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Characterization of Poor Visual Outcomes of Neovascular Age-related Macular Degeneration Treated with Anti–Vascular Endothelial Growth Factor Agents

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Purpose: To investigate the incidence, characteristics, and baseline predictors of poor visual outcomes in eyes with neovascular age-related macular degeneration (nAMD) receiving intravitreal anti–vascular endothelial growth factor (anti-VEGF) agents in daily clinical practice.

Design: Observational study.

Participants: Treatment-naive eyes starting anti-VEGF therapy for nAMD between 2007 and 2012 tracked in the Fight Retinal Blindness! registry. Eyes had sustained ≥15 letters of loss from baseline without recovery of visual acuity (VA) at final end point. A subgroup analysis included eyes that sustained ≥30 letters of loss. Controls had not sustained ≥15 letters of loss.

Methods: Kaplan–Meier curves estimated time to first development of loss of ≥15 letters. Cox proportional hazards models evaluated predictors of loss of ≥15 letters.

Main Outcome Measures: The proportion of eyes with sustained VA loss within 5 years, the time to development of sustained VA loss, and baseline predictors of sustained VA loss.

Results: There were 1760 eyes in total and 856 eyes that completed 5 years follow-up. The proportion of eyes with sustained VA loss of ≥15 letters at 5 years was 22.9% (95% confidence interval [CI], 20.7%–25.1%) and VA loss of ≥30 letters was 10.8% (95% CI, 9.1%–12.5%). Factors independently associated with higher incidence of sustained ≥15-letter loss included age >80 years (odds ratio [OR], 1.33 for patients >80 years vs. ≤80 years; 95% CI, 1.05–1.69; $P = 0.02$), fewer injections (OR, 0.97 per injection; 95% CI, 0.96–0.98; $P = 0.0005$), and more visits at which the choroidal neovascularization was graded as active (OR, 1.97 for eyes in upper quartile of active visits vs. eyes in lowest quartile of active visits; 95% CI, 1.39–2.79; $P = 0.0001$). Baseline VA ≥70 letters was associated with reduced risk of sustained ≥30-letter loss (OR, 0.61; 95% CI, 0.38–0.98; $P = 0.04$). Baseline angiographic lesion criteria were not significantly associated with sustained VA loss.

Conclusions: Twenty-three percent of eyes with nAMD developed sustained VA loss of ≥15 letters over 5 years of anti-VEGF therapy. Baseline predictors of poor outcomes provide more accurate assessment of the potential benefit from anti-VEGF therapy. *Ophthalmology 2019;126:735-742 © 2018 by the American Academy of Ophthalmology*

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Despite the effectiveness of anti–vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (nAMD), significant loss of vision can still occur.[1–11] The major clinical trials of ranibizumab, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA), and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR), reported a loss of 15 or more letters of visual acuity (VA) in 8% to 10% of eyes at 2 years.[4,6] In the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW 1 and VIEW 2), 4.9% to 6.3% of patients treated with aflibercept or ranibizumab had lost 15 letters of VA by 2 years.[11]

Visual outcomes from such clinical trials may not readily translate into routine clinical practice for many reasons, such as differences in patient selection and treatment protocols. Knowledge of the incidence of poor outcomes in eyes receiving therapy in the clinical setting will complement data from clinical trials that may be more relevant to practitioners and patients. Understanding the factors that contribute to loss of vision in patients receiving therapy for nAMD may lead to better outcomes and provide a more accurate prediction of the potential benefit of anti-VEGF therapy.

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Here we describe the incidence, characteristics, and baseline predictors of poor visual outcomes in eyes with nAMD receiving intravitreal anti-VEGF therapy in daily clinical practice over 5 years.

Methods

Design and Setting

We analyzed anonymized data from the Fight Retinal Blindness! (FRB!) registry that were captured during routine clinical practice. The project includes contributing centers located in Australia, New Zealand, and Switzerland. All treatment decisions and visit schedules were entirely at the discretion of the treating clinician and patient. Details of the FRB! project data tracking system have been reported previously.[12] At the baseline visit, patient demographic and clinical information were obtained, including gender, year of birth, prior treatments for nAMD, and angiographic lesion size (greatest linear dimension, GLD) and type. Data were collected at each visit on VA letters read on a logarithm of the minimum angle of resolution (logMAR) chart (on which Early Treatment of Diabetic Retinopathy Study charts are based), type of treatment given, adverse events, and activity of the choroidal neovascular (CNV) lesion. Activity of the CNV lesion was judged by the treating clinician according to a prespecified definition of activity: fluid, hemorrhage, or loss of vision felt to be due to activity of the lesion as seen on any of biomicroscopy, fluorescein angiography, or optical coherence tomography. The best reading of uncorrected, corrected, or pinhole VA was used. Since April 2016, the presence and location of geographic atrophy (GA), subretinal fibrosis (SRFi), and pigment epithelial detachment were also recorded to comply with the International Consortium for Healthcare Outcome Measures macular degeneration standard set.[13]

Institutional ethics approval was obtained from the Human Research Ethics Committees of the Universities of Sydney, Melbourne, Western Australia, and Zurich Hospital. Overarching ethical approval for the private centers was obtained from the Royal Australian and New Zealand College of Ophthalmologists' Human Research Ethics Committees. The research described adhered to the tenets of the Declaration of Helsinki.

