IMPORTANCE Although multiple imputation models for missing data and the use of mixed-effects models generally provide better outcome estimates than using only observed data or last observation carried forward in clinical trials, such approaches usually cannot be applied to visual outcomes from retrospective analyses of clinical practice settings, also called real-world outcomes.

OBJECTIVE To explore the potential usefulness of survival analysis techniques for retrospective clinical practice visual outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study covered a 12-year observation period at a tertiary eye center. Of 10,744 eyes with neovascular age-related macular degeneration receiving anti–vascular endothelial growth factor (VEGF) therapy between October 28, 2008, and February 1, 2020, 7,802 eyes met study criteria (treatment-naive, first-treated eyes starting anti-VEGF therapy). Eyes were excluded from the analysis if they received photodynamic therapy or macular laser, any previous anti-VEGF therapy, treatment with anti-VEGF agents other than ranibizumab or aflibercept, or had an unknown date or visual acuity (VA) value at first injection.

MAIN OUTCOMES AND MEASURES Kaplan-Meier estimates and Cox proportional hazards modeling were used to consider VA reaching an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 70 (Snellen equivalent, 20/40) or better, duration of VA sustained at or better than 70 (20/40), and VA declining to 35 (20/200) or worse.

RESULTS A total of 7,802 patients (mean [SD] age, 78.7 [8.8] years; 4,776 women [61.2%]; and 4,785 White [61.3%]) were included in the study. The median time to attaining a VA letter score greater than or equal to 70 (20/40) was 2.0 years (95% CI, 1.87-2.32) after the first anti-VEGF injection. Predictive features were baseline VA (hazard ratio [HR], 1.43 per 5 ETDRS letter score or 1 line; 95% CI, 1.40-1.46), baseline age (HR, 0.88 per 5 years; 95% CI, 0.86-0.90), and injection number (HR, 1.12; 95% CI, 1.10-1.15). Of the 4,439 of 7,802 patients (57%) attaining this outcome, median time sustained at an ETDRS letter score of 70 (20/40) or better was 1.1 years (95% CI, 1.1-1.2).

CONCLUSIONS AND RELEVANCE In this cohort study, patients with neovascular age-related macular degeneration beginning anti-VEGF therapy were more likely to experience positive visual outcomes within the first 2.0 years after treatment, typically maintaining this outcome for 1.1 years but then deteriorating to poor vision within 8.7 years. These findings demonstrate the potential usefulness of the proposed analyses. This data set, combined with the statistical approach for retrospective analyses, may provide long-term prognostic information for patients newly diagnosed with this condition.

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Neovascular ARMD is characterized by the development of aberrant blood vessels (macular neovascularization) that are prone to leakage and hemorrhage, ultimately leading to fibrosis and rapid central vision loss. The development of vascular endothelial growth factor (VEGF) inhibitors to reduce macular neovascularization activity has revolutionized the treatment of neovascular ARMD. Yet, long-term, clinically significant outcomes remain uncertain.

Randomized clinical trials (RCTs) evaluating anti-VEGF therapy in neovascular ARMD primarily report visual outcomes by averaging and dichotomizing vision at predefined time points (eg, mean visual acuity [VA] and percentage of patients attaining a visual threshold at 1 year). Clinical trials typically have limited missing data rates. In a review of RCTs published between July and December 2013, the median proportion of participants with a missing outcome was 9%. Missing observations in RCTs are assumed to occur randomly, and the appropriate statistical methods to analyze outcomes are chosen; that is, it is generally accepted that multiple imputation models for missing data and the use of mixed-effects models provide better outcome estimates than using only observed data or last observation carried forward in clinical trials. Such approaches typically cannot be used in retrospective studies of clinical practice data, or so-called real-world studies, which also usually have a high rate of missing data (17%-34% at 1 year); the circumstances of nonobservation are rarely described, and the underlying reasons cannot be assumed to be random. Hence, generalizing available data to the target population without addressing missingness is prone to survival bias. There is no consensus when considering missing observations in real-world clinical data. Hence, it is not feasible to apply the superior statistical approaches used in RCTs for missing data to clinical practice data.

