Ten-Year Survival Trends of Neovascular Age-Related Macular Degeneration at First Presentation

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Abstract

Background: To describe 10-year trends in visual outcomes, anatomical outcomes, and treatment burden of patients receiving anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (nAMD).

Methods: Retrospective cohort study of treatment-naïve, first-affected eyes with nAMD started on ranibizumab before January 1, 2009. The primary outcome was time to best-corrected visual acuity (BCVA) falling ≤ 35 early treatment diabetic retinopathy study (ETDRS) letters after initiating anti-VEGF therapy. Secondary outcomes included time to BCVA reaching ≥ 70 letters; proportion of eyes with BCVA ≥ 70 and ≤ 35 letters at 10 years; mean trend of BCVA and central retinal thickness (CRT) over 10 years; and mean number of injections.

Results: For our cohort of 103 patients, Kaplan-Meier analyses demonstrated median time to BCVA reaching ≤35 and ≥70 letters were 37.8 (95% CI 22.2-65.1) and 8.3 (95% CI 4.8-20.9) months after commencing anti-VEGF therapy, respectively. At the final follow-up, BCVA was ≤35 letters and ≥70 letters in 41.1% and 21%, respectively, in first-affected eyes, whilst this was the case for 5.4% and 48.2%, respectively, in a patient's better-seeing eye. Mean injection number was 37.0 ± 24.2 per eye and 53.6 ± 30.1 at patient-level (63.1% of patients required injections in both eyes).

Conclusions: The chronicity of nAMD disease and its management highlights the importance of long-term visual prognosis. Our analyses suggest that one in five patients will retain good vision (BCVA ≥70 ETDRS letters) in the first-affected eye at 10 years after starting anti-VEGF treatment; yet one in two patients will have good vision in their better-seeing eye. Moreover, our data suggest that early treatment of nAMD is associated with better visual outcomes.

Abbreviations

AMD - age related macular degeneration

GA - geographic atrophy

CNV - choroidal neovascularization

UK - United Kingdom

nAMD - neovascular AMD

VEGF - vascular endothelial growth factor

RCT - randomized controlled trial

MEH - Moorfields Eye Hospital

BCVA - best-corrected visual acuity

ETDRS - Early Treatment Diabetic Retinopathy Study

CRT - central retinal thickness

OCT - optical coherence tomography

PRN - pro re nata

LTFU - lost to follow-up

DNA - did not attend

CFP - color fundus photograph

IRF - intraretinal fluid

SRF - subretinal fluid

Introduction

Age-related macular degeneration (AMD) is a progressive disease which frequently necessitates long-term treatment. Photoreceptor dysfunction is likely to occur, with the development of geographic atrophy (GA) and choroidal neovascularization (CNV).[1] Left untreated, CNV leads to legal blindness in 76% of individuals at 3 years.[1,2] In the United Kingdom (UK), it is estimated that 1 in every 2000 individuals aged 60 or over are diagnosed with late AMD, defined as GA or CNV, rising to 1 in every 5 individuals aged 90 or more.[3] Over 40,000 individuals are diagnosed with neovascular AMD (nAMD) in the UK every year.[4] Intravitreal injections of anti-vascular endothelial growth factor (VEGF) have been proven to be the most effective treatment for nAMD,[5–7] although there is a lack of supported data from randomized controlled trials (RCTs) on long-term outcomes.[8–10] The unquestionable level of benefit achieved in RCTs is nonetheless seldom achieved in a real-life setting, as per selection criteria, monthly assessments, and strict treatment protocols. Furthermore, long-term RCTs would be cost-prohibitive. In clinical practice, frequent examinations can pose an added burden to the overstretched healthcare system. The question of whether a frequent dosing regimen in the first 1-2 years of treatment could grant better long-term visual outcomes, or if it delays a drop in vision occurring when adopting a less frequent dosing regimen, remains unanswered. Additionally, morphological changes, such as GA, may be either the result of cumulative damage over years, or the presumed effect of persistent VEGF blockage. As the long-term natural history of nAMD is discouraging, one of the biggest challenges is preserving patients' expectations and level of independence in activities of daily living.

This study aimed to interrogate the 10-year visual function, anatomical outcome, and treatment burden of anti-VEGF treatment in the first-affected eye of nAMD patients. These findings inform long-term prognosis and treatment expectations, with potential impact on promoting patient engagement. Moreover, a deidentified version of our dataset and its analysis in step-by-step code will be made open-source digital to permit replication, follow-up analyses, and promote open-science as has been carried out by our group previously.

Methods

Study design

This was a retrospective cohort study of patients that had commenced intravitreal therapy for nAMD at Moorfields Eye Hospital (MEH) NHS Foundation Trust before January 1, 2009. Baseline was defined as the date of the first injection of the first-affected eye. Final visit was defined as the appointment nearest to and within 6 months of 120 months from baseline. Data extracted from electronic medical records included demography, appointment date, anti-VEGF agent administered, and fellow eye involvement for each visit. All data points were manually cross-referenced by three researchers. For each appointment, best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters and central retinal thickness (CRT) were extracted. This study was conducted in accordance with the Declaration of Helsinki and the UK's Data Protection Act. Permission for data collection and analysis was registered as a clinical audit (reference CA17/MR/28).

Cohort selection

Eligibility criteria were: (i) age ≥ 50; (ii) treatment with ranibizumab 0.5 mg/0.05 mL (Lucentis; Genentech, South San Francisco, CA) for nAMD before January 1, 2009; (iii) treatment-naïve eyes; (iv) first-affected eye. Exclusion criteria were: (i) previous/concomitant treatment with photodynamic therapy or macular laser; (ii) previous treatment with intravitreal bevacizumab, pegaptanib or ranibizumab; (iii) missing baseline BCVA; (iv) macular scar secondary to nAMD in the fellow eye (thus being the first-treated eye the second-affected eye).

Treatment regimen

All patients were started on a *pro re nata* (PRN) ranibizumab regimen until 2015, when a treat-and-extend protocol was adopted. All eyes were treated according to MEH AMD intravitreal treatment guidelines (**Supplementary Figure 1**).[13] Briefly, all patients starting on ranibizumab undergo 3 monthly injections, followed by a PRN treatment if dry. They are otherwise offered a treat-and-extend protocol i.e. monthly injections until dry after which injection visits increase by 2-week increments up to 12 weekly injections. If a patient undergoes 12-weekly injections for 3 consecutive visits alongside features of stability, they are monitored at 6-weekly intervals for 6 months without injections and then at 3-monthly intervals without injections. Here, disease stability (or disease inactivity) is defined as absence of the following features when compared with the previous visit: new or enlargement of fluid on OCT; new or persistent haemorrhage or exudates; decreased VA attributable to CNV; fluorescein leakage or increase in lesion size on FFA. Disease stability at the last follow-up appointment was assessed by considering whether patients had received anti-VEGF treatment in the 6 months leading up to and including the last appointment. Those who responded suboptimally to ranibizumab were switched to aflibercept 2 mg/0.05 mL (Eylea; Regeneron, Tarrytown, NY).

Loss to follow-up

Patients who did not reach the 10-year timepoint were considered lost to follow-up (LTFU). Underlying reasons for LTFU were categorised as: deceased; non-attendance of appointments despite physician's recommendation (DNA; did not attend); clinician decision to discharge; or relocation to another hospital.

Image analysis

SD-OCT scans and colour fundus photographs (CFP) at baseline and last visit were reviewed by two reading centre graders to assess morphological features, including: CNV type, intraretinal fluid (IRF), subretinal fluid (SRF), foveal/extrafoveal GA or fibrotic scar, subretinal hyperreflective material, intraretinal/subretinal haemorrhages. GA was defined on OCT as presence of ≥ 1 patch, within the macular vascular arcades, of partial/complete retinal pigment epithelium or outer retinal atrophy ≥ 250 μm, increase in choroidal reflectivity below Bruch's membrane, external limiting membrane absence/descent, and sharply demarcated borders, and/or visibility of underlying choroidal vessels on CFP.[14,15] CRT values were extracted using Topcon OCT Data Collector Software. This was defined as thickness from inner limiting membrane to outer photoreceptor segments/retinal pigment epithelium junction boundary within the central ETDRS grid region when centred on the fovea. Manual measurements of CRT were performed on OCT scans at fixed time points to check for accuracy.

