Neovascularization in Fellow Eye of Unilateral Neovascular Age-related Macular Degeneration According to Different Drusen Types

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• PURPOSE: To investigate the incidence of fellow eye (FE) neovascular age-related macular degeneration (nAMD) in patients with unilateral nAMD according to FE drusen type.

• DESIGN: Retrospective cohort study.

• METHODS: Between January 2013 and June 2016, 434 consecutive patients with naïve nAMD were enrolled. We selected 280 eligible patients with treatment-naïve, unilateral nAMD for analysis (280/280 = 100% patients were followed up at 2 years; 50/280 = 17.9% patients were followed up at 5 years). The incidence and hazard ratios (HR) of FE nAMD according to age, sex, choroidal thickness, nAMD subtype, and drusen type were analyzed.

• RESULTS: The 5-year incidence of FE nAMD was 20.9%. The incidences of the soft plus subretinal drusenoid deposits (SDD), soft drusen only, and SDD only groups were 76.4%, 46.2%, and 25.7%, respectively; they were significantly higher than the no drusen group (vs 3.6%; $P < .001$, $P < .001$, $P < .001$). There was no significant difference between the pachydrusen and no drusen groups (7.1% vs 3.6%; $P = .101$). The multivariate Cox regression hazard model revealed older age (HR, 1.053; $P = .031$) and drusen type were significant ($P = .001$). Compared with the no drusen group, the soft drusen plus SDD, soft drusen only, and SDD groups showed an HR of 18.460 ($P = .001$), 8.302 ($P = .015$), and 5.465 ($P = .082$), respectively. Pachydrusen was not shown to be a significant risk factor compared to the no drusen group (HR, 2.417; $P = .281$).

• CONCLUSION: The incidence of FE nAMD was significantly different with respect to drusen type. Soft drusen plus SDD had the highest risk of neovascular AMD, followed by soft drusen only and SDD only. (Am J Ophthalmol 2019;208:103–110. © 2019 Elsevier Inc. All rights reserved.)

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AGE-RELATED MACULAR DEGENERATION (AMD) IS the leading cause of blindness in developed countries. Based on studies on the natural course of AMD,[1–3] efforts have been made to predict the risk for AMD progression. Drusen size, drusen position, and pigmentary abnormalities are thought to be important factors for the progression of AMD.[1–6]

Beyond the era of historical AMD cohort studies, drusen (extracellular deposits) have been further differentiated with the development of various imaging modalities. In addition to conventional soft drusen, a newly classified subretinal drusenoid deposit (SDD; reticular pseudodrusen) is also known to be a risk factor for advanced AMD.[7] Recently, pachydrusen, a new type of drusen exhibiting a wider distribution pattern that spares the macula center and is associated with a thicker choroid, has been introduced.[8] However, there has been no definite correlation found between the presence of pachydrusen and the progression to advanced AMD.

The development of a neovascular AMD (nAMD) in a single eye implies a major risk of developing a similar condition in the fellow eye.[9–15] The development of nAMD in the fellow eye is of great significance to patients because it is usually the better-seeing eye, and its visual outcome will ultimately have a great impact on their quality of life. More precise knowledge of the development of nAMD in the fellow eye can lead to more appropriate follow-up, an early diagnosis, and better treatment. However, the timing and factors that could influence the occurrence of this event are not completely understood.

In this study, we investigate the occurrence of nAMD in the fellow eye and analyze the drusen types as a risk factor in patients with unilateral nAMD.

METHODS

• PATIENTS: A retrospective study was conducted on patients newly diagnosed with nAMD in the Department of Ophthalmology at Yonsei Medical Center (Severance Hospital) between January 2013 and June 2016. A total

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of 434 consecutive patients were selected for medical record review from a clinical database containing patients' ophthalmologic examinations and ocular history. This retrospective study was approved by the Institutional Review Board (IRB) at Yonsei University Medical Center before the review of data began, and the requirement to obtain informed consent from the subjects was waived by the IRB (IRB number: 4-2018-1076). All study protocols adhered to the tenets of the Declaration of Helsinki.

