

Visual Acuity Outcomes and Anti–Vascular Endothelial Growth Factor Therapy Intensity in Neovascular Age-Related Macular Degeneration Patients

A Real-World Analysis of 49 485 Eyes

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Purpose: This study assessed anti–vascular endothelial growth factor (VEGF) therapy intensity and its relationship with visual acuity (VA) change in real-world neovascular age-related macular degeneration (nAMD) patients.

Design: This retrospective analysis was performed on a large database of aggregated, longitudinal, de-identified electronic medical records from a geographically and demographically diverse sample of patients of United States retina specialists (Vestrum Health Retina Database).

Participants: Treatment-naïve nAMD patients who underwent anti-VEGF injections between January 1, 2012, and October 31, 2016, were eligible if follow-up data were available before October 31, 2017.

Methods: Age, gender, anti-VEGF treatment type, number of treatments, and VA were extracted from the database.

Main Outcome Measure: Mean VA change assessed at 1 year and stratified based on number of anti-VEGF injections received over 1 year.

Results: In this analysis, 49 485 eyes were included. The mean age was 80.9 years, and 64% were female. Mean baseline VA was 53.8 letters (Snellen equivalent, 20/80). At 1 year, after a mean of 7.3 anti-VEGF injections, there was a mean gain of 1 letter (0.95 letter; 95% confidence interval [CI] for change in VA, +0.77 to +1.13 letter; $P < 0.001$). When stratified by anti-VEGF agent, the mean VA changes were nearly identical at 1 year. There was a linear relationship between mean letters gained and mean number of injections, between 4 and 10 injections over 1 year, with 4 or fewer or 10 or more injections associated with loss of vision or a plateau, respectively. Greater mean 1-year change in VA also trended with worse baseline VA; those patients with better VA at presentation tended to be particularly vulnerable to vision loss. Those who received the fewest injections tended to be older and have worse baseline VA.

Conclusions: Real-world nAMD patients receive fewer anti-VEGF injections and experience worse visual outcomes compared with patients receiving fixed, frequent therapy in randomized controlled trials. Mean change in VA correlates with treatment intensity at 1 year, but with ceiling effects related to treatment intensity and baseline VA. Older patients and those with poor baseline VA may be particularly prone to undertreatment. *Ophthalmology Retina* 2020;4:19–30 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

See Editorial on page 1.

Anti–vascular endothelial growth factor (VEGF) therapy currently is the standard of care for neovascular age-related macular degeneration (nAMD). Registration trials for ranibizumab (monthly) and aflibercept (every 2 months after 3 monthly loading doses), as well as the monthly ranibizumab and bevacizumab arms of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT; described further in Table 1), suggest that these anti-VEGF agents can perform similarly, with an average 1-year improvement of 8.5

letters across these studies (Table 1).^{1–4} However, real-world studies of anti-VEGF therapy in nAMD, based on chart reviews, electronic medical records (EMRs), or claims analyses, have reported less favorable visual outcomes.^{5–19} For example, our prior study showed no improvement in visual acuity (VA) in the 1-year cohort,¹⁸ and another United States–based real-world study reported a 1-year improvement of only 2.5 letters, with both studies excluding nAMD patients receiving fewer than 3 anti-VEGF injections.¹⁹

Table 1. Ranibizumab Registration Trials, Aflibercept Registration Trials, and Comparison of Age-Related Macular Degeneration Treatments Trials

Study	Mean Age (yrs) at Baseline	Mean Visual Acuity (Early Treatment Diabetic Retinopathy Study Letters) at Baseline	Mean Change Visual Acuity (Early Treatment Diabetic Retinopathy Study Letters) at 1 Year
ANCHOR, ranibizumab 0.5 mg monthly	76	47.1	11.3
MARINA, ranibizumab 0.5 mg monthly	77	53.7	7.2
VIEW 1, aflibercept 2 mg every 2 months after 3 monthly doses	78	55.7	7.9
VIEW 1, ranibizumab 0.5 mg monthly	78	54.0	6.9
VIEW 2, aflibercept 2 mg every 2 months after 3 monthly doses	74	51.6	8.9
VIEW 2, ranibizumab 0.5 mg monthly	73	53.8	9.4
CATT, ranibizumab 0.5 mg monthly	79	60.1	8.5
CATT, bevacizumab 1.25 mg monthly	80	60.2	8.0
Mean	76.9	54.5	8.5

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; MARINA = Minimally Classic/Occlud Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD.

The studies show a mean baseline age of 76.9 years, a mean baseline visual acuity (VA) of 54.5 letters (Snellen equivalent, 20/80), and a mean 1-year improvement of 8.5 letters (unweighted means).¹⁻⁴

As the healthcare system shifts from volume-based fee-for-service systems to value-based systems, real-world outcomes become increasingly important. Although the cause of discrepancies between real-world nAMD studies and randomized controlled trials (RCTs) is unknown, possibilities include patient characteristics and undertreatment associated with variable frequency treatment regimens (not regularly repeating monthly injections for ranibizumab or bevacizumab, or not regularly repeating bimonthly injections for aflibercept). In the current study, we relaxed the requirement for 3 initial anti-VEGF loading injections and increased the sample size specifically to assess anti-VEGF therapy intensity, as well as its relationship with mean change in VA at 1 year, in treatment-naïve nAMD patients using a demographically diverse sample of United States retina specialists' EMRs.