Outcome measures

The primary outcome was time to BCVA falling to or below 35 ETDRS letters after starting anti-VEGF therapy. Secondary outcomes were: time to BCVA reaching 70 letters or above; proportion of first-affected eyes with BCVA ≥ 70 and ≤ 35 letters at 10 years; proportion of patients with better-seeing eye BCVA ≥ 70 and ≤ 35 letters at 10 years; mean BCVA and CRT over the observation period; mean change in BCVA and CRT from baseline over the observation period; mean number of injections; and morphological outcomes.

Statistical analysis

Statistical analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).[17] Cox proportional hazards regression models were performed to evaluate the effects of demography (gender, ethnicity), baseline features (age and BCVA) as time-independent continuous variables, and intravitreal injections (included as time-dependent covariates) on each outcome.

Time to each of the visual outcomes were visualised with Kaplan-Meier time-event plots. Patients lost to follow-up during the observation period were censored. Survival plots were stratified by covariates identified as statistically significant in the Cox models. For visualisation purposes, baseline BCVA was sub-stratified into ≥ 70, 50-69, 36-49, and ≤ 35; and baseline age sub-stratified into ≥80, 70-79, and 60-69.

Data distribution was tested by the Shapiro-Wilk test. Means of non-parametric groups were compared using Wilcoxon Signed-rank, Wilcoxon Rank-sum, and Kruskal-Wallis tests as appropriate. For more than two groups, multiple pairwise-analyses were carried out with the Wilcoxon Rank-sum test. P-value <0.05 was considered statistically significant. Mean values are expressed with ± standard deviation unless otherwise specified.

Data sharing statement

De-personalised data for this study will be openly available from the Mendeley Digital Repository: doi:10.17632/kd8774f5jd.1

Results

Cohort demography

Data were extracted for 8,467 eyes of 6,778 patients receiving a total of 122,010 anti-VEGF injections for nAMD at MEH between June 2007 and July 2018. Before 1 January 2009, 128 treatment-naïve eyes of 122 patients received intravitreal ranibizumab for nAMD. The cohort taken forward for analysis comprised 103 eyes from 103 patients, of which 56 patients (54.4%) were followed-up for the whole ten-year duration (**Figure 1**). Mean baseline BCVA was 54.6 ± 14.9 ETDRS letters, with 26 (25.2%) patients having BCVA ≥ 70 letters, and 19 (18.4%) patients having BCVA ≤ 35 letters (**Table 1**).

Visual outcomes

Time to event analyses revealed median event time for reaching BCVA ≤ 35 letters to be 37.8 (95% CI 22.2-65.1) months (**Figure 2**), and 8.3 (95% CI 4.8-20.9) months for reaching BCVA ≥ 70 letters (**Figure 3**). Cox modelling was used to interrogate gender, baseline age, baseline BCVA and foveal thickness, and number of injections as covariates for reaching BCVA ≤ 35 and ≥ 70 letters. Reaching BCVA ≤ 35 letters was negatively associated with baseline BCVA (HR 0.91; 95% CI 0.89-0.94) and positively associated with age (HR 1.08; 95% CI 1.04-1.12). Conversely, BCVA ≥ 70 letters was only positively associated with baseline BCVA (HR 1.13; 95% CI 1.10-1.17). To illustrate the association of baseline BCVA on these outcomes, we stratified our cohort into four groups: baseline BCVA ≤ 35, 36-49, 50-69, and ≥ 70 letters. The observed trend in mean BCVA change from baseline showed increases at month 6 (+1.9 ± 14.5 letters) and month 12 (+2.6 ± 16.5). All subsequent timepoints exhibited negative and

progressively decreasing mean VA-change peaking at -13.7 ± 6.5 at 120 months (**Figure 4** and **Supplementary Table 1**).

At the 10 year follow-up timepoint, mean BCVA was 42.9 ± 27.0 letters and the proportion of eyes with BCVA ≥ 70 and ≤ 35 letters were 21.4% and 41.1%, respectively (**Table 2**). However, when visual outcomes were considered at the patient-level (i.e. the better-seeing eye), 48.2% had BCVA ≥ 70 letters in at least one eye and only 5.4% of the patients had BCVA ≤ 35 letters in both eyes (**Supplementary Figure 2)**. Interestingly, each of the better-seeing eyes with BCVA ≥ 70 letters at 10 years had all received anti-VEGF injections prior to the timepoint suggesting disease-involvement.

Treatment status

Mean total number of injections per eye at 10 years was 37.0 ± 24.2. Of those who completed the follow-up, 29 (51.8%) were receiving injections at the 10 year timepoint (**Table 2**). Mean number of injections was 5.3 ± 3.1, 3.3 ± 2.8 and 3.0 ± 2.9 during years 1, 2 and 3, respectively, to decrease to 1.1 ± 2.2 during year 10 (**Supplementary Table 3**). Over the observation period, 65 patients (63.1%) required injections in both eyes. Mean time to fellow eye involvement was 30.6 ± 30.5 months. Mean total number of injections per patient, inclusive both first and second eye, was 53.6 ± 30.1 up to 10 years. All eyes started treatment with ranibizumab, and 60 (58.3%) were switched to aflibercept after an average of 65.6 ± 9.5 months following baseline (**Table 2**).

Anatomic observations and OCT features

Average CRT was 298.9 ± 92.6 μm at baseline and 237.5 ± 87.3 μm at 10 years. An initial decline of 55.8 μm in CRT was evidenced at 6 months from baseline and maintained until year 7, increasing to baseline values at year 9 (**Supplementary Table 2**).

At 10 years, 21 eyes (37.5%) had IRF only, 5 (8.9%) had SRF only, and 3 (5.4%) had both IRF and SRF, while 43 (76.8%) and 32 (57.1%) presented GA and fibrotic scar, respectively. Median event time to GA was 44.8 months (**Supplementary Figure 3)**. We further stratified patients according to foveal involving lesions, where 5 patients (8.9%) had foveal-involving GA, and 21 (37.5%) had subfoveal fibrosis. OCT images were examined to investigate morphological outcomes in eyes with poor BCVA (≤ 35 letters) at 10 years; foveal-involving fibrosis was the most common cause, accounting for 70% of this subcohort, followed by foveal GA (17%) and subfoveal IRF/SRF (13%). Cox modelling suggested that gender, baseline age, baseline BCVA and foveal thickness, and number of injections were not statistically significant covariates for development of GA (**Supplementary Figure 3**). Here we also queried baseline OCT features. Presence of IRF was positively associated with GA development (HR 2.21; 95% CI 1.02-4.79) while SRF was negatively associated with it (HR 0.52; 95% CI 0.28-0.97).

Loss to follow-up

Forty-seven patients (45.6%) were LTFU before 10 years. Mean time for LTFU was 61.0 ± 32.3 months (**Table 2**). The main cause was death, represented by 42.6% of this cohort, followed by DNA patients (34.0%). Fifty-six percent of the DNA patients received their last injection 6 months or more prior to their last visit. Thirteen percent of LTFU patients were discharged as

per clinician's opinion, with a median time to event at 49.5 months. A comparison of baseline demographics and clinical features was made between subgroups of patients who did and did not complete the 10-year follow-up; patients who completed it were younger at the time of first injection compared to LTFU patients (74.6 ± 5.7 vs 81.8 ± 5.8 years, respectively; p-value <0.001), but no difference was found between the two cohorts in terms of baseline BCVA, gender and ethnicity (**Table 1**).

