

## Patterns of treatment discontinuation in patients receiving anti-vascular endothelial growth factor for neovascular age-related macular degeneration

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**Purpose:** To report the reasons for treatment discontinuation within 5 years in patients receiving intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (nAMD). **Methods:** A retrospective case-notes review of patients commenced on anti-VEGF for nAMD who failed to complete 5 years of follow-up was undertaken. The reasons for treatment discontinuation, baseline age, baseline visual acuity (VA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and the VA change at the last follow-up were recorded. Age-specific all-cause mortality was calculated for deceased patients. **Results:** Of the 1177 patients, 551 patients (46.8%) failed to complete the 5-year follow-up. The reasons for treatment discontinuation were death (251), early discharge due to stable disease (110), further treatment deemed futile (100), failure to attend (15), ill health (14), patient choice (7), and transfer of care (1). In 53 patients, no reason was documented. The mean baseline age of those who completed the 5-year follow-up ( $77.4 \pm 7.8$  years, 95% confidence interval (CI): 76.8–77.9) was significantly lower than those who discontinued the treatment for any reason ( $82 \pm 7.7$  years, 95% CI: 81.4–82.6) ( $P < 0.0001$ ). Survival analysis showed that baseline VA was not a factor in treatment discontinuation; however, visual stability ( $\pm 5$  letters from baseline) was associated with treatment continuation. The age-specific all-cause mortality in deceased patients was lower than that in the general population. **Conclusion:** At 5 years, only 53% of patients remained in active care, and death was the most common reason for treatment discontinuation. Lower baseline age and VA stability during therapy were associated with treatment continuation.

**Key words:** Anti VEGF, nAMD, treatment discontinuation

Neovascular age-related macular degeneration (nAMD) is the most common cause of visual impairment in people over the age of 55 years.<sup>[1]</sup> Untreated, it causes irreversible central visual loss in 76% of patients within 3 years.<sup>[2]</sup> Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has decreased the rate of legal blindness in over 50% of such patients.<sup>[3]</sup> Despite the initial visual acuity (VA) gain with monthly injections, around 10% of eyes lose 15 letters of vision within 2 years, as seen in various studies.<sup>[4–6]</sup> Visual decline of 8–14 letters has been reported on exit from clinical trials.<sup>[7,8]</sup>

Real-world evidence suggests that the visual gains seen in trials cannot be matched by pro-re-nata (PRN) or treat and extend (TAE) regimens, possibly due to non-adherence or non-persistence with the treatment.<sup>[9]</sup> Given the chronicity of the disease, treatment discontinuation is a significant concern. Literature shows that two-thirds of patients complete 5 years of continuous follow-up, which drops to one-third by 10 years.<sup>[10–12]</sup>

Reporting on patients in whom treatment is discontinued for clinical reasons or who are lost-to-follow-up (LTFU) is important. Many retrospective studies reporting 5-year outcomes have not provided this vital information.<sup>[13–16]</sup> A 5-year study from the

UK reported a completion rate of 66%, with death as the most common reason for LTFU.<sup>[17]</sup> The Fight for Retinal Blindness (FRB) registry study reported a treatment discontinuation rate of 42% over 6 years.<sup>[18]</sup> Higher LTFU rate has been reported with older age, African American and Asian ethnicity, lower gross income, lower baseline VA, unfavorable VA outcome, greater distance to clinic, and in patients with unilateral eye disease.<sup>[19–21]</sup> Non-adherence and non-persistence with intravitreal treatment have led to inferior clinical outcomes; thus, knowledge of contributing factors is important to combat this.

The objective of this study was to evaluate the reasons for treatment discontinuation over 5 years in the UK, where cost is funded by National Health Service (NHS). The age, baseline VA, and VA change in patients who completed 5 years of follow-up (“completers”) were compared to those in patients who discontinued treatment (“non-completers”) for any reason. Additionally, the age-specific all-cause mortality rate was calculated for the deceased patients and compared to that for the general population.

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## Methods

In this single-center retrospective study, data were extracted for treatment-naïve eyes that were initiated on intravitreal anti-VEGF therapy for nAMD between January 2009 and December 2014 from electronic records (Medisoft®). Only patients who had three loading injections of anti-VEGF therapy were included, and the results were recorded for 5 years. All patients had clinical signs of active nAMD with VA between 24 and 74 letters [number of Early Treatment of Diabetes Retinopathy Study (ETDRS) letters on a logarithm of the minimum angle of resolution (LogMAR) chart]. Further information collected included patient demographics; VA at baseline, 4 months (4 weeks after the three loading injections), and last follow-up; reason for treatment discontinuation; anti-VEGF agent used; and number of injections. The VA was recorded in a clinic setting by using the patient's own spectacle correction and VA of "counting fingers" or worse was given a value of 0 letters.