Methods

Database

The database consisted of aggregated, longitudinal, de-identified EMRs from a demographically and geographically diverse patient sample that was obtained from a panel of United States retina specialists (Vestrum Health, LLC, Naperville, IL). Specifically, the panel includes more than 240 private practice retina physicians with 65%, 32%, and 3% located in urban, suburban, and rural settings, respectively. They are geographically diversified by region into the Mid Atlantic (24%), Southeast (24%), West (20%), Southwest (12%), Northeast (8%), Great Lakes (7%), and North Central (4%) regions. At the time of this study, the database included more than 800 000 unique patients and more than 4.5 million encounters. Aggregated data included detailed information on in-office and outpatient pharmaceutical use, clinical findings, diagnostic test interpretation, ocular and systemic diagnoses, surgical use, outcomes, and adverse events. All information was de-identified, in accordance with the regulations of the Health Insurance Portability and Accountability Act of 1996, by a proprietary process during which patient identifiers are removed and replaced with an alphanumeric identifier that is generated using an industry-standard 1-way algorithm. The names of treating physicians and practices were

removed from the data. The database is refreshed on a weekly basis. Visual acuity score is reported using an Early Treatment Diabetic Retinopathy Study approximation, calculated as follows: $85 + 50 \times \log(\text{Snellen fraction})$, as described by Gregori et al.²⁰ With this formula, Snellen visual acuity of 20/20 is converted appropriately to 85 letters, 20/40 to 70 letters, 20/80 to 55 letters, 20/160 to 40 letters, and so forth.

Study Design, Dates for Data Collection, and Inclusion Criteria

This project was considered exempt from institutional review board review because the research involved only the collection of existing data, which had been de-identified, as noted above. This research adhered to the tenets of the Declaration of Helsinki. This retrospective, uncontrolled analysis studied treatment-naïve nAMD patients treated from January 1, 2012, through October 31, 2016, if follow-up data were available before October 31, 2017. Patients must have received at least 1 anti-VEGF injection for nAMD to be included in the analysis. Patients with other retinal diagnoses were excluded. One-year follow-up data were assessed with the visit closest to 1 year, within months 11 to 12. Patients who lacked 1-year follow-up data were excluded. Data beyond 1 year of follow-up were not assessed in this study. Age, gender, anti-VEGF treatment type, number of treatments, and VA were extracted from the database. Visual acuity measurements were not standardized in this retrospective uncontrolled review; VA score was calculated as described above.

Statistical Analysis

All analyses were carried out at the patient eye level. For bilaterally treated patients, each patient eye was treated independently. As a sensitivity analysis, an analysis of top-line results was performed, excluding nAMD patients who underwent bilateral treatment during the 5-year study period. Baseline characteristics were summarized with descriptive statistics. Mean values for patient demographics, number of anti-VEGF injections, and baseline and final VA (letters) were calculated. Mean change in VA from baseline was calculated, along with 95% confidence intervals (CIs) and nominal *P* values, using paired *t* tests.

Breakdown by initial anti-VEGF agent and mean baseline VA by initial anti-VEGF agent were assessed. Mean change in VA at 1

Table 2. Baseline Characteristics and Results for the Real-World Outcomes Study Group Overall and Stratified by Initial Anti-Vascular Endothelial Growth Factor Therapy

	All Anti-Vascular Endothelial Growth Factor Agents	Bevacizumab	Aflibercept	Ranibizumab
Eyes				
No.	49 485	19 501	12 520	17 464
%	100.0	39.4	25.3	35.3
Gender (%)				
Male	36	36	37	35
Female	64	64	63	65
Mean age (yrs)	80.9	80.5	80.8	81.4
No. of injections per patient per yr				
Mean	7.3	7.3	7.3	7.3
Median	7	8	7	7
Mean VA (letters)				
Baseline BCVA	53.8	52.9	56.4	52.9
Change at 1 yr	0.95	1.41	0.22	0.96
P value	<0.001	<0.001	0.18	<0.001
95% Confidence interval	0.77 to 1.13	1.12 to 1.71	-0.11 to 0.55	0.65 to 1.26

BCVA = best-corrected visual acuity; VA = visual acuity; VEGF = vascular endothelial growth factor.

