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ARTICLE

Transition from intermediate to late AMD and associated changes in vision by two years in a multicentre cohort study in Europe- INTERCEPT-AMD Report 3

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BACKGROUND/OBJECTIVES: The aim was to evaluate the incidence of late AMD in eyes with intermediate AMD (iAMD) over two years.

SUBJECTS/METHODS: In this multicentre cohort study, participants with iAMD were classified as: (i) iAMD without incomplete retinal pigment epithelium or outer retinal atrophy (iRORA) or subretinal drusenoid deposits (SDD); (ii) iAMD with SDD with no iRORA; (iii) iAMD with iRORA with no SDD and (iv) iAMD with iRORA and SDD. Factors associated with the incidence of late AMD were analysed using an interval-censored Weibull parametric proportional hazards model.

RESULTS: 983 eyes from 805 participants were analysed. Model-based cumulative incidence at nominal 2 years was 13.1% (95% CI 10.8–15.6%) for late AMD, 7.6% (95% CI 5.9–9.3%) for nAMD as the cause and 5.5% (95% CI 4.1–7.3%) for cRORA as the cause. Participants aged 75–84 (adjusted HR [aHR] 1.66, 95% CI 1.13–2.46; $P = 0.01$), 85 years+ (aHR 2.48, 95% CI 1.49–4.15; $P = 0.001$), presence of iRORA (aHR 1.50, 95% CI 1.05–2.16; $P = 0.03$), fellow-eye nAMD (aHR 3.23, 95% CI 2.04–5.12; $P < 0.001$) and BRVA 70–79 (vs 80 or better ETDRS letters: aHR 1.65, 95% CI 1.09–2.49; $P = 0.02$) had increased hazard of late AMD. Eyes that transitioned to neovascular AMD (nAMD) by 2 years (within tolerance window) displayed the greatest loss in BRVA compared to other phenotypes (–6.01 letters, SD 11.35).

CONCLUSIONS: Approximately 13% of eyes with iAMD progressed to late AMD within 2 years. Eyes that transitioned to nAMD experienced the greatest loss in BRVA.

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INTRODUCTION

Age-related macular degeneration (AMD) is a common degenerative disease in older individuals that is predicted to affect 288 million people by 2040 [1]. The advanced forms of the disease are geographic atrophy (GA) and exudative neovascular AMD (nAMD). The economic burden of advanced AMD is high [2]. Prevention of progression to advanced AMD is key to preventing visual loss.

Intermediate AMD (iAMD) is the strongest ocular risk factor for disease progression to advanced stages [3]. Several optical coherence tomography (OCT) based clinical phenotypes of iAMD exist and may signify different disease pathways. Some of these include drusen size, morphology and volume; hyperreflective foci (HRF); subretinal drusenoid deposits (SDD) and incomplete retinal pigment epithelium and outer retinal atrophy (iRORA) [4–6]. Signs of SDD and iRORA can be identified by clinicians in routine practice without the assistance of automated algorithms. The rate of decline of visual acuity VA over time by transitioning from the absence of any of these features in iAMD to its presence is also not reported [7]. In addition, the change of VA in eyes that

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progress to cRORA or advanced forms of GA and nAMD may be different based on the status of their fellow eye. Previous reports have shown that the second eye of unilateral nAMD presents with better VA when they transition to nAMD [8, 9].

INTERCEPT AMD was a collaborative network study conducted by EVICR.net Members in Europe to develop a multimodal image database of eyes with iAMD in at least one eye with a two-year follow-up linked to the age, sex and records of visual acuity of the participants during this period to further define iAMD. In the study, we classified iAMD into four groups based on multimodal imaging. Eyes with iAMD with no evidence of iRORA or SDD, which we believe have the lowest risk of fast progression, were considered as the eyes with the slowest rate of progression. The other three categories included iAMD with SDD, with no iRORA; iAMD with iRORA, with no SDD and iAMD with iRORA and SDD. In addition, age and AMD severity level of the fellow eye were collected as they are strong predictors of disease progression.

The aims of this study are to:

1) Evaluate the incidence of any late AMD over two years.
2) To evaluate the change in visual acuity based on progression of AMD disease phenotypes over 2 years to either cRORA or exudative nAMD (defined by the presence of nAMD as per CONAN classification on OCT) or to another category of iAMD.

METHODS

The study was conducted in accordance with the Declaration of Helsinki and was registered in clinicaltrials.gov (NCT05698316). The study was managed by EVICR.net, Coimbra, Portugal, which obtained the overarching institutional review board approval for the study. The EVICR.net also established data sharing agreements from sites to the EVICR.net platform and data and image transfer to Moorfields Eye Hospital via the EVICR.net platform. Each site then obtained the regulatory approval required in its own country. Informed consent from patients was obtained at sites where national regulations required it, whereas in sites where the study was classified as retrospective use of routinely collected data, ethics committees granted waivers of consent. The study was funded by Boehringer Ingelheim, Germany.

Details on the identification of patients with iAMD from respective electronic medical records or imaging datasets have been reported previously [7]. In summary, patients with iAMD in one or both eyes with multimodal imaging on Spectralis macular OCT scans with or without enhanced depth imaging and infrared imaging (IR) and optional fundus autofluorescence (FAF) were identified by site personnel and graded into the four categories: iAMD with no atrophy and no SDD; iAMD with no atrophy with SDD; iAMD with iRORA with no SDD; iAMD with iRORA with SDD. Eyes with evidence of any other atrophy less than 250 microns, such as vitelliform maculopathy at baseline phenotyping, were excluded from the analysis, however, they were allowed as a transition state at follow-up visits [7, 10]. If only one eye had iAMD, the macula status of the non-study eye was graded on multimodal imaging as the presence of cRORA: exudative nAMD, early AMD, healthy macula (no drusen or retinal pigment epithelium (RPE) changes suggestive of AMD) or ungradable due to poor image quality. If both eyes met the eligibility criteria of iAMD, they were both enrolled as study eyes. The best recorded VA (BRVA) in ETDRS letters was obtained from the medical records from the index date and included VA with pinhole, visual acuity with the patient's glasses or best-corrected visual acuity (BCVA) if patients were refracted at the time of their VA assessment. Images were linked to demography and visual acuity data in the Eye Platform and the pseudonymised data were transferred to Moorfields Eye Hospital for analysis.

