

## Progression from Early/Intermediate to Advanced Forms of Age-Related Macular Degeneration in a Large UK Cohort: Rates and Risk Factors

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# Progression from Early/Intermediate to Advanced Forms of Age-Related Macular Degeneration in a Large UK Cohort: Rates and Risk Factors

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**Purpose:** To estimate rates and risk factors for progression to geographic atrophy (GA) or choroidal neovascularization (CNV) among eyes diagnosed with early or intermediate age-related macular degeneration (AMD) in clinical practice.

**Design:** Retrospective cohort analysis of a multicenter electronic medical record (EMR) database from the United Kingdom.

**Participants:** Patients aged 50 years or more with diagnosis of early/intermediate AMD in at least 1 eye (the study eye) and no evidence of CNV or GA in the study eye, from 10 clinical sites using the EMR.

**Methods:** Anonymized data for 40 543 patients with a diagnosis of early/intermediate AMD were extracted between October 2000 and February 2016 from EMR database records held in the 10 sites. A sample of records randomly selected from each center was used to validate disease definitions. Records were analyzed by subgroup, based on the AMD status of the fellow eye. Multivariate Cox regression models identified other predictors of disease progression.

**Main Outcome Measures:** Progression rate (per 100 person-years) to GA or CNV in study eyes with early/intermediate AMD by fellow eye status and identified risk factors for progression.

**Results:** Study eyes with early/intermediate AMD and a diagnosis of CNV in the fellow eye progressed to CNV fastest (at a rate of 15.2 per 100 person-years), and those with a diagnosis of GA in the fellow eye progressed to GA fastest (11.2 per 100 person-years), compared with the rates per 100 person-years of progression to CNV (3.2–11.9) or GA (2.0–7.8) in the other subgroups. In individuals with bilateral early/intermediate AMD, rates of progression to GA or CNV were 2.0 and 3.2 per 100 person-years, respectively. In the multivariate model, age, female sex, and cardiovascular disease were associated with an increased risk for progression to advanced AMD, whereas diabetes and glaucoma were associated with a decreased rate of progression (hazard ratios, 0.45 and 0.64, respectively).

**Conclusions:** Progression to GA or CNV was observed frequently in eyes with early/intermediate AMD, with the status of the fellow eye affecting the rate of progression. Novel associations with risk factors were observed and require replication in other cohorts. *Ophthalmology Retina* 2020;4:662-672 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at <https://www.opthalmologyretina.org/>.

Age-related macular degeneration (AMD) is a progressive, chronic disease of the retina and a major cause of blindness worldwide.<sup>1</sup> Age-related macular degeneration has been estimated to affect some 170 million of the worldwide population,<sup>2</sup> with this figure predicted to increase to 196 million in 2020 and 288 million in 2040.<sup>3</sup> The clinical hallmarks of AMD are features indicating degenerative

change in the posterior pole of the eye and consist of drusen or pigmentary abnormalities, the presence of which defines the early/intermediate stage of the disease<sup>4</sup>; at this stage, visual function is generally unaffected.

Vision loss can vary in severity across the spectrum of AMD, and when this is significant, it is due to 2 late-stage manifestations, namely geographic atrophy (GA) and

neovascular AMD (nAMD).<sup>1</sup> Geographic atrophy is a progressive and irreversible loss of the outer retina consisting of the choriocapillaris, retinal pigment epithelium, and photoreceptors; nAMD is the term used to describe an exudative pathology that is due to the presence of leaking blood vessels that originate from the choriocapillaris to invade the outer retinal layers or develop de novo within the retina.<sup>5</sup>

The prevalence and incidence of early and late manifestations of AMD<sup>6-9</sup> and associations with diet, medication, and lifestyle<sup>10-14</sup>; genetic factors<sup>14,15</sup>; cardiovascular disease<sup>16,17</sup>; and vitamin supplementation<sup>18</sup> have been reported and reviewed in detail.<sup>1,2</sup> Although progression rates have been reported in longitudinal epidemiologic studies (Rotterdam, Beaver Dam, Blue Mountains, and Los Angeles Latino Eye Studies), these are limited by the small numbers of incident late-stage cases.<sup>12,19-21</sup> Other data on progression also exist but come from small studies (e.g., Sunness et al)<sup>22</sup>; thus, estimates have wide confidence intervals (CIs). Rates of progression have been estimated from longitudinal clinical trials of nutritional supplementation in individuals with early AMD that were conducted in the United States.<sup>18,23</sup> Data from clinical trials are likely to be confounded by bias due to the healthy participant effect (whereby the more medically complex or sicker patients are excluded) and as a consequence of Age-Related Eye Disease Study (AREDS) supplementation, which was associated with lower rates of progression.<sup>18</sup>

In the United Kingdom, a large number of retina clinics use electronic medical records (EMRs), and these have been used to form longitudinal clinical repositories. In the present study, we analyzed data captured at 10 retina clinics that used the Medisoft Ophthalmology EMR software system (Medisoft Limited, Leeds, UK). This EMR system uses structured data fields similar to a clinical case report form. We have previously reported findings on the burden of macular disease in a cohort of patients with bilateral GA.<sup>24</sup> In the current article, we report on our findings regarding progression from early/intermediate AMD to the late forms of GA, choroidal neovascularization (CNV), or both.

## Methods

### Study Design

This was a retrospective cohort study using anonymized data from 10 retina clinics across the United Kingdom. Data were collected between October 2000, the date of first EMR record at earliest site, and February 16, 2016 (date of data extraction), using the Medisoft Ophthalmology EMR software system, which is the most widely used electronic database in the United Kingdom.<sup>25</sup> The exact timeframe was variable for each center and patient. Classified as a service evaluation study, in line with UK National Health Service (NHS) National Research Ethics guidance, institutional review board/ethics committee approval was not required, and governance was provided by the NHS hospital service providers, known as hospital trusts in the United Kingdom. The Caldicott Guardian at the Belfast Trust provided overall governance for the study, and a project oversight committee comprising 4 clinical

retina specialists, data specialists (IQVIA), and representatives from the funder (Hoffmann-La Roche, Basel, Switzerland) ensured the scientific integrity of the study. The study had the approval of the Caldicott Guardian at each site to allow sharing of anonymized EMR data and was conducted in accordance with the codes of conduct of the UK NHS regulations for the collection and use of patient-level data (as defined in the Data Protection Act of 1998). Because all data were fully anonymized, collected retrospectively, and in line with the aforementioned ethics guidelines and codes of conduct, patient consent was not required. The study adhered to the tenets of the Declaration of Helsinki. Further information on the design, participating centers, and study oversight was published previously.<sup>24</sup>

### Study Population

The patients included in this study were part of the larger UK EMR study of patients with early/intermediate AMD or GA (Fig 1). All patient records were stripped of patient identifying information before biostatistical analysis at IQVIA (London, UK).