This real-world analysis included 49 485 neovascular age-related macular degeneration patient eyes, which demonstrated a mean baseline VA of 53.8 letters (Snellen equivalent, 20/80), received a mean of 7.3 anti-VEGF injections, and improved by 1.0 letter at 1 year on average. Compared with those patients in the randomized clinical trials cited in Table 1, these real-world patient eyes showed nearly identical mean baseline VA, but were 4 years older, on average, at presentation. In this real-world analysis, there were no clinically meaningful differences in mean 1-year change in VA when stratified by initial anti-VEGF agent. As a sensitivity analysis, a similar assessment was performed, excluding those patients who switched between agents, with no clinically meaningful differences. However, comparison of outcomes based on anti-VEGF agent is limited in this study by the higher mean baseline VA for patients treated with aflibercept versus other agents by approximately 4 letters.

year was analyzed for the entire group. One-year mean change in VA also was stratified by initial anti-VEGF agent, and as a sensitivity analysis, a similar assessment was performed, excluding those patients who switched between agents.

Anti-VEGF injection frequency over 1 year was assessed and compared with baseline demographic features. Mean 1-year change in VA was stratified by anti-VEGF injection frequency and by baseline VA. Five-year trends, stratified by initial anti-VEGF agent, were assessed for presenting VA, mean number of first-year injections, and mean 1-year change in VA.

Results

Demographics

Based on the inclusion criteria, 49 485 eyes were included in this analysis. Baseline demographics are summarized in Table 2. The mean age was 80.9 years, 36% of patients were men, and 64% of patients were women. The mean baseline VA was 53.8 letters (Snellen equivalent, 20/80). The initial anti-VEGF agent was as follows: 25% aflibercept, 35% ranibizumab, and 39% bevacizumab. Patient eyes initially treated with aflibercept showed a higher mean baseline VA of 56.4 letters compared with those treated with bevacizumab and ranibizumab (52.9 letters each).

Mean 1-Year Change in Visual Acuity for the Entire Group and Stratified by Anti-Vascular Endothelial Growth Factor Agent

Overall, patients demonstrated a baseline mean VA of 53.8 letters (Snellen equivalent, 20/80), received a mean of 7.3 anti-VEGF injections, and improved by 1.0 letter at 1 year (0.95 letter; 95% CI for change in VA, +0.77 to +1.13 letter; $P < 0.001$; Table 2). As a

sensitivity analysis, a similar assessment was performed, excluding nAMD patients who underwent bilateral treatment during the 5-year study period. Nearly identical 1-year outcomes resulted. Among patients treated for unilateral nAMD, 32 922 eyes with a mean baseline VA of 53.2 letters (Snellen equivalent, 20/80) received a mean of 7.3 anti-VEGF injections and showed improvement of 1.47 letters.

The 1-year VA outcomes, stratified by initial anti-VEGF agent, are shown in Table 2. Despite different initial anti-VEGF agents, all groups received a mean of 7.3 injections and showed very similar mean change in VA at 1 year. Of 12 520 patient eyes initially treated with aflibercept, the mean 1-year improvement was +0.2 letter (95% CI for change in VA, -0.11 to +0.55 letter; $P = 0.18$), with similar outcomes for bevacizumab (19 501 eyes; +1.4 letter; 95% CI for change in VA, +1.12 to +1.71 letter; $P < 0.001$) and for ranibizumab (17 464 eyes; +1.0 letter; 95% CI for change in VA, +0.65 to +1.26 letter; $P < 0.001$). As a sensitivity analysis, a similar assessment was performed, excluding those patients who switched between agents. Nearly identical mean 1-year change in VA resulted. Of 10 727 patient eyes treated with a mean of 7.1 aflibercept-only injections, the mean 1-year improvement was +0.4 letter, with similar outcomes for bevacizumab only (13 928 eyes; 6.7 injections; +1.2 letter) and for ranibizumab only (14 032 eyes; 6.9 injections; +1.1 letter). The aflibercept-only group showed a greater mean baseline VA (56.5 letters) than the bevacizumab-only and ranibizumab-only groups (52.5 and 52.6 letters, respectively), approximating a 4-letter difference.

One-Year Anti-Vascular Endothelial Growth Factor Injection Frequency and Baseline Features

The mean and median number of anti-VEGF injections per eye were 7.3 and 7.0, respectively, in the first year of treatment.