Sample size

This study aimed to collect a large research database for future studies and a sample size of 1000 eyes with VA records at baseline and over 2 years (5 visits, every 6 months, with a tolerance of approximately +/- 3 months) was considered a feasible resource for studying the progression of different categories of iAMD and the change in VA. Visit windows were narrow and consistent, though visit 5 had a wider tolerance window compared to other visits: −3.22 to +3.33 months at 6 months, −3.60 to +3.60 months at 12 months, −2.83 to +3.40 months at 18 months and −3.53 to +4.17 months at 24 months.

Outcomes

The primary outcome was time to late AMD (presence of the earliest of nAMD or cRORA as reported by investigators at clinical sites). The recorded causes of late AMD (i.e. nAMD and cRORA) were investigated secondarily. Additionally, the change in VA at the final visit (2 years within the tolerance window) was evaluated based on stage transitions and progression of iAMD from baseline to summarise the level of visual decline across different transition patterns.

Statistical analysis

Baseline characteristics were summarised using mean (SD) and/or median (IQR) for continuous variables and n (%) for categorical variables, overall and by data completeness. The primary analysis included all eyes, regardless of missing intermediate visits, with missing visits handled via interval-censored models.

Fellow eye late AMD status was categorised in two ways: (1) binary presence or absence of late AMD in the fellow eye and (2) phenotype-specific categories of no recorded late AMD, nAMD or cRORA. The no recorded late AMD group combined eyes with bilateral iAMD or absent fellow-eye late AMD due to low event counts. A sensitivity analysis was conducted, excluding observations with missing or insufficient fellow-eye data.

The intccr package in R was used to estimate cumulative incidence functions (CIF's) using Fine-Gray subdistribution hazard models for interval-censored competing risks data [11]. Progression to late AMD subtypes was modelled with nAMD and cRORA treated as competing risks, to estimate absolute (population) risk. As death was not recorded and therefore unmodelled as a competing risk, individual CIFs were summed to approximate the composite late AMD outcome. Interval censoring accounted for progression occurring between scheduled 6-monthly visits, using the last event-free visit as the left endpoint and the first observed event visit as the right endpoint, accommodating missing intermediate visits. Two-year cumulative incidence and 95% confidence intervals (CIs) were estimated overall and stratified by demographic factors, baseline visual acuity, iAMD phenotype and fellow-eye status. CI's were derived using a cluster-robust bootstrap approach (500 replicates, percentile-based 95% CI's), preserving the cohort distribution of baseline unilateral and bilateral eligibility. Observed event counts reflected progression by the final attended visit within the tolerance window, whereas model-based cumulative incidence estimates were evaluated at a nominal 2 years.

Univariate and adjusted parametric proportional hazards models (Weibull distribution) assessed associations with progression to composite late AMD and cause-specific progression to nAMD and cRORA. In cause-specific analyses, the first occurrence of one subtype was treated as a censoring event when modelling the other subtype. Models were fitted using Stata's stintreg command for interval-censored time-to-event data [12], with robust variance estimators accounting for inter-eye correlation. Model selection was guided by the generalised gamma distribution and goodness of fit was visually assessed using Cox-Snell residuals. Hazard ratios, 95% CIs and *p*-values were reported.

Adjusted analyses included separate models for each covariate, controlling for age and sex, to estimate total effects. A multivariable model including age, sex, bilateral/fellow eye status, baseline iAMD phenotype and baseline VA was fitted to provide clinically interpretable conditional associations for risk stratification. Interaction terms were evaluated between age and sex, given reports of differences in sex in older age categories [13] and between fellow-eye status and iRORA presence. As frailty terms could not be incorporated into the interval-censored proportional hazards model due to software limitations, a sensitivity analysis used semi-parametric Cox models (exact event times) and a gamma-distributed frailty term to assess unobserved heterogeneity between participants.

Baseline and visit 5 BRVA, mean change and categorical VA outcomes (>=10-letter and 15-letter loss), were summarised across AMD transitions and by better-and worse-seeing eyes, based on complete baseline and visit 5 data. A sensitivity analysis using BCVA was also performed. All summary data reflect assessments obtained within the allowable visit tolerance windows, while model-based incidence estimates are reported at the nominal 2-year time point. Statistical analyses were conducted using StataNow MP version 18 and R version 4.4.1 [14, 15].

RESULTS

Summary statistics

A total of 805 participants (983 eyes) were included, completing a mean of 4.24 (SD 0.87) visits [median 5 (IQR 3-5)]. The interval between all observed consecutive assessments had a mean 7.40 (SD 2.99) [median 6.47, IQR 5.52-8.34]. Complete visit imaging data were available for 442 participants (518 eyes) (Table S2). Eyes with fellow-eye nAMD (i.e. frequent anti-VEGF injections) were more likely to have complete imaging (71.3% vs 50.3%), while incomplete follow-up had higher bilateral eligibility (27.0% vs 17.2%). This suggests differential follow-up related to clinical status, although distributions of key structural phenotypes (iRORA and SDD) were similar. All eyes were included, regardless of missing intermediate visits, minimising selection bias from restricting to complete follow-up.

A total of 178 of 805 participants (22.1%) had bilateral eligibility and 627 had iAMD in one eye only; with 499 (62.0%) with nAMD in the fellow eye and 72 (8.9%) with cRORA in the fellow eye; the rest of the cohort had fellow eyes that were either not recorded/insufficient data ($n = 8$, 1.0%), early AMD ($n = 11$, 1.4%), healthy macula ($n = 5$, 0.6%) or other retinal disease than AMD related ($n = 32$, 4.0%). Visits 2 and 4 had the highest proportion of missing scans (Figure S1).