Study Population and Groups

Study enrollment criteria included treatment-naive patients starting treatment with intravitreal therapy for nAMD between January 2007 and March 2012. Cases consisted of those patients who had sustained VA loss, defined as at least 2 consecutive visits in which there was loss of $\geq$15 letters from baseline without recovery of VA, either at 5 years or at their last visit if they did not complete 5 years, after starting treatment irrespective of when the loss of vision occurred. A subgroup analysis included eyes that sustained $\geq$30 letters of loss. Controls were eyes that had not sustained $\geq$15 letters of loss from baseline during the period of observation. Eyes with baseline VA <35 letters were excluded because the lower likelihood of such eyes suffering a 15- or 30-letter loss even if they had suffered a significant adverse event might have biased the control group. Patients who were treated by clinicians that stopped participating in the project before the patients could have been followed for 5 years were also excluded.

Study Outcomes

The main outcomes were the proportion of eyes with sustained VA loss within 5 years, the time to development of sustained VA loss, and baseline predictors of sustained VA loss.

Statistical Analysis

The proportion of eyes with sustained loss of $\geq$15 or $\geq$30 letters and time to first development of a $\geq$15- or $\geq$30-letter loss was estimated using Kaplan–Meier curves. The baseline predictors of $\geq$15 or $\geq$30 letters of loss were evaluated by multivariate analysis using Cox proportional hazards models. The variables included baseline age, VA, angiography lesion criteria and lesion size, total number of injections, and CNV activity. Adjusted hazard ratios and associated 95% confidence intervals (CIs) were calculated from a multivariate Cox proportional hazards model. Nesting effects of the variables were analyzed to correlate outcomes between eyes within the same patient and same practice.

Descriptive statistics included mean, standard deviation, 95% CI, median, range, first and third quartiles, and percentages where appropriate. Characteristics at baseline were compared between eyes with and without sustained VA loss $\geq$15 letters, using the *t* test and Pearson chi-square test where appropriate. Locally weighted regression smoothing curves were used to visualize longitudinal observations of VA throughout the follow-up period.

All data analyses were performed using R version 3.4.1 with the survival package (version 2.41-3) for Kaplan–Meier survival analysis and the coxme package (version 2.2-7) for mixed-effects Cox proportional hazards models.[14]

Results

Study Participants

There were 1760 treatment-naive eyes from 1586 patients with nAMD that began intravitreal treatment between January 2007 and March 2012 with baseline VA >35 letters (Fig 1). Of these, 856 eyes (48.6%) of 774 patients completed 5 years of follow-up. Table 1 summarizes the baseline characteristics of the eyes observed. The mean baseline VA of the eyes that developed sustained VA loss of $\geq$15 letters was similar to the group without sustained VA loss (59.6 vs. 59.3 letters, $P = 0.72$). The distribution of angiographic lesion gradings was also similar between the 2 groups, with most lesions being occult ($P = 0.36$). The mean baseline age and median CNV lesion GLD of eyes that developed sustained VA loss of $\geq$15 letters were greater compared with the group without sustained VA loss (80.7 vs. 79.0 years, $P = 0.001$; and 2685 vs. 2200 μm, $P = 0.03$, respectively).

Baseline characteristics of eyes that completed 5 years of follow-up were compared with those that did not. The mean baseline age of noncompleters was greater, and mean baseline VA of noncompleters was worse than completers (80.4 vs. 78.2 years, $P = 0.0004$; and 56.7 vs. 62.2 letters, $P < 0.0001$, respectively). The distribution of angiographic lesion gradings and median CNV lesion GLD of eyes was similar between the 2 groups ($P = 0.40$ and $P = 0.95$, respectively).

Incidence of Sustained Visual Acuity Loss

The proportion of eyes with sustained VA loss of $\geq$15 letters was estimated to be 11.0% (95% CI, 9.4–12.5) at 2 years and 22.9% (95% CI, 20.7–25.1) at 5 years. The proportion of eyes with sustained VA loss of $\geq$30 letters was estimated to be 3.6% (95% CI, 2.7%–4.6%) at 2 years and 10.8% (95% CI, 9.1%–12.5%) at 5 years (Fig 2).