### Inclusion and Exclusion Criteria

The EMR database included all patients referred to ophthalmology clinics and is therefore representative of a broad spectrum of ophthalmic disorders. An algorithm was needed to identify and select the AMD patient population that was included in the present analysis. Case definitions for early/intermediate AMD, GA, and CNV were previously published.<sup>24</sup> For the purposes of the present analysis, we only included patients with 1 or both eyes meeting the case definition for early/intermediate AMD, without advanced AMD (GA or CNV), before their first record for that eye in the EMR dataset. For inclusion in the analysis, the patient's fellow eye had to be classifiable as having early/intermediate AMD, GA, or CNV. The inclusion and exclusion criteria are shown in Table S1 (available at [www.opthalmologyretina.org/](http://www.opthalmologyretina.org/)). For all patients, a study eye and a fellow (contralateral) eye were designated.

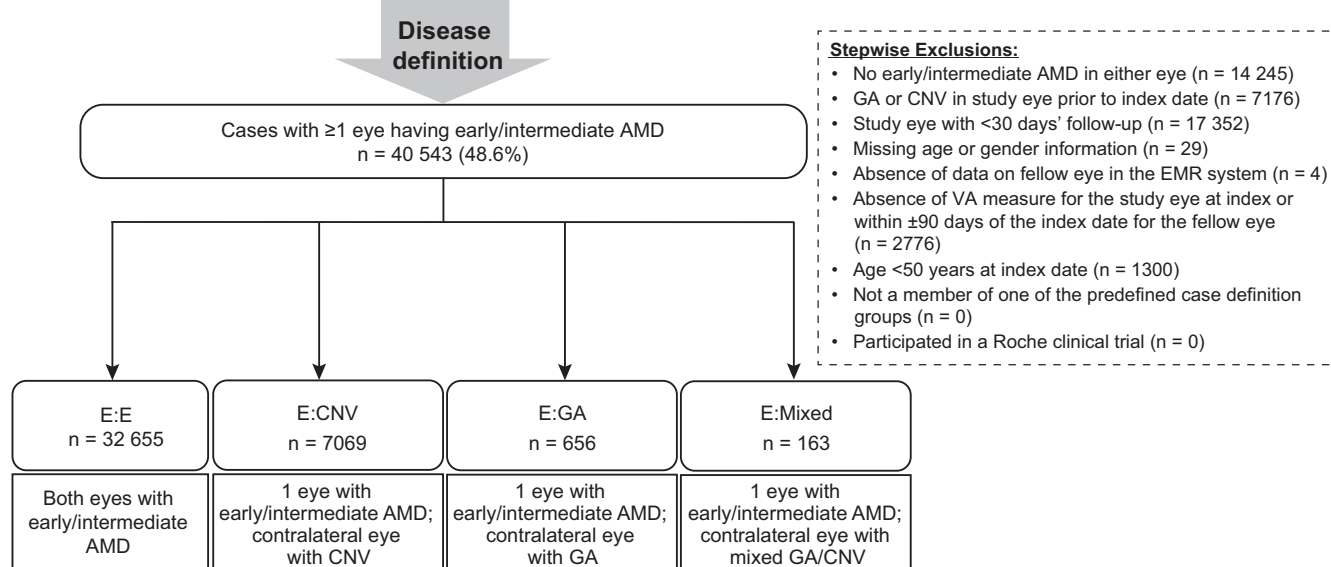
The earliest record indicating presence of early or intermediate AMD was taken as the index date for the patient. In patients with 2 eyes meeting the criteria for inclusion, the study eye was the eye with worse visual acuity (VA) at index, the eye with VA measures if only 1 eye had baseline measurements, or the right eye if VA was the same for both eyes at index.

Patients meeting the criteria for inclusion were divided into the following 4 subgroups on the basis of eye condition at index (Fig 1): early:early (both study eye and fellow eye classified as having early/intermediate AMD); early:GA (early/intermediate AMD in the study eye and GA in the fellow eye); early:CNV (early/intermediate AMD in the study eye and CNV in the fellow eye); and early:mixed (early/intermediate AMD in the study eye and both GA and CNV in the fellow eye).

### Objectives and Outcomes Assessed

The objectives of this study were to estimate the rates of progression to GA or CNV among eyes diagnosed with early/intermediate AMD and identify clinical risk factors for progression. Outcomes included the rate of progression to GA or CNV, expressed as number of cases progressed per 100 person-years. In addition, in patients with early/intermediate AMD in both eyes, progression to GA or CNV was evaluated for the worse-seeing eye, better-seeing eye, or either eye. Time to progression was calculated as time from index to first time when the GA or CNV definition was met.

Anonymized data from 83 425 patients with diagnosis or clinical findings suggesting early/intermediate AMD or GA extracted across 10 UK clinical sites between 2000 and 2016



**Figure 1.** Flow diagram showing the study population identified in the electronic medical record (EMR) database, extracted from 10 clinical sites in the United Kingdom. Patients with early/intermediate age-related macular degeneration (AMD) in at least 1 eye are the focus of this article. Subgroup definitions: E:CNV = early/intermediate AMD in study eye, choroidal neovascularization (CNV) in fellow eye; E:E = early/intermediate AMD in both eyes; E:GA = early/intermediate AMD in study eye, geographic atrophy (GA) in fellow eye; E:mixed = early/intermediate AMD in study eye, both GA and CNV in fellow eye. VA = visual acuity.