Model-based incidence of late AMD (nAMD or cRORA) by 2 years, overall and by recorded cause

The mean observed follow-up from baseline to the last completed assessment was 1.96 years (SD 0.20) [median 1.99, IQR 1.92-2.07]. By the final visit (visit 5 window), 132 eyes (130 participants) developed late AMD- 53 caused by cRORA and 79 by nAMD. Among eyes with events, the mean width of the censoring intervals was 0.61 years (SD 0.27) [median 0.56 years, IQR 0.42-0.68].

The cumulative incidence at nominal 2 years of the composite outcome late AMD was 13.1% (95% CI 10.8–15.6%), with cause-specific estimates 7.6% (5.9–9.3%) for nAMD and 5.5% (4.1–7.3%) for cRORA, based on a competing risks framework (Table 1). Restricting to eyes with complete imaging modestly increased cumulative incidence to 16.0% (95% CI 13.3–20.1%), consistent with greater follow-up intensity among clinically higher-risk patients, justifying the inclusion of all eyes, regardless of intermediate missing visits. A sensitivity analysis using non-parametric Turnbull's intervals yielded an overall incidence rate of 11.6% (95% CI 9.1–14.9%) (Table S3).

Cumulative incidence of late AMD and cRORA increased with age, while rates were similar between sexes. Incidence was higher in eyes with baseline BRVA and BCVA 70-79 ETDRS letters and in eyes with iRORA, which more clearly stratified progression to cRORA than to nAMD. This reflects the competing-risks structure; earlier progression to cRORA in eyes with iRORA reduces the remaining risk set for neovascular conversion, so the lower nAMD counts should not be interpreted as protective. Differences by SDD were minimal. Compared with other fellow eye categories, fellow-eye nAMD had a higher late AMD incidence in the study eye, while fellow-eye cRORA had a higher incidence of study-eye cRORA, but did not clearly stratify risk of progression to nAMD with interpretation limited by small numbers ($n = 1$ of 6 eyes; Table 1).

Univariate and age-sex adjusted analysis using Weibull proportional hazards models

Univariate associations are presented in Table S4. Increasing age was associated with a higher hazard of late AMD by visit 5: adjusted HR [aHR] 1.66, 95% CI 1.13–2.46; $P = 0.01$ for ages 75–84 years and aHR 2.48, 95% CI 1.49–4.15; $P = 0.001$ for >=85 years relative to <75 years (Table 2).

Eyes with iRORA and no SDD had increased hazard of late AMD (vs no atrophy and no SDD: aHR 2.04, 95% CI 1.15–3.61; $P = 0.02$), as did presence of iRORA (vs absence of iRORA: aHR 1.50, 95% CI 1.05–2.16; $P = 0.03$). Additionally, iRORA was associated with increased hazard of cRORA in the study eye (aHR 3.98, 95% CI 2.26–7.02, $P < 0.001$) but not nAMD. This pattern reflects a competing-risks structure and should not be interpreted as a protective association.

Fellow-eye late AMD conferred increased hazard of late AMD (aHR 3.03, 95% CI 1.92–4.79, $P < 0.001$), nAMD (aHR 4.08, 95% CI 2.13–7.83, $P < 0.001$) and cRORA in the study eye (aHR 2.02, 95% CI 1.03–3.95, $P = 0.04$). Stratifying by phenotype, nAMD in the fellow eye conferred increased hazard of late AMD (aHR 3.23, 95% CI 2.04–5.12, $P < 0.001$) and nAMD in the study eye (aHR 4.56, 95% CI 2.38–8.77, $P < 0.001$). While fellow-eye cRORA showed increased hazard for progression to cRORA in the study eye, the p-value did not reach statistical significance (adjusted HR 2.62, 95% 0.97–7.1, $P = 0.06$). A sensitivity analysis excluding 8 eyes with unavailable fellow eye status (insufficient data or missing) showed similar results (Table S5).

Relative to >=80 ETDRS letters, eyes with 70-79 BRVA (aHR 1.65, 95% CI 1.09–2.49, $P = 0.02$) had increased hazard of late AMD, with similar associations for BCVA 70–79 ETDRS letters (vs BCVA > = 80 ETDRS letters: aHR 1.61, 95% CI 1.04–2.51, $P = 0.04$). A similar trend was observed for progression to cRORA for BRVA 70–79 ETDRS letters (aHR 2.90, 95% CI 1.50–5.60, $P = 0.002$) and BCVA 70–79 (aHR 3.31, 95% CI 1.65–6.64, $P = 0.001$) relative to eyes with >=80 BRVA or BCVA, respectively.

No significant interactions were observed (age vs sex and between fellow-eye nAMD vs iRORA) in models for late AMD and by cause. Due to the small number of eyes with fellow-eye cRORA that progressed to nAMD in the study eye, interaction analysis with iRORA was not performed. Gamma frailty models showed no significant participant-level heterogeneity ($P = 0.21$ for the frailty term).

Multivariable-adjusted associations

In multivariable analyses (mutually adjusted), factors associated with a higher hazard of late AMD were BRVA 70-79 ETDRS letters (aHR 1.57, 95% CI 1.04–2.38, $P = 0.03$) and fellow-eye nAMD (aHR 3.27, 95% CI 1.98–5.40, $P < 0.001$) (Table S6). Progression to nAMD was associated only with baseline fellow-eye nAMD (aHR 5.56, 95% CI 2.58–11.98, $P < 0.001$). In contrast, progression to cRORA was associated with age >=85 years (vs age<75 years: aHR 2.56, 95% CI 1.03–6.35, $P = 0.04$), BRVA 70-79 (aHR 2.66, 95% CI 1.35–5.24, $P = 0.005$), iRORA & no SDD (aHR 3.62, 95% CI 1.41–9.30, $P = 0.008$) and iRORA with SDD (aHR 2.81, 95% CI 1.19–6.67, $P = 0.02$).

