

Characterizing Disease Burden and Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration

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Purpose: To understand levels of disease burden and progression in a real-world setting among patients from the United Kingdom with bilateral geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Design: Retrospective cohort analysis of a multicenter electronic medical record (EMR) database.

Participants: Patients who were aged ≥ 50 years with bilateral GA and no history of choroidal neovascularization (CNV) and who attended 1 of 10 clinical sites using the EMR.

Methods: A deidentified data set was constructed from the records held at the 10 sites. An algorithm was used to extract cases with a GA diagnosis, of which 1901 had bilateral GA and form the basis of this report. A sample of records randomly selected from each center was used to validate disease definitions.

Main Outcome Measures: Progression to blindness (visual acuity [VA] < 20 letters or Snellen 3/60 in the better-seeing eye), driving ineligibility (VA ≤ 70 letters or Snellen 6/12 in the better-seeing eye), progression to CNV, loss of 10 or more letters, and mean change in VA over time.

Results: At first record of GA, 7.1% had a VA in the better-seeing eye equal to or lower than the cutoff for blindness registration and 71.1% had a VA that would have rendered them ineligible to drive. Over time, 16% became legally blind (median time to outcome, 6.2 years) and 66.7% became ineligible to drive (median time to outcome, 1.6 years). In the worse-seeing eye, 40.1% lost ≥ 10 letters in 2.4 years. Among patients with baseline and 24-month VA measurements, mean VA decline was 6.1 letters in the worse-seeing eye ($n = 413$) and 12.4 letters in the better-seeing eye ($n = 414$). The rate of progression to CNV in either eye was 7.4% per patient-year.

Conclusions: At initial diagnosis, based on VA in the better-seeing eye, a high proportion of patients with bilateral GA were ineligible to drive and approximately 7% were eligible for UK blindness registration. The subsequent reduction in VA that occurred in the better-seeing eye would render a further two-thirds ineligible to drive. These findings emphasize the severity of the visual disability associated with GA secondary to AMD. *Ophthalmology* 2018;125:842-849 © 2018 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/>).



See Editorial on page 794.

Supplemental material available at www.aaojournal.org.

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD), characterized by progressive and irreversible loss of the retinal pigment epithelium, photoreceptors, and underlying choriocapillaris.^{1,2} Geographic atrophy has been estimated to afflict some 5 million people worldwide and has similar prevalence rates to neovascular AMD, both in the United States and globally.^{3–5} It was previously estimated that GA accounted for one-tenth of the blindness due to AMD and neovascular AMD for the remainder.⁶ However, the global incidence of

blindness due to neovascular AMD has been significantly reduced over the last decade with the introduction of anti-vascular endothelial growth factor therapy.^{7–10} Recent studies have reported that GA accounts for approximately one-quarter of legal blindness in the United Kingdom and the United States.^{1,2}

It has also been reported that even when distance visual acuity (VA) is marginally reduced or indeed unaffected, patients with GA experience difficulty with reading and seeing in low-light conditions, problems that may not be

reflected in VA measurements.¹¹ Currently, there are no approved treatments to prevent GA or limit its progression when already present, nor are there treatments that can reverse pathology. Geographic atrophy is usually bilateral, and with its major impact on vision-related quality of life, this lack of a treatment for GA represents an important unmet need.^{2,11,12}

Both GA and neovascularization are manifestations of the advanced stages of AMD. Epidemiologic studies, while estimating prevalence and incidence of these 2 phenotypes, have mainly classified eyes with both manifestations under the category of neovascular. Also, for the purposes of analyzing risk factors at a person level, most studies classify persons with neovascular AMD in 1 eye under this label. Thus, the historical classification regimens are likely to have underestimated the prevalence and incidence of GA. Additionally, relationships between GA and choroidal neovascularization (CNV) remain largely unexplored.

Data on the development and progression of GA have been well characterized in prospective, longitudinal studies.^{13–18} However, natural history data on visual function decline and the temporal changes of clinically relevant functional end points remain limited,¹⁹ and existing evidence has been mainly derived from small clinic-based GA cohorts or from the few GA cases that were found within large epidemiologic studies.^{20,21} Particularly important are the outstanding questions on the interrelationship between GA and neovascular AMD,²² and the functional impact of GA when it is the sole manifestation, as well as when occurring concomitantly with neovascular AMD.