Time-to-event analyses, such as Kaplan-Meier survival and Cox proportional hazards regression tests, address some limitations of clinical practice data by making use of all available data through the extrapolation of outcome probabilities. Kaplan-Meier survival and Cox proportional hazards regression tests are not biased in the same way as group means, which are not designed to handle missing data. Thus far, time-to-event analyses have been used minimally in ophthalmology and only to evaluate fellow eye involvement, retreatment, dropout rate, and visual stability. This study used time-to-event methodologies to analyze visual outcomes with clinical relevance rather than using mean VA at arbitrary time points. The Moorfields Eye Hospital (MEH) data set holds a large, single-center cohort (10 000 eyes over 12 years) of patients with neovascular ARMD receiving anti-VEGF therapy on a standardized treatment schedule according to national guidelines. Moreover, our data set and analyses were deidentified and made open source to enable independent replication of our results and follow-up analyses.

Methods

Study Design and Setting
This retrospective cohort study included patients with neovascular ARMD undergoing intravitreal anti-VEGF therapy at MEH National Health Service Foundation Trust, a tertiary center in London, UK. This study was conducted in compliance with the Declaration of Helsinki and with approval from the Institutional Review Board of the hospital (research reference: ROAD17/031, clinical audit reference: CA17/MR/28) and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The requirement for informed consent was waived by the ethics committee, as this is the standard when using retrospective, deidentified data for research within the UK National Health Service.

Cohort

The cohort comprised treatment-naive patients with neovascular ARMD who started anti-VEGF therapy between October 28, 2008, and February 1, 2020. First-affected eyes were considered; if both eyes initiated treatment simultaneously, 1 was selected at random using the sample function of base R software, version 3.6.2 (R Foundation for Statistical Computing). Patients were excluded if they (1) received photodynamic therapy or focal or grid macular laser, (2) received any anti-VEGF therapy before arriving at MEH, (3) received treatment with anti-VEGF agents other than ranibizumab or aflibercept (ie, pegaptanib and bevacizumab), or (4) had an unknown treatment date or VA value at first injection.

Anti-VEGF Treatment

All patients were treated according to MEH guidelines with ranibizumab (Lucentis; Novartis) or aflibercept (EYLEA; Bayer) during the observation period, 1923 patients (195 [10.1%] receiving aflibercept and 1728 [89.9%] receiving ranibizumab) were switched from their initial anti-VEGF agent because of a suboptimal response. Post-switch data were censored to isolate drug effects. The induction (or loading) phase comprised 3 injections at 1-month intervals. The induction phase was appropriately completed if done within 90 days.

Aflibercept was first introduced at MEH in October 2013, which means that all patients were initiated on ranibizumab between 2008 and 2013. The aflibercept (3951 of patients 7802 [50.6%]) and ranibizumab (3851 of 7802 [49.4%]) subcohorts were compared in terms of...
Survival Analyses During 12 Years of Anti-VEGF Therapy for Neovascular ARMD

Original Investigation Research

Results

Cohort Demographics and Clinical Features
Between October 28, 2008, and February 1, 2020, 10,744 eyes of 8,670 patients with neovascular ARMD received anti-VEGF therapy. A total 7802 eyes from 7802 patients (mean [SD] age, 78.7 [8.8] years; 4776 were women [61.2%]; and 4785 were White [61.3%]) met inclusion criteria and were monitored for 1.3.1056 (RStudio PBC) from February 16, 2020, to September 1, 2020. As per formulations of Andersen and Gill, Cox proportional hazards models were used to relate visual outcomes to both time-independent (age at baseline, VA at baseline, sex, race/ethnicity, anti-VEGF drug, induction status, mean loading injection interval, and treatment initiation before or after introduction of aflibercept) and time-dependent (anti-VEGF injections given) clinical covariates.