Disease transition and corresponding VA change by study end (visit 5)

Among 935 eyes with BRVA recorded at baseline and visit 5, eyes that transitioned to late AMD ($N = 123$) showed a greater BRVA loss (mean change: −5.58 letters, SD 12.60, Table 3 and Fig. 1) and lower visit 5 BRVA (72.18 ETDRS letter score, SD 13.60, Table S7 and Fig. 1) than non-late AMD phenotypes, with 30.9% ($n = 38$) and 17.9% ($n = 22$) losing >= 10 and >= 15 letters, respectively (Table S8). BRVA decline was slightly greater in eyes progressing to nAMD (−6.01 letters, SD 11.35; >= 10-letter loss, $N = 24$ of 74, 32.4%) than to cRORA (−4.92 letters, SD 14.40; >=10-letter loss, $N = 14$ of 49, 28.6%) (Table S9). BCVA sensitivity analyses in 582 eyes showed comparable patterns to BRVA (Table S9).

Progression with fellow-eye nAMD to late AMD in the study eye experienced greater BRVA loss (−5.44 letters, SD 13.44, $N = 95$, Table 3 and Fig. 1 and $N = 28$, 29.5% >=10 letter loss; Table S8) compared with transition to other phenotypes. Similarly, in eyes with fellow-eye cRORA (−1.67 letters, SD 5.32, $N = 6$, Table 3 and Fig. 1 and $N = 1$, 16.7% >=10 letter loss, Table S8) and across all baseline phenotypes: No iRORA & No SDD (−5.00 letters, SD 10.52; $N = 30$), No iRORA & SDD present (−7.92 letters, SD 10.52; $N = 50$), iRORA & No SDD (−1.72 letters, SD 15.96; $N = 18$) and both iRORA & SDD present (−4.36 letters, SD 15.58; $N = 25$, Table 3 and Fig. 2).

Table 1. Incidence of late AMD by 2 years based on the competing risks framework with nAMD and cRORA as causes of late AMD, by demographic and clinical characteristics.

	Study end (2 years visit 5 window)[a]			Incidence at nominal 2 years (95% bootstrap percentile CI)[b]		
Characteristics	**Sample size**	**Number of late AMD**	**Percentage with late AMD**	**Late AMD (composite)**	**nAMD as the cause**	**cRORA as the cause**
Overall	983	132	13.4%	13.1% (10.8–15.6%)	7.6% (5.9–9.3%)	5.5% (4.1–7.3%)
Age, years						
<75	434	42	9.7%	9.6% (7.2–12.4%)	5.2% (3.5–7.2%)	4.4% (2.6–6.1%)
75–84	437	66	15.1%	15.0% (11.5–18.0%)	9.9% (7.0–13.0%)	5.1% (3.0–6.9%)
85+	112	24	21.4%	22.8% (14.6–31.2%)	7.7% (3.5–12.0%)	15.0% (8.7–21.8%)
Sex						
Female	645	87	13.5%	12.8% (10.1–15.8%)	7.3% (5.2–9.5%)	5.5% (3.8–7.5%)
Male	338	45	13.3%	13.8% (9.7–17.7%)	8.3% (5.8–10.9%)	5.6% (3.3–8.4%)
BRVA, Study eye, ETDRS letters, categories						
80 or better	630	66	10.5%	10.0% (8.1–13.1%)	6.4% (4.9–8.8%)	3.6% (2.3–5.2%)
70–79	252	47	18.7%	18.2% (13.4–23.7%)	8.1% (5.4–11.9%)	10.1% (5.9–14.2%)
<=69	68	10	14.7%	16.1% (8.9–25.4%)	9.3% (4.1–16.4%)	6.9% (2.9–12.0%)
BCVA, Study eye, ETDRS letters, categories						
80 or better	429	61	14.2%	13.3% (10.7–17.0%)	9.2% (6.8–11.9%)	4.1% (2.7–6.6%)
70–79	169	40	23.7%	24.1% (17.2–30.7%)	10.0% (5.9–14.5%)	14.1% (8.3–19.8%)
<=69	36	6	16.7%	20.5% (7.9–30.3%)	10.5% (2.2–19.5%)	9.9% (2.5–18.1%)
iAMD Diagnosis, study eye						
No atrophy & no SDD	321	32	10.0%	10.3% (7.3–12.7%)	6.6% (4.4–8.6%)	3.7% (2.2–5.1%)
No atrophy & with SDD	385	52	13.5%	13.0% (9.7–16.7%)	9.4% (6.8–12.8%)	3.5% (1.7–5.4%)
iRORA & no SDD	114	20	17.5%	18.7% (12.1–26.4%)	6.8% (3.0–10.9%)	11.9% (6.3–19.6%)
iRORA & SDD	163	28	17.2%	17.2% (12.1–23.6%)	5.5% (2.5–9.6%)	11.7% (7.2–16.5%)
iRORA						
Absent	706	84	11.9%	11.6% (9.1–14.0%)	8.2% (6.3–10.3%)	3.4% (2.1–5.1%)
Present	277	48	17.3%	17.6% (13.3–23.4%)	5.9% (3.5–9.2%)	11.8% (8.1–16.0%)
SDD						
Absent	435	52	12.0%	12.2% (8.8–14.4%)	6.8% (4.3–8.7%)	5.4% (3.2–7.2%)
Present	548	80	14.6%	13.3% (11.0–17.4%)	7.8% (5.9–10.9%)	5.5% (3.8–8.0%)
Fellow eye status						
Bilateral or no recorded late AMD in the fellow eye	412	25	6.1%	6.9% (5.0–9.9%)	3.1% (2.0–5.2%)	3.9% (2.3–5.8%)
nAMD in the fellow eye	499	100	20.0%	19.2% (15.4–23.4%)	11.7% (9.2–15.6%)	7.5% (4.6–9.6%)
cRORA in the fellow eye	72	7	9.7%	15.0% (6.6–22.0%)	3.4% (0.8–6.6%)	11.6% (4.3–17.7%)

iAMD intermediate age-related macular degeneration, *cRORA* complete retinal and retinal pigment epithelial atrophy, *iRORA* incomplete retinal and retinal pigment epithelial atrophy, *nAMD* neovascular age-related macular degeneration, *SDD* subretinal drusenoid deposits, *BRVA* best recorded visual acuity, *BCVA* best corrected visual acuity.

