neovascular events occurring in our cohorts over the follow-up interval was rather small (26 eyes in AREDS, 6 eyes in PTAMD), our model could not predict the probability of event occurrence in a robust fashion. We did, however, plot the rough probability of an eye developing wet AMD as a function of drusen area, measured at baseline in the two regions of regard for our AREDS subjects (Fig. 1). For the 26 AREDS event eyes in aggregate, the probability of an event increased with increasing drusen area initially, but then the curve flattened out. As 10 of the 26 AREDS event eyes were in subjects whose fellow eye was affected at baseline (category 4), we plotted this event group separately. In the 3000-micron region, the curve for fellow-eye–affected eyes actually inverted as a total drusen area of approximately 0.75 mm^2 was reached (an area equivalent to approximately 60 large drusen).

Our results, taken in aggregate, challenge the belief that an eye is necessarily at a correspondingly higher risk of developing wet AMD as more and more drusen develop and drusen area increases. The risk of CNV imparted from the presence of drusen in an eye seems, in fact, to reach a maximum threshold in some cohorts. In addition, we found that where the drusen are located is also relevant.

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