The mean VA of eyes with sustained $\geq$15-letter loss decreased gradually over time (Fig 3). There were 856 eyes that completed 5 years of follow-up. There was a higher rate of dropout of eyes with sustained VA loss of $\geq$15 letters (56%) than eyes without sustained VA loss (50%). There was a mean decrease of 31 letters from baseline at 5 years compared with a mean gain of 7 letters in eyes without sustained VA loss. The group of eyes with sustained

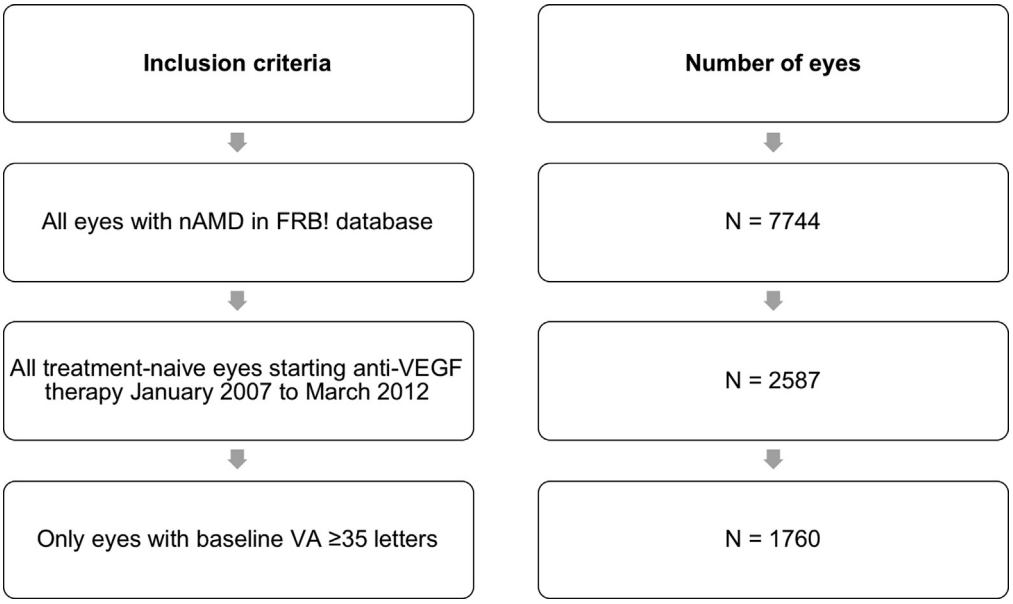

Figure 1. Consolidated Standards Of Reporting Trials (CONSORT)-style diagram showing the number of eyes in the study, the number excluded, and the reasons for exclusion. Anti-VEGF = anti–vascular endothelial growth factor; FRB! = Fight Retinal Blindness!; nAMD = neovascular age-related macular degeneration.

VA loss of ≥30 letters had a mean decrease of 44 letters from baseline at 5 years (Table 2). The mean VA of the 145 eyes with sustained VA loss of ≥15 letters at year 5 was 33 letters (Snellen equivalent of $20/200^{-2}$) and 18 letters (Snellen equivalent of $20/400^{-2}$) for the 63 eyes that lost ≥30 letters from baseline (Table 2). Kaplan–Meier curves for time to develop a sustained loss of ≥15 letters in VA showed that the onset of VA loss occurred at a steady rate throughout the 5-year follow-up period (Fig 2). Recovery of ≥15 letters occurred in 25% of eyes that completed 1 year follow-up after the sustained VA loss occurred, with mean VA recovery of 24.7 (standard deviation 10.4) letters.

Characteristics Associated with Sustained Visual Acuity Loss at 5 Years

Features in eyes with and without sustained VA loss at 5 years are listed in Table 2. Eyes with sustained VA loss of ≥15 letters at 5 years were observed in older patients compared with eyes without sustained VA loss (aged 79.8 years vs. 77.9 years, $P = 0.007$). Eyes that developed sustained VA loss were more likely to have had an adverse event than eyes without sustained VA loss (0.5% vs. 0.3% of visits, $P = 0.004$), had a higher mean proportion of visits with CNV graded as active (53.7% vs. 46.8%, $P = 0.02$), and received fewer anti-VEGF injections on average (25.5 vs. 28.0, $P = 0.04$) (Fig 4). The eyes that developed sustained VA loss completed a similar number of visits over 5 years as eyes without sustained VA loss (39.8 vs. 38.3, $P = 0.34$). The injection interval at the time of sustained VA loss was 4 weekly for 44% of eyes with loss of ≥15 letters and for 35% of eyes with VA loss of ≥30 letters.