Discussion

This study offers one of the longest reports on anti-VEGF treatment for nAMD and one of the first UK-based studies on patients followed-up for 10 years.[18] By analysing results for the first-affected eye and accounting second eye involvement, we offer a realistic insight of disease burden and visual prognosis. Encouragingly, among those who completed the follow-up, approximately one out of two patients was able to maintain a BCVA ≥ 70 letters in the better-seeing eye while only 5.4% of the patients were accounted as legally blind at 10 years. By illustrating visual outcomes through survival curves, we hope to provide clinicians information which could be easily conveyed to patients. As expected, poor visual outcomes could be deferred by early treatment.

TIme event analyses revealed that median time to BCVA ≤ 35 letters was approximately 3 years, which was negatively associated with baseline BCVA and positively associated with age. Patients with baseline BCVA between 36 and 49 letters were 50% likely for BCVA to fall ≤ 35 letters 1.5 years after starting treatment, while patients with baseline BCVA ≥70 letters had the same likelihood of reaching ≤ 35 letters after almost 8 years. This suggests that treating patients at an earlier stage (with higher VA and younger age) could delay poor visual outcomes. Noticeably, while patients with baseline BCVA ≤ 35 letters were not observed to achieve good BCVA (≥ 70 letters), patients with baseline BCVA ≥ 70 letters could achieve poor BCVA (≤ 35 letters). This might be a reason for maintaining a close follow-up with those with good vision instead of discharging them, supported by the evidence that treatment is frequently resumed in patients dismissed because of disease inactivity.[19]

More than half of our cohort were followed-up after 10 years (54%) and approximately half of these were still receiving treatment. This rate of attendance is greater than those reported in other RCTs and real-life studies,[9,10,20–24] with death being the main cause of LTFU. First-affected eyes received a mean 37.04 ± 24.19 injections over the whole observation period, comparably to a recent report on 10-year outcomes of a Swiss cohort.[24] Sixty-three percent of our patients required bilateral injections by a median time of approximately 2.5 years, with a total number of injections per patient, considering both the first and the second eye, corresponding to a mean of 53.6 ± 30.1 injections over 10 years. As no previous studies have investigated bilateral involvement at 10 years, comparison of long-term outcomes is limited to studies with shorter follow-up, such as the SEVEN-UP study (bilateral involvement of 51% at 7 years). Of note, it has been put forth that the participants of the SEVEN-UP study were potentially under-treated at the beginning thereby limiting the visual potential.

When considering short-term outcomes, the 2-year mean BCVA change observed amongst our cohort (-0.3 letters) was inferior to major RCTs, including PrONTO (+11.1 letters), MARINA (+7.2 letters), and ANCHOR (+11.3 letters).[16,25,26] These differences could be partially attributable to baseline differences, as patients with poor baseline BCVA are usually excluded by RCTs. Patients recruited for the ANCHOR and MARINA trials were not all treatment-naïve and received monthly injections for 2 years. In contrast, our patients received about five injections in the first year, and three injections in both the second and third year. This was lower compared to the aforementioned RCTs and to other real-life studies.[9,10,27,28] A model-based analysis on VA-guided treatment regimen showed that 8.1 injections over the first and 6 over the second year were necessary to maintain the vision gained during the loading phase, ensuring the same efficacy as pivotal trials with less injections.[29] This could partially

explain why, in our study, the letters gained in the first year were not maintained at two years; insufficient treatment of our cohort cannot be ruled out, leaving space for additional improvement.

At 10 years, the proportion of first-affected eyes with BCVA ≥ 70 and ≤ 35 letters were 21.4% and 41.1%, respectively. Considering other real-life studies, similar proportions of eyes with BCVA ≥ 70 letters were reported,[23,30] while Gillies *et al.* reported discordant outcomes between their two groups.[24] To query visual function, we considered these visual outcomes at the patient-level. At 10 years, almost half of the patients retained a single eye with BCVA ≥ 70 letters - the minimum threshold for a driver's licence in most European countries and for reading small prints. Only 5.4% of the patients had BCVA ≤ 35 letters in the better-seeing eye i.e. ≤ 35 letters in both eyes and potentially certifiable as visually impaired in the UK.[32]

Anatomical analysis in a subcohort of patients with final BCVA ≤ 35 letters suggested that poor vision was more likely due to foveal fibrosis rather than foveal GA, as the proportion of eyes with subfoveal scarring and foveal GA was 70% and 17%, respectively. Overall, at 10 years, 51.8% of our patients had evidence of exudation, while the incidence of subfoveal fibrosis was analogous to the one detected in the SEVEN-UP study (37.5% vs. 38.6%, respectively). Furthermore, we detected GA in 76.8% of our patients, with median time to GA development (approximately 4 years) being temporally concomitant with a drop of mean BCVA under its baseline values.[30,33] Interrogating predictive factors of GA development is beyond the purpose of this study, but our survival analyses did not reveal an association between the number of injections and development of GA, in agreement with the HARBOR and SEVEN-UP studies.[33,34] GA might be part of a degeneration caused by the disease itself and develop

insofar as intravitreal therapy is administered at the onset of a more flogogenous process like exudation.

This report has some limitations, including the retrospective observational study design, lack of a uniform treatment protocol, heterogeneous treatment intervals and patients' management at the discretion of different physicians. Nonetheless, such heterogeneity is implicit in real-life studies and reflects routine medical practice, and retrospective studies represent the only affordable option to investigate long-term outcomes. We should remark that we excluded patients whose fellow eye was affected by advanced AMD, as second-treated eyes maintain better vision at all time points.[36] Given these strict inclusion/exclusion criteria and data collection at each visit, this study offers a plausible real-life overview of outcomes 10 years after the commencement of nAMD treatment.

Here we present a deidentified, real-world dataset of treatment-naïve, first-affected eyes from nAMD patients treated with anti-VEGF over a 10-year observation period. Our analyses reveal insights into the long-term visual and anatomical prognosis of anti-VEGF therapy and suggest that initiating treatment at early stages of disease may improve likelihood of achieving good vision and delay deterioration towards poor vision. Moreover, these data may inform policy and planning of healthcare service delivery, as well as enable patients to gain further understanding of what they can expect from this chronic condition.

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Figure legends

Figure 1. Figure shows the number of patients who received anti-VEGF injections for neovascular age-related macular degeneration (nAMD) between June 2007 and July 2018. Before 1 January 2009, 128 treatment-naïve eyes of 122 patients received intravitreal injections for nAMD; 6 patients were treated in both eyes in the selected time period, hence only the first-affected eye was taken forward for statistical analysis; 18 patients were excluded as they presented a pre-existing contralateral disciform scar at baseline; 1 patient was excluded due to missing baseline BCVA. The evaluable sample consisted of 103 eyes from 103 patients; of these, 56 patients (54.4%) were followed-up for the whole ten-year duration.

Figure 2. Kaplan-Meier plot for time to reach visual acuity (VA) ≤ 35 letters (20/200) for all patients (top panel), as well as, sub-stratified by age groups (middle panel) and visual acuity at baseline (bottom panel) - 20 [20/400] ETDRS letters [Snellen equivalent]), 30 [20/250], 40 [20/160], 50 [20/100], 60 [20/63], 70 [20/40], 80 [20/25]). As reaching VA ≤ 35 is the event, the y-axis represents the inverse of the event (VA ≥ 36) i.e. as more patients reach VA ≤ 35 the probability of VA remaining ≥ 36 and never reaching 35 falls. Cox-modelling was carried out with gender, baseline age, baseline best-corrected VA, baseline central retinal thickness (CRT), and injection number included as covariates. Hazard ratios (HR), 95% confidence intervals (CI), and p-values are displayed for the individual covariate.