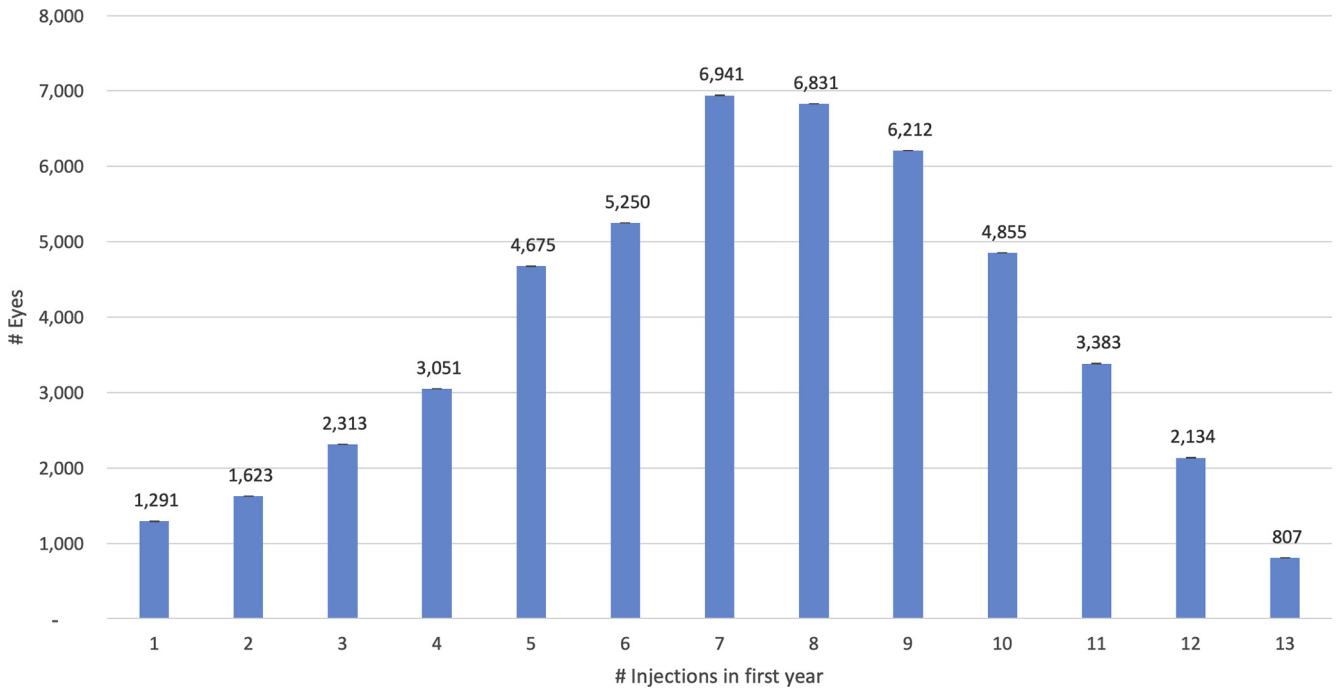


Figure 1. Histogram showing a nearly normal distribution of neovascular AMD patient eyes stratified by number of anti-vascular endothelial growth factor (VEGF) injections received in the first year of treatment. The median number of anti-VEGF injections received in the first year of treatment was 7.

Figure 1 depicts a histogram showing a nearly normal distribution of eyes stratified by number of anti-VEGF injections received in 1 year, between 1 and 13. A small number of eyes (119, or 0.024%) of the 49 485 total received more than 13 injections in 1 year, but were not assigned their own injection cohort because of this small subsample size.

Patient eyes that received 4 anti-VEGF injections or fewer over 1 year generally showed worse mean baseline VA than those patient eyes that received a greater number of injections over 1 year. In particular, those who received the fewest anti-VEGF injections, only 1 or 2 injections in 1 year, showed the worse mean baseline VA, between 41 and 45 letters (Snellen