This study aimed to address and bridge current knowledge gaps on the progression of GA to CNV and the impact of the former on VA change using a large patient cohort assimilated within a common electronic medical record (EMR) platform used by multiple centers in the United Kingdom. The primary objective was to better understand the natural history of patients with bilateral GA using large, longitudinal, real-world data. Specifically, we evaluated baseline characteristics and progression to precise or unambiguous clinical outcomes. The secondary objective was to explore risk factors associated with disease progression. A validation exercise was also conducted across all sites to ensure that the algorithm to identify disease and assess progression was valid.

Methods

Study Design

This was a retrospective cohort study using anonymized data collected using the Medisoft EMR software system.²³ All patient data were fully compliant with UK National Health Service (NHS) rules governing the use of patient-level health care data (as defined in the Data Protection Act of 1998) and had approval of the individual NHS center's Caldicott Guardian. Ten NHS clinical sites (Table S1, available at www.aaojournal.org) contributed data that had been accumulated between October 2000 (date of first EMR record at earliest site) and February 16, 2016 (date of data extraction from all sites), although the exact time frame was variable for each center and patient, depending on when the EMR system was introduced. The centers were selected as they fulfilled the following criteria: EMR system adoption and utilization by center

physicians and staff for routine clinical management; willingness to provide EMR data and undertake the necessary governance procedures to allow extraction of the data; sufficient duration of use of the EMR and adequate size of early/intermediate AMD and GA populations under clinical management; geographic spread of centers; year from which there was continuous data recording; and consistency of VA data entry by the center.

A project oversight committee comprising key members with clinical expertise (4 retina specialists from the contributing sites), statistical and data expertise (QuintilesIMS), and the funder (Roche, Basel, Switzerland), whose representatives had epidemiology, study design, and interpretation expertise, ensured the scientific integrity of this study.

Study Population

After confirmation from each of the selected sites that permission from the local NHS data guardian was granted to provide data for the construction of the amalgamated data set, the software provider (Medisoft Limited, Leeds, United Kingdom) created data files for transfer to the biostatistics support unit (QuintilesIMS). These files consisted of patient data in which the diagnoses or clinical findings suggested early/intermediate AMD or GA. The data were stripped of all patient identifiers and pseudonymized before transfer to the biostatistics support unit. Research ethics committee review and approval were not required. An algorithm was used to identify the study population and consisted of patients meeting prespecified inclusion criteria.

Inclusion and Exclusion Criteria

For inclusion, patients had to have at least 1 eye meeting the GA case definition (Table S2, available at www.aaojournal.org) and no evidence of CNV in that eye before the first GA record during the study period. The earliest record indicating the diagnosis of GA was taken as the index date for the patient.

Main exclusion criteria were age <50 years at index date; study eye with <30 days' follow-up (defined as the absence of any record of visits, measures, or procedures); missing age or sex information; no information for the fellow eye in the EMR system, or fellow eye not classifiable (i.e., not meeting the early/intermediate AMD, GA or CNV case definition, and VA missing within ± 90 days of index date).

For all patients, a study eye and a fellow eye were designated. If both eyes met the inclusion criterion on the same day, then the eye with the worse VA was designated as the study eye. If both eyes had the same VA, then the right eye was designated as the study eye. For outcomes of functional measures (blindness eligibility and driving ineligibility), the eye with better VA was used. For all other outcomes, the study eye was used. The study time period for all patients was from the index date to the end of follow-up, defined as the date of the last available record for that eye in the EMR.

The patients were divided into 3 subgroups depending on the conditions of both eyes at the index date: GA:GA (both study and fellow eye with GA); GA:CNV (study eye with GA, fellow eye with CNV); and GA:early/intermediate AMD (study eye with GA and fellow eye with early/intermediate AMD). The aim of this analysis was to characterize the subgroup of patients with GA in both eyes (i.e., GA:GA).