Figure 3. Kaplan-Meier plot for time to reach visual acuity (VA) ≥ 70 letters (20/40) for all patients (top panel), as well as, sub-stratified by visual acuity at baseline (bottom panel) - 20

[20/400] ETDRS letters [Snellen equivalent]), 30 [20/250], 40 [20/160], 50 [20/100], 60 [20/63], 70 [20/40], 80 [20/25]). As reaching VA ≥ 70 is the event, the y-axis represents the inverse of the event (VA ≤ 69) i.e. as more patients reach VA ≥ 70 the probability of VA remaining ≤ 69 and never reaching 70 even once falls. Cox-modelling was carried out with gender, baseline age, baseline best-corrected VA, baseline central retinal thickness (CRT), and injection number included as covariates. Hazard ratios (HR), 95% confidence intervals (CI), and p-values are displayed for the individual covariate.

Figure 4. Mean trends in visual acuity (VA) of first-affected eyes with nAMD. Mean VA (a) and mean change in VA following baseline (b) in early treatment diabetic retinopathy study (ETDRS) letters over the 120 month observation period. Baseline was considered timepoint at which the first anti-VEGF therapy was delivered. Error bars denote 95% confidence intervals of the mean.

Tables

		All	10-year follow-up	LTFU	p-values
Patients, n (%)		**103**	56 (54.36%)	47 (45.63%)	
Gender (%)	Female	**75 (72.8)**	41 (73.2)	34 (72.3)	0.087
	Male	**28 (27.2)**	15 (26.8)	13 (27.7)	
Ethnicity (%)	Asian	**5 (4.9)**	4 (7.1)	1 (2.1)	0.093
	Mixed	**2 (1.9)**	0 (0)	2 (4.2)	
	Other Ethnic Groups	**6 (5.8)**	5 (8.9)	1 (2.1)	
	Unknown	**17 (16.5)**	7 (12.5)	10 (21.3)	
	Caucasian	**73 (70.9)**	40 (71.4)	33 (70.2)	
Mean baseline age, years (SD)		**77.90 (6.75)**	74.61 (5.69)	81.83 (5.78)	<0.001
Baseline age, years (%)	80 or over	**44 (42.7)**	12 (21.4)	32 (68.1)	<0.001
	70-79	**49 (47.6)**	34 (60.7)	15 (31.9)	
	60-69	**10 (9.7)**	10 (17.9)	0 (0.0)	
Mean baseline VA, ETDRS letters (SD)		**54.6 (14.9)**	56.6 (13.2)	52.2 (16.6)	0.139
Baseline VA, ETDRS letters (%)	70 or over	**26 (25.2)**	13 (23.2)	13 (27.7)	0.772
	50-69	**45 (43.7)**	29 (51.8)	16 (34.0)	
	36-49	**13 (12.6)**	8 (14.3)	5 (10.6)	
	35 or less	**19 (18.4)**	6 (10.7)	13 (27.7)	0.098

Table 1. Patient demography comparing 10-year cohort to lost-to-follow-up cohort.

		All	10-year follow-up	LTFU	p-value
Patients, n (%)		**103**	56 (54.36%)	47 (45.63%)	
Mean baseline VA, ETDRS letters (SD)		**54.6 (14.9)**	56.6 (13.2)	52.2 (16.6)	0.139
Mean VA at 10 years or last visit, ETDRS letters (SD)		**42.2 (26.3)**	42.9 (27.0)	41.4 (25.8)	0.767
Mean change in VA at 10 years or last visit, ETDRS letters (SD)		**-12.4 (25.0)**	-13.7 (24.4)	-10.7 (25.8)	0.566
Fellow eye involved? (%)	No	**38 (36.9)**	17 (30.4)	21 (44.7)	0.195
	Yes	**65 (63.1)**	39 (69.6)	26 (55.3)	
Mean time to fellow eye involvement, months (SD)		**30.55 (30.53)**	37.90 (33.32)	19.54 (22.09)	0.016
Mean injection number (SD)		**26.95 (22.86)**	37.04 (24.19)	14.94 (13.7)	<0.001
Mean injection number between both eyes (SD)		**42.7 (29.8)**	53.6 (30.1)	24.9 (19.15)	<0.05
Mean time of loss-to-follow-up, months (SD)		**61.04 (32.26)**	-	61.04 (32.26)	
Stable at 10 years or at loss-to-follow-up? (%)	No	**51 (49.5%)**	29 (51.8)	22 (46.8)	
	Yes	**52 (50.5%)**	27 (48.2)	25 (53.2)	
Switch from ranibizumab to aflibercept (%)		**60 (58.3)**	47 (83.9)	13 (27.7)	
Mean time of switch from ranibizumab to aflibercept, months (SD)		**65.58 (9.50)**	65.55 (10.29)	65.69 (6.12)	0.963
VA ≥ 70 at 10 years or last visit (%)		**20 (19.4)**	12 (21.4)	8 (17.0)	0.754

VA ≤ 35 at 10 years or last visit (%)		**41 (39.8)**	23 (41.1)	18 (38.3)	0.933
Mean CRT at baseline, μm (SD)		**298.89 (92.58)**	292.20 (93.93)	307.04 (91.27)	0.28
Mean CRT at 10 years or last visit, μm (SD)		**237.13 (74.47)**	237.46 (87.32)	236.72 (55.93)	0.96
Mean change in CRT at 10 years or last visit, μm (SD)		**-63.33 (101.82)**	-54.73 (109.91)	-74.02 (90.83)	0.229
Geographic atrophy at 10 years or last visit (%)	Total	**77 (74.8%)**	43 (76.8%)	34 (72.0)	0.77
	Foveal	**14 (13.6%)**	5 (8.9%)	9 (19.0%)	0.17
	Non-foveal	**63 (61.2%)**	38 (67.9%)	25 (53.2%)	
Fibrotic scar at 10 years or last visit (%)	Total	**57 (55.3%)**	32 (57.1%)	25 (53.2%)	0.84
	Foveal	**45 (43.7%)**	21 (37.5%)	24 (51.1%)	0.01
	Non-foveal	**12 (11.7%)**	11 (19.6%)	1 (2.1%)	
IRF only at 10 years or last visit (%)		**31 (30.9%)**	21 (37.5%)	10 (21.7%)	0.63
SRF only at 10 years or last visit (%)		**10 (9.7%)**	5 (8.9%)	5 (10.1%)	0.24
IRF and SRF at 10 years or last visit (%)		**10 (9.7%)**	3 (5.4%)	7 (15.9%)	0.31
Missing OCT (%)		**1 (0.9%)**	1 (1.8%)	0 (0.0%)	

Table 2. Comparison of 10-year cohort to lost-to-follow-up cohort.