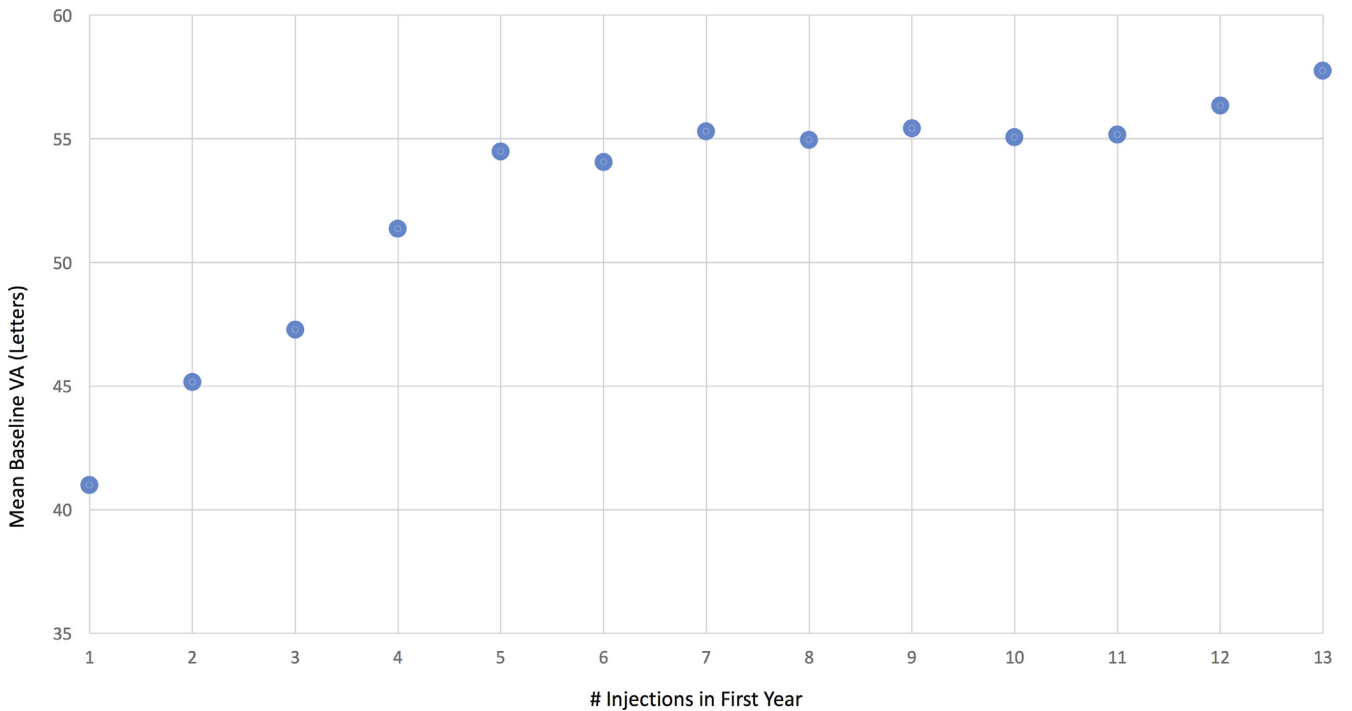


Figure 2. Scatterplot suggesting a trend in which neovascular AMD patient eyes with worse mean baseline visual acuity received fewer anti-vascular endothelial growth factors injections in the first year of treatment, on average.

Table 3. Mean 1-Year Changes in Visual Acuity, Stratified by Anti-Vascular Endothelial Growth Factor Injection Frequency

	1	2	3	4	5	6	7	8	9	10	11	12	13
Eyes	1291	1623	2313	3051	4675	5250	6941	6831	6212	4855	3383	2134	807
No.	3	3	5	6	9	11	14	14	13	10	7	4	2
%	34	35	36	34	34	35	34	36	36	38	38	40	39
Gender (%)	66	65	64	66	66	65	66	64	64	62	62	60	61
Male	81.1	81.8	81.6	81.3	81.9	81.6	81.7	81.1	80.6	80.0	79.5	78.7	78.4
Female													
Mean													
age (yrs)													
Mean VA													
(letters)													
Baseline	41.0	45.2	47.3	51.4	54.5	54.0	55.3	54.9	55.4	55.0	55.2	56.3	57.8
BCVA	-2.3	-2.1	-1.7	-2.3	-1.6	-0.4	0.7	2.1	2.4	3.3	4.3	3.0	3.2
Change	<0.001	<0.001	<0.001	<0.001	<0.001	0.20	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
at 1 yr	-3.46 to -1.17	-3.13 to -1	-2.52 to -0.79	-3.08 to -1.57	-2.13 to -1.03	-0.93 to 0.19	0.2 to 1.13	1.62 to 2.56	1.95 to 2.94	2.71 to 3.86	3.57 to 4.95	2.18 to 3.9	1.85 to 4.64
P value													
95% Confidence interval													

BCVA = best-corrected visual acuity; VA = visual acuity.

equivalent, 20/160–20/125), whereas those who received 13 injections in 1 year showed the highest mean baseline VA at nearly 58 letters (Snellen equivalent, 20/60), as demonstrated in Figure 2 and Table 3. In addition, those who received 7 anti-VEGF injections or fewer generally were older at baseline. The mean age of the entire group was nearly 81 years. Those who received 1 anti-VEGF injection had a mean baseline age of 81.1 years, whereas those who received 13 injections over 1 year had a mean baseline age of 78.4 years (Fig 3; Table 3).

Mean 1-Year Change in Visual Acuity Stratified by Anti-Vascular Endothelial Growth Factor Injection Frequency and Baseline Visual Acuity

Important trends were observed between mean 1-year change in VA and anti-VEGF injection frequency, depicted in Table 3 and Figure 4A. At the lower range, those patient eyes that received 4 anti-VEGF injections or fewer in the first year of treatment generally lost vision, approximately 2 to 3 letters at 1 year. In the mid range, a linear relationship was found between mean letters gained and mean number of anti-VEGF injections, up to 10 injections over 1 year, after which the relationship plateaued at approximately 3 to 4 letters gained. For example, the mean 1-year change in VA was -1.7 letters, -0.4 letters, +2.4 letters, and +3.0 letters in those 2313, 5250, 6212, and 2134 patient eyes that received a mean of 3 injections, 6 injections, 9 injections, and 12 injections, respectively.

Greater mean 1-year change in VA trended with worse baseline VA (Table 4). Specifically, when stratified by baseline VA of 20/200 or worse (6926 eyes), 20/70 to 20/200 (12 524 eyes), 20/40 to 20/70 (15 604 eyes), and 20/40 or better (14 312 eyes), the mean 1-year change in VA was +13.9 letters, +0.8 letters, -0.8 letters, and -3.3 letters, respectively. This result did not correlate with the relative number of anti-VEGF injections administered, because these patients all received a similar number of injections over 1 year. Specifically, patients with baseline VA of 20/200 or worse, 20/70 to 20/200, 20/40 to 20/70, and 20/40 or better received 6.5, 7.4, 7.5, and 7.3 anti-VEGF injections, respectively, over 1 year.