Patients who did not progress from an early to late stage during the course of their follow-up in the EMR were censored at their final record for the nominated study eye.

### Validation Exercise

A case-validation exercise was undertaken to verify the accuracy of the algorithm used to identify disease stage and progression that was applied to the EMR data. From the cohort of patients with early/intermediate AMD at index, 120 patients were selected randomly from the 10 study sites, stratified by whether progression to GA or CNV was recorded or not. Clinicians from each participating center checked their clinical and imaging repositories for correct classification of study and fellow eye at index and progression to GA or CNV. Any discrepancies were noted, and the percentage of patients with correct diagnoses for study eye and fellow eye at index and with correct identification of progression was calculated. The positive predictive value (PPV; proportion of true positives), negative predictive value (NPV; proportion of true negatives), sensitivity (proportion correctly classified), and specificity (proportion correctly classified as not experiencing the event) were calculated.

### Statistical Analyses

A Cox proportional hazards model was used to estimate rates of progression from early/intermediate AMD to GA or CNV. Multivariate models were run, which included the following potential predictors of progression: age at index, sex, cardiovascular disease, diabetes, gastrointestinal disease, glaucoma, hypertension, other comorbidities, smoking, cataract status, and VA at index. No imputation of missing data was conducted.

## Results

### Validation Exercise

Disease definition in the study and fellow eye and progression from early/intermediate AMD to GA and CNV were correctly identified in a high proportion of the sample (Table 1). Table 2 shows the number and proportion of patients with study and fellow eyes correctly classified and number of patients correctly classified, where these were (1) study eye classification, (2) fellow eye classification, (3) progression to GA in study eye, and (4) progression to CNV in study eye. The PPV was 0.96 for the study eye and 0.95 for the fellow eye with regard to classification at index. For progression from early/intermediate AMD to GA, the PPV was 0.92, and for progression to CNV, the PPV was 0.98. The corresponding NPVs for progression to GA and CNV were 0.99 and 1.00, respectively. The progression of early/intermediate AMD to GA had a sensitivity of 0.92 and specificity of 0.99; progression from early/intermediate AMD to CNV had a sensitivity of 1.00 and specificity of 0.95.

### Patient Population

In total, records for 83 425 patients were extracted from 10 retina centers across the United Kingdom between October 2000 and February 16, 2016, of whom 40 543 patients with early/intermediate AMD were included in the analysis. The numbers of patients in each of the previously defined 4 subgroups were as follows: early:early (n = 32 655); early:CNV (n = 7069); early:GA

Table 1. Results of the Validation Exercise\*

	Study Eye (Early/Intermediate AMD Definition)	Fellow Eye (Early/Intermediate AMD Definition)	Progression from Early/Intermediate AMD Degeneration to:	
			GA	CNV
PPV	0.96	0.95	0.92	0.98
NPV	NA	NA	0.99	1.00
Sensitivity	NA	NA	0.92	1.00
Specificity	NA	NA	0.99	0.95

AMD = age-related macular degeneration; CNV = choroidal neovascularization; GA = geographic atrophy; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value.

\*A total of 120 patients were included in the validation exercise. Ten patients were randomly selected from 9 of the 10 sites with the following stratification: 5 randomly selected from those diagnosed as progressing to CNV, and 5 randomly selected from those who did not progress to CNV; 30 patients were randomly selected from 1 site, with 15 randomly selected from those diagnosed as progressing to CNV and 15 randomly selected from those who did not progress to CNV.

(n = 656); early:mixed (n = 163). The baseline characteristics of patients across these subgroups are summarized in Table 3.

The mean age of patients was 76 years in the early:early subgroup, 78 years in the early:CNV group, and 80 years in the early:GA and early:mixed subgroups. The majority of patients in all subgroups were female (59.5% overall). The median (interquartile range [IQR]) time of follow-up for the entire group was 1.7 (0.7–3.6) years. The early:CNV and early:mixed subgroups had longer periods of follow-up (median, 2.1 years) compared with the early:early subgroup (median, 1.6 years). Median (IQR) VA in the study eye ranged from 70 (60–75) to 75 (65–80) Early Treatment Diabetic Retinopathy Study (ETDRS) letters across subgroups, whereas median (IQR) VA in the fellow eye was best in the early:early subgroup (84 [75–85] ETDRS letters) and worst in the early:GA subgroup (60 [35–75] ETDRS letters). The VA was better in the study eye than in the fellow eye for the early:CNV, early:GA, and early:mixed subgroups but worse in the study eye in the early:early group (reflecting the selection criteria for this subgroup, which required that the eye with worse VA be designated the study eye). Glaucoma was present in 4.1% of study eyes overall, with the highest rate (4.6%) in the early:GA subgroup and lowest rate (2.6%) in the early:CNV subgroup. The percentage of pseudophakic study eyes was 12.8% overall, highest (14.3%) in the early:GA subgroup and lowest (7.7%) in the early:CNV subgroup. Diabetes was present in 26% of patients overall but varied between subgroups, reported at baseline for 29.9% of patients in the early:early subgroup, in 16.9% of the early:GA subgroup, and less than 10% of the early:CNV and early:mixed subgroups. Cardiovascular disease also varied between subgroups, reported in 13% of the early:early subgroup and in more than 20% of the other subgroups. Hypertension was reported for 28.9% of patients at

baseline, ranging from 26.1% in the early:CNV subgroup to 34.9% in the early:GA subgroup.

### Progression from Early/Intermediate Age-Related Macular Degeneration to Geographic Atrophy or Choroidal Neovascularization in Patients with Late-Stage Age-Related Macular Degeneration in 1 Eye

The rates of progression to GA and CNV varied by the advanced stage phenotype of the fellow eye, as shown in Table 4 and Figure 2. Progression to GA in the study eye was 11.2 per 100 person-years when GA was present in the fellow eye at index (n = 656) and the rate of progression to CNV was 8.5 per 100 person-years. Among patients in the early:GA subgroup with at least 2 years of follow-up (n = 238), the proportion of study eyes that progressed by 2 years to GA was 13.4% (n = 32), and the rate was identical for those that progressed to CNV (13.4%; n = 32).