Figures

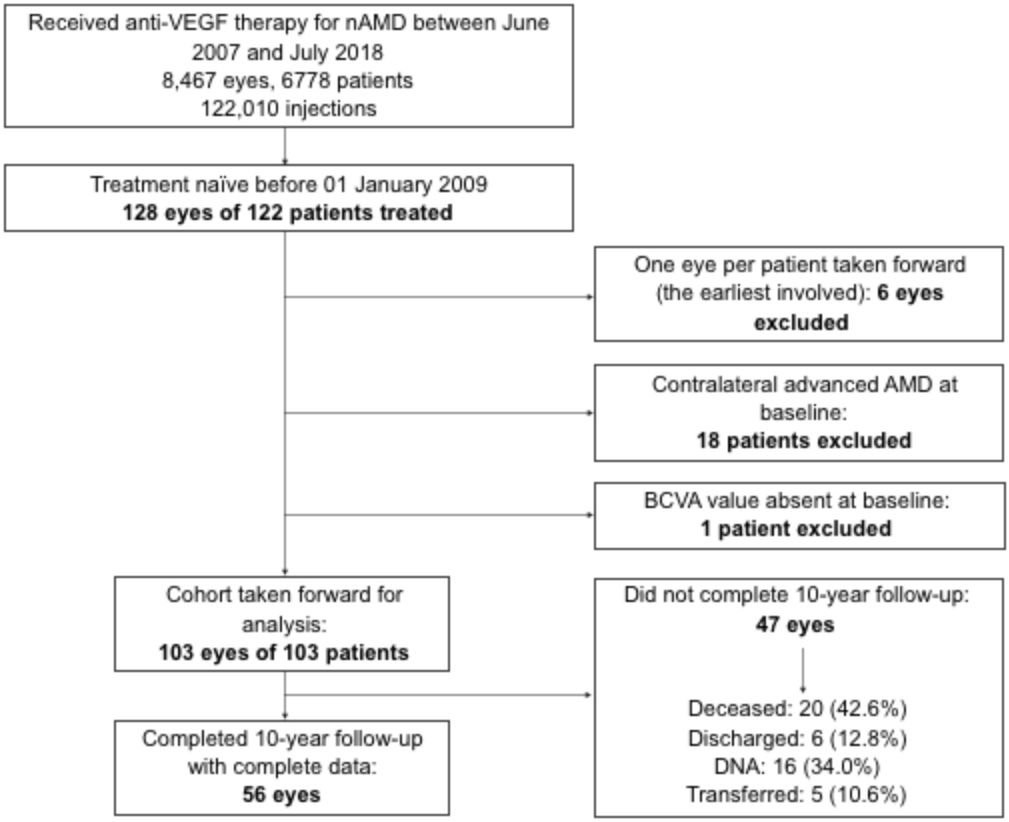
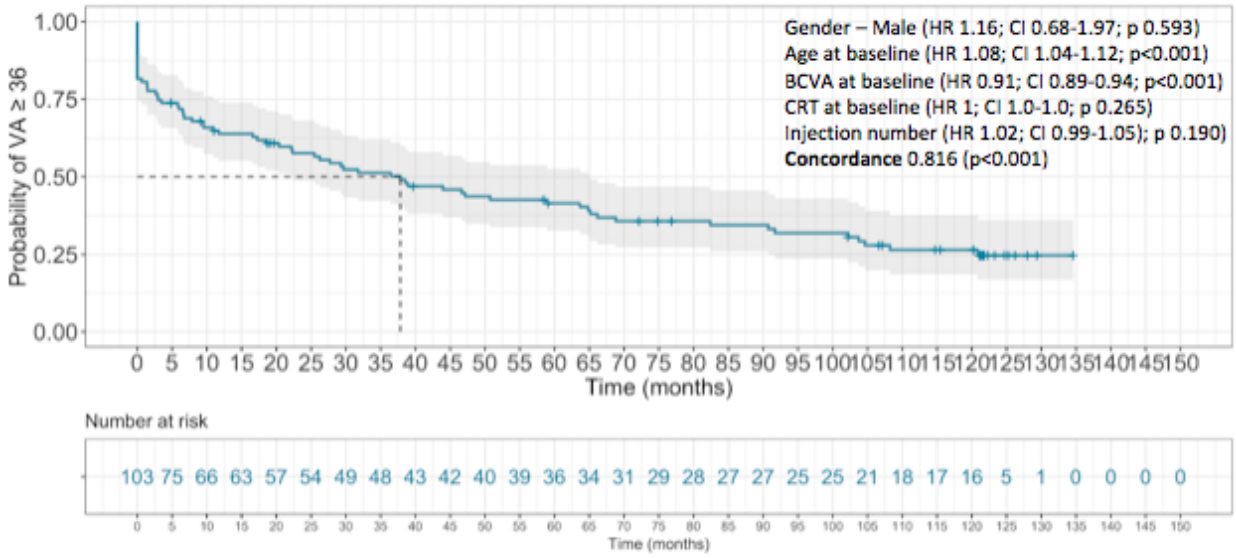
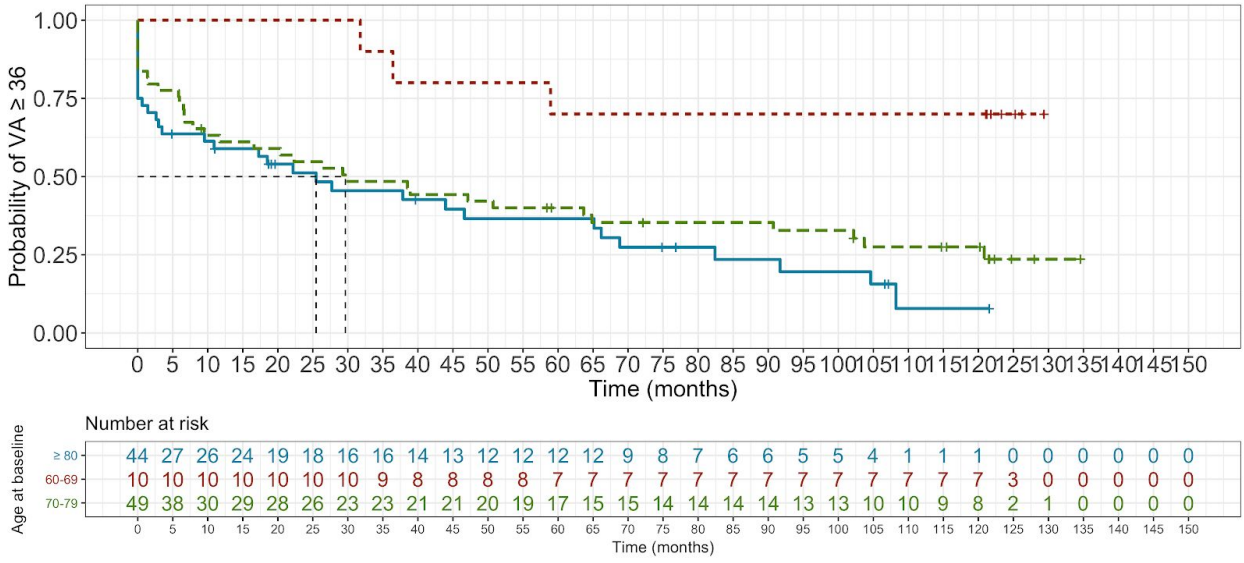


Figure 1. Patient cohort.


Gender – Male (HR 1.16; CI 0.68-1.97; p 0.593)
Age at baseline (HR 1.08; CI 1.04-1.12; p<0.001)
BCVA at baseline (HR 0.91; CI 0.89-0.94; p<0.001)
CRT at baseline (HR 1; CI 1.0-1.0; p 0.265)
Injection number (HR 1.02; CI 0.99-1.05); p 0.190)
Concordance 0.816 (p<0.001)
Probability of VA ≥ 36
Time (months)
Number at risk
103 75 66 63 57 54 49 48 43 42 40 39 36 34 31 29 28 27 27 25 25 21 18 17 16 5 1 0 0 0 0


Probability of VA ≥ 36
Time (months)
Number at risk
Age at baseline
≥ 80
60-69
70-79
44 27 26 24 19 18 16 16 14 13 12 12 12 12 9 8 7 6 6 5 5 4 1 1 1 0 0 0 0 0 0
10 10 10 10 10 10 10 9 8 8 8 8 7 7 7 7 7 7 7 7 7 7 7 7 3 0 0 0 0 0
49 38 30 29 28 26 23 23 21 21 20 19 17 15 15 14 14 14 14 13 13 10 10 9 8 2 1 0 0 0 0
Time (months)