When mean 1-year change in VA was stratified by both anti-VEGF injection frequency and baseline VA, the trends generally persisted (Fig 4B). Mean 1-year change in VA tended to increase in patients with both increased anti-VEGF injection frequency and decreased baseline VA. At the upper range of anti-VEGF injection frequency, VA gain plateaued, regardless of baseline VA. Similarly, at the upper range of baseline VA, a ceiling effect occurred, regardless of anti-VEGF injection frequency. Patients with better VA at presentation tended to be particularly vulnerable to vision loss. Specifically, those patients with baseline VA of 20/40 or better tended to lose VA at 1 year, regardless of anti-VEGF injection frequency. However, these patients also showed better final VA compared with those patients with worse baseline VA.

Five-Year Trends in Presenting Visual Acuity, Mean Number of First-Year Anti-Vascular Endothelial Growth Factor Injections, and Mean 1-Year Change in Visual Acuity

Presenting VA, mean number of first-year anti-VEGF injections, and mean 1-year change in VA were assessed for trends over a

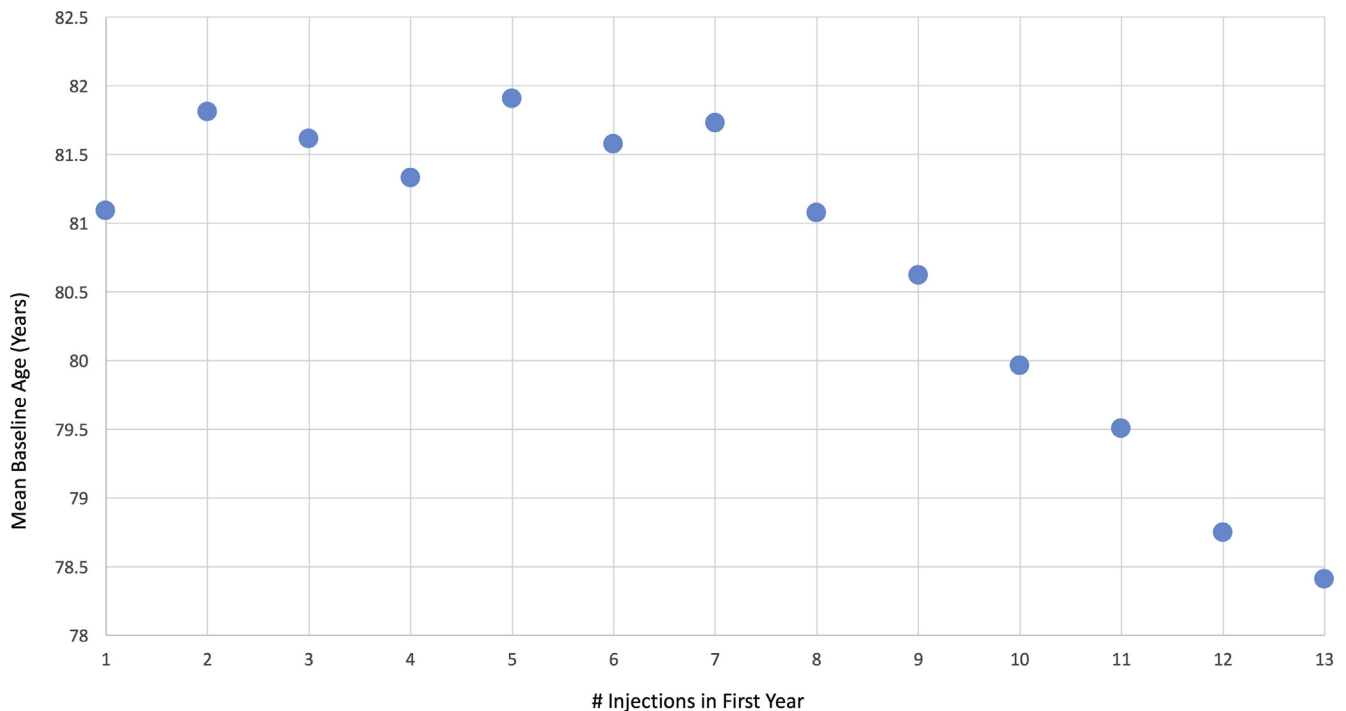


Figure 3. Scatterplot suggesting a trend in which older neovascular age-related macular degeneration patients generally received fewer anti-vascular endothelial growth factor injections in the first year of treatment, on average.

5-year period, stratified by initial anti-VEGF agent (Table 5). Declining trends were found in presenting VA over this 5-year period, which were more prominent in those eyes initially treated with ranibizumab or bevacizumab (Fig 5). In particular, the mean baseline VA in 2012 approximated 57 letters (Snellen equivalent, 20/80) for patient eyes treated with all 3 anti-VEGF agents. By 2016, mean baseline VA approximated 51 letters (Snellen equivalent, 20/100) for those patient eyes treated with ranibizumab and bevacizumab and approximated 56 letters (Snellen equivalent, 20/80) for those patient eyes initially treated with aflibercept.