Survival curves were plotted using the classical Kaplan-Meier estimator based on tabulation of the number at risk and number of events at each unique event time. For stratified curves, averages for subpopulations were fitted for each of these models to plot the cumulative hazard function with each grouping variable. Two-sided P values were reported, and P < .05 was considered significant. Mean (SD) values were reported unless otherwise specified. All clinical data were recorded within an electronic medical record application (OpenEyes Foundation) as previously described.

Statistical Analysis
All data analyses were carried out with RStudio, version 1.3.1056 (RStudio PBC) from February 16, 2020, to September 1, 2020. As per formulations of Andersen and Gill, Cox proportional hazards models were used to relate visual outcomes to both time-independent (age at baseline, VA at baseline, sex, race/ethnicity, anti-VEGF drug, induction status, mean loading injection interval, and treatment initiation before or after introduction of aflibercept) and time-dependent (anti-VEGF injections given) clinical covariates.

Survival curves were plotted using the classical Kaplan-Meier estimator based on tabulation of the number at risk and number of events at each unique event time. For stratified curves, averages for subpopulations were fitted for each of these models to plot the cumulative hazard function with each grouping variable. Two-sided P values were reported, and P < .05 was considered significant. Mean (SD) values were reported unless otherwise specified. All clinical data were recorded within an electronic medical record application (OpenEyes Foundation) as previously described.

Study Outcomes
The primary outcome was time from starting anti-VEGF therapy to VA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score reaching 70 (Snellen equivalent, 20/40) among those not already above 70 at baseline (5978 of 7802 patients [76.6%]). Secondary outcomes were time to VA ETDRS letter score declining to 35 (20/200) among those with a score greater than 35 (20/200) at baseline (6453 of 7802 [82.7%]) and time with VA sustained at or above 70 (20/40), ie, time between letter score reaching 70 (20/40) and then declining below 70 (20/40). Hazards were modeled with Kaplan-Meier and covariate effects with Cox models, with potential confounding variables included as independent covariates.

Probability of Attaining a Positive Visual Outcome
Attaining an ETDRS letter score of at least 70 (20/40 or better) is often used to signify positive visual outcome. Kaplan-Meier modeling demonstrates the median time for patients to reach a letter score of 70 (20/40) (or time by which 50% of the patients reach this score) is 2.0 (95% CI, 1.8-2.3) years after starting anti-VEGF therapy; 42% of patients reach this score by 1.0 (95% CI, 0.97-1.02) years (Figure 1A). Cox proportional hazards models were used to identify covariates predictive of patients attaining VA of at least 70 (20/40 or better) (Table 2).

Baseline VA (hazard ratio [HR], 1.43 per 5 letter score; 95% CI, 1.40-1.46; P < .001) (Figure 1B) and number of intravitreal injections (HR, 1.12 per injection; 95% CI, 1.10-1.15; P < .001) were associated with attaining a letter score of at least 70 (20/40 or better) (Table 2). That is, the incremental likelihood of reaching a letter score of 70 (20/40) increased by 43% with each additional 5 ETDRS letter score (1 line) at treatment initiation. Older patients (HR, 0.88 per 5 years; 95% CI, 0.86-0.90; P < .001) (Figure 1C) and those with incomplete induction phase (HR, 0.87; 95% CI, 0.77-0.98; P = .02) were less likely to reach this target. Moreover, the probability of patients attaining a VA of at least 70 (20/40 or better) did not differ between those receiving ranibizumab and aflibercept (HR, 0.92; 95% CI, 0.77-1.11; P = .39) (Figure 1D).
Figure 1. Kaplan-Meier Curve Showing Probability of Visual Acuity (VA) Reaching or Surpassing ETDRS Letter Score of 70