Outcome Measures

Primary and secondary outcome measures are shown in Table 1. Most outcomes were derived from measures of routinely collected VA, which was primarily captured in the clinical sites as Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the majority of patients. In a minority of patients, Snellen VA may have been recorded and converted to logarithm of the

minimum angle of resolution. Progression to blindness was defined as VA <20 letters or Snellen 3/60 (equivalent to US Snellen 20/400)^{24–26} in the better-seeing eye, which is the level specified by the United Kingdom for eligibility for blindness registration. Progression to loss of eligibility to drive was defined as VA ≤70 letters or Snellen 6/12 (equivalent to US Snellen 20/40)^{26,27} in the better-seeing eye, which is the commonly used driving standard threshold internationally.²⁸

Validation of Algorithm Used to Define Cases and Assess Progression

The aim of the validation exercise was to confirm the accuracy of the clinical diagnosis and to ensure that the automated extraction algorithm had been effective in the correct identification of the status of both eyes of each case. Because the EMR users can record the diagnosis using both drop-down diagnostic fields and text fields, the algorithm was constructed to also search for strings of text. A total of 120 patients with GA across all 3 subgroups were randomly selected from the 10 sites using a random sampling method stratified by progression to CNV outcomes. Clinicians from each site then reviewed each of these cases along with findings from the image repositories (high-resolution optical coherence tomography and any other imaging modalities that were available at the site) to confirm the accuracy of the information (i.e., presence of GA, CNV, or early/intermediate AMD by eye and for progression to GA or CNV). Three clinical states of each of the patients in the validation sample were verified: correct classification of study eye at index; correct classification of fellow eye at index; and correct identification of progression of the study eye to CNV. When discrepancies were detected, arbitration was performed by a retina expert. The positive predictive value (PPV) (proportion of true positives among all classified as positive), negative predictive value (proportion of true negatives among all classified as negative), sensitivity (proportion of patients who were correctly classified as experiencing the event among all who experienced the event), and specificity (proportion of patients who were correctly classified as not experiencing the event among all who did not experience the event) were calculated.

Statistical Analyses

Data analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). Eye- and patient-level data are presented. Summary statistics of the covariates in the analyses were used to identify outliers and check the data. Missing data were not imputed, and a complete case analysis was carried out. Patient characteristics at index date and time to progression were assessed using descriptive statistics, and Kaplan–Meier curves were used to determine median time to progression. Rates of progression were calculated as the number of patients/eyes experiencing progression divided by the total person-years at risk. The Cox proportional hazard model was used to estimate the risk of disease progression in the worse-seeing eye and to identify potential predictors of progression. Covariates that were controlled for in the multivariate model included patient characteristics of age and sex along with the index VA, lens status (phakic vs. pseudophakic), and glaucoma status of the worse-seeing eye. Significant predictors were identified at $P < 0.05$.

Results

Validation Exercise

High positive and negative predictive values were observed in the validation study. A PPV of 0.95 and 0.89 in study and fellow eyes

Table 1. Outcome Measures Evaluated in Patients with Bilateral Geographic Atrophy Identified in the Electronic Medical Record System from 10 Clinical Sites in the United Kingdom

Objective	Outcome Measure
Primary	<ul style="list-style-type: none"> • Mean change in VA over time* • Progression to CNV[†] • Progression to loss of ≥10 or ≥15 letters[‡] • Progression to blindness[‡] • Progression to loss of driving eligibility[§]
Secondary	<ul style="list-style-type: none"> • Risk factors for progression to loss of driving eligibility[§]

CNV = choroidal neovascularization; VA = visual acuity.

*Among patients with VA data available at months 12, 24, and 60 (±1.5 months).

[†]Among patients who did not meet the CNV disease definition at baseline (Table S2, available at www.aaojournal.org).

[‡]Among patients with VA follow-up and who were not blind at baseline.

[§]Among patients with VA follow-up and who were eligible to drive at baseline.

showed that the disease state was correctly classified in 95% and 89% of eyes, respectively. Progression to CNV had a PPV of 0.88, a negative predictive value of 1.00, a sensitivity of 1.00, and a specificity of 0.90.