Over the 5-year period, rising trends were found in mean numbers of first-year anti-VEGF injections, which were more prominent in those eyes initially treated with ranibizumab or bevacizumab (Fig 6). In 2012, there were 6.7 yearly injections, 7.3 yearly injections, and 7.2 yearly injections on average in the groups initially treated with bevacizumab, aflibercept, and ranibizumab, respectively. By 2016, the mean number of yearly injections in the groups initially treated with bevacizumab and ranibizumab had increased by approximately 1, to 7.8 and 8.0 yearly injections, respectively. The mean number of yearly injections in the groups initially treated with aflibercept (which is Food and Drug Administration approved for every 8-week dosing after 3 monthly loading doses) remained stable at 7.3 injections.

Over the 5-year period, there were rising trends in mean 1-year change in VA (Fig 7). In 2012, patients experienced a mean loss of vision at 1 year, ranging between 1 and 2 letters, but by 2016, they experienced a mean gain in vision, ranging between 2 and 4 letters

at 1 year. The magnitude of improvement was similar, regardless of initial anti-VEGF agent.

Discussion

This study specifically assessed the relationship between mean 1-year change in VA and injection frequency in real-world anti-VEGF-treated nAMD patients from the United States. The real-world sample was derived from a database of aggregated, longitudinal, de-identified EMRs representing a geographically and demographically diverse group of patients examined by retina specialists in the United States.

This real-world study is limited by its retrospective nature, use of aggregated data from numerous clinical sites, and nonstandardized visual acuity assessment. Given these constraints, correlation between eyes from bilaterally treated patients was not statistically modelled, although mean 1-year VA change did not differ clinically when excluding bilaterally treated patients from the dataset. Another limitation includes the possibility of prior treatment in a previous practice not in the Vestrum Health Retina Database, but the results are consistent with other real-world treatment-naïve nAMD studies,^{5–19} including 2 United States–based studies that required at least 3 anti-VEGF loading injections, generally administered to treatment-naïve patients.^{18,19} In addition, statistical testing in retrospective studies is inherently limited by selection bias, with resulting *P* values that are only nominal.