Only patients with treatment-naïve, unilateral neovascularization and without signs of nAMD in the fellow eye and those who underwent more than 24 months of follow-up were included in the analysis. All patients underwent anti–vascular endothelial growth factor (VEGF) therapy (ranibizumab, aflibercept, bevacizumab). Photodynamic therapy (PDT) was added in few patients with polypoidal choroidal vasculopathy (PCV). Patients presented for follow-up at 1- to 3-month intervals, depending on the disease activity.

All included patients had undergone a comprehensive ophthalmologic examination at the initial presentation, which included measurement of the best-corrected Snellen visual acuity (BCVA), slit-lamp biomicroscopy, indirect funduscopy, color fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICGA) using the Heidelberg retinal angiography device (HRA-II; Heidelberg Engineering, Dossenheim, Germany), and spectral-domain OCT (SDOCT; Spectralis; Heidelberg Engineering, Heidelberg, Germany)—including enhanced depth imaging (EDI) OCT. SDOCT consisted of 6-mm horizontal raster scans with 30- to 60-μm spacing that covered a 1500-μm diameter centered on the fovea. We also included high-resolution and EDI mode images of 9-mm horizontal and vertical scans. At every follow-up, all examinations except angiography were performed. When nAMD of the fellow eye was suspected, FA and ICGA were performed.

The subtype of neovascular AMD (typical nAMD, PCV, and retinal angiomatous proliferation [RAP]) was comprehensively diagnosed on the basis of the findings from funduscopy, angiography, and OCT. Typical nAMD was characterized by the presence of exudative changes due to choroidal neovascularization (CNV) on FA and ICGA. The diagnosis of PCV was based on ICGA findings, including polypoidal structures at the borders of the branching choroidal vascular networks.[16] In some cases, subpigment epithelial orange-red protrusions were biomicroscopically observed; these corresponded to the polypoidal lesions revealed by ICGA. The diagnosis of RAP was based on the characteristic findings of retinal pigment epithelial detachment with overlying cystic retinal edema on OCT images, intraretinal hemorrhage, and intraretinal vascular anastomoses.[17]

The patients were excluded if any of the eyes exhibited the following signs: CNV secondary to other macular disorders such as angioid streaks; a refractive error of >6.0 diopters; amblyopia; media opacities significant enough to limit the quality of imaging; and a history of ocular inflammation, retinal detachment, retinal vascular occlusive diseases, epiretinal membrane, macular holes, ocular trauma, and previous vitreoretinal surgery and/or laser photocoagulation. Patients exhibiting any sign of advanced AMD in the fellow eye were also excluded.

• **IMAGING ANALYSIS:** The type of drusen (extracellular deposit) in the fellow eye was determined using color fundus photographs and SDOCT according to the criteria presented in a previous study.[8] Eyes without drusen, with small drusen (<63 μm), or with few intermediate drusen (<20, <125 μm) were classified into a no significant drusen group. Positivity for drusen was defined by the presence of at least 1 large (≥125 μm) druse or numerous intermediate drusen (≥20, 125 μm > size ≥63 μm), according to the Age-Related Eye Disease Study (AREDS).[18]

Soft drusen was diagnosed when yellowish-white aggregates observed on color fundus photographs were evaluated as homogeneous subretinal pigment epithelium (sub-RPE) deposits that formed mounds on OCT images. SDDs were diagnosed when ≥10 discrete whitish deposits were observed on color fundus photographs and infrared reflectance images provided by Spectralis OCT; these deposits corresponded to material accumulated in the subretinal space on OCT images. Pachydrusen were considered present if there were isolated or scattered yellowish-white deposits on color fundus photographs that corresponded to homogenous material accumulation under RPE on OCT images. Pachydrusen are scattered over the posterior pole and may aggregate around the optic nerve and occur in isolation or in groups of only a few drusen. Eyes with pachydrusen and conventional soft drusen were classified into the soft drusen group.

SDD may or may not be accompanied by soft drusen. Thus, we divided the patients into 5 subgroups according to the accompanying drusen type in the fellow eye: soft drusen plus SDD, soft drusen only, SDD only, pachydrusen, and no significant drusen groups.