[a]Observed event counts were based on follow-up through each participant's final attended visit within the visit 5 assessment window (nominally 2 years, allowing visits within the tolerance window).

[b]Competing risk regression on interval-censored competing risk data using proportional subdistribution hazards model (Fine and Gray) with 500 cluster-robust bootstrap replicates to estimate confidence intervals. Models were estimated using the intccr package in R [14]. Model-based cumulative incidence was evaluated at the nominal 2-year timepoint, while observed event counts were based on follow-up up to the final attended visit within the Visit 5 assessment window.

Table 2. Adjusted baseline associations with the incidence of late AMD (composite and by cause) by study end (2-year visit 5 window) using an interval-censored parametric survival model (Weibull proportional hazards models) with cluster-robust standard errors a.

Baseline characteristic	Category	*N*	Composite (late AMD)		nAMD as the recorded cause of late AMD		cRORA as the recorded cause of late AMD	
			Adjusted HR [b] (95% CI)	*P*-value	Adjusted HR [b] (95% CI)	*P*-value	Adjusted HR [b] (95% CI)	*P*-value
Age, years	<75	983	Ref	–	Ref	–	Ref	-
	75–84		1.66(1.13,2.46)	0.01	1.95(1.2,3.16)	0.007	1.22(0.63,2.38)	0.55
	85+		2.48(1.49,4.15)	0.001	1.35(0.61,3.02)	0.46	4.04(2,8.17)	<0.001
Sex	Female	983	Ref	–			Ref	
	Male		0.98(0.68,1.40)	0.89	1.03(0.65,1.65)	0.89	0.90(0.50,1.60)	0.71
Study eye BRVA categories, ETDRS letters	80 or better	950	Ref	–	Ref	–	Ref	-
	70 to 79		1.65(1.09,2.49)	0.02	1.1(0.64,1.89)	0.75	2.90(1.50,5.60)	0.002
	<=69		1.25(0.62,2.5)	0.54	1.15(0.46,2.87)	0.76	1.53(0.52,4.44)	0.44
Study eye BCVA categories with 80 or better as ref, ETDRS letters	80 or better	634	Ref	–	Ref	–	Ref	-
	70 to 79		1.61(1.04,2.51)	0.04	0.92(0.51,1.66)	0.78	3.31(1.65,6.64)	0.001
	<=69		1.03(0.44,2.40)	0.95	0.78(0.23,2.6)	0.69	1.65(0.49,5.51)	0.42
Study eye diagnosis	No atrophy & no SDD	983	Ref	–	Ref	–	Ref	-
	No atrophy & SDD		1.22(0.78,1.90)	0.38	1.37(0.82,2.26)	0.23	0.93(0.37,2.32)	0.87
	iRORA & no SDD		2.04(1.15,3.61)	0.02	0.95(0.41,2.23)	0.91	4.91(2.05,11.8)	<0.001
	iRORA & SDD		1.51(0.90,2.52)	0.12	0.71(0.33,1.54)	0.38	3.28(1.46,7.39)	0.004
iRORA	Absent	983	Ref	–	Ref	–	Ref	-
	Present		1.50(1.05,2.16)	0.03	0.66(0.38,1.15)	0.14	3.98(2.26,7.02)	<0.001
SDD	Absent	983	Ref	–	Ref	–	Ref	-
	Present		1.06(0.74,1.52)	0.77	1.19(0.76,1.86)	0.46	0.88(0.49,1.6)	0.68
Presence or absence of late AMD in the fellow eye	Bilateral or absence of recorded late AMD in the fellow eye	983	Ref		Ref	–	Ref	-
	Late AMD in the fellow eye		3.03 (1.92–4.79)	<0.001	4.08(2.13,7.83)	<0.001	2.02(1.03,3.95)	0.04
Presence or absence of nAMD and cRORA in the fellow eye	Bilateral or absence of recorded late AMD in the fellow eye	983	Ref	–	Ref	–	Ref	-
	nAMD in the fellow eye		3.23 (2.04–5.12)	<0.001	4.56 (2.38–8.77)	<0.001	1.94(0.98,3.84)	0.06
	cRORA in the fellow eye		1.67 (0.71–3.93)	0.24	NA[c]	NA[c]	2.62(0.97,7.1)	0.06

iAMD intermediate age-related macular degeneration, *cRORA* complete retinal and retinal pigment epithelial atrophy, *iRORA* incomplete retinal and retinal pigment epithelial atrophy, *nAMD* neovascular age-related macular degeneration, *SDD* subretinal drusenoid deposits, *BRVA* best recorded visual acuity, *BCVA* best corrected visual acuity.

[a]Separate models were fitted using an interval-censored parametric survival model (Weibull Regression) for incident late AMD (composite and by cause) by study end (visit 5 within the tolerance window) with cluster-robust standard errors to account for intra-subject correlation due to some participants contributing 2 eyes (combination of unilateral and bilateral eye data). Hazard ratio estimates were based on follow-up up to each participant's final attended visit within the Visit 5 assessment window (nominally 2 years up to the tolerance window).

[b]Separate models were fitted, adjusting for age (< 75, 75–84, 85 +) and sex in each.