In eyes where further therapy was deemed futile due to permanent macular damage (secondary to macular atrophy/scarring), baseline color fundus photographs (CFP) were reviewed. Additionally, optical coherence tomography (OCT, spectral-domain Spectralis, Heidelberg Engineering, Germany) findings at the last follow-up were revisited to confirm the reason for treatment withdrawal. On CFP, macular atrophy (MA) was recorded to be present when a discrete area of hypopigmentation or depigmentation of retinal pigment epithelium (RPE) within the vascular arcade, causing increased visibility of choroidal vessels, was seen. Presence of a well-defined area of yellowish-white tissue was recorded as macular fibrosis. On OCT images, MA was recorded to be present in eyes that showed a zone of choroidal hypertransmission with absence of RPE homogenous band, while macular fibrosis was recorded in eyes that showed a hyper-reflective sheet-like material above or below the RPE. All the images were reported by the treating clinician.

### Treatment protocol

All eyes commencing treatment between 2009 and 2013 received intravitreal ranibizumab with three monthly loading injections. In eyes that received intravitreal aflibercept, from 2014 onwards, the treatment regimen included three loading injections followed by fixed bimonthly dosing in the first year. The treatment was given on PRN basis until 2016, after which TAE became the preferred regimen.

The study adhered to the tenets of the Declaration of Helsinki and was registered as a clinical audit with the hospital quality improvement team.

### Outcome measures

The outcome measures were the number of patients discontinuing treatment, reasons for discontinuation, and patient factors that may have contributed to discontinuation. Additionally, where the decision to discontinue further treatment was made on clinical grounds (due to disease stability or deemed futility of further treatment), the reasons were compared in patients where treatment was stopped early (within 2 years) to those where treatment was stopped late (between 4<sup>th</sup> and 5<sup>th</sup> year). In addition to these results, the outcome measures in patients aged  $\geq 90$  years at treatment initiation were reported separately. Finally, the age-specific all-cause mortality rate was calculated for the deceased patients and compared with the rate in the general population.<sup>[22]</sup>

### Statistical analysis

The data were entered into an Excel sheet and analyzed using GraphPad Prism 6.0. The data were not found to be normally distributed (D'Agostino and Pearson omnibus test). Descriptive data included mean, standard deviation, standard error, median, range, and percentages. The Mann-Whitney test was used to compare the mean parameters of completers with all non-completers and with each of the non-completer categories. Time to treatment discontinuation ("dropout") based on age, baseline VA, and change in VA was analyzed using Kaplan-Meier survival, and curves were compared using the Mantel-Cox test.  $P < 0.05$  was considered statistically significant.

## Results

Of the 1177 patients (1322 eyes) commenced on anti-VEGF therapy for nAMD, 626 patients (687 eyes) completed the 5 years follow-up and were still in active care. Of the 551 non-completers, 251 patients (45.6%) deceased over 5 years. The reasons for treatment discontinuation in the remaining 300 patients (353 eyes) were early discharge due to stable disease (110, 20.0%), further treatment deemed futile (100, 18.1%), non-attendance (15, 2.7%), ill health (14, 2.5%), patient choice (7, 1.3%), and care transferred elsewhere (1, 0.2%). In 53 patients (9.6%), there was no documented reason for treatment discontinuation.