Neovascular AMD was diagnosed when there was evidence of CNV associated with nondrusenoid retinal pigment epithelium detachment, serous or hemorrhagic retinal detachment, subretinal hemorrhage, or subretinal exudation.[19]

All color fundus photographs, OCT images, and FA and ICGA findings were reviewed by 2 independent examiners (J.L., S.H.B.) to determine the occurrence of nAMD, the presence of drusen, and the drusen type. The agreement between the 2 examiners was good. The subfoveal choroidal thickness was measured from the outer surface of the RPE band to the inner surface of the choroidal–scleral interface under the fovea on EDI OCT images.[20,21]

• **STATISTICAL ANALYSIS:** Differences in the variables among the drusen groups were analyzed using 1-way

analysis of variance (ANOVA) or Fisher exact test. Time-to-event endpoint (nAMD occurrence of fellow eye) was analyzed using the Kaplan-Meier method, and subgroups according to different druse types were compared using the log-rank test. Univariate analysis was performed to determine whether demographic and clinical variables affect nAMD occurrence in the fellow eye. Factors likely to have an association in the univariate analysis ($P < .15$) were tested using multivariate analysis to identify independent factors associated with the occurrence using the Cox proportional hazard regression model. Assessment of collinearity between variables in the logistic regression model was performed using the variance inflation factor. Additionally, 2 Cox proportional hazard models were constructed including each nAMD subtypes (model 1) and drusen types (model 2). Harrell's C-index was used to quantify the predictive accuracy of both multivariate Cox models.[22] Paired comparisons of the C-indexes were performed using a bootstrap resampling procedure. Briefly, the difference between the 2 C-indexes was calculated on each of the 10,000 bootstrap samples to obtain the bootstrap 95% confidence interval (CI) of the difference. Almost statistics were determined using SPSS software (IBM SPSS Statistics, Armonk, New York, USA). Harrell's C-indexes were obtained using R software (version 3.5.3). A P value of <.05 was considered statistically significant.

RESULTS

A TOTAL OF 434 CONSECUTIVE PATIENTS WHO WERE NEWLY diagnosed with nAMD between January 2013 and June 2016 were enrolled in the study. Among the enrolled patients, the follow-up duration of 71 patients was less than 24 months. Nineteen patients were excluded as nAMD was diagnosed in both eyes at the initial presentation. Fifty patients were excluded because of the presence of scar change in the fellow eye or by a past ocular history of diagnosis, surgery, or any treatments. Fourteen patients whose drusen types were undetermined by media opacity were also excluded. Finally, 280 patients with unilateral nAMD who underwent at least a 24-month follow-up period were included. Typical nAMD, PCV, and RAP accounted for 56.1% (n = 157), 32.5% (n = 91), and 11.4% (n = 32) of the cases, respectively. The mean (± standard deviation [SD]) age of the patients was 69.3 ± 8.5 (range, 51.61-89.36) years, and there were 128 (45.7%) women and 152 (54.3%) men. The number (%) of followed-up patients at 3, 4, and 5 years was 216 (216/280 = 77.1%), 116 (116/280 = 41.4%), and 50 (50/280 = 17.9%), respectively. At 5 years, the number of followed-up patients in the soft drusen plus SDD, soft drusen only, SDD only, pachydrusen, and no significant drusen groups was 9 of 39 (23.1%), 4 of 26 (15.4%), 2 of 19 (10.5%), 17 of 100 (17.0%), and 18 of 96 (18.8%), respectively. The mean follow-up duration was 44.8 ± 12.1 months and was not significantly different among the subgroups (1-way ANOVA; F = 0.577, $P = .680$).