When the fellow eye had CNV at index (n = 7069), the rate of progression to CNV in the study eye was 15.2 per 100 person-years and progression to GA occurred at a rate of 4.1 per 100 person-years. Among patients in the early:CNV group with at least 2 years of follow-up (n = 3690), the proportion of study eyes that progressed by 2 years to CNV was 28% (n = 1032) and the proportion that progressed by 2 years to GA was 7.0% (n = 259).

In the early:mixed subgroup (n = 163), where the fellow eye exhibited both GA and CNV at index, the progression rates to GA and CNV were 7.8 and 11.9 per 100 person-years, respectively (Fig 2). Among patients with at least 2 years of follow-up (n = 83), the proportion of study eyes that progressed by 2 years to GA was

Table 2. Additional Details from the Validation Exercise: Correct Diagnoses by 4 States\*

Study Eye Correct (N = 120)	Fellow Eye Correct (N = 120)	No. of Correct States				
113 (94%)	113 (94%)	4	3	2	1	0
		101 (84%)	15 (13%)	4 (3%)	0	0

A total of 120 patients were included in the validation exercise. Ten patients were randomly selected from 9 of the 10 sites with the following stratification: 5 randomly selected from those diagnosed as progressing to choroidal neovascularization (CNV) and 5 randomly selected from those who did not progress to CNV; 30 patients were randomly selected from 1 site, with 15 randomly selected from those diagnosed as progressing to CNV and 15 randomly selected from those who did not progress to CNV.

\*The 4 states were (1) study eye classification; (2) fellow eye classification; (3) progression to geographic atrophy in study eye; and (4) progression to CNV in study eye.

Table 3. Baseline Patient and Ocular Characteristics

Variable	All Patients (N = 40 543)	E:E (n = 32 655)	E:CNV (n = 7069)	E:GA (n = 656)	E:Mixed (n = 163)
Mean age (SD), yrs	76 (8)	76 (9)	78 (7)	80 (7)	80 (6)
Median (IQR)	78 (72–83)	78 (71–82)	80 (74–83)	82 (77–85)	82 (78–85)
Female, %	59.5	58.5	64.2	55.5	60.7
Median follow-up time (IQR), yrs	1.7 (0.7–3.6)	1.6 (0.6–3.6)	2.1 (1.0–3.9)	1.3 (0.6–2.7)	2.1 (1.1–3.4)
Median study eye VA at baseline (IQR), ETDRS letters*	70 (60–75)	70 (60–75)	75 (65–80)	70 (60–75)	73 (63–79)
Median fellow eye VA at baseline (IQR), ETDRS letters	N/A	84 (75–85)	70 (50–78)	60 (35–75)	63 (41–75)
Pseudophakic, no. (%)	5195 (12.8)	4534 (13.9)	547 (7.7)	94 (14.3)	20 (12.3)
Glaucoma, no. (%)*	1641 (4.0)	1421 (4.4)	185 (2.6)	30 (4.6)	5 (3.1)
Cardiovascular disease, no. (%)*	5909 (14.6)	4228 (12.9)	1481 (21.0)	161 (24.5)	39 (23.9)
Diabetes, no. (%)*	10 555 (26.0)	9761 (29.9)	669 (9.5)	111 (16.9)	14 (8.6)
Gastrointestinal disease, no. (%)*	382 (0.9)	230 (0.7)	138 (2.0)	8 (1.2)	6 (3.7)
Hypertension, no. (%)*	11 726 (28.9)	9604 (29.4)	1846 (26.1)	229 (34.9)	47 (28.8)
Other systemic comorbidities, no. (%)*	1967 (4.9)	1419 (4.3)	491 (6.9)	51 (7.8)	6 (3.7)
Smoking (ever), no. (%)†	3474 (8.6)	2371 (7.3)	994 (14.1)	82 (12.5)	27 (16.6)

ETDRS = Early Treatment Diabetic Retinopathy Study; IQR = interquartile range; N/A = not available; SD = standard deviation; VA = visual acuity. Subgroup definitions: E:CNV = early/intermediate age-related macular degeneration (AMD) in study eye, choroidal neovascularization (CNV) in fellow eye; E:GA = early/intermediate AMD in study eye, geographic atrophy (GA) in fellow eye; E:mixed = early/intermediate AMD in study eye, both GA and CNV in fellow eye.

\*All comorbidities except cataract were calculated as any record within 6 months of index.

†Smoking status and smoking history were missing for approximately 65% of patients.

16.9% (n = 14) and the proportion that progressed by 2 years to CNV was also 16.9% (n = 14). For all patients with a diagnosis of early/intermediate AMD in one eye, the overall rate of progression to GA was 2.5 per 100 person-years and to CNV was 5.1 per 100 person-years.

### Progression from Early/Intermediate Age-Related Macular Degeneration to Geographic Atrophy or Choroidal Neovascularization in Patients with Bilateral Early/Intermediate Age-Related Macular Degeneration

In this subgroup of patients (n = 32 655), the rate of progression to GA in the study eye was 2.0 per 100 person-years and the rate of progression to CNV was 3.2 per 100 person-years; when either eye was considered (n = 25 835), the rates of progression to GA

and CNV were 2.5 and 4.5 per 100 person-years, respectively, and the rate of progression to any advanced AMD was 6.3 per 100 person-years overall. In patients with at least 2 years of follow-up (n = 14 383), the proportion of study eyes that progressed to GA by 2 years was 2.4% (n = 339), and the proportion of study eyes that progressed to CNV by 2 years was 7.1% (n = 1020).

On testing the effect of VA on rates of progression after classification of eyes within persons as better- or worse-seeing eyes, better-seeing eyes showed slightly lower progression rates to both GA and CNV compared with the worse-seeing eyes (study eyes). Of the 25 835 better-seeing eyes, the rate of progression per 100 person-years was 1.8 for progression to GA and 2.4 for progression to CNV (Table 5, Fig 3).