Predictors of Sustained Visual Acuity Loss

In multivariate analysis, factors independently associated with higher incidence of sustained ≥15-letter loss included age >80 years (odds

Table 1. Demographics and Lesion Characteristics at Baseline

	≥15-Letter Losers	≥30-Letter Losers	Rest of the Cohort	*P* Value[‡]
No. of eyes (%)*	326 (18.5)	150 (8.5)	1434	
No. of patients	310	146	1276	
Mean age, yrs (SD)	80.7 (7.4)	81.2 (7.0)	79.0 (8.1)	**0.001**
Mean baseline VA, letters (SD)	59.6 (13.5)	57.6 (12.6)	59.3 (13.3)	0.72
Angiography lesion criteria, n (%)				
Occult	168 (51.5)	80 (53.3)	793 (55.3)	0.36
Predominantly classic	67 (20.6)	30 (20.0)	245 (17.1)	
Minimally classic	38 (11.7)	20 (13.3)	183 (12.8)	
Other[†]	20 (6.1)	8 (5.3)	98 (6.8)	
Not recorded	33 (10.1)	12 (8.0)	115 (8.0)	
Median GLD, μm (Q_1, Q_3)	2685 (1500, 3700)	2500 (1534, 3600)	2200 (1484, 3200)	**0.03**

GLD = greatest linear dimension; Q_1, Q_3 = first quartile, third quartile; SD = standard deviation; VA = visual acuity.
Boldface indicates statistical significance.
*Eyes with baseline VA < 35 letters were excluded.
[†]Includes disciform scar, idiopathic polypoidal choroidal vasculopathy, juxtapapillary, retinal angiomatous proliferation.
[‡]*t* test and Pearson chi-square test comparing ≥15-letter losers with the rest of the cohort.

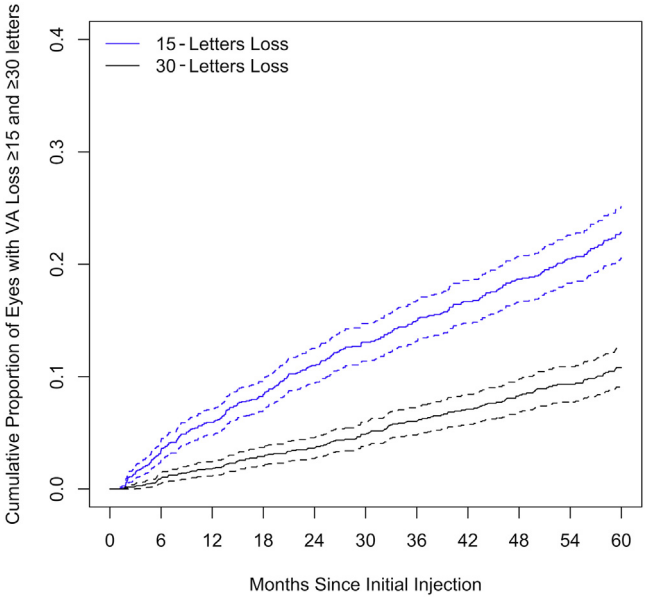

Figure 2. Kaplan–Meier curve for time to first loss of ≥15 and ≥30 letters of visual acuity (VA) over 5 years. The solid line is the point estimate of the proportion of eyes with VA loss. The dashed lines are the 95% confidence intervals.

ratio [OR], 1.33 for patients >80 years vs. ≤80 years; 95% CI, 1.05–1.69; $P = 0.02$), lower total number of injections (OR, 0.97 per injection; 95% CI, 0.96–0.98; $P = 0.0005$), and higher proportion of visits at which the CNV lesion was graded as active (OR, 1.97 for eyes in upper quartile of active visits vs. eyes in lowest quartile of active visits; 95% CI, 1.39–2.79; $P = 0.0001$) (Table 3). The same factors were associated with increased risk of sustained ≥30-letter loss. Baseline CNV lesion GLD was somewhat associated with sustained ≥15-letter loss of vision (OR, 1.27 for patients >2500 μm vs. ≤2500 μm; 95% CI, 0.99–1.62; $P = 0.06$). In eyes with ≥30-letter loss, baseline VA >70 letters was associated with reduced risk of loss of vision (OR, 0.61; 95% CI, 0.38–0.98; $P = 0.04$) (Table 4). Baseline angiographic lesion criteria were not significantly associated with sustained VA loss.