The soft drusen plus SDD, soft drusen only, SDD only, pachydrusen, and no significant drusen groups accounted for 13.9% (n = 39), 9.3% (n = 26), 6.8% (n = 19), 35.7% (n = 100), and 34.3% (n = 96) of all the enrolled patients, respectively. The mean (± SD) age of patients with soft drusen plus SDD, soft drusen only, SDD only, pachydrusen, and no significant drusen was 76.0 ± 6.1 years, 73.2 ± 7.0 years, 71.7 ± 7.1 years, 69.9 ± 8.5 years, and 64.5 ± 7.3 years, respectively; the mean age of the no significant drusen group was significantly lower than the other 4 groups (1-way ANOVA; F = 19.822, $P < .001$). In total, 34 of the 39 patients (87.2%) with soft drusen plus SDD, 9 of the 26 patients (34.6%) with soft drusen, 14 of the 19 patients (73.7%) with SDD, 39 of the 100 patients (39.0%) with pachydrusen, and 32 of the 96 patients (33.3%) with no drusen were women, and the proportions of women in the subgroups with SDD were significantly higher; Fisher exact test revealed a significant difference in the proportion of women among the 5 groups ($P < .001$).

The mean subfoveal choroidal thickness of the first involved eye in the total cohort was 282.4 ± 123.7 (range, 39.0-616.0) μm. The mean subfoveal choroidal thicknesses were 157.1 ± 61.0 (range, 54.0-311.0) μm, 236.0 ± 62.4 (range, 83.0-354.0) μm, 138.6 ± 53.4 (range, 39.0-254.0) μm, 343.4 ± 109.2 (range, 115.0-616.0) μm, and 310.7 ± 116.5 (range, 93.0-604.0) μm in the soft drusen plus SDD, soft drusen only, SDD only, pachydrusen, and no significant drusen groups, respectively (1-way ANOVA; F = 37.653, $P < .001$) (Table 1). The mean subfoveal choroidal thickness of the fellow eye in the total cohort was 260.4 ± 109.3 (range, 47.0-560.0) μm. The mean subfoveal choroidal thicknesses were 155.5 ± 56.3 (range, 61.0-295.0) μm, 239.8 ± 85.9 (range, 109.0-457.0) μm, 147.4 ± 62.7 (range, 47.0-275.0) μm, 308.4 ± 101.2 (range, 91.0-558.0) μm, and 281.0 ± 101.9 (range, 71.0-560.0) μm in the soft drusen plus SDD, soft drusen only, SDD only, pachydrusen, and no significant drusen groups, respectively (1-way ANOVA; F = 27.593, $P < .001$). The choroidal thickness of first and fellow eyes showed a similar tendency according to each subgroup (Table 1).

The analysis according to the nAMD subtype is presented in Supplemental Table 1 (Supplemental Material available at AJO.com).

• INCIDENCE OF FELLOW EYE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION ACCORDING TO DRUSEN TYPE OF FELLOW EYE AND NEOVASCULAR AGE-RELATED MACULAR DEGENERATION SUBTYPE OF FIRST EYE: The 5-year incidence of nAMD in the fellow eye was 20.9%, and the 2-year incidence was 10.4%. The 5-year incidences of nAMD in the fellow eye in the soft plus SDD, soft drusen only, and SDD only groups were

TABLE 1. Demographics and Clinical Characteristics of Patients With Unilateral Neovascular Age-related Macular Degeneration According to Drusen Type in the Fellow Eye

	Total (N = 280)	Soft Drusen + SDD (N = 39)	Soft Drusen Only (N = 26)	SDD Only (N = 19)	Pachydrusen (N = 100)	No Drusen (n = 96)	*P* Value
Age (years), mean ± SD	69.3 ± 8.5	76.0 ± 6.1	73.2 ± 7.0	71.7 ± 7.1	69.9 ± 8.5	64.5 ± 7.3	<.001*
Sex (M:F), n (%)	152:128 (54.3%:45.7%)	5:34 (12.8%:87.2%)	17:9 (65.4%:34.6%)	5:14 (26.3%:73.7%)	61:39 (61.0%:39.0%)	64:32 (66.7%:33.3%)	<.001*
AMD subtype (typical AMD, PCV, RAP, n; %)	157, 91, 32 (56.1%, 32.5%, 11.4%)	17, 1, 21 (43.6%, 2.6%, 53.8%)	21, 3, 2 (80.8%, 11.5%, 7.7%)	10, 0, 9 (52.6%, 0.0%, 47.4%)	55, 45, 0 (55.0%, 45.0%, 0.0%)	54, 42, 0 (56.3%, 43.8%, 0.0%)	<.001*
FU duration (months), mean ± SD	44.8 ± 12.1	47.4 ± 12.5	44.0 ± 11.0	43.1 ± 12.8	44.5 ± 11.6	44.7 ± 12.7	.680
SubF CT of first involved eye (μm), mean ± SD	282.4 ± 123.7	157.1 ± 61.0	236.0 ± 62.4	138.6 ± 53.4	343.4 ± 109.2	310.7 ± 116.5	<.001*
SubF CT of fellow eye (μm, mean ± S.D.)	260.4 ± 109.3	155.5 ± 56.3	239.8 ± 85.9	147.4 ± 62.7	308.4 ± 101.2	281.0 ± 101.9	<.001*