Baseline Characteristics

The initial extract of the data set consisted of 83 425 unique patients in the 10 clinical sites with data ranging from 2000 to 2016. There were a total of 11 240 (13.5%) cases with at least 1 eye with a clinical record of GA recorded at any visit; the first record of a GA patient meeting inclusion/exclusion criteria for this analysis was March 2006, and the last record was December 2015, resulting in 4769 (5.7%) patients in the eligible GA cohort. Of these, 1901 (39.9%) had bilateral GA (Fig 1). In the bilateral GA subgroup, the mean age was 81 years (standard deviation, 6 years) and 63.9% of patients were female (Table 2). The median VA of the worse-seeing (study) and better-seeing (fellow) eyes at index was 45 letters (interquartile range [IQR], 16–60) and 64 letters (IQR, 49–75), respectively. The median follow-up time was 1.4 years (IQR, 0.6–2.8). Comorbidities at baseline are shown in Table S3 (available at www.aaojournal.org).

At the index date, 7.1% of those with bilateral GA were eligible according to the VA criterion of Snellen 3/60 (US Snellen 20/400) in the better-seeing eye for blindness registration in the United Kingdom, increasing to 16.2% when using the US definition of blindness [Snellen 20/200]). Just fewer than three-quarters of patients (71.1%) were classified as having a VA in the better-seeing eye that was worse than Snellen 6/12 (US Snellen 20/40) (Table 2), rendering them ineligible to drive in the United Kingdom.

Visual Acuity Decline Over Time

In the worse-seeing eye, mean VA decreased over 2 years and continued to decline over 60 months (Fig 2). Mean loss of ETDRS letters from baseline was 2.0 letters (95% confidence interval [CI], 0.7–3.3) at month 12, 6.1 letters (95% CI, 4.3–7.9) at month 24, and 10.9 letters (95% CI, 5.5–16.4) at month 60. Over this same timeframe, the better-seeing eye exhibited a steeper trajectory of VA loss; 5.7 letters (95% CI, 4.6–6.9), 12.4 letters (95% CI, 10.6–14.2), and 22.6 letters (95% CI, 17.3–27.9) by months 12, 24, and 60, respectively (Fig 2).

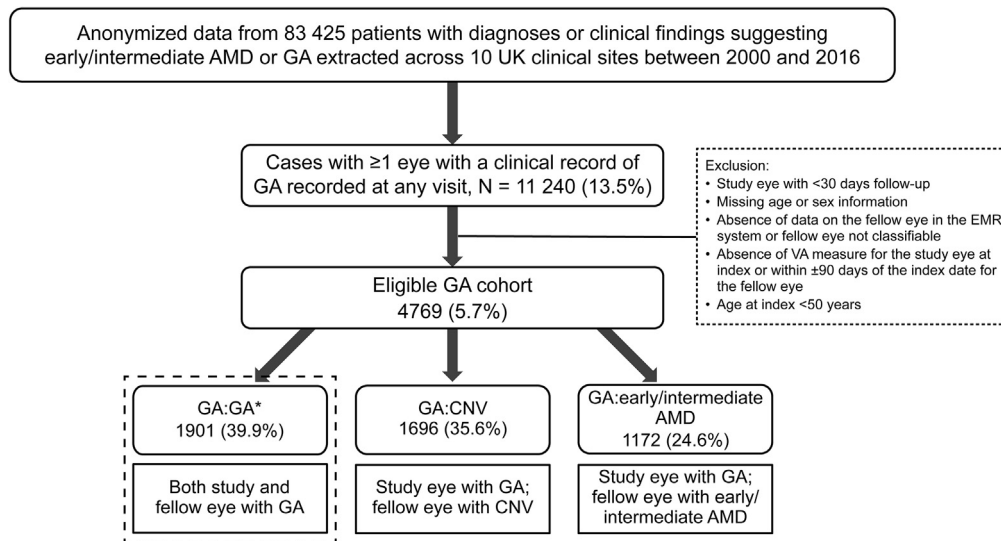


Figure 1. Flow diagram showing the study population identified in the electronic medical record (EMR) system from 10 clinical sites in the United Kingdom. *Patients with bilateral geographic atrophy (GA) secondary to age-related macular degeneration (AMD) are the focus of the analyses reported in this article. CNV = choroidal neovascularization; VA = visual acuity.