A  Entire cohort

B  Baseline VA

C  Baseline age

D  Anti-VEGF agent

Kaplan-Meier estimates of achieving good vision (defined as VA ETDRS letter score ≥70 [Snellen equivalent 20/40]) was assessed for the A, cohort stratified by B, baseline VA; C, baseline age; and D, anti–vascular endothelial growth factor (anti-VEGF) agent. Median outcome time and the 95% CI is displayed for each subcohort. Here, only those whose ETDRS letter score was not already ≥70 (20/40) at baseline were considered (5978 of 7802 eyes [76.6%]). Tick marks indicate censored data with remaining numbers at risk shown in the legend below. Nonparametric log-rank test comparing survival for each of the subcohort variables was carried out: baseline VA, P < .001; baseline age, P < .001; and anti-VEGF agent, P = .07. Cumulative event number is presented in eFigure 4A in the Supplement. AFB indicates aflibercept; RBZ, ranibizumab.
**Table 2. Cox Proportional Hazards Regression Models for Visual Outcomes**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>VA reaching ETDRS letter score ≥70 (20/40)</th>
<th>Falling to sustain VA ≥70 (20/40)</th>
<th>VA deteriorating ≤35 (20/400)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Sex</td>
<td>Men</td>
<td>0.99 (0.91-1.07)</td>
<td>.75</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>White</td>
<td>0.82 (0.64-1.05)</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>Chinese</td>
<td>0.97 (0.55-1.73)</td>
<td>.93</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>1.21 (0.58-2.51)</td>
<td>.61</td>
</tr>
<tr>
<td></td>
<td>Southeast Asian</td>
<td>0.72 (0.55-0.94)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>0.77 (0.60-0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>0.88 (0.86-0.90)</td>
<td>&lt;.001</td>
<td>1.12 (1.10-1.15)</td>
</tr>
<tr>
<td>VA at baseline</td>
<td>1.43 (1.40-1.46)</td>
<td>&lt;.001</td>
<td>0.89 (0.88-0.91)</td>
</tr>
<tr>
<td>Drug</td>
<td>Ranibizumab</td>
<td>0.92 (0.77-1.11)</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>Treatment start date before 2013</td>
<td>1.24 (1.03-1.50)</td>
<td>.20</td>
</tr>
<tr>
<td></td>
<td>Anti-VEGF injections</td>
<td>1.12 (1.10-1.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Induction phase not completed</td>
<td>0.87 (0.77-0.98)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Loading injection interval</td>
<td>1.00 (0.99-1.00)</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td>Concordance</td>
<td>0.763</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** ETDRS, Early Treatment Diabetic Retinopathy Study; HR, hazard ratio; NA, not applicable; VA, visual acuity; VEGF, vascular endothelial growth factor.

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**Evaluating Duration of Sustained Positive Visual Outcome**

The majority of the cohort attained the primary visual outcome (ETDRS letter score of at least 70 [20/40]) within the observation period (4439 of 7802 patients [56.9%]). Because the duration for which patients with neovascular ARMD receiving anti-VEGF therapy can expect to sustain this positive outcome has yet to be reported, we modeled the duration between attaining the positive outcome to declining below the same threshold (i.e., letter score ≤70). Here, Kaplan-Meier modeling suggests a 50% probability of deteriorating below 70 (20/40) at a median 1.1 (95% CI, 1.1-1.2) years after reaching the primary outcome and 75% by 3.0 years (Figure 2A).