AMD = age-related macular degeneration; CT = choroidal thickness; FU = follow-up; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; SDD = subretinal drusenoid deposits; SubF = subfoveal.
P values designated by asterisk (*) are significantly different.

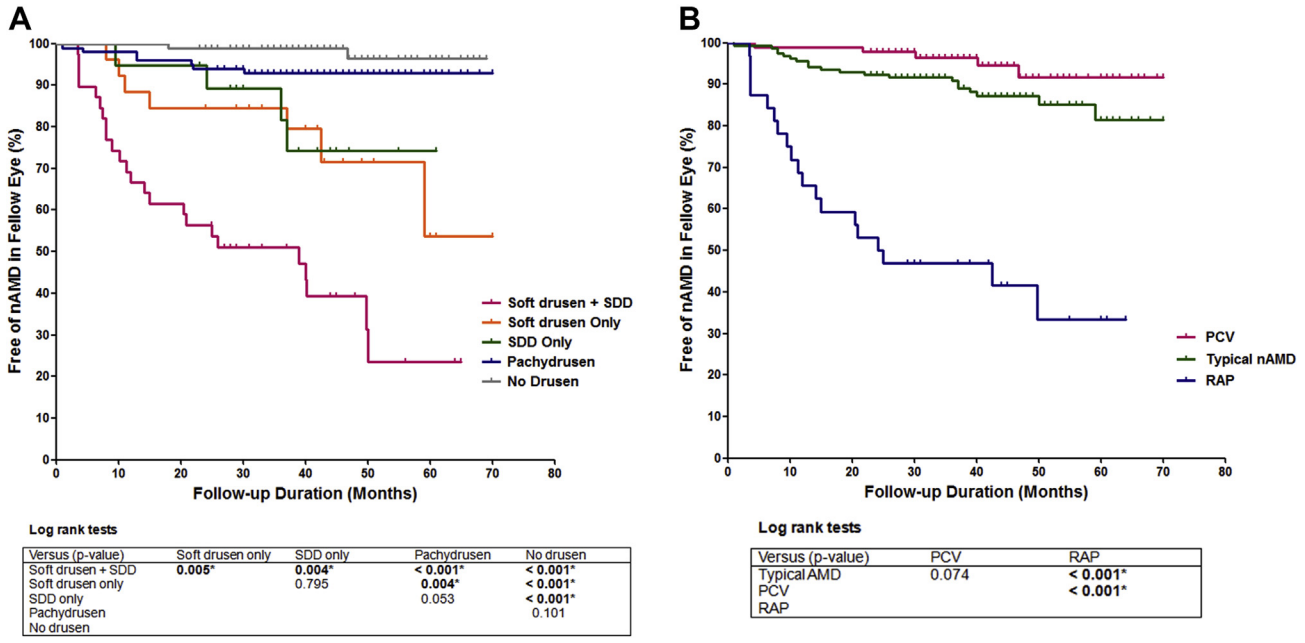
76.4%, 46.2%, and 25.7%, respectively, which were significantly higher than the no significant drusen group (vs 3.6%; $P < .001$, $P < .001$, $P < .001$; log-rank test; Figure). However, there was no significant difference between the pachydrusen group and no significant drusen group (7.1% vs 3.6%; $P = .101$; log-rank test; Figure). The 2-year incidences of nAMD in the fellow eye in the soft plus SDD, soft drusen only, SDD only, pachydrusen, and no significant drusen groups were 43.6%, 15.4%, 5.3%, 6.0%, and 1%, respectively.