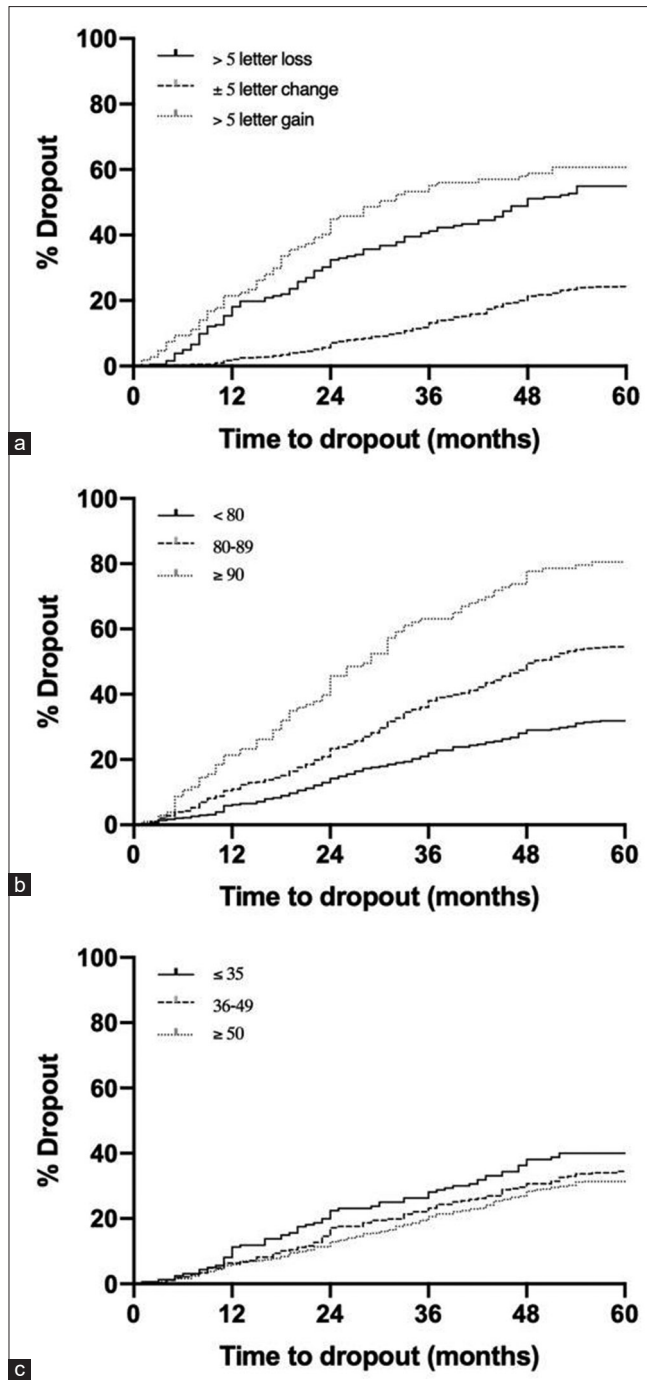
### Age

The mean baseline age of completers ( $77.4 \pm 7.8$  years, 95% confidence interval CI: 76.8–77.9) was significantly lower than that of non-completers ( $82 \pm 7.7$  years, 95% CI: 81.4–82.6) ( $P < 0.0001$ ). The mean baseline age of deceased patients ( $84.3 \pm 6.3$  years, 95% CI: 83.5–85) was significantly higher than that of the completers ( $P < 0.0001$ ), as was the age of patients in whom further treatment was deemed futile ( $81.1 \pm 7.6$  years, 95% CI: 79.7–82.6) ( $P < 0.001$ ). The mean baseline age of patients in whom treatment was terminated early due to stable disease ( $78.7 \pm 8.6$  years, 95% CI: 54–90) was not significantly different from that of the completers ( $P = 0.3$ ). Survival analysis showed a significantly higher discontinuation rate with increasing age at treatment initiation ( $P < 0.0001$ ) [Graph 1a].

### Visual acuity

Fig. 1 shows the baseline and final VA of all the completers and non-completers. A mean decline of 1.7 letters (95% CI: -3.1 to -0.3,  $P = 0.19$ ) was seen in the completers (baseline VA:  $52.4 \pm 13.5$  letters, VA at 5 years:  $50.6 \pm 20.8$  letters). The baseline VA of non-completers was significantly lower than that of the completers ( $49.0 \pm 15.4$  letters,  $P < 0.0001$ ). Comparing with completers, eyes where further treatment was deemed futile had significantly worse baseline VA ( $40.2 \pm 15$  letters,  $P < 0.0001$ ); however, no significant difference was seen when comparing completers with eyes where treatment was terminated early due to stable disease (baseline VA  $54.4 \pm 14.4$ ,  $P = 0.12$ ). Patients who were less than 70 years of age at treatment initiation had significantly better VA ( $53.4 \pm 14.1$  letters) than patients greater than 80 years ( $49.4 \pm 13.7$  letters,  $P = 0.02$ ).