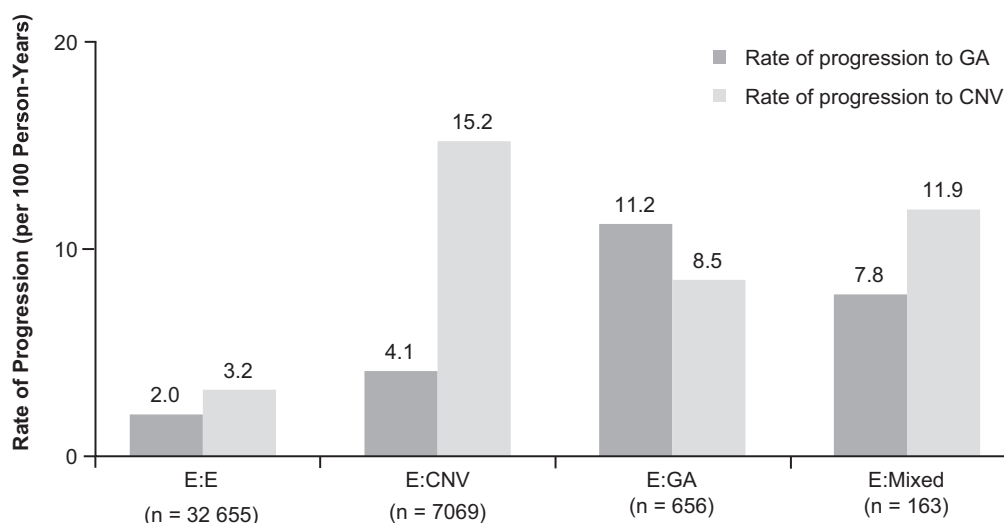
The progression outcomes for all patients with at least 2 years of follow-up (n = 18 394) are reported in Appendix S1 and Fig S1 (available at [www.opthalmologyretina.org/](http://www.opthalmologyretina.org/)).

Table 4. Progression to GA or CNV in Study Eyes with Early/Intermediate AMD

	E:E (N = 32 655)	E:CNV (N = 7069)	E:GA (N = 656)	E:Mixed (N = 163)
Progression to GA				
Progressed, n (%)	1495 (4.58)	709 (10.03)	122 (18.6)	27 (16.56)
Person-yrs	76 524	17 194	1087	344
Rate per 100 person-yrs	2.0	4.1	11.2	7.8
Progression to CNV				
Progressed, n (%)	2333 (7.14)	2066 (29.23)	91 (13.87)	38 (23.31)
Person-yrs	73 233	13 620	1067	320
Rate per 100 person-yrs	3.2	15.2	8.5	11.9

AMD = age-related macular degeneration; CNV = choroidal neovascularization; GA = geographic atrophy.

Subgroup definitions: E:CNV = early/intermediate AMD in study eye, CNV in fellow eye; E:E = early/intermediate AMD in both eyes; E:GA = early/intermediate AMD in study eye, GA in fellow eye; E:mixed = early/intermediate AMD in study eye, both GA and CNV in fellow eye.



**Figure 2.** Rate of progression from early/intermediate age-related macular degeneration (AMD) to geographic atrophy (GA) or choroidal neovascularization (CNV) by status of fellow eye. Subgroup definitions: E:CNV = early/intermediate AMD in study eye, CNV in fellow eye; E:E = early/intermediate AMD in both eyes; E:GA = early/intermediate AMD in study eye, GA in fellow eye; E:mixed = early/intermediate AMD in study eye, both GA and CNV in fellow eye.

### Risk Factors for Progression to Advanced Age-Related Macular Degeneration

Multivariate Cox regression models show the hazard ratios (HRs) for the risk factors that were tested for progression to the late AMD phenotypes in persons with early/intermediate AMD (Table 6). Age at index, female sex, history of cardiovascular disease, and history of smoking were significantly associated with an increased rate of progression from early/intermediate AMD to GA, CNV, and either GA or CNV. A history of diabetes or glaucoma and better VA at index were significantly associated with a decreased rate of progression to GA or CNV, or either type of advanced AMD.

After adjustment for all of the risk factors determined to be significant in the multivariate regression, HRs for the progression to GA or CNV in the study eye by late-stage AMD phenotype in the fellow eye are shown in Figures 4 and 5. The adjusted progression rates in the study eye were more than 2.5-fold greater for GA, with a point estimate for the HR of 4.5 compared with 1.7 for CNV, when the fellow eye had GA (Fig 4). The adjusted

progression rate to CNV in the study eye was 1.8-fold greater than progression to GA when the fellow eye had CNV (Fig 5).

### Discussion

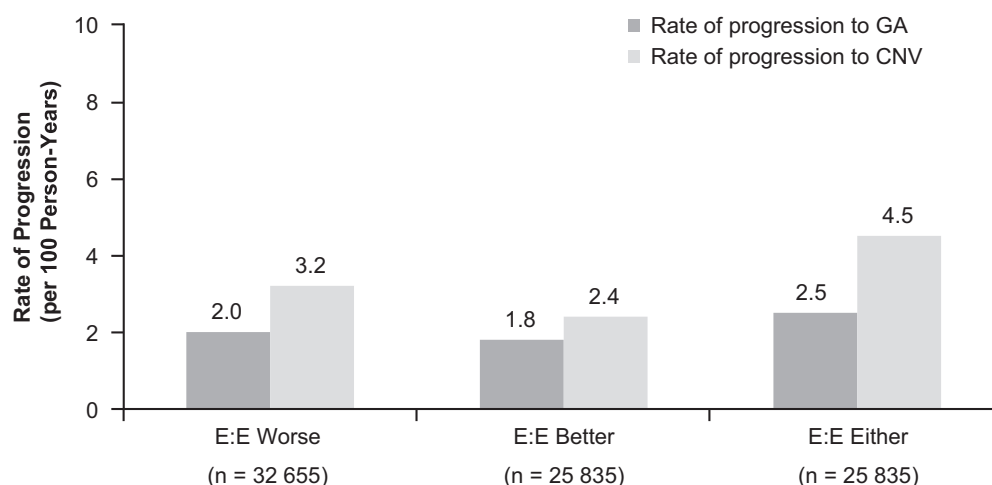
The present study has provided valuable information on the rate of progression from early/intermediate presentations of AMD to more advanced forms of the disease in a large population of clinical patients. It is the only EMR dataset that has undertaken systematic validation of assignment to the correct disease state of AMD and for the progression from early to late AMD phenotypes. The finding of high PPVs and NPVs supports the robustness of the algorithm used to classify the cases and testifies to the quality of the data entered into the EMR. It is also the largest study that has examined risk factors for progression from early/intermediate AMD to advanced AMD.