[c]Only 1 eye developed nAMD as the cause for late AMD in eyes with cRORA in the fellow eye and therefore, we omitted this category from this adjusted analysis between the covariate and nAMD event. The analysis was done on a subset ($N = 911$) with bilateral or absence of late AMD in the fellow eye and nAMD in the fellow eye only.

Table 3. Progression of disease state and BRVA decline in the study eye at Visit 5 (2-year visit 5 window): Mean Change from baseline.

	Visit 5 (2-year visit 5 window) phenotype							
	No atrophy		iRORA		Other atrophy[a]		Late AMD	
Baseline	N[b]	Change, Mean (SD)	N[b]	Change, Mean (SD)	N[b]	Change, Mean (SD)	N[b]	Change, Mean (SD)
All eyes ($N = 935$ eyes)	482	−1.53 (8.81)	303	−1.69 (6.97)	27	−0.78 (6.59)	123	−5.58 (12.60)
Bilateral/Fellow eye status								
Bilateral iAMD Worse-Seeing Eye	91	−0.41 (6.03)	58	−1.09 (7.31)	4	−4.75 (14.17)	13	−5.77 (9.18)
Bilateral iAMD Better-Seeing Eye	96	−3.46 (5.11)	60	−1.47 (4.84)	3	−3.33 (3.06)	7	−5.57 (6.75)
iAMD Study eye (nAMD in fellow eye)	241	−0.89 (9.20)	135	−2.04 (6.47)	13	0.31 (4.94)	95	−5.44 (13.44)
iAMD study eye (cRORA in fellow eye)	19	0.79 (10.38)	39	−1.54 (8.81)	4	2.25 (4.50)	6	−1.67 (5.32)
iAMD diagnosis, Study eye								
No iRORA & No SDD	236	−1.97 (9.06)	42	−1.29 (7.92)	1	NA[c]	30	−5.00 (10.52)
No iRORA & SDD	243	−1.09 (8.62)	60	−1.53 (6.24)	9	−4.56 (8.00)	50	−7.92 (10.52)
iRORA & No SDD	3	−1.67 (2.89)	84	−1.32 (6.65)	5	−0.80 (1.79)	18	−1.72 (15.96)
iRORA & SDD	0	NA[d]	117	−2.19 (7.25)	12	1.33 (5.60)	25	−4.36 (15.58)

iAMD intermediate age-related macular degeneration, *cRORA* complete retinal and retinal pigment epithelial atrophy, *iRORA* incomplete retinal and retinal pigment epithelial atrophy, *nAMD* neovascular age-related macular degeneration, *SDD* subretinal drusenoid deposits, *BRVA* best recorded visual acuity, *SD* standard deviation.

[a]Other atrophy includes drusenoid PED, vitelliform degeneration.

[b]N reported on those with available VA data at baseline and visit 5 (2 years within the visit 5 window)

[c]Summary statistics were not reported, as only 1 eye contributed data

[d]Summary statistics were not reported as no eyes were observed in this transition category

DISCUSSION

In this multicentre cohort study, we observed that the incidence of late AMD was 13.1% in eyes with iAMD within 2 years. Incidence increased with age with no sex predilection, substantiated by our models assessing age and sex interaction, but our hospital-based cohort may not mirror population-level data [16]. In addition, fellow eye nAMD had a substantially increased risk for transition to late AMD. There were 499 participants with fellow-eye nAMD compared with 72 with cRORA. These findings mirror real-life patient cohorts in Europe, as treatment is only available for nAMD [17]. The incidence of late AMD was 15.0% in those with fellow-eye cRORA compared to 19.2% in those with fellow-eye nAMD. Fellow-eye nAMD conferred a threefold higher risk of conversion compared to those with bilateral eligibility or absence of late AMD. Although more frequent anti-VEGF therapy in fellow-eye nAMD eyes may potentially introduce detection bias, interval-censored analyses partially mitigated this, unlike other routine EMR studies. Interestingly, these events included both nAMD and cRORA, suggesting that other risk factors such as iRORA, SDD or drusenoid PEDs or vitelliform-related atrophy in the study eye may explain the development of cRORA [18]. Indeed, we found the presence of iRORA to be a precursor to the development of cRORA, having nearly 4 times the risk. No clear association with SDD was observed, possibly due to inconsistent site-based grading in routine practice, given its subtle appearance and sensitivity to imaging quality and grader experience compared with iRORA on OCT.

Out of the 950 study eyes with recorded BRVA, only 68 (7.2%) eyes had fewer than 70 letters. Baseline VA between 70–79 letters was associated with a 1.65-fold higher risk of transition to late forms compared to those with ≥80 letters. Interestingly, the associations with baseline VA were maintained for cRORA but not nAMD. This suggests poorer baseline vision may reflect underlying structural damage (e.g. iRORA or drusen, among other markers not collected), predisposing them to cRORA, whereas it does not reliably indicate progression to nAMD.

Another important finding was that eyes that transitioned to nAMD experienced the greatest loss in BRVA (−6.01 ETDRS letters, SD 11.35), more so than cRORA (−4.92 ETDRS letters, SD 14.40). Moreover, among eyes with late AMD at visit 5, those with fellow-eye nAMD lost about 1 line (−5.4 ETDRS letters, $N = 95$ eyes) of vision compared with a smaller decline in fellow-eye cRORA (-1.67 ETDRS letters, $N = 6$ eyes) on the ETDRS chart. This suggests that nAMD involvement in one eye may signal a more aggressive disease course to late AMD with earlier functional impact than participants with fellow eyes with cRORA. This is consistent with our finding that fellow-eye nAMD increases the hazard of progression to nAMD, which are prone to sudden large drops in VA (from foveal involvement). In contrast, cRORA typically progresses more gradually (extrafoveal) with less functional decline.