We found that baseline age (HR, 1.12 per 5 years; 95% CI, 1.10-1.15; P < .001), baseline VA (HR, 0.89 per 5 ETDRS letter score; 95% CI, 0.88-0.91; P < .001), and number of intravitreal injections (HR, 1.04; 95% CI, 1.02-1.05; P < .001) were associated with VA letter score deterioration below 70 (20/40) (Table 2). As such, greater baseline age decreased the likelihood of attaining a positive VA outcome (HR, 0.88 per 5 years; 95% CI, 0.86-0.90; P < .001) and increased the likelihood of a negative VA outcome (HR, 1.12 per 5 years; 95% CI, 1.10-1.15; P < .001) (Table 2). Indeed, the median time to VA ETDRS letter score deterioration below 70 (20/40) increased from 0.92 (95% CI, 0.87-1.02) years to 1.66 (95% CI, 1.16-2.76) years as the baseline age range decreased from age 80 years or older to 50 to 59 years, respectively (Figure 3C). A similar trend was observed with baseline VA; a positive association was observed for both reaching (HR, 1.43 per 5 ETDRS letter score; 95% CI, 1.40-1.46; P < .001) and retaining a letter score of at least 70 (20/40) (Table 2). The latter can be inferred as baseline VA was inversely associated with letter scores of 69 or less (20/40 or worse) with an HR of 0.89 per 5 letter score or 1 line (95% CI, 0.88-0.91; P < .001) (Figure 3B). Injection number was a time-dependent covariate associated with both the positive outcome (VA letter score ≥70 [20/40]; HR, 1.12; 95% CI, 1.10-1.15; P < .001) and the negative outcome (VA ≤69 [20/40] after reaching 70 [20/40]; HR, 1.14; 95% CI, 1.02-1.05; P < .001) (Table 2).

**Predicting Poor Vision**

Poor vision is an important visual outcome and commonly signified by an ETDRS letter score of 35 (20/200) or less in macular disease research.34 Of the 6453 of 7802 patients (82.7%) who started therapy above this threshold, the median time to a letter score of 35 (20/200) or less was 8.7 years (95% CI, 6.6-10.8) (Figure 3A). The analyses found the following to be predictive covariates (Table 2): baseline age (HR, 1.14 per 5 years; 95% CI, 1.11-1.18; P < .001) (Figure 3C), baseline VA (HR, 0.71 per 5 letter score [1 line]; 95% CI, 0.69-0.72; P < .001) (Figure 3B), injection number (HR, 1.01; 95% CI, 1.00-1.02; P = .17), failing to complete induction phase (HR, 1.19; 95% CI, 1.03-1.38; P = .02), and anti-VEGF drug (HR, 1.44; 95% CI, 1.13-1.84; P = .003) (Figure 3D). Indeed, the time at which 50% of patients were likely to decline to a letter score of 35 (20/200) or less occurred substantially sooner in those with a lower baseline VA (2.3 years with baseline letter score between 49 and 36 [20/100-20/200]) compared with those who had a greater baseline VA, such as 69 to 50 (7.5 years [20/40-20/100]) or ≥70 (20/40). Only 20% reached a VA ETDRS letter score of 35 or less by 5.5 years (Figure 3B). Initiating injections at older ages was also associated with a marked risk toward poor visual outcome. The median survival time for the subcohort with baseline age of 80 years or older (6.0 years; 95% CI, 5.35-7.84) was...
Figure 2. Kaplan-Meier Estimates of Failure to Sustain Visual Acuity (VA) Equal to or Greater Than Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score of 70