The 5-year incidences of nAMD in the fellow eye in typical nAMD, PCV, and RAP of the first eye were 18.5%, 8.2%, and 66.7%, respectively. The incidence in the RAP group was significantly higher than that of the other groups (both $P < .001$); however, there was no significant difference between the typical nAMD and PCV groups ($P = .074$; log-rank test; Figure). The 2-year incidences of nAMD in the fellow eye in typical nAMD, PCV, and RAP of the first eye were 7.6%, 2.2%, and 46.9%, respectively.

• **CLINICAL FEATURES PREDICTING THE OCCURRENCE OF FELLOW EYE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION:** Results of the univariate analysis demonstrated that older age, female sex, RAP subtype, drusen type (soft drusen and/or SDD), and thinner subfoveal choroidal thickness of first eye and fellow eye showed a significantly higher risk (all $P < .001$). The multivariate Cox regression model revealed that older age was statistically significant (hazard ratio [HR], 1.053; 95% CI, 1.005-1.104; $P = .031$), as well as drusen type ($P = .001$). Compared with the no significant drusen group, the soft drusen plus SDD, soft drusen only, and SDD group showed an HR of 18.460 (95% CI, 3.338-102.081; $P = .001$), 8.302 (95% CI, 1.521-45.313; $P = .015$), and 5.465 (95% CI, 0.808-36.963; $P = .082$), respectively. Pachydrusen did not show a higher risk than the no significant drusen group (HR, 2.417; 95% CI, 0.485-12.043; $P = .281$). The variance inflation factors of all variables were under 2, indicating collinearity of independent variables was not a substantive concern (Table 2). Additionally, 2 Cox proportional hazard models were constructed including each nAMD subtype (model 1) and drusen type (model 2). The predictive capacity, using Harrell's C-index, was 82.52% for model 1 and 83.35% for model 2 and there was no significant difference between both models (difference = -0.0283 [95% CI = -0.0744-0.0111]) (Supplemental Table 2; Supplemental Material available at AJO.com).

DISCUSSION

IN OUR STUDY, THE 5-YEAR INCIDENCE OF NAMD IN THE fellow eye was 20.9%, and the 2-year incidence was 10.4%. The largest drusen size, soft indistinct drusen



Log rank tests

Versus (p-value)	Soft drusen only	SDD only	Pachydrusen	No drusen
Soft drusen + SDD	**0.005***	**0.004***	**< 0.001***	**< 0.001***
Soft drusen only		0.795	**0.004***	**< 0.001***
SDD only			0.053	**< 0.001***
Pachydrusen				0.101
No drusen				

Log rank tests

Versus (p-value)	PCV	RAP
Typical AMD	0.074	**< 0.001***
PCV		**< 0.001***
RAP		

FIGURE. Time to developing neovascular age-related macular degeneration (nAMD) in the fellow eye in unilateral nAMD patients according to drusen type (A) and nAMD subtypes (B). The occurrence of nAMD in the fellow eye was used as an endpoint. AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; SDD = subretinal drusenoid deposits.

type, larger drusen area, and increased pigment and depigmentation have been thought to be risk factors for advanced AMD progression; the 5-year progression rates varied from approximately 10% to 30% depending on the extent of the drusen size, type, area, and pigmentary abnormalities.[5] The AREDS was designed to investigate the natural history and risk factors of AMD. According to the AREDS, the 5-year progression rate of nAMD in patients with unilateral nAMD at baseline was 30.8%. The prominent researches of the AMD progression risk calculation based on natural course were AREDS report 17 (detailed severity scale)[5] and AREDS report 18 (simplified severity scale).[6] The simplified severity scale results in a scoring system that assigns 1 point or risk factor for the presence of 1 or more large (≥125 mm) drusen, 1 point for the presence of any retinal pigment abnormalities in an eye, and 1 point for bilateral medium drusen if there are no large drusen in either eye. An eye with advanced AMD contributes 2 points to the score. Risk factors are summed across both eyes, forming a 5-step scale (steps 0-4) for which the 5-year risk of advanced AMD developing in at least 1 eye increases as follows: 0 factors, 0.5%; 1 factor, 3%; 2 factors, 12%; 3 factors, 25%; and 4 factors, 50%. Our study cases were all unilateral advanced AMD. Thus, if we applied the AREDS scale to our series, the 5-year risk of advanced AMD would range from 12% to 50%.