Ultimately, our findings suggest that the presence of iRORA, baseline VA 70-79 ETDRS letters and fellow-eye nAMD were associated with incident late AMD, irrespective of age and sex. Moreover, iRORA and baseline VA were found to be a precursor to the incidence of cRORA as the cause of late AMD, but not to nAMD.

The strengths of this study are the large sample size of the cohort from across Europe, ensuring generalisability unlike prior EMR-based and trial-enriched populations [19, 20] and the detailed study on transitions between OCT phenotypes of iAMD and their influence on VA. Moreover, the relatively low incidence of late AMD (13%) highlights the need for surrogate endpoints in prevention trials, as traditional progression to late disease may occur too infrequently to power studies efficiently. iRORA in the study eye and fellow-eye nAMD identified eyes at higher risk of progression to late AMD in the study eye, while fellow-eye nAMD experience worse functional decline once late AMD develops. These features may help enrich trial populations, shorten follow-up and increase trial efficiency, but their role as predictive biomarkers of treatment response should be established before they are used to define eligibility criteria, as any modification of treatment effect could alter the expected

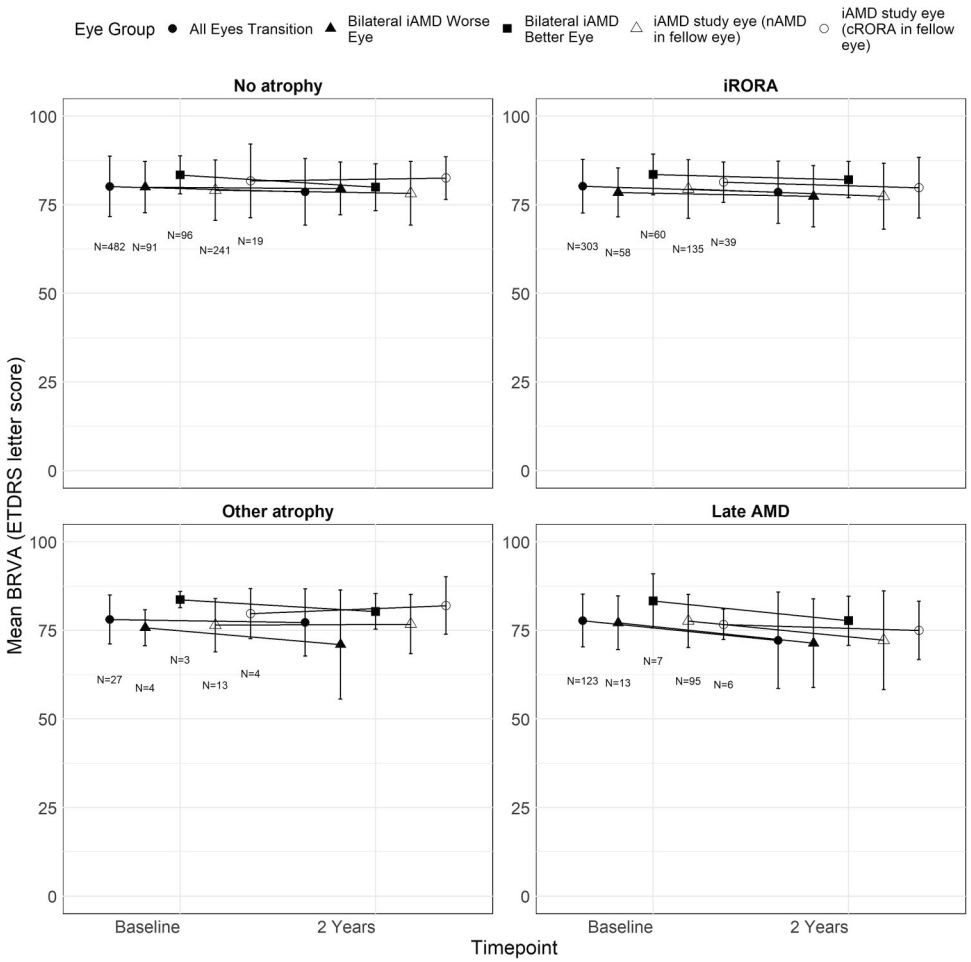

Fig. 1 Mean (±SD) BRVA in the study eye at baseline and visit 5 (2-year visit 5 window) by disease progression in better- and worse-seeing eyes (bilateral) and fellow eyes (unilateral)[a]. iAMD-intermediate age-related macular degeneration; cRORA- complete retinal and retinal pigment epithelial atrophy; iRORA- incomplete retinal and retinal pigment epithelial atrophy; nAMD-neovascular age-related macular degeneration; SDD-subretinal drusenoid deposits; BRVA-best recorded visual acuity. [a] Eyes with BRVA assessed at baseline and visit 5 (2-year visit 5 window) were included; with numbers observed in the transition category, used for the calculation of mean and SD, labelled on the graph.

benefit and sample size requirements. Furthermore, knowing which eyes are likely to experience functional decline (fellow eye nAMD) might help define meaningful primary and secondary endpoints.

Despite a large sample size, the study has several limitations. Firstly, there was no independent reading centre grading of OCT images. Moreover, the optional nature of FAF imaging may have further contributed to the misclassification of SDD, which could attenuate observed associations in adjusted models. Therefore, the null association for SDD should be interpreted with caution in light of ascertainment limitations. Secondly, we did not include other known risk factors such as genetic factors and other OCT features (e.g. drusen volume/size) [21, 22]. Finally, there is potential for measurement variability in using BRVA over BCVA. However, BRVA reflects routine clinical practice and a sensitivity analysis using BCVA showed a similar direction of effect.

In conclusion, only 13% of eyes with iAMD progress to late AMD within 2 years, highlighting the limitation of using late AMD incidence as a primary endpoint in prevention trials. Alternative endpoints should also be considered to ensure adequate event rates for detecting clinically meaningful differences. Moreover, eyes that transitioned to nAMD experienced the greatest visual loss and fellow-eye nAMD remained an important risk factor for progression, associated with greater visual decline compared to fellow eyes with cRORA.