Progression to Specified Clinical Outcomes

Progression from Geographic Atrophy to Choroidal Neovascularization. Among the 1901 patients with bilateral GA, 160 progressed to CNV in the worse-seeing eye over 3361 patient-years of follow-up (a progression rate of 4.8% per patient-year) (Fig 3),

Table 2. Characteristics of Patients with Bilateral Geographic Atrophy Identified in the Electronic Medical Record System from 10 Clinical Sites in the United Kingdom

Variable	Total (n = 1901)
Age, yrs, mean \pm SD	81 \pm 6
Female, n (%)	1214 (63.9)
Follow-up time, yrs,* median (IQR)	1.4 (0.6–2.8)
Study eye VA at baseline, ETDRS letters,* median (IQR)	45 (16–60) (Snellen 20/125)
Fellow eye VA at baseline, ETDRS letters, median (IQR)	64 (49–75) (Snellen <20/50)
Intraocular pressure at baseline (n = 1246),* mmHg, mean \pm SD	16 \pm 4
Glaucoma,* n (%)	100 (5.3)
Phakic,* n (%)	1531 (80.5)
Pseudophakic,* n (%)	370 (19.5)
Eligible for blindness registration, n (%)	
UK definition [†]	135 (7.1)
US definition [‡]	308 (16.2)
Ineligible to drive, [§] n (%)	1351 (71.1)

ETDRS = Early Treatment Diabetic Retinopathy Study; IQR = inter-quartile range; SD = standard deviation; VA = visual acuity.

*Reported variables are based on the predefined study eye diagnosed with geographic atrophy except for the measures relating to blindness/UK driving standard definitions.

[†]UK blindness definition: <20 VA letters or Snellen 3/60 (US Snellen 20/400) in the better-seeing eye.

[‡]US blindness definition: Snellen 20/200.

[§]UK and US driving standard (VA measure >70 letters or Snellen 6/12 [US Snellen 20/40] in the better-seeing eye).

and 152 patients progressed to CNV in the better-seeing eye over 3352 patient-years of follow-up (a progression rate of 4.5% per patient-year). Finally, the earliest time of progression to CNV in either eye was evaluated with 239 patients progressing to CNV over 3213 patient-years (a progression rate of 7.4% per patient-year).

Progression to Loss of 10 or More Letters. In the 1693 patients with bilateral GA who had VA follow-up and did not meet the UK definition of blindness at baseline, 679 (40%) lost ≥ 10 letters in the worse-seeing eye in a median time to progression of 2.4 years (IQR, 1.1–5.0), as estimated from the Kaplan–Meier curve. In this same cohort, 523 (31%) lost ≥ 15 letters in a median time to progression of 3.3 years (IQR, 1.5–6.2), as estimated from the Kaplan–Meier curve (Fig 3).

Progression to Blindness. Of the 1693 patients with bilateral GA who had VA follow-up and who did not meet the UK definition of blindness at baseline, 264 (16%) progressed to blindness in the better-seeing eye with a median time to progression of 6.2 years (IQR, 3.3–8.5), as estimated from the Kaplan–Meier curve (Fig 4).

Progression to Loss of Driving Eligibility. Of the 523 patients who had VA follow-up and a level of VA in their better-seeing eye that would have placed them in a category of eligible to drive at baseline, 349 (67%) became ineligible to drive with a median time to progression of 1.6 years (IQR, 0.7–2.7) from the index date, as estimated from the Kaplan–Meier curve (Fig 4).

Risk Factors Associated with Progression to Loss of Driving Eligibility

On the basis of a multivariate model, older age and worse VA at index were significant ($P < 0.05$) predictors for risk of progression to loss of VA to a level below the driving standard for the United Kingdom (Table 3).