A. Entire cohort

B. Baseline VA

C. Baseline age

D. Anti-VEGF agent

Following initiation of anti–vascular endothelial growth factor (anti-VEGF) therapy, 5978 of 7802 (76.6%) eyes reached VA ETDRS letter score equal to or greater than 70 (Snellen equivalent 20/40). Herein, the A, overall probability of VA deteriorating below this threshold is shown. Moreover, event estimates are also shown for substratifications by B, baseline VA; C, baseline age; and D, anti-VEGF agent. Median outcome time and the 95% CI is displayed for each subgroup. Tick marks indicate censored data with remaining numbers at risk shown in the legend below. Nonparametric log-rank test comparing survival for each subcohort variables was carried out: baseline VA, \( P < .001 \); baseline age, \( P < .001 \); and anti-VEGF agent, \( P < .004 \). Cumulative event number is presented in eFigure 4B in the Supplement. AFB indicates aflibercept; RBZ, ranibizumab.
Kaplan-Meier estimates of reaching poor vision (defined as VA ETDRS letter score ≤35 [Snellen equivalent 20/200]) was assessed for the A, cohort stratified by B, baseline VA; C, baseline age; and D, anti–vascular endothelial growth factor (anti-VEGF) agent. Median outcome time and the 95% CI is displayed for each subcohort. Tick marks indicate censored data with remaining numbers at risk shown in the legend below. Nonparametric log-rank test comparing survival for each of the subcohort variables was carried out: baseline VA, \( P = .05 \); baseline age, \( P < .001 \); and anti-VEGF agent, \( P = .2 \). Cumulative event number is presented in eFigure 4C in the Supplement. AFB indicates aflibercept; RBZ, ranibizumab.
much shorter than for those aged 70 to 79 years (8.0 years; 95% CI, 6.56-9.36) (Figure 3C). Our analyses suggest that patients who did not appropriately complete the induction phase (HR, 1.19; 95% CI, 1.03-1.38; \( P = .02 \)) and who received ranibizumab (HR, 1.44; 95% CI, 1.13-1.84; \( P = .003 \)) were more likely to reach a letter score of 35 (20/200) or less (Table 2).

### Discussion

**Visual Outcomes in Anti-VEGF Therapy**

The ETDRS letter score threshold of 70 (20/40) has been viewed as an indicator of patient independence and thus is commonly used to signify positive visual outcomes.\(^{25}\) A VA of 70 (20/40) is (1) the International Council of Ophthalmology’s threshold for good independent vision\(^{22,23}\); (2) the legal threshold for driving in the UK\(^{24}\); and (3) the minimum VA required to read small print.\(^{25}\) Therefore, this threshold is recommended as a key visual outcome by numerous consortia.\(^{35}\) Our analyses suggest that approximately 57% of first eyes treated with anti-VEGF therapy for neovascular ARMD attained a VA of at least 70 (better than 20/40). This finding is consistent with single time point analyses reported in prospective trials with comparable cohorts, in which 31% to 68% of patients (42%-58% in retrospective reports) had a letter score of at least 70 (20/40) 2 years after treatment initiation.\(^{26,36,37}\) This result means that an eye is most likely to experience a positive visual outcome within the first 2 years after treatment initiation.

The proportion of eyes with VA of at least 70 (20/40) is commonly reported in RCTs and retrospective studies, yet the duration for which patients can expect to sustain this level of visual function remains unclear. With up to 12 years of follow-up and time-to-event analyses, the current study is, to our knowledge, uniquely positioned to examine this question. If a patient has VA greater than or equal to 70 (20/40) during anti-VEGF therapy, our analyses suggest there is a 50% chance of sustaining this function beyond 1.1 years and a 25% likelihood beyond 3.0 years (Figure 3). Such metrics have implications for expectation management, as well as anticipation and surveillance of vision deterioration.

### Initiating Treatment at Earlier Disease Stages

Our models consider established prognostic factors of good visual outcome, namely, baseline VA and age. Consistent with previous evidence,\(^{26}\) our analyses suggest that initiating anti-VEGF early (ie, younger patients with better VA) increased the likelihood of positive visual outcomes and was protective against vision deterioration.\(^{26}\) Notably, baseline ETDRS letter score exerted a greater hazard outcome in terms of reaching VA greater than or equal to 70 (20/40) and less than or equal to 35 (20/200) than baseline age (Table 2). This outcome may occur because higher baseline VA can reflect overall milder disease. As such, our analyses suggest that early detection of neovascular ARMD and early inception of anti-VEGF therapy were key factors in optimizing the likelihood of positive outcomes.