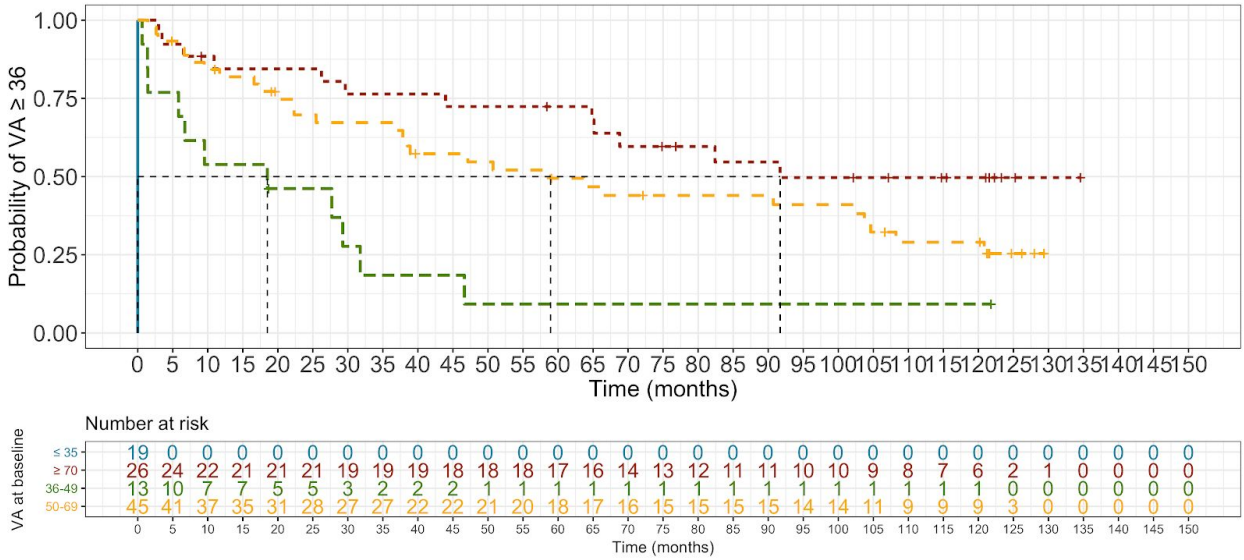
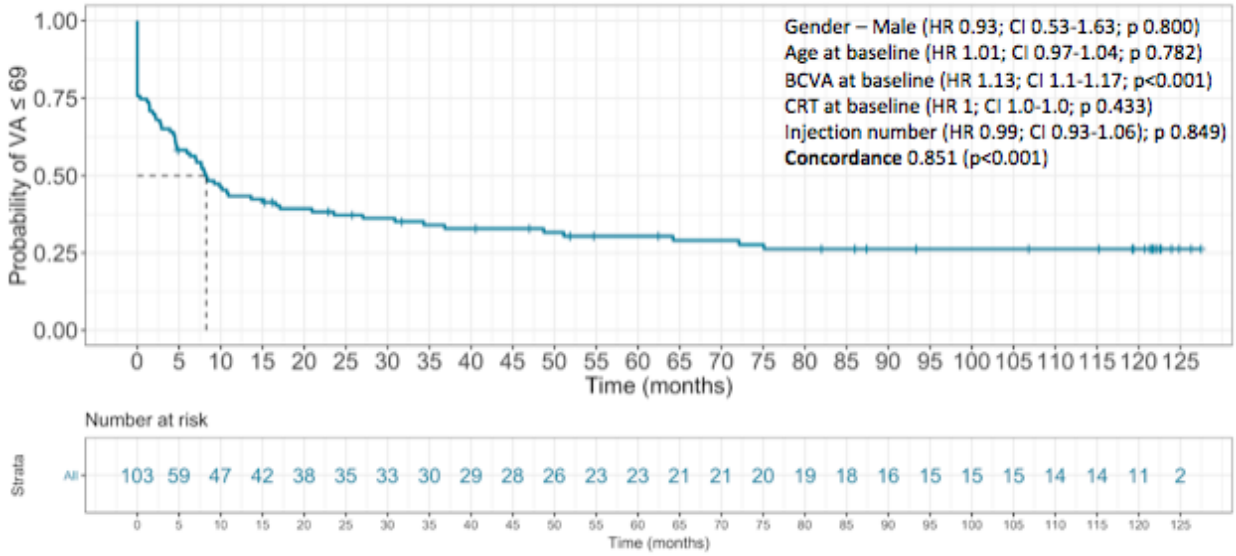


Figure 2. Time-to-event analysis with outcome being visual acuity of less than or equal to 35 ETDRS (early treatment diabetic retinopathy study) letters.



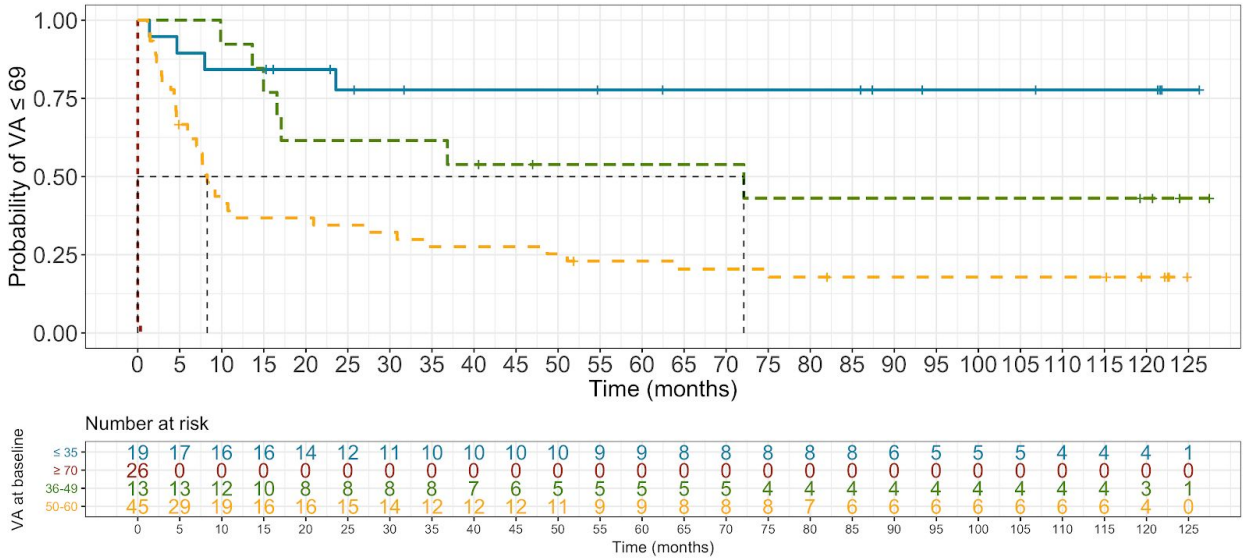


Figure 3. Time-to-event analysis with outcome being visual acuity of greater than or equal to 70 ETDRS (early treatment diabetic retinopathy study) letters.