Discussion

This large, retrospective EMR database analysis characterized the rates of VA loss and progression to CNV in patients

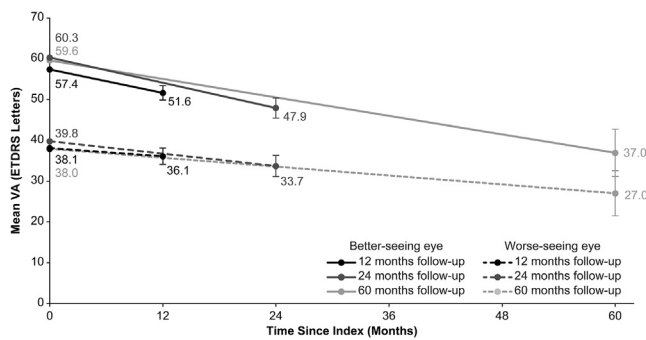


Figure 2. Change in mean visual acuity (VA) from baseline in the worse-seeing (study) eye and better-seeing (fellow) eye through 60 months' follow-up in patients with bilateral geographic atrophy identified in the electronic medical record system from 10 clinical sites in the United Kingdom. For each time point, patients had to have VA measurement at index and at the specific time point of 12, 24, or 60 months after post index. For the better-seeing eye the sample comprised 726, 414, and 80 patients for the 12-, 24-, and 60-month time points, respectively. For the worse-seeing eye, the sample comprised 724, 413, and 80 patients for the 12-, 24-, and 60-month time points, respectively. Error bars represent 95% confidence intervals. ETDRS = Early Treatment Diabetic Retinopathy Study.

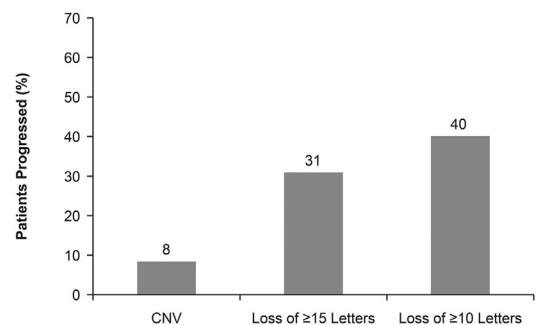
with bilateral GA secondary to AMD. We showed that patients with GA exhibit high levels of visual impairment at levels that would result in loss of mobility and independence. We also provided robust estimates of rates of progression to CNV in the context of GA.

Although the data come from a repository of information that was retrospective, the information on VA was obtained directly from the standardized, mandated EMR fields, making this aspect of the data more analogous to that which is collected using case report forms characteristic of prospectively designed studies. In addition, the findings of the validation exercise were highly reassuring, confirming that the performance of the classification algorithm used to extract the cases of interest had high positive and negative predictive values for the different clinical states and testifies to the robustness and accuracy of the data set. However, we did not undertake tests for whether cases with the diagnosis of interest had been missed within the unselected patient groups. Therefore, we cannot be confident that our data have not underestimated the true number of cases with GA.

At initial GA diagnosis, 7.1% of the bilateral GA cohort were eligible for blindness registration in the United Kingdom (16.2% using the US definition of blindness) and more than two-thirds (71.1%) had a level of vision that would have not passed the UK driving standard for VA in the better-seeing eye. We contend that this represents an enormous limitation to mobility and thus a significant burden of disease affecting independence. Also, in the following 2 years, a further two-thirds (67%) became sufficiently visually impaired in their better-seeing eye such that driving would have been compromised and another one-sixth (16%) would have become eligible for registration as blind. Therefore, our data support those of Sunness et al,¹⁷ who observed that rates of vision loss to 20/200 or worse in eyes with GA were 14% at 2 years and 31% at 4 years in patients with VA better than 20/200 at baseline.

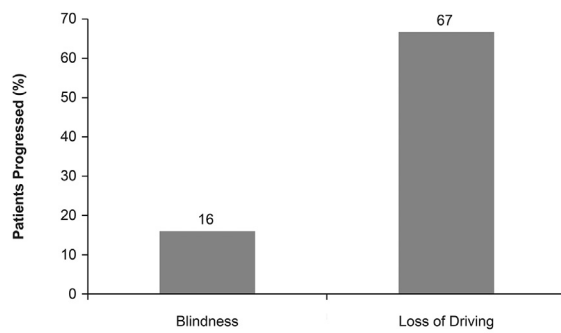
Because visual standards for driving in the United Kingdom are the ability to read at least Snellen 6/12 (20/40) binocularly, it is possible that loss of driving ability in the present study may have been marginally overestimated because only monocular vision was considered in the analysis. However, our study does not consider reduced peripheral field of vision as a criterion for loss of driving ability; therefore, our estimates of the proportions of patients who had levels of VA worse than those permitted for driving is more likely to be an underestimate of the true burden of disease.