### Considering Injection Numbers as a Time-Dependent Covariate

Previous studies have highlighted the importance of reporting outcomes from clinical practice because injection dosing patterns differ markedly between trials and routine clinical practice.\(^{26,38,39}\) Injections were integrated into our models as a cumulative, time-dependent variable to account for observed variations in injection numbers, interinjection intervals, and follow-up periods. Our results suggest that completing the induction phase appropriately (the first 3 injections within 90 days) increased the likelihood of VA reaching a score of greater than or equal to 70 (20/40).

Interestingly, injection number increased the probability of both achieving positive (VA=70 [20/40 or better]) and negative (VA=69 [20/40 or worse]) outcomes after reaching 70 (20/40) (Table 2). This result can be reconciled by considering that injection schedules for patients with neovascular ARMD treated at MEH follow a decision tree that includes treatment response rather than administration solely by rote, fixed schedules, or randomness (eFigure 1 in the Supplement). Patients receiving more injections may therefore also reflect more aggressive disease. By querying negative outcomes that occur years after initiating treatment, differences in injection number are more apparent, and those with greater injection numbers likely reflect more advanced or aggressive disease. Accordingly, one would expect those with more injections to have a greater likelihood of experiencing negative visual events. Conversely, patients who achieve a VA score greater than or equal to 70 earlier in their treatment course will most likely receive a similar number of injections, thereby enabling the model to reflect the efficacy of anti-VEGF therapy.

### Comparison of Treatment Drugs

Our results suggest that ranibizumab was more likely to result in a VA score of less than or equal to 35 (20/200 or worse) (Table 2) compared with aflibercept. However, ranibizumab was initially used on a pro re nata regimen until a treat-and-extend protocol was introduced in 2013 alongside aflibercept. The association with a VA score of less than or equal to 35 (20/200 or worse) may therefore, in part, have arisen from the pre-2013 treatment schedule or yet-to-be-efficient, scaled-up treatment-delivery service. Differences were also apparent in baseline and treatment parameters between our aflibercept and ranibizumab subcohorts (eTable in the Supplement). Although each potential confounder was considered as an independent covariate, it still may not be possible to disentangle differences between the 2 drugs and adjust analyses fully. Certainly, a cause-and-effect relationship cannot be established from such observational data.\(^{40}\)

### Strengths and Limitations

A key assumption implicit to time-event analyses is that censored patients have the same chance of experiencing an event as those still under observation. The nature of missing data means that this assumption, as well as the underlying reason for missing data, can never be tested—no analytical technique of missing data can adequately substitute for a complete data set. Survival analyses make use of all available data.
Survival Analyses During 12 Years of Anti-VEGF Therapy for Neovascular ARMD

Conclusions

In this cohort study, patients with neovascular ARMD beginning anti-VEGF therapy were more likely to experience positive visual outcomes within the first 2.0 years after treatment; these outcomes were typically maintained for 1.1 years, with deterioration to poor vision within 8.7 years. These findings suggest that analysis of clinical practice (real-world) data may offer a broader representation of the patient experience than RCTs. However, the known superior analytical approaches in RCTs are not applicable to real-world data. Namely, analyses of real-world data cannot incorporate multiple imputation models for missing data and use of mixed-effects models to provide better outcome estimates. Such analyses can only be performed by using observed data or last observation carried forward in clinical trials. For retrospective analyses of clinical practice data, survival analysis can account for variable and biased follow-up duration and can be used to evaluate clinically meaningful categorical variables. In the present study, multi-variable modeling revealed potentially important factors associated with visual trajectories. Our findings underscore the importance of early diagnosis of neovascular ARM and the initiation of anti-VEGF therapy to improve visual outcomes.

ARTICLE INFORMATION

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Additional Information: A deidentified version of the data set and our analyses in step-by-step, open-source R code was released via the Dryad Digital Repository (https://doi.org/10.5061/dryad.nvx0k6dqs).

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