We computed annual progression rates from early/intermediate AMD to both GA and CNV in a large patient

**Table 5.** Progression to GA or CNV in Worse-Seeing (Study Eyes), Better-Seeing (Fellow Eyes), or Either Eye in Patients with Bilateral Early/Intermediate AMD

	Worse-Seeing Eye (N = 32 655)	Better-Seeing Eye (N = 25 835)	Either Eye (N = 25 835)
Progression to GA			
Progressed, n (%)	1495 (4.58)	1114 (4.3)	1561 (6.0)
Person-yrs	76 524	62 499	61 892
Rate per 100 person-yrs	2.0	1.8	2.5
Progression to CNV			
Progressed, n (%)	2333 (7.14)	1489 (5.8)	2606 (10.1)
Person-yrs	73 233	60 806	58 182
Rate per 100 person-yrs	3.2	2.4	4.5

AMD = age-related macular degeneration; CNV = choroidal neovascularization; GA = geographic atrophy.



**Figure 3.** Rate of progression to geographic atrophy (GA) or choroidal neovascularization (CNV) in eyes with bilateral early/intermediate age-related macular degeneration (AMD), with eyes classified by relative visual acuity (VA) at patient level. Subgroup definitions (patients with early/intermediate AMD in both eyes): E:E worse = rate of progression in eye with worse VA; E:E better = rate of progression in eye with better VA; E:E either = rate of progression to GA or CNV in either eye.

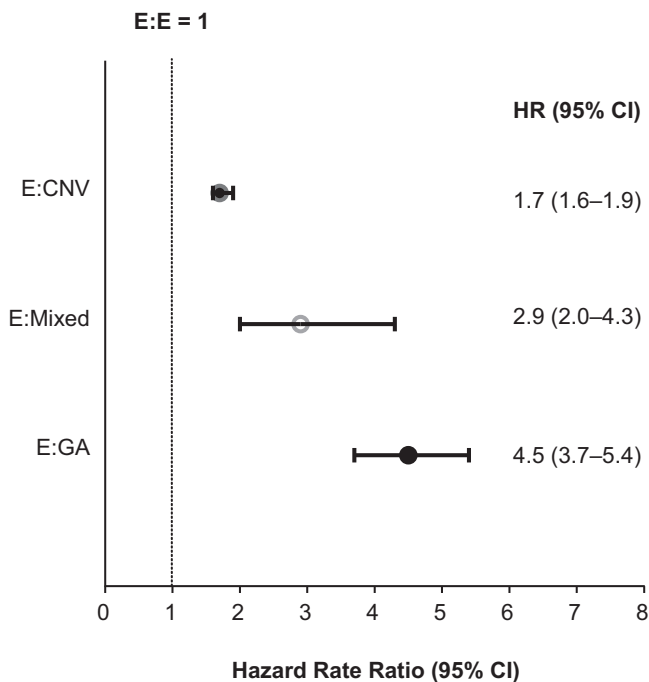
population, which included approximately 8000 patients with late-stage AMD in 1 eye. Although the phenotype of the eye with late-stage AMD has been identified as a predictor of the potential phenotype of late-stage AMD in the early/intermediate AMD fellow eye of a person,<sup>19,26,27</sup> our data not only support past observations but also provide progression rates for estimating risk from a large clinical sample and thus having small confidence limits. The finding that progression from an early/intermediate AMD state to GA can occur at a rate of approximately 11.2 per 100 person-years (in those with existing GA in fellow eye) is inconsistent with the relative prevalences of GA and CNV that have been reported in the major epidemiologic studies, which often suggest a lower prevalence or cumulative incidence of GA compared with CNV.<sup>7-9,12,19,28,29</sup> There was more CNV present in the study population at baseline (more patients had CNV in the fellow eye than

had GA), and yet a high rate of progression from early/intermediate AMD to GA was observed. In our previous report from this database, we showed that the rate of development of CNV in eyes with GA was considerable.<sup>24</sup> Furthermore, epidemiologic studies review their participants in 5 and 10 yearly intervals, unlike the EMR repository in which patients were reviewed at more frequent intervals and which could allow detection of the onset of even small areas of GA before the onset of neovascularization. Our findings together support the view that GA may be a precursor to CNV and that this event may mask the presence of the former. In this context, it is worth noting that AREDS found that in eyes with incident GA without neovascular disease, the 4-year risk of subsequent neovascular disease was 29%.<sup>30</sup> Along with the findings of the present study, these event frequencies suggest that atrophy is likely to be the initial step in the

**Table 6.** Risk of Progression from Early/Intermediate AMD to Advanced AMD: Multivariate Predictive Cox Regression Model Results