Table 1 compares the baseline VA, final VA, and VA change between the completers and all the categories of non-completers. Eyes in the treatment futile group lost more vision and had a significantly higher proportion reaching the blind registration level (VA  $< 35$  letters). Survival analysis showed a significantly reduced rate of treatment discontinuation in eyes that experienced VA stability (change  $\pm 5$  letters) over the study

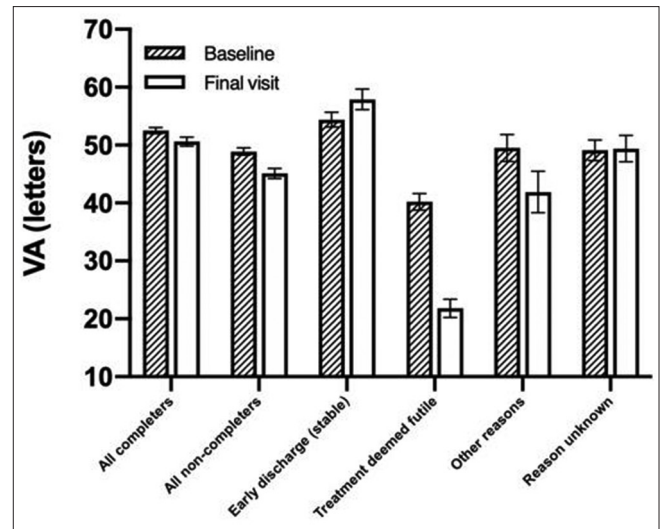


**Graph 1:** Kaplan–Meier survival plot for time to dropout according to age in years (a), change in visual acuity in letters (b), and baseline visual acuity in letters (c)

period compared to eyes that experienced gain or loss in VA [Graph 1b], while there was no difference in drop-out rate when comparing the baseline VA [Graph 1c].

**Central foveal thickness (CFT)**

The mean CFT of all the eyes that completed the 5-year follow-up was  $390.7 \pm 100.8 \mu$  and was not statistically different to those where treatment was stopped early due to stable disease (mean CFT:  $397.4 \pm 110.4, P = 0.97$ ). However, eyes in which further treatment was considered futile had a



**Figure 1:** Bar graph showing baseline and final visual acuity (ETDRS letters) in completers and various categories of non-completers

significantly higher mean CFT ( $451.5 \pm 153.8 \mu, P = 0.01$ ) than completers.

**Monitoring visits and clinic delays**

The number of monitoring visits reduced significantly after the 3<sup>rd</sup> year of follow-up. The mean number of clinic visits for all the patients was 10, 6.8, 6.6, 5.5, and 4.6 in the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> year of follow-up, respectively. Only 40% of patients were seen within 7 days of their scheduled follow-up time, and in 30% of patients, the delay was more than 14 days.

**Number of injections**

Of the 1322 eyes, 1276 eyes received intravitreal ranibizumab (of which 8 switched to aflibercept) and 46 eyes had aflibercept as the initial therapy. The cumulative mean number of injections in completers by the end of 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> year of therapy was 6.1, 9.3, 12.2, 14.4, and 17.1 respectively, compared to 3.5, 5, 5.8, 7.4, and 10 injections in non-completers.

**Deceased patients**

Of the 300 patients who died during the 5-year period, 5.9% deceased in the first year after treatment initiation and 22.8% in the 5<sup>th</sup> year. The cause of death in these patients was not recorded, but the age-specific all-cause mortality rate (per 100,000) in every age category was lower than that in the general population [Table 2] (Public Health England PHE) records between 2009 and 2016).<sup>[22]</sup>

**Early discontinuation due to treatment futility**

Over 5 years, therapy was withdrawn in 100 patients (113 eyes) because further treatment was deemed futile. These patients suffered a significant visual loss (median decline of 17 letters, interquartile range (IQR): -4 to -32) over the course of follow-up. Eyes where treatment was withdrawn in the first 2 years (“early stoppers”; n = 46) were compared with those where treatment was withdrawn in the 4<sup>th</sup> and 5<sup>th</sup> years (“late stoppers”; n = 34) [Table 3]. There was no difference in the baseline VA or overall visual decline; however, VA change at 4 months (4 weeks after the three loading injections) was a major factor determining the timing of treatment withdrawal. At 4 months, a mean decline of 1 letter was seen in the early stoppers compared to a gain of 4



**Table 1: Proportion of change in visual acuity change (%) in completers and various categories of non-completers**

	VA gain $\geq 10$ letters	VA loss $\geq 10$ letters	VA change $\pm 5$ letters	VA $\geq 70$ letters (baseline/final)	VA $\leq 35$ letters (baseline/final)
All completers	30.5	30.8	23.4	10.7/19.9	13.9/25.4
All non-completers	21.4	29.4	32.5	7.5/14.9	22.3/36.6
Futile treatment	4.4	64.6	20.3	0/2.2	43.3/84.9
Deceased	22.8	23.9	14.5	7.2/13	19.5/25
Treatment cessation	31.8	14.4	32	13.6/32.8	9.6/16
Unknown cause	18.6	25.3	37.3	9.3/14.6	24/34.6