In this study, the 5-year incidence of nAMD in the fellow eye in the soft plus SDD, soft drusen only, and SDD only groups were 76.4%, 46.2%, and 25.7%, respectively; they were significantly higher than the no significant drusen group (vs 3.6%). However, there was no significant difference between the pachydrusen group and no significant drusen group (7.1% vs 3.6%; $P = .101$). The fellow eye nAMD incidences in the pachydrusen group and no significant drusen group were much lower than the predicted value of 12%, according to the AREDS simplified severity score. Drusen type was the most significant risk factor, even after adjusting for confounding factors. Compared with the no significant drusen group, the soft drusen and/or SDD groups showed significantly higher risks, whereas pachydrusen did not (Table 2). Because SDD is not always accompanied by soft drusen,[23] we performed an analysis after subgrouping soft drusen and SDD. As previously shown, soft drusen was considered to be associated with a higher risk of neovascularization than SDD,[23] with the highest risk. The most widely used AREDS severity score was based solely on color fundus photographs. The development of new image modalities has enabled the identification of new subtypes of extracellular deposits, such as SDD—a risk factor for advanced AMD. For example, under the severity score, the new risk factor such as small SDD would be classified as being meaningless, and extramacular large drusen such as pachydrusen could have been calculated as a risk factor same as macular drusen.

Beyond the AREDS era, the clinical features of nAMD have been further elucidated,[23] which was not sufficiently identified by the color fundus photography used in the AREDS. Additionally, a recent study has shown that the

TABLE 2. Univariate and Multivariate Analyses of Fellow Eye Neovascular Age-related Macular Degeneration Occurrence in Patients With Unilateral Neovascular Age-related Macular Degeneration

	Fellow Eye nAMD Occurrence				
	Univariate Analysis		Multivariate Analysis		
Characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*	Variance Inflation Factor
Age, years	1.102 (1.059-1.147)	<.001*	1.053 (1.005-1.104)	.031*	1.227
Sex					1.161
Female	3.862 (1.952-7.642)	<.001*	1.412 (0.623-3.202)	.408	
Male	1		1		
nAMD subtype		<.001*		.086	1.253
Typical AMD	2.386 (0.896-6.359)	.082	0.986 (0.321-3.030)	.980	
RAP	16.138 (6.012-43.321)	<.001*	2.248 (0.596-8.481)	.232	
PCV	1		1		
Drusen type		<.001*		.001*	1.101
Soft drusen + SDD	46.760 (11.021-198.391)	<.001*	18.460 (3.338-102.081)	.001*	
Soft drusen	14.660 (3.044-70.605)	.001*	8.302 (1.521-45.313)	.015*	
SDD	11.315 (2.071-61.832)	.005*	5.465 (0.808-36.963)	.082	
Pachydrusen	3.502 (0.727-16.859)	.118	2.417 (0.485-12.043)	.281	
No drusen	1		1		
SubF CT of first eye, μm	0.993 (0.990-0.996)	<.001*			
SubF CT of fellow eye, μm	0.994 (0.991-0.997)	<.001*	1.002 (0.997-1.006)	.453	1.296

CI = confidence interval; CT = choroidal thickness; HR = hazard ratio; nAMD = neovascular age-related macular degeneration; SDD = subretinal drusenoid deposit; SubF = subfoveal.

P values designated by asterisk (*) are significantly different.

AREDS severity score does not fit well in PCV.[24] A new classification and risk calculation system that reflects various new knowledge about AMD may be required. Our approach, which reflects the new types of extracellular deposits as a simple, easy, and intuitive method, can provide new insight to AMD research. Pachydrusen, a newly introduced drusen mainly located in the extramacular regions, is associated with thick choroid, pachyvessels, choroidal hyperpermeability in nonexudative AMD, PCV, and typical nAMD.[8,25,26] Pachydrusen is more prevalent in Asian patients than in white patients,[27] and its location is related to the underlying pachyvessels.[28] However, it is not yet known whether pachydrusen is a risk factor for the development of advanced AMD. According to the results of our study, pachydrusen was not found to be a statistically significant risk factor for nAMD progression in the fellow eye when compared to conventional soft drusen or SDD (HR, 2.417; 95% CI, 0.485-12.043; $P = .281$). Because pachydrusen is not typically present in the macula center, it is less likely to be directly related to the development of neovascularization or geographic atrophy.