In a subset of patients with VA measurements at baseline and 24 months, clinically meaningful vision loss occurred in both the worse-seeing eye (−6.1 letters) and the better-seeing eye (−12.4 letters), and we noted that the latter rate was twice as rapid compared with the worse-seeing eye. It is possible that more shallow VA decline observed in the worse-seeing eye could represent a floor effect because the change in vision is dependent on baseline VA. This finding is supported by data from another study in patients with GA, which found a 40% 2-year rate of VA loss (≥ 3 lines) in those with a baseline VA 20/50 or better versus 13% for the patients with worse baseline VA.²⁹ In the present study, 40% of patients who did not meet the UK definition of blindness at baseline lost ≥ 10 letters in the worse-seeing eye in a median time to progression of 2.4 years. Other studies that have included patients with GA have provided progression rates of vision loss that vary considerably²⁰; furthermore, none of them have reported their findings by better-seeing and worse-seeing eye functional status.^{13,14,20} In a study by Sunness et al,³⁰ patients with bilateral GA without CNV at enrollment ($n = 91$) progressed to CNV at a rate of 2% by 2 years and 11%



Study sample eligible for analyses (N)	1901	1693*	1693*
Median (IQR) time to outcome (years) [†]	N/A [‡]	3.3 (1.5–6.2)	2.4 (1.1–5.0)

Figure 3. Percentage of patients with bilateral geographic atrophy identified in the electronic medical record system from 10 clinical sites in the United Kingdom who progressed from GA to choroidal neovascularization (CNV), lost 15 or more letters, or lost 10 or more letters in the worse-seeing (study) eye. *Among patients with visual acuity (VA) follow-up and who did not meet the UK definition of blindness at baseline (VA measurement of < 20 Early Treatment Diabetic Retinopathy Study letters or Snellen 3/60 [US Snellen 20/400] in the better-seeing eye). [†]Estimated using the Kaplan–Meier survival method. [‡]Median time to development of CNV unavailable because $< 50\%$ of patients progressed to CNV. IQR = interquartile range; N/A = not available.



Study sample eligible for analyses (N)	1693*	523†
Median (IQR) time to outcome (years)‡	6.2 (3.3–8.5)	1.6 (0.7–2.7)

Figure 4. Percentage of patients with bilateral geographic atrophy identified in the electronic medical record system from 10 clinical sites in the United Kingdom who progressed to blindness or were rendered ineligible to drive by the better-seeing (fellow) eye. *Among patients with visual acuity (VA) follow-up and who did not meet the UK definition of blindness at baseline (VA measurement of <20 Early Treatment Diabetic Retinopathy Study letters or Snellen 3/60 [US Snellen 20/400] in the better-seeing eye). †Among patients with VA follow-up and who were eligible to drive at baseline according to the UK driving standard (VA measure >70 letters or Snellen 6/12 [US Snellen 20/40] in the better-seeing eye). ‡Estimated using the Kaplan–Meier survival method. IQR = interquartile range.

by 4 years. These rates are lower than those observed in the present study, which estimated that 7.4% of patients with bilateral GA progressed to CNV per year.

In the current study, older age and worse VA at baseline were the only significant predictors of risk of progression to worse levels of vision. This is not surprising given that increasing age is a risk factor for GA³ and vision declines with age, even in the absence of GA.³¹ Previous studies have shown that vision impairment in patients with advanced AMD, including GA, is associated with difficulty performing functional reading activities,³² reduced physical activity,³³ and fewer outings away from home.³³ Because GA commonly spares the foveal center until later in the disease course, problems with visual functioning may not be reflected in distance VA measurements. Taken together, these data are of importance, because limiting the progression of vision loss even in patients with early GA must be a priority to maintain vision-dependent quality of life and mobility.