Parameter	Progression to GA			Progression to CNV			Progression to GA or CNV		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Age at index (+1 yr)	1.06	1.06–1.07	<0.0001	1.02	1.02–1.03	<0.0001	1.04	1.03–1.04	<0.0001
Sex (female vs. male)	1.11	1.02–1.21	0.019	1.19	1.12–1.27	<0.0001	1.18	1.12–1.25	<0.0001
Cataract status (phakic vs. pseudophakic)	1.04	0.91–1.18	0.603	1.19	1.07–1.32	0.001	1.12	1.03–1.22	0.008
VA at index (+1 letter)	0.98	0.98–0.98	<0.0001	0.99	0.99–0.99	<0.0001	0.98	0.98–0.98	<0.0001
History of glaucoma (yes vs. no)	0.75	0.62–0.91	0.003	0.57	0.48–0.68	<0.0001	0.64	0.56–0.74	<0.0001
History of cardiovascular disease (yes vs. no)	1.20	1.04–1.38	0.010	1.23	1.12–1.36	<0.0001	1.24	1.14–1.35	<0.0001
History of diabetes (yes vs. no)	0.52	0.46–0.59	<0.0001	0.43	0.40–0.48	<0.0001	0.45	0.42–0.49	<0.0001
History of gastrointestinal disease (yes vs. no)	1.29	0.88–1.89	0.195	1.05	0.80–1.37	0.716	1.17	0.93–1.46	0.187
History of hypertension (yes vs. no)	0.95	0.85–1.06	0.334	0.96	0.88–1.04	0.312	0.94	0.88–1.01	0.079
History of other conditions (yes vs. no)	1.00	0.81–1.23	0.987	1.17	1.03–1.33	0.019	1.16	1.04–1.30	0.011
History of smoking (ever vs. never)	1.25	1.06–1.47	0.008	1.29	1.16–1.45	<0.0001	1.29	1.17–1.43	<0.0001

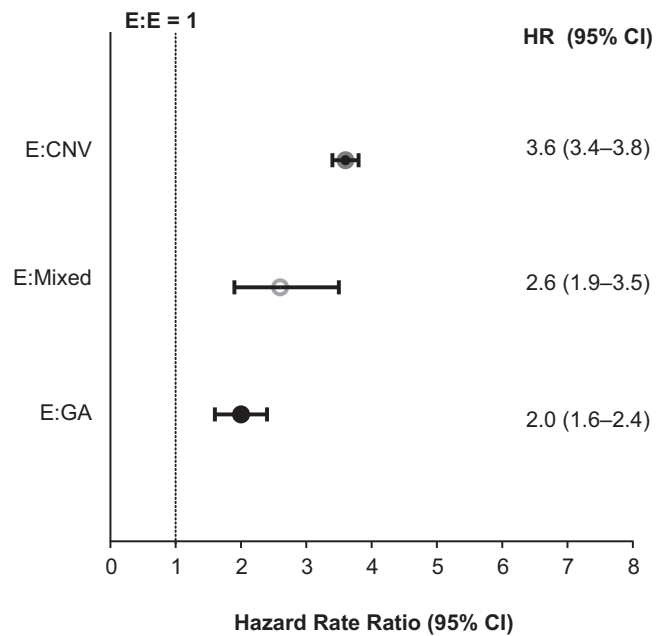
AMD = age-related macular degeneration; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; HR = hazard ratio; VA = visual acuity.



**Figure 4.** Adjusted\* rate of progression from early/intermediate age-related macular degeneration (AMD) to geographic atrophy (GA) in patients with advanced AMD in fellow eye, compared with patients with early/intermediate AMD in both eyes. \*Multivariate Cox proportional hazards model, adjusted for covariates if proportional hazards assumption violated (covariates: age, sex, cardiovascular disease, diabetes, gastrointestinal disease, glaucoma, hypertension, other comorbidities, smoking, presenting visual acuity, and cataract status). Subgroup definitions: E:CNV = early/intermediate AMD in study eye, CNV in fellow eye; E:E = early/intermediate AMD in both eyes; E:GA = early/intermediate AMD in study eye, geographic atrophy (GA) in fellow eye; E:mixed = early/intermediate AMD in study eye, both GA and CNV in fellow eye. CI = confidence interval; HR = hazard ratio.

progression to late-stage AMD and development of CNV is linked to photoreceptor and retinal pigment epithelium loss. It is also notable that the rate at which CNV occurred in AREDS2 in eyes with GA (29% in 4 years, approximating to 7 per 100 person-years) is close to the 8.5 per 100 person-years rate of progression to CNV seen in study eyes in the early:GA group in the present study.

The recording of clinical history with information on smoking and VA data, and the large sample size constituted by the EMR records, allowed the characterization of the trajectory of progression to either form of late AMD in patients with bilateral early/intermediate AMD, with high degrees of confidence. In patients with bilateral early AMD, the progression rates per 100 person-years to GA or CNV were 2.5 and 4.5, respectively. Previous epidemiologic studies have observed low rates of progression to GA and higher rates of progression to CNV. In the Blue Mountains Eye Study, incident GA without CNV was observed at a rate of 2.6% overall over a 15-year period.<sup>12</sup> This is an extremely low rate of incident GA compared with both the present study and that of AREDS, in which, of the 6530 eyes at risk, 17% developed GA without neovascular



**Figure 5.** Adjusted\* rate of progression from early/intermediate age-related macular degeneration (AMD) to choroidal neovascularization (CNV) in patients with advanced AMD in fellow eye, compared with patients with early/intermediate AMD in both eyes. \*Multivariate Cox proportional hazards model, adjusted for covariates if proportional hazards assumption violated (covariates: age, sex, cardiovascular disease, diabetes, gastrointestinal disease, glaucoma, hypertension, other comorbidities, smoking, presenting visual acuity, and cataract status). Subgroup definitions: E:CNV = early/intermediate AMD in study eye, CNV in fellow eye; E:E = early/intermediate AMD in both eyes; E:GA = early/intermediate AMD in study eye, geographic atrophy (GA) in fellow eye; E:mixed = early/intermediate AMD in study eye, both GA and CNV in fellow eye. CI = confidence interval; HR = hazard ratio.

disease during 4.4 years (mean follow-up).<sup>30</sup> However, the age of the Blue Mountains Eye Study population was considerably lower than that in the present study and AREDS because the lower age cutoff was 49 years, thus permitting younger participants to be enrolled. The numbers developing late AMD were small, and follow-up was at 5, 10, and 15 years; it is possible that foci of incident GA may have been obscured by CNV that occurred in the intervals between follow-up assessments.