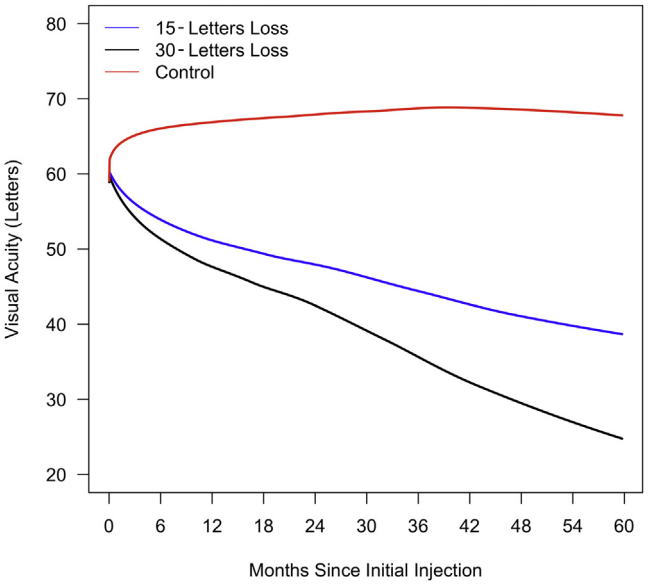

Figure 3. Locally weighted regression smoothing curves for mean visual acuity over time up to 5 years.

Causes of Sustained Visual Acuity Loss

Eyes with sustained VA loss of ≥15 letters at 5 years had more cases of hemorrhage reducing VA ≥15 letters or retinal pigment epithelium (RPE) tears than eyes without sustained VA loss (0.27% vs. 0.07% of visits and 0.05% vs. 0.02% of visits, respectively).

There were 510 eyes that completed 5 years follow-up that had information available on GA and SRFi. The group of eyes with sustained VA loss of ≥30 letters had more GA and SRFi than those with VA loss of ≥15 letters, which in turn had more than the group of eyes without sustained VA loss. Most cases of GA and SRFi were graded as subfoveal (Table 5).

Discussion

Our study evaluated the incidence, characteristics, and predictors of sustained VA loss among 1760 treatment-naive eyes that began anti-VEGF therapy for nAMD in routine clinical practice. The proportion of eyes with sustained VA loss of ≥15 letters within 5 years was 22.9% and was 10.8% in the subgroup with sustained VA loss of ≥30 letters. Factors independently associated with higher incidence of sustained ≥15-letter loss included age >80 years, fewer injections, and higher proportion of visits at which the CNV lesion was graded active. Baseline lesion size was somewhat associated with sustained ≥15-letter loss of vision. Baseline VA >70 letters was associated with reduced risk of sustained ≥30-letter loss. Baseline angiographic lesion criteria were not significantly associated with sustained VA loss.

The primary efficacy end point in the pivotal phase III randomized controlled trials (RCTs) was the proportion of patients who had lost fewer than 15 letters of VA. In the MARINA and ANCHOR trials, 8% and 10% of patients, respectively, treated with ranibizumab had lost 15 letters of VA by 2 years.[4] In the CATT study, 9.2% of patients treated with ranibizumab or bevacizumab lost 15 or more letters at 2 years.[5,6] In the VIEW 1 and VIEW 2 studies, 4.9% to 6.3% of patients treated with aflibercept or ranibizumab had lost 15 letters of VA by 2 years.[11] In our study, the proportion of eyes with sustained VA loss of ≥15 letters was estimated to be 11.0% at 2 years and 22.9% at 5 years, higher than the pivotal clinical trials. Our study may differ from these RCTs, as we defined sustained VA loss as loss of ≥15 letters from baseline at 2 consecutive visits without recovery of VA either at 5 years or at their last visit if they did not complete 5 years. This definition of sustained VA loss excluded random VA fluctuations over time or episodes of sporadic loss of vision owing to, for example, CNV reactivation or keratitis related to the antiseptic agent used prior to the injection. We had an inclusion criterion of eyes with baseline VA ≥35 letters (Snellen equivalent of 20/200), whereas the pivotal trials had a lower threshold with inclusion criteria of VA of 70 to 25 letters (Snellen equivalent of 20/40 to 20/320). Eyes with poor baseline VA may be less likely to lose ≥15 letters,

Table 2. Outcomes of ≥15- and ≥30-Letter Losers at 5 Years of Follow-up

	≥15-Letter Losers	≥30-Letter Losers	Rest of the Cohort	*P* Value*
No. of eyes (%)	145 (16.9)	63 (7.4)	711	
No. of patients	139	62	635	
Mean baseline age, yrs (SD)	79.8 (7.0)	81.1 (6.8)	77.9 (7.8)	**0.007**
Mean baseline VA, letters (SD)	63.8 (13.3)	62.1 (12.4)	61.8 (12.9)	0.09
Mean final VA, letters (SD)	32.9 (19.9)	18.17 (15.6)	68.4 (12.6)	**<0.0001**
Mean ΔVA from baseline, letters (SD)	−31.0 (15.3)	−43.9 (13.3)	6.7 (12.3)	**<0.0001**
CNV activity (proportion of visits active, %)	53.7	50.9	46.8	**0.02**
Mean no. of visits completed (SD)	39.8 (15.8)	40.3 (15.5)	38.3 (17.1)	0.34
Mean no. of anti-VEGF treatments (SD)	25.5 (14.1)	22.4 (12.7)	28.0 (14.0)	**0.04**
Adverse events (proportion of visits, %)	0.54	0.63	0.33	**0.004**