This study has several strengths. Data were collected from a large, geographically representative patient cohort examined at 10 clinical sites across the United Kingdom. Thus, it provides a real-world snapshot of the clinical characteristics of a wide patient group and offers evidence beyond that obtainable in a clinical trial setting where eligibility criteria may be restrictive and participation restricted to healthier and younger cohorts. The validation exercise demonstrated the robustness of the algorithm used for case selection based on disease definitions and progression states. Notably, in this data set, the diagnosis was clinician-reported GA rather than being identified through Systematized Nomenclature of Medicine or International Classification of Diseases (ICD) codes. Although the latter

Table 3. Significant Risk Factors for Progression to Loss of Driving Eligibility (Visual Acuity ≤70 Letters in the Better-Seeing Eye) among Patients with Bilateral Geographic Atrophy Identified in the Electronic Medical Record System from 10 Clinical Sites in the United Kingdom Who Were Eligible to Drive at Geographic Atrophy Diagnosis (n = 523)

Significant Predictors	Hazard Ratio	95% CI	P Value
Age (per 5-yr increase)	1.223	1.115–1.332	<0.001
Index VA (per 5 ETDRS letter-score increase)	0.970	0.946–0.995	0.025

CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; VA = visual acuity.

Covariates included age, sex, index VA, lens status (phakic vs. pseudophakic), and glaucoma. All covariates were included in the multivariate model and were analyzed simultaneously. Significant predictors were identified at $P < 0.05$ in the multivariate model.

did not include GA as a distinct disease entity in older versions,³⁴ the present US version, ICD, 10th Revision, Clinical Modification,³⁵ has recently been expanded to include GA, and proposals have been made to include GA in ICD-11,³⁶ which is currently in development. In addition, mandatory variables were captured consistently and accurately with very low levels of missing data in the recording of VA (ETDRS) in both eyes at every visit along with details of treatment with anti-vascular endothelial growth factor agents. The former allowed us to specify key markers of visual impairment at the index visit, and change over time and the latter allowed us to exclude patients with bilateral neovascular AMD at the index visit and identify the development of incident neovascular AMD with high precision.

As with most studies involving retrospective databases, there are some limitations. Specifically, the duration of follow-up varied considerably but is reflective of routine practice. It was also not possible to attribute the VA loss to a specific diagnosis because there is considerable comorbidity in this age group, such as cataract. However, in this context, information was available on the phakic status of patient eyes and a sensitivity analysis using only data from pseudophakic patients was consistent with the findings from the entire bilateral GA cohort (data not shown). Another potential limitation with studies involving retrospective databases is selection bias. It is likely that patients with certain comorbidities (e.g., diabetes, glaucoma), patients with more severe disease or vision loss, or those with neovascular AMD in 1 eye who were receiving active treatment may have been reviewed more frequently and thus may have more comprehensive data collected and entered into the database. In addition, there is the potential for under-reporting of patients with GA and good central VA because they may not be referred to the hospital eye care system. Likewise, patients with GA and very poor VA may be underrepresented because they may not return to the clinic because of a lack of treatment options. Other limitations include incomplete medical history information, inconsistent capture of smoking status, noncapture of secondary health care outcomes (e.g., hospital admissions, social care,

and vision aids), and incomplete capture of ocular comorbidities, which would underestimate eligibility for blindness registration and capacity to continue driving.

In summary, the GA phenotype is commonly encountered in the clinical setting and is associated with high levels of visual impairment. Our study demonstrated that a significant proportion of patients with bilateral GA have VAs at a level that will preclude driving. Our study also showed that in those with milder levels of impairment at the time of diagnosis of GA, there is a high risk of loss of vision over time. We also investigated the incidence of CNV among those with bilateral GA and provided robust estimates of risk of progression to the neovascular stage by eye. Further analysis of this and other real-world data sets will help fully characterize the burden of GA on patients, caregivers, and society for this currently untreatable disease.

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Abbreviations and Acronyms:

AMD = age-related macular degeneration; **CI** = confidence interval; **CNV** = choroidal neovascularization; **EMR** = electronic medical record; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **GA** = geographic atrophy; **ICD** = International Classification of Diseases; **IQR** = interquartile range; **NHS** = National Health Service; **PPV** = positive predictive value; **VA** = visual acuity.

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