In a detailed review of the pachydrusen group cases, we found that combined RPE undulations (or abnormalities) or pigmentation changes were related with the development of nAMD, suggesting that neovascularization develops through the so-called pachychoroidal pigment epitheliopathy (PPE). All pachydrusen cases without RPE abnormalities were not found to have developed nAMD during the follow-up period. Therefore, the presence of PPE was thought to be more important than the presence of pachydrusen for nAMD progression. PPE is already known to be a risk factor for neovascular AMD.[29] Pachydrusen and pachychoridal spectrum disorder are often accompanied by a thick choroid. Comprehensively thinking, it is possible that pachydrusen may be just an innocent bystander in relation with the thick choroid. As this was a small retrospective cohort study and fellow eye study, our findings may be insufficient to confirm whether pachydrusen is a risk factor for AMD progression. Further population-based prospective studies are needed to elucidate this issue. Because the drusen area is a stronger predictor than drusen size, subgrouping pachydrusen may more accurately predict the risk by separating extramacular large drusen from the large drusen of the AREDS severity score in this study.[30]

Results of previous studies have suggested that different subtypes of neovascularization, such as typical nAMD, PCV, and RAP, have different natural courses, visual prognoses, and risk levels for developing neovascularization in the fellow eye.[9–15] The incidence of nAMD in the fellow eye showed comparable trends to those reported in previous papers in that the incidence in the PCV group was not significantly different from that in the typical nAMD group,[24] and the incidence in the RAP group was significantly higher than that of the other groups.[31] In

this study, the 2-year incidence of nAMD in the fellow eye in typical nAMD, PCV, and RAP of the first eye were 7.6%, 2.2%, and 46.9%, respectively. In previous studies, the incidence of neovascularization in the fellow eye of the senile disciform lesion was 18% at 2 years.[9] According to the Submacular Surgery Trials report, the 2-year neovascularization incidence was 22% in the fellow eye of those with choroidal CNV.[12] In RAP, the 2-year fellow eye neovascularization incidence was reported to be much higher, at 56%.[32] The incidence of each nAMD subtype varies significantly according to ethnicity of the study group. It is generally known that the prevalence of PCV and RAP is higher and lower, respectively, in Asian individuals than in white individuals.[33–36] The fellow eye incidence in total nAMD may differ depending on the predominant ethnicity of each cohort. In the present study, nAMD subtype was found to be a risk factor for the development of nAMD in the fellow eye in univariate analysis, but not in multivariate analysis. On the other hand, even after adjusting for other potential risk factors, the drusen type remained as the most significant risk factor for the event.

This study has the inherent limitations of a retrospective study and a relatively limited number of cases and follow-up durations. Some risk factors, such as a history of smoking,[37] genetic factors,[37] and the use of an AREDS supplement that could affect the progression of AMD, were not included. Because this study considered only unilateral typical nAMD patients in a Korean population and the incidence of each AMD subtype varies significantly according to ethnicity,[33–36] the characteristics and progression rates of advanced AMD may not represent those of the general population. Therefore, future large-scale studies are required to better reflect ethnicity and nAMD subtypes and risk factors, including genetic factors. Another limitation is that we did not consider pigmentary abnormalities as another risk factor apart from drusen type. In fact, the occurrences of nAMD in the fellow eye with pachydrusen or no significant drusen were mostly related to pigmentary abnormalities. If the pigmentary abnormalities, including pachychoroid pigment epitheliopathy,[29] are reflected in addition to the proposed drusen types, the prediction for AMD progression may be more precise.

Despite these limitations, this study presented simple and intuitive results suggesting that the risk of developing nAMD in the fellow eye can be predicted according to the different drusen types in patients with unilateral typical nAMD.

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