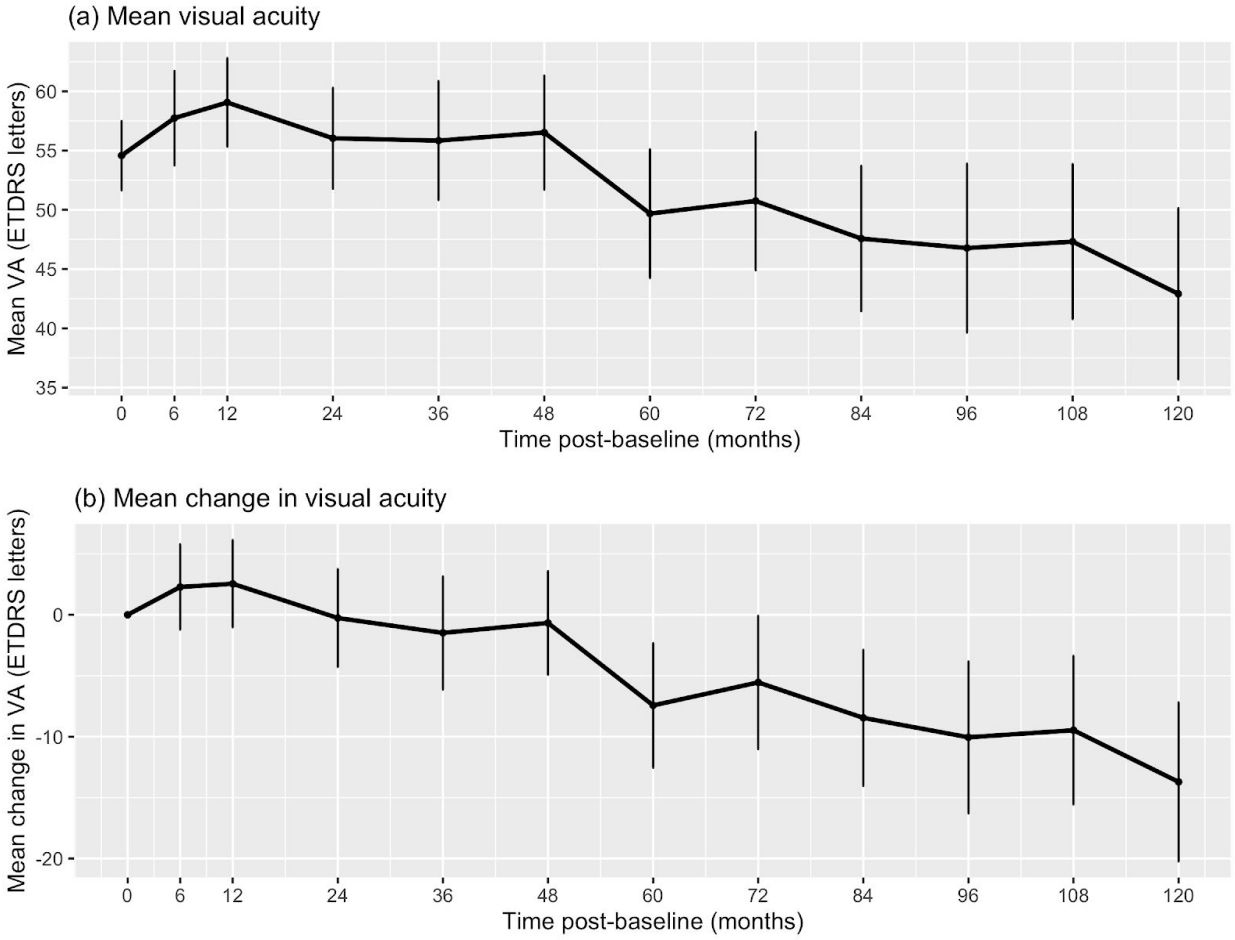


Figure 4. Mean trends in visual acuity (VA) of first-affected eyes with nAMD. Mean VA (a) and mean change in VA following baseline (b) in early treatment diabetic retinopathy study (ETDRS) letters over the 120 month observation period. Baseline was considered timepoint at which the first anti-VEGF therapy was delivered. Error bars denote 95% confidence intervals of the mean.

Timepoint in months from baseline	Mean VA (ETDRS)	95% CI	Mean change in VA (ETDRS) from baseline	95% CI
0	54.6	2.9	0	0
6	57.9	4.0	1.9	3.3

12	59.1	3.8	2.6	3.6
24	56	4.3	-0.3	4.0
36	55.8	5.0	-1.5	4.6
48	56.5	4.8	-0.7	4.3
60	49.7	5.4	-7.5	5.1
72	50.7	5.8	-5.6	5.5
84	47.6	6.1	-8.4	5.6
96	46.8	7.1	-10.1	6.2
108	47	6.6	-9.8	6.2
120	42.9	7.2	-13.7	6.5

Supplementary Table 1. Mean visual acuity (VA) and change in VA from baseline in early treatment diabetic retinopathy study (ETDRS) letters over the 10-year study period.

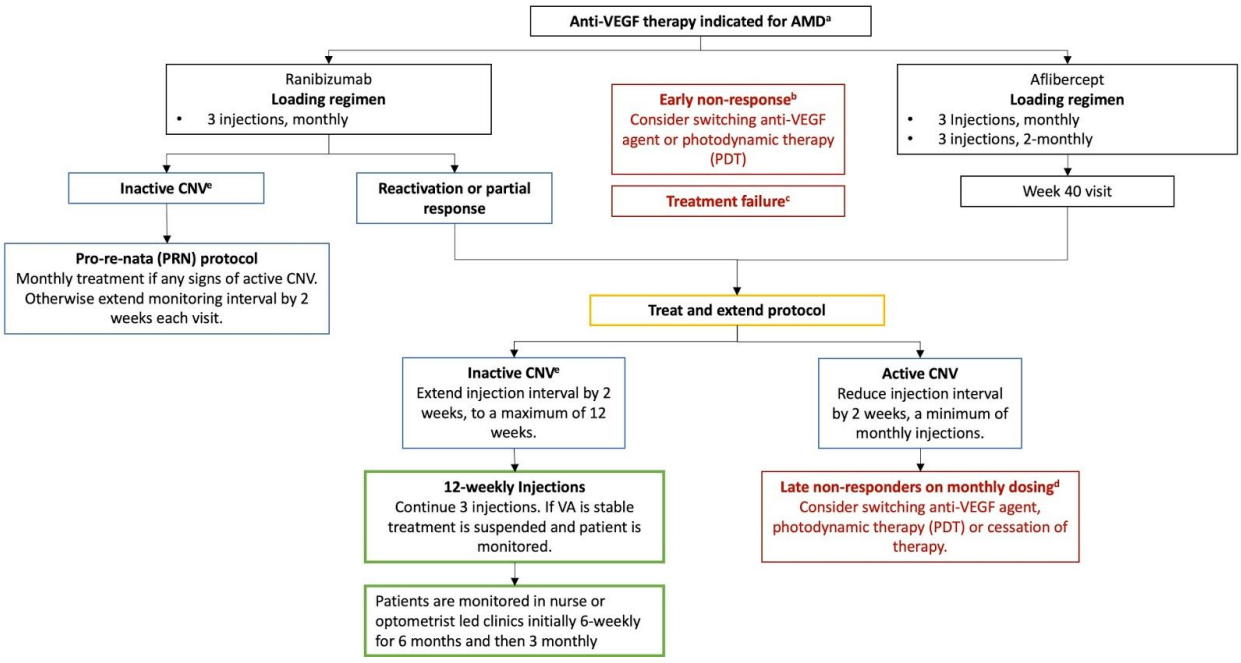
Timepoint in months from baseline	Mean CRT thickness (µm)	95% CI	Mean change in CRT thickness (µm) from baseline	95% CI
0	299	18.2	0	0
6	246	23.5	-55.8	29.5
12	262	14.9	-36.8	22.9
24	249	15.4	-57.2	23.3
36	241	18.3	-55.3	25.8
48	242	15.9	-54.3	28.4
60	245	19.8	-55.3	25.8
72	253	54.9	-49.8	59.6
84	237	22.4	-72.5	27.2
96	266	52.5	-33.4	54.9
108	299	46.3	1.59	49.7