Supplemental materials are available at Eye's website

SUMMARY

What is known about this topic

- Not all eyes with intermediate AMD (iAMD) progress to late stages during an individual's lifetime.
- The trajectory of visual acuity (VA) change in eyes that progress can vary depending on several factors, such as fellow eye status and baseline disease characteristics.
- Clinical trials typically enroll eyes with a VA of 70 ETDRS letters or better. However, it remains unclear whether this criterion limits the ability of studies to capture sufficient progression events

What this study adds

- Approximately 13% of eyes with iAMD progressed to late AMD within 2 years, with eyes developing nAMD experiencing the greatest loss in VA.
- Presence of iRORA, VA 70–79 ETDRS letters relative to 80 or better and fellow eye status were associated with progression

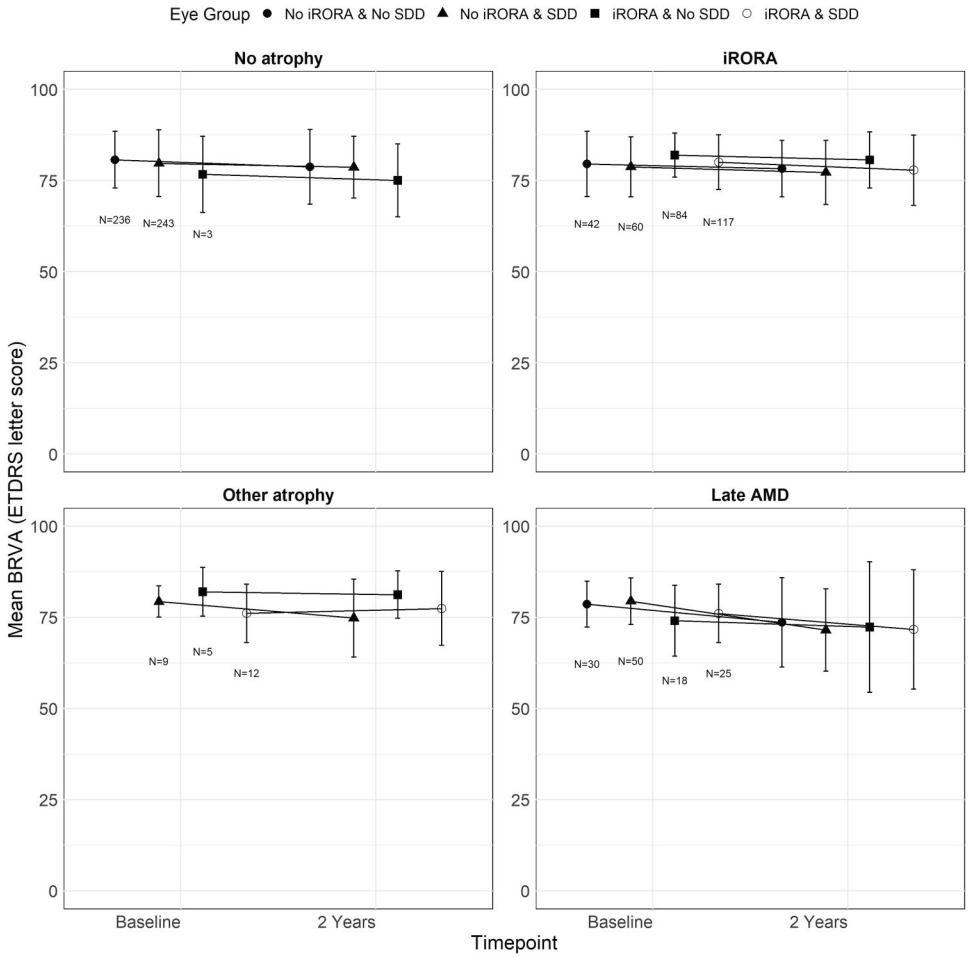

Fig. 2 Mean (±SD) BRVA in the study eye at baseline and visit 5 (2-year visit 5 window) by iAMD disease progression[a,b]. iAMD-intermediate age-related macular degeneration; iRORA- incomplete retinal and retinal pigment epithelial atrophy; SDD-subretinal drusenoid deposits; BRVA-best recorded visual acuity. [a]Data points for the following groups were not plotted due to no eyes or only 1 eye being observed in that transition category with available BRVA data: i) iRORA & SDD to no atrophy and ii) no iRORA & no SDD to other atrophy. [b]Eyes with BRVA at baseline and visit 5 (2-year visit 5 window) included; with numbers observed in the transition category used for the calculation of mean and SD labeled on the graph.

to late AMD irrespective of age and sex, while iRORA and VA 70–79 ETDRS were associated with progression to cRORA as the first late AMD event but not with progression to nAMD.

- Late AMD prevention trials may require large sample sizes or long follow-up periods to accrue sufficient events for analysis; biomarker-based enrichment may improve efficiency but should first be evaluated for treatment-effect modification before sample size planning.

DATA AVAILABILITY

The data that support the findings of this study are all reported in this paper. Further details are available from the corresponding author and/or in the EVICR.net Eye Platform upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualisation: SG, IM, JFG, YL, MCP, LB, HA, SB, ET, JM, LS, RS, HPNS, AL, BS, SV and SS; Data curation: SG; Formal analysis: SG; Funding acquisition: IM, JFG, YL, MCP, LB, HA, SB, ET, JM, LS, RS, HPNS, AL, BS, SV and SS; Methodology: SG and SS; Supervision: SS; Visualisation: SG; Writing – original draft: SG and SS; Writing—review and editing: SG, IM, JFG, YL, MCP, LB, HA, SB, ET, JM, LS, RS, HPNS, AL, BS, SV and SS; Review and approval of final manuscript: SG, IM, JFG, YL, MCP, LB, HA, SB, ET, JM, LS, RS, HPNS, AL, BS, SV and SS.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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