CNV = choroidal neovascularization; ΔVA = change in VA; SD = standard deviation; VA = visual acuity; VEGF = vascular endothelial growth factor. Boldface indicates statistical significance.
**t* test and Pearson chi-square test comparing ≥15-letter losers with the rest of the cohort.

which could have contributed to our higher incidence of vision loss. The protocol-based regimens used in RCTs, particularly monthly treatment, which is rarely performed in routine clinical practice, may also explain the lower incidence of loss of VA in RCTs than we found in the present study.

Several cohort studies and clinical trials have highlighted the risk of visual loss in patients with nAMD treated with anti-VEGF agents. The FRB! Study Group[1] has previously reported outcomes of 1212 eyes treated with anti-VEGF agents. Loss of ≥10 letters occurred in 32% (42 of 131) of eyes that continued treatment for more than 6.5 years. The CATT study reported 24% (153 of 647) of eyes losing 15 or more letters after 5 years.[15] Zhu et al[16] reported a retrospective case series in which 20% (42 of 208) of patients had lost more than 15 letters at the end of 5 years of ranibizumab treatment on an as-needed regimen. Our results were comparable with these prior cohort studies and clinical trials, even though we included a wider range of patients from daily clinical practice who may have had a tendency to worse outcomes than those who meet the inclusion criteria of the clinical trials.

Our study found that eyes that had sustained VA loss had poor final VA outcomes. Of the 145 eyes with sustained ≥15-letter VA loss in our study, the mean final VA was 33 letters at 5 years; results were worse for the 63 that had sustained ≥30-letter VA loss, with mean final VA of 18 letters. Eyes with sustained VA loss were more likely to have dropped out, had an adverse event, had a higher proportion of visits at which the CNV lesion was graded as active, and received fewer anti-VEGF injections than eyes without sustained VA loss. Factors we identified that were independently associated with sustained ≥15-letter loss included age >80 years, fewer injections, and a higher proportion of visits at which the CNV lesion was active. Some of the differences in groups that were labeled significant statistically were small, but they are likely to reflect underlying influences of undertreatment and general infirmity (age) that could have

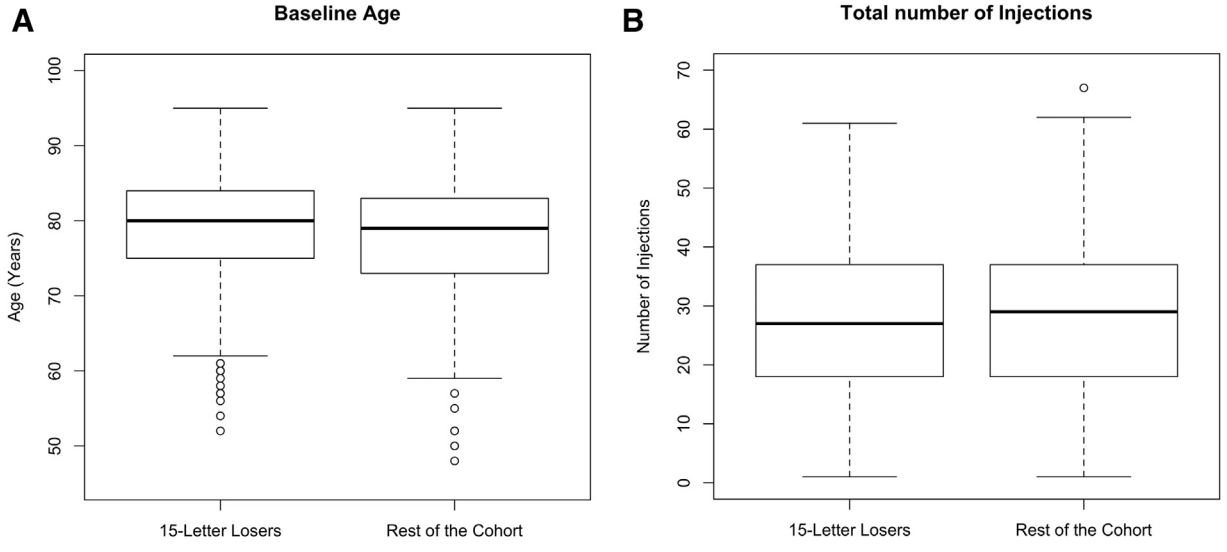

Figure 4. Box plot of baseline age and total number of injections in 15-letter losers and the rest of the cohort at 5 years.