120	237	23.4	-54.7	29.5

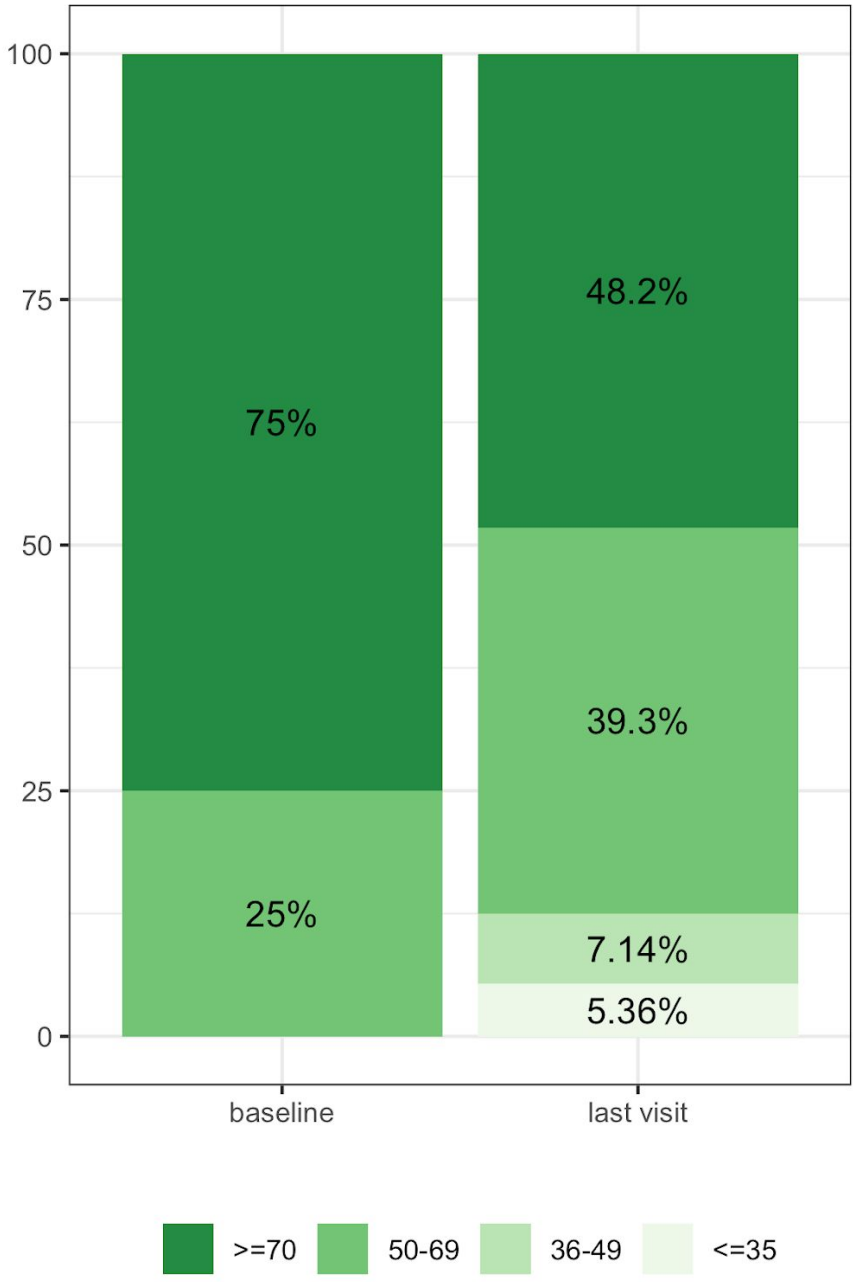
Supplementary Table 2. Mean central retinal thickness (μm) and change in central retinal thickness from baseline over the 10-year study period.

Timepoint in months from baseline	Mean injections	SD
0	0	0
12	5.33	3.09
24	3.33	2.82
36	3.01	2.90
48	2.75	3.14
60	2.86	3.22
72	2.74	2.93
84	2.42	2.92
96	1.90	2.80
108	1.67	2.88
120	1.10	2.19

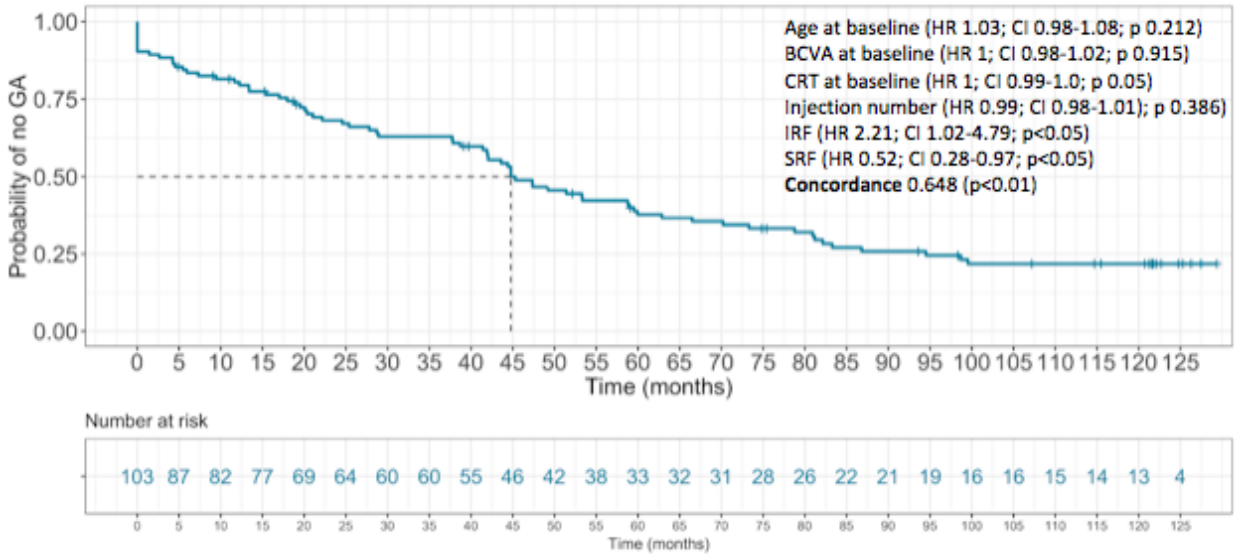
Supplementary Table 3. Mean injections per annum



Supplementary Figure 1. Overview of MEH AMD anti-VEGF treatment guidelines. (a) As per NICE guidelines, AMD patients are indicated for anti-VEGF therapy given the following: best-corrected visual acuity (VA) is between 6/12 and 6/96 Snellen (circa 73 to 25 ETDRS letters); no permanent structural damage to the central fovea; lesion size is less than or equal to 12 disc areas in greatest linear dimension; evidence of recent presumed disease progression. At MEH, some patients initiated treatment with VA < 25 ETDRS letters as funding for therapy had been sought and approved at a time when VA was > 25 letters. (b) Early non-response was defined as worsening VA and/or OCT on the 3rd injection visit. Patients were reviewed in 4 weeks for consideration of switching anti-VEGF agent or consideration of photodynamic therapy (PDT). (c) Therapy response-failure (as per NICE) refers to VA decline by 30 letters despite anti-VEGF. Here, a switch is considered if failure to one drug) or a drop to below 15 letters caused by the AMD lesion and no other cause can explain the visual loss. Treatment is otherwise withheld permanently. (d) Patients who failed to respond to aflibercept after 12 months despite reducing dosing interval may consider switching to ranibizumab. (e) Disease and CNV inactivity is defined as absence of the following features when compared with the previous visit: new or enlargement of fluid on OCT; new or persistent haemorrhage or exudates; decreased VA attributable to CNV; fluorescein leakage or increase in lesion size on FFA. With aflibercept, the monthly injections for initial 3 months are followed by 3 injections at 2-monthly intervals. At the 7th visit, if OCT imaging demonstrates wet features and/or VA decreases with residual fluid present the treatment interval is reduced down to 6 weekly and then 4 weekly until desired response is achieved. Once dry and/or stable, injection visits increase by 2-week increments (6-weekly, and then 8- weekly, etc). However, if at the 7th visit the OCT is dry and VA stable, intervals can increase to 10-weekly and then 12 weekly injections. As with ranibizumab, if a patient undergoes 12-weekly injections for 3 consecutive visits alongside features of disease stability, they are monitored at 6-weekly intervals for 6 months without injections and then at 3-monthly intervals.



Supplementary Figure 2. Outcomes of the better-seeing eye at baseline and at 10 years, stratified by visual acuity.



Supplementary Figure 3. Time to GA.