**Table 2: Comparison of all-cause age-specific mortality rate in this study with PHE data**

Age range (years)	Age-specific mortality rate (per 100,000)	
	National	Present study
70-74	2000	1717
75-79	3000	2770
80-84	6000	4459
85-89	11,000	6718
$\geq 90$	20,000	9800

**Table 3: Comparison of “early” and “late” stoppers in the treatment futile group, visual acuity in ETDRS letters (standard deviation)**

Parameter	Treatment futile		
	Early (46)	Late (34)	P
Baseline VA	38.1 (15.2)	41.1 (16.6)	0.4
Final VA	21.5 (19)	20.4 (14.9)	0.7
Median VA change at 4 months	-1	4	0.01
VA $\geq 70$ letters (baseline/final)%	0/6.5	0/0	
VA $< 35$ letters (baseline/final)%	47.8/82.6	44.1/85.3	
Injections (mean)	4.8 (2.4)	9.1 (5.9)	0.0002

letters in the late stoppers. Additionally, at 4 months, the CFT was less significantly reduced in the early stoppers (baseline:  $432.3 \pm 188.8 \mu$ , at 4 months:  $345.1 \pm 166 \mu$ ;  $P = 0.01$ ) than in the late stoppers (baseline:  $427.9 \pm 160.7 \mu$ , at 4 months:  $266.2 \pm 97.8 \mu$ ;  $P < 0.0001$ ). Baseline CFP revealed the presence of macular atrophy/scarring in 20 eyes in the early stoppers compared to five eyes in the late stoppers. At last follow-up, CFP was not available, but OCT showed the presence of these changes in 46 eyes in the early stoppers and 34 in the late stoppers.

#### Early discontinuation due to disease stability

In 110 patients (125 eyes), treatment was withdrawn because the disease was considered clinically stable by the clinician, based on stable VA, and absence of macular fluid on OCT on multiple serial visits. The treatment cessation decision was made in 35 eyes in the first 2 years (“early stoppers”) and in 58 eyes in the last 2 years (“late stoppers”). Early stoppers showed a median visual gain of 4 letters (IQR: 0–12) at 4 months compared to 8 (IQR: 0–14) letters in the late stoppers.

#### Patients aged $\geq 90$ years

Of 108 patients (8.6% of the total cohort) who were  $\geq 90$  years at treatment initiation, 54 deceased (50%) and only 18 (16.6%) completed the 5-year follow-up. There were no patients with bilateral disease. Mean VA change of +0.4 letters was seen in the completers. The reasons for treatment discontinuation were early discharge due to disease stability (8), further treatment deemed futile (11), non-attendance (5), and no documented reason (10).

#### Discussion

Neovascular age-related macular degeneration is a chronic condition, the necessity for frequent clinic visits and injections poses a significant burden on patients and clinicians. This study looked at the reasons for treatment discontinuation over 5 years in the NHS setting, where the cost of treatment is not a factor. Patient death was the main reason for treatment discontinuation. In the majority of surviving non-completers, the decisions to terminate treatment early were based on clinical judgment. The decision to discontinue treatment depended not only on the visual gain or loss but also on the timing of these gains/losses.

In eyes with stable disease, if a significant visual gain was obtained in the first 2 years of treatment, a clinical decision was made to discharge the patients by the 3<sup>rd</sup> year, based on the stable OCT changes and VA. It is important that some of these patients were the first in our service to receive anti-VEGF for nAMD and the chronic nature of the disease was unknown then. Additionally, we did not review the number of patients who returned with disease recurrence. Soares *et al.*<sup>[23]</sup> has shown that patients who return to follow-up after being lost to follow-up (LTFU) experience a significant visual decline at the return visit, which persists despite normalization of macular thickness.