Table 3. Multivariate Analysis of Predictors Associated with ≥15-Letter Visual Acuity Loss

	Hazard Ratio (95% CI)	P Value
Baseline age, yrs		
≤80	1.00	**0.02**
>80	1.33 (1.05–1.69)	
Baseline VA, letters		
≤70	1.00	0.23
>70	1.18 (0.89–1.56)	
Baseline angiography lesion criteria		
Minimally classic	1.00	0.18
Other*	0.92 (0.53–1.61)	
Occult	0.96 (0.67–1.37)	
Predominantly classic	1.32 (0.88–1.98)	
Baseline greatest linear dimension, μm		
≤2500	1.00	0.06
>2500	1.27 (0.99–1.62)	
Total number of injections	0.97 (0.96–0.98)	**0.0005**
CNV activity (quartiles)		
Low	1.00	**0.0001**
Medium	1.24 (0.87–1.77)	
High	1.27 (0.88–1.82)	
Very high	1.97 (1.39–2.79)	

CI = confidence interval; CNV = choroidal neovascularization; VA = visual acuity.
Boldface indicates statistical significance.
*Includes disciform scar, idiopathic polypoidal choroidal vasculopathy, juxtapapillary, retinal angiomatous proliferation.

Table 4. Multivariate Analysis of Predictors Associated with ≥30-Letter Visual Acuity Loss

	Hazard Ratio (95% CI)	P Value
Baseline age, yrs		
≤80	1.00	**0.006**
>80	1.64 (1.15–2.34)	
Baseline VA, letters		
≤70	1.00	**0.04**
>70	0.61 (0.38–0.98)	
Baseline angiography lesion criteria		
Minimally classic	1.00	0.29
Other*	0.63 (0.26–1.49)	
Occult	0.87 (0.53–1.43)	
Predominantly classic	1.01 (0.57–1.80)	
Baseline greatest linear dimension, μm		
≤2500	1.00	0.71
>2500	1.07 (0.75–1.53)	
Total number of injections	0.96 (0.94–0.97)	**0.0004**
CNV activity (quartiles)		
Low	1.00	**0.002**
Medium	1.23 (0.74–2.06)	
High	1.18 (0.70–2.01)	
Very high	2.22 (1.35–3.66)	

CI = confidence interval; CNV = choroidal neovascularization; VA = visual acuity.
Boldface indicates statistical significance.
*Includes disciform scar, idiopathic polypoidal choroidal vasculopathy, juxtapapillary, retinal angiomatous proliferation.

contributed to poor outcomes in some but not all cases. Baseline GLD >2500 μm was somewhat associated with an increased risk of sustained ≥15-letter loss. Baseline angiographic lesion type was not significantly associated with sustained VA loss.

There have been retrospective analyses of predictors of VA loss in some phase III RCTs. Rosenfeld et al[17] evaluated the characteristics of eyes that lost vision when receiving monthly ranibizumab in the MARINA and ANCHOR trials. They compared eyes receiving monthly treatment with ranibizumab that lost ≥15 letters (71 patients) with those that gained ≥15 letters (271 patients) during the 2-year studies. The baseline characteristics found to be associated with the risk of VA loss included increased patient age, larger size of the neovascular lesion, and better VA at baseline. Ying et al[18] performed a retrospective analysis of a cohort of 61 patients from the CATT study who suffered sustained VA loss of ≥15 letters during monthly or pro re nata treatment with ranibizumab or bevacizumab for 2 years. As in the present study, Ying et al[18] compared morphologic features between eyes with sustained VA loss with all other eyes without sustained VA loss, rather than only eyes that gained ≥15 letters as Rosenfeld et al[17] did. They reported that 5.9% of eyes of CATT participants developed sustained VA loss of ≥15 letters over 2 years of treatment with ranibizumab or bevacizumab, with their VA decreasing gradually over time. Foveal scar, pigmentary abnormalities, and GA were reported to have contributed to most cases (83.7%) of sustained VA loss. The presence of baseline GA, larger CNV area at baseline, and bevacizumab treatment were independently associated with higher risk of sustained VA loss. Other risk factors, such as age and baseline VA, were not significant predictors of sustained VA loss.[19] Ying et al[15] recently reported baseline predictors of VA outcomes at 5 years after initiating treatment with ranibizumab or bevacizumab in the cohort of patients (647) enrolled in CATT. Worse baseline VA, larger CNV area at baseline, and presence of baseline RPE elevation (which we did not measure) remained independently associated with worse VA at 5 years. We found that increased age (>80 years) was associated with sustained ≥15-letter VA loss in the present study, whereas better baseline VA (>70 letters) reduced the risk of ≥30-letter VA loss. This difference could be related to our larger cohort and longer follow-up. Better baseline VA was reported to be associated with reduced risk of VA loss in the study by Westborg et al[20] of patients with nAMD treated with ranibizumab or bevacizumab in routine clinical practice. These data came from 3912 patients tracked by the Swedish Macula Register from 2011 to 2014. For patients with VA more than 60 letters at baseline, the risk of having a VA lower than 60 letters after 1 or 2 years of treatment was 20%. For patients with lower VA at diagnosis (<60 letters), this risk was 60%.[20]