The Antioxydants, Lipids Essentiels, Nutrition et Maladies Oculaires (ALIENOR) study has also computed progression rates to advanced AMD.<sup>14</sup> However, there were only 45 incident cases of late AMD, and thus the CIs for progression were wide and within the range found in the present study. In ALIENOR, the risk of progression to advanced AMD (GA or CNV) was associated with the AMD grade in the fellow eye, with a multivariate-adjusted HR (95% CI) of 18.60 (2.5–141.1) if there was GA in the fellow eye and 22.54 (2.6–195.9) when CNV was found in the fellow eye.<sup>14</sup> Also, a diagnosis of early AMD in 1 eye was associated with the highest HR for progression to advanced AMD in the fellow eye, which is in contrast to the findings in this study where the highest risk of

progression in any eye was related to the presence of late-stage AMD in the fellow eye. However, compared with the present study, ALIENOR had smaller numbers of eyes included ( $n = 264$ ), and few ( $n = 10$ ) fellow eyes had late AMD at baseline. Thus, the low event rate and small sample likely affected their ability to provide robust estimates of risk and progression rates. The effect of phenotype in the fellow eye has also been reported for eyes with GA by Sunness et al<sup>31</sup> in a study in which 18% of eyes with GA developed CNV by year 2 if the fellow eye had CNV at baseline, compared with 2% of eyes in patients with bilateral GA at baseline. As in the present study, the AMD phenotype in the fellow eye appeared to influence the nature of progression in the study eye.

It was reassuring to note that factors associated consistently with AMD in many populations were similarly identified as increasing risk in the present study. Notably, for GA we observed that age at index, female sex, worse VA, and smoking were significantly associated with increased risk. For CNV, in addition to the factors listed for GA, cardiovascular disease was also associated with an increased risk. Analyses of data from previous studies have found smoking and total serum cholesterol, but not diabetes, to be risk factors for advanced AMD.<sup>32,33</sup> Of note, we found a history of glaucoma and diabetes to be protective, with that of diabetes having a profound effect. One possible explanation is that glaucoma and diabetes account for a large proportion of the hospital population in the EMR, and this may account for a spurious protective association with respect to progression to AMD. Another possible explanation is that, at least in diabetes, the presence of retinopathy may have masked features of AMD. However, onset of late AMD characteristics are detectable on OCT and it is unlikely that expert retinal clinicians would have missed the onset of CNV or areas of GA. However, drugs used in treating glaucoma have been credited with neuroprotective effects, and thus it is possible that patients on intraocular pressure-reducing strategies might have benefited through a trophic effect on the photoreceptors of the retina. A high proportion of the patients with diabetes mellitus had the type 2 form (data not shown), for which a cornerstone of treatment is the biguanide compound, metformin. Metformin has been noted to be protective against cancer, inflammation, and age-related pathologies.<sup>34</sup> Because the pathogenesis of AMD has been strongly linked to gene variants in the complement pathways that promote inflammation at a local level,<sup>35</sup> it is possible that the long-term use of such compounds in patients with type 2 diabetes, which was common in our dataset, may have provided protection in this manner. These findings merit further scrutiny. An analysis of the Beaver Dam Study found no relationship for diabetes with early AMD or GA.<sup>33</sup> Likewise, pooled data from the Beaver Dam, Blue Mountains, and Rotterdam Eye Studies found no relationship of diabetes with advanced AMD.<sup>32</sup>

Our study has a number of strengths. Data were drawn from a large cohort of patients from 10 different clinical sites across the United Kingdom. By using EMR data, we captured clinician diagnoses representative of clinical practice. The validation exercise supported the accuracy of the algorithm used for case selection and confirmed both disease classification and evidence of progression.

## Study Limitations

Our study suffers from a number of limitations. First, the sample had more patients with nAMD than GA. This likely reflects the inherent bias operating in UK NHS clinics where patients with treatable disorders are retained in the hospital eye care systems and, furthermore, the lack of an approved treatment for GA likely resulted in a filtering out of such cases from our referral sources. Another important weakness of our model is that the sample, although large, may have higher frequencies of confounding ophthalmic conditions, unlike that of a population-based dataset. We made no imputation in the present analysis for smoking history, a high proportion of which was missing at baseline, and therefore the regression analyses may have been affected by unobserved differences between patients. However, we made an effort to select centers based on quality of data capture to mitigate this limitation. In this analysis of the early/intermediate AMD cohort, we censored patients at the point at which they developed advanced AMD in the nominated study eye, and thus no information was gained on progression from GA to CNV or to a mixed morphology. In a previous study in patients with bilateral GA from the same EMR dataset, we showed that eyes with GA can progress to CNV at a rate of 7.4 per 100 person-years.<sup>24</sup> Findings from AREDS, which also had a clinic population, after 10 years of follow-up show an average rate of progression from GA to CNV of 5.8 per 100 person-years in patients with CNV in their fellow eye (average rate ranged from 4.9 to 8.6) and 3.2 per 100 person-years if no CNV was present (average rate ranged from 2.0 to 3.3).<sup>36</sup> A major limitation of our study is the variable follow-up both across centers and between patients, which is a weakness. Nonetheless, it is reflective of routine clinical practice. Other limitations of this study were that the analyses could not be controlled for use of AREDS supplements<sup>18</sup> by individual patients, it did not capture severity of early/intermediate AMD features, and selection bias may have arisen in that patients with select comorbidities or advanced AMD in 1 eye may have been reviewed more frequently.

## Conclusions

We have shown that in eyes with early or intermediate AMD, progression to GA or CNV occurs frequently, and that if GA or CNV is present in the fellow eye then there is a high risk for progression to the same form of advanced AMD. Further studies are needed to confirm the novel risk factor relationships observed for progression from early AMD to advanced AMD.

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Abbreviations and Acronyms:

**AMD** = age-related macular degeneration; **AREDS** = Age-Related Eye Diseases Study; **CI** = confidence interval; **CNV** = choroidal neovascularization; **EMR** = electronic medical record; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **GA** = geographic atrophy; **HR** = hazard ratio; **IQR** = interquartile range; **nAMD** = neovascular age-related macular degeneration; **NHS** = National Health Service; **NPV** = negative predictive value; **PPV** = positive predictive value; **VA** = visual acuity.

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