The Royal College of Ophthalmologists guidelines recommend permanent suspension of anti-VEGF treatment in eyes where the absolute VA reduces below 15 letters on two consecutive visits, where visual decline of  $> 30$  letters from baseline is noted, or worsening of lesion morphology is seen despite optimal anti-VEGF therapy.<sup>[24]</sup>

Sixty of the 113 eyes in the treatment futile group met these criteria for treatment suspension. Poor response to treatment at 4 months was the primary driver for stopping treatment within the first 2 years. Amoaku *et al.*<sup>[25]</sup> defined eyes that lose more than 5 letters from baseline at 4 months as “non-responsive.” This criterion was met in 37% of eyes where the decision was taken to withdraw treatment in the first 2 years. The knowledge that response to anti-VEGF treatment for nAMD is heterogeneous and that a subset of patients could show a delayed response was unknown at the time.<sup>[26]</sup> Additionally,

the option of switching to a different anti-VEGF agent was not available in the first 5 years of this study. Treatment futility in the 4<sup>th</sup> and 5<sup>th</sup> year was possibly due to permanent macular damage, and given the PRN nature of disease monitoring, these eyes were undertreated (as highlighted by the significantly reduced number of injections in this group of patients). Under-treatment with PRN monitoring has been reported as the main reason for visual decline in various real-world studies from the UK and other countries.<sup>[27,28]</sup> A higher rate of macular fibrosis (61%) and macular atrophy (98%) were seen in the SEVEN-UP study<sup>[7]</sup> compared to patients managed on TAE in the FRB study.<sup>[29]</sup> Recently, the Vision Academy Steering Committee has published guidance on the management of patients who show poor response to anti-VEGF and the various factors to be considered in cases of treatment futility.<sup>[30]</sup>

Previous studies have reported that the mortality rate among patients receiving anti-VEGF for nAMD is comparable to the normal population, with a 5-year all-cause mortality of 30%.<sup>[31,32]</sup> We noted an all-cause mortality of nearly 6% in the 1<sup>st</sup> year of treatment, which increased to nearly 23% by the 5<sup>th</sup> year. We did not compare the mortality among our patients with a matched group; however, comparison with the PHE averages showed that the age-specific all-cause mortality rate was lower in these patients. Nevertheless, this could be due to the low number of patients in our study in each age category.

A previous publication on patients aged  $\geq 90$  years showed a high rate of treatment discontinuation due to patient death or unacceptable treatment burden.<sup>[33]</sup> It has been suggested that these patients may not seek help early in the course of the disease and may accept age-related vision decline. This was not true in our cohort, and the baseline VA in these patients was similar to that in patients aged 80–89 years at treatment initiation. The age-specific all-cause mortality in patients aged  $\geq 90$  years was 50% over 5 years. Only 18 patients (16.6%) completed the 5 years of follow-up, and the visual outcome in these eyes was comparable to the outcomes in completers from other age groups. Further, 40.7% (44 eyes) discontinued within the first 2 years as compared to 51% in the previously published study.<sup>[32]</sup>

Our study provides an insight into the early cohort of patients who received anti-VEGF for nAMD in the first 5 years after its introduction in the NHS. This study has several limitations, including retrospective data collection, PRN treatment strategy, treatment withdrawal decisions based on subjective clinical discretion, no documented reason for treatment discontinuation in a significant number of patients, absence of CFP at the last follow-up, and that the study was carried out in the UK, where patient affordability of the cost of treatment is not a factor.<sup>[34]</sup> Additionally, this information has to be used with caution in the current setting, where TAE is the preferred disease monitoring regimen; however, it is helpful in planning service delivery where PRN is still followed.

Our study has multiple strengths: It is the first study reporting in detail on treatment discontinuation rates over 5 years in the NHS, looking at factors associated with early withdrawal of treatment, reporting visual results in the very old ( $\geq 90$  years of age), and providing all-cause age-specific mortality data.

## Conclusion

In conclusion, only 53% of patients remain in active care 5 years after initiation of anti-VEGF therapy for nAMD, and death

was the most common reason for treatment discontinuation. Lower baseline age and VA stability during therapy were associated with treatment continuation while age  $>80$  years and early visual gain and loss were associated with treatment discontinuation.

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## Conflicts of interest

ND- Travel grant and advisory board fees from Novartis, Bayer, and Allergan. Lecture fees from Novartis.

FDG- Institutional research grants from: Allergan, Bayer, Boehringer Ingelheim, Chengdu Pharma, Clearside, Novartis, and Roche. Travel Grants from Allergan, Bayer, Novartis. Lecture fees from: Allergan, Alimera, Bayer, Heidelberg, Novartis, Roche, Advisory board/Consultancy for Allergan, Alimera, Apellis, Bayer, Boehringer Ingelheim, Novartis, Roche.

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