We found that eyes with sustained VA loss had a higher proportion of visits with an adverse event compared with those without sustained VA loss. The adverse events captured in our study were unlikely to be a significant contributor to VA loss, given their low incidence.

Table 5. Frequency of Geographic Atrophy and Subretinal Fibrosis at 5 Years

	Number of Eyes (%)*			
	≥15-Letter Losers, N = 63	≥30-Letter Losers, N = 22	Rest of the Cohort, N = 447	P Value†
Geographic atrophy				
Not present	19 (30.2)	5 (22.7)	233 (52.1)	**0.01**
Present	44 (69.8)	17 (77.3)	214 (47.9)	
Subfoveal	32	15	98	
Extrafoveal	12	2	116	
Subretinal fibrosis				
Not present	27 (42.9)	6 (27.3)	303 (67.8)	**0.01**
Present	36 (57.1)	16 (72.7)	144 (32.2)	
Subfoveal	32	14	104	
Extrafoveal	4	2	40	

Boldface indicates statistical significance.
*Geographic atrophy and subretinal fibrosis data were not obligatory in the Fight Retinal Blindness! data entry system until after April 2016.
†Pearson chi-square test comparing ≥15-letter losers with the rest of the cohort.

Seventy percent of eyes that sustained VA loss of ≥15 letters had GA, and 57% had SRFi at 5 years. In comparison, 48% of eyes without sustained VA loss of ≥15 letters had GA, and 32% had SRFi at 5 years. This significant difference could partly explain the major causes of vision loss; however, we were unable to analyze baseline GA and SRFi as risk factors for vision loss because these data for the FRB! data entry system were not obligatory until April 2016.

Study Limitations and Strengths

Data collected in observational studies such as the present study have strengths and weaknesses.[21] Data completeness was high for all variables (>99.5% VA, treatment given, activity grading fields, and adverse event completed) owing to the quality assurance features of the FRB! web-based data entry system, with the exception of CNV lesion size (GLD; 80% completed) and lesion type (88% completed). It is likely that adverse events are under-reported in the FRB! database. Lack of consistent GA and SRFi grading for a period of time is another limitation. The measurement of logMAR VA is reasonably objective. Case selection and treatment regimens in observational studies may be different than in clinical trials and among different clinicians. In contrast to phase III trials, clinicians made treatment decisions in routine practice without reference to reading center adjudications and study protocols. Subjective criteria, such as lesion activity or lesion type, may not be graded uniformly in observational studies because clinicians may have different opinions of whether a lesion is active. This would result in lower internal validity compared with RCTs; however, our results are more generalizable to actual clinical practice because this better reflects how treatment decisions are made in daily clinical practice.[2,12] More than half of the eyes in our analysis did not complete 5 years of follow-up, which could have biased the results. Patients that lost 15 or 30 letters prior to dropping out would still be included in our estimated proportions of poor outcomes. However, the proportion of eyes losing ≥15 or ≥30 letters may have been underestimated if, for example, patients experienced poor outcomes but dropped out of the study before loss of 15 or 30 letters was observed. We also note that many patients were also discontinued owing to reasons unrelated to treatment outcomes, including patient going to another doctor and patient death.

Twenty-three percent of eyes with nAMD managed with anti-VEGF therapy developed sustained VA loss of ≥15 letters over 5 years of treatment in daily clinical practice. Older age, fewer injections, and higher proportion of visits at which the CNV lesion was graded as active were independently associated with less improvement in VA. Identification of the incidence and predictors of poor outcomes provides more accurate assessment of the potential benefit from anti-VEGF therapy.

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Footnotes and Financial Disclosures

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No animal subjects were used in this study.

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Abbreviations and Acronyms:
CI = confidence interval; **CNV** = choroidal neovascular; **FRB!** = Fight Retinal Blindness!; **GA** = geographic atrophy; **GLD** = greatest linear dimension; **LogMAR** = logarithm of the minimum angle of resolution; **nAMD** = neovascular age-related macular degeneration; **OR** = odds ratio; **RCT** = randomized controlled trial; **RPE** = retinal pigment epithelium; **SRFi** = subretinal fibrosis; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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