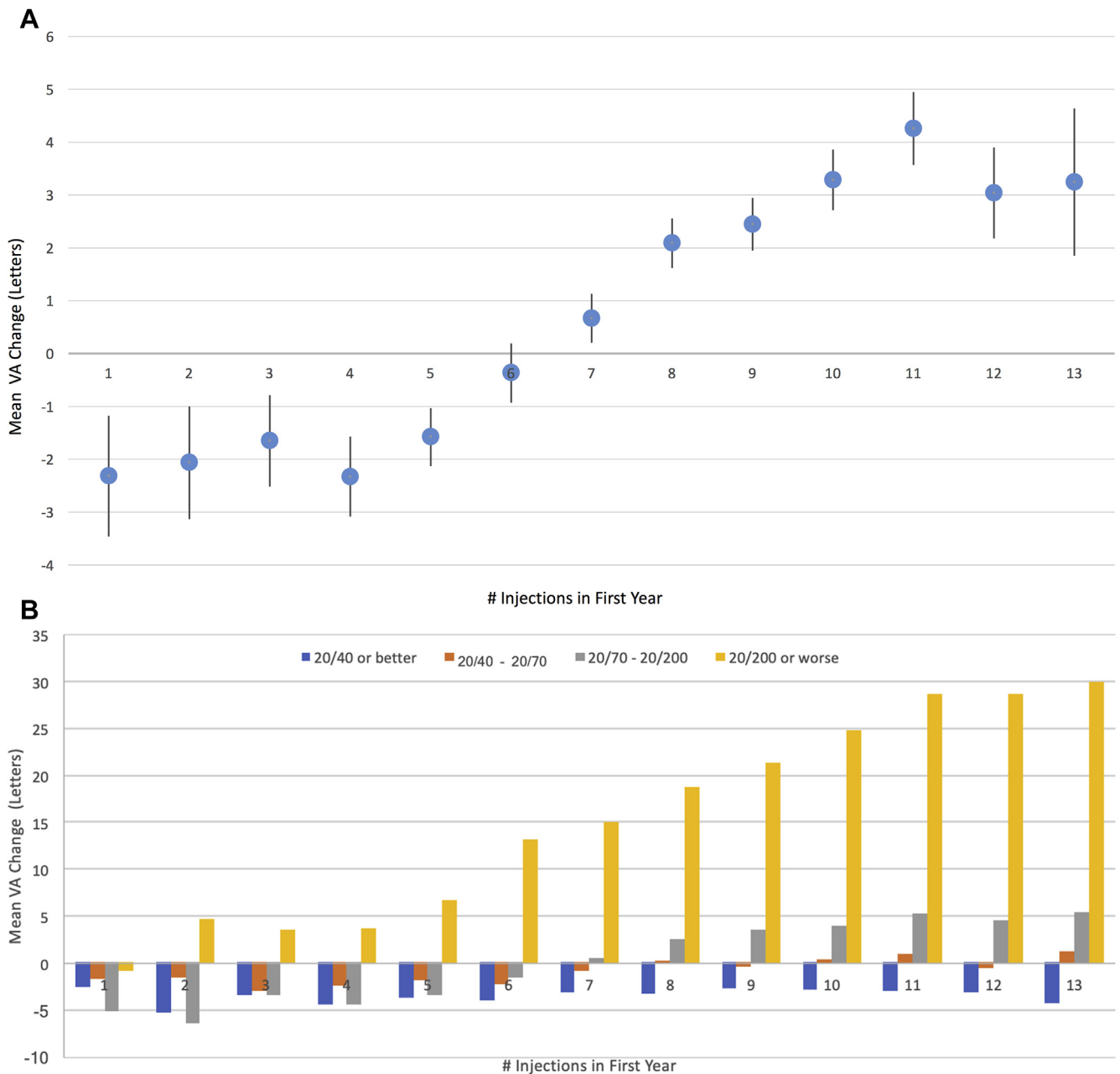


Figure 4. **A**, Graph showing change in visual acuity (VA) versus anti-vascular endothelial growth factor (VEGF) injections administered in the first year of treatment. The 95% confidence intervals are included. There appears to be a linear relationship between mean letters gained and mean number of anti-VEGF injections, between 4 and 10 injections over the first year of treatment, after which the relationship plateaus. At the lower range, those patient eyes that received 4 or fewer anti-VEGF injections in 1 year generally lost vision at 1 year. **B**, Graph showing the mean change in VA over 1 year, stratified by both anti-VEGF injection frequency and baseline VA. Mean 1-year change in VA tended to increase in patients with both increased anti-VEGF injection frequency and decreased baseline VA. There were ceiling effects related to both baseline VA and treatment intensity. Patients with baseline VA of 20/40 or better tended to lose VA at 1 year, regardless of anti-VEGF injection frequency. However, these patients also show better final VA compared with those patients with worse baseline VA.

Although mining EMRs has numerous limitations, the resulting data can yield important longitudinal insights to understand better patient outcomes in clinical practice. Most importantly, this study revealed multiple pertinent insights. First, in the United States, real-world nAMD patients received fewer anti-VEGF injections and experienced worse visual outcomes compared with patients receiving fixed,

frequent therapy in RCTs. Second, mean change in VA correlated with treatment intensity at 1 year, but with ceiling effects related to both treatment intensity and baseline VA; older patients and those with poor baseline VA may be particularly prone to undertreatment. Finally, over a recent 5-year period, trends in both treatment intensity and mean 1-year change in VA rose.

Table 4. Mean 1-Year Changes in Visual Acuity, Stratified by Baseline Visual Acuity

	20/40 or Better	20/40–20/70	20/70–20/200	20/200 or Worse
Eyes				
No.	14 312	15 604	12 524	6926
%	29	32	25	14
Gender (%)				
Male	37	35	35	34
Female	63	65	65	66
Mean age (yrs)	79.1	81.2	82.0	82.2
Mean VA (letters)				
Baseline BCVA	75.8	63.6	46.1	0.2
Change at 1 yr	–3.3	–0.8	0.8	13.9
P value	<0.001	<0.001	<0.001	<0.001
95% Confidence interval	–3.51 to –3.16	–0.98 to –0.52	0.45 to –1.21	13.07 to –14.68
Mean no. of anti-VEGF injections per patient per yr	6.5	7.4	7.5	7.3

BCVA = best-corrected visual acuity; VA = visual acuity; VEGF = vascular endothelial growth factor.

Real-World Neovascular Age-Related Macular Degeneration Patients Receive Fewer Anti-Vascular Endothelial Growth Factor Injections and Experience Worse 1-Year Outcomes Compared with Randomized Controlled Trials

Real-world nAMD patients in our United States-based study received fewer anti-VEGF injections and experienced worse visual outcomes on average, compared with patients receiving fixed, frequent therapy in RCTs. Registration trials for ranibizumab (monthly) and aflibercept (every 2 months after 3 monthly loading doses) and the monthly ranibizumab and bevacizumab arms of CATT show an average 1-year improvement of 8.5 letters across these studies (Table 1),^{1–4} whereas the current real-world study showed a mean gain of only 1 letter after a mean of 7.3 anti-VEGF injections. Numerous real-world studies of anti-VEGF therapy in nAMD have reported similar poor visual outcomes.^{5–19} In one particularly relevant real-world study using a database of American Academy of Ophthalmology members (Intelligent Research in Sight [IRIS] registry),

13 859 nAMD patients received an average of 6.1 anti-VEGF injections and experienced a mean improvement of 0.05 logarithm of the minimum angle of resolution (2.5 letters).¹⁹ Cross-trial comparisons are difficult because this IRIS registry study differed in several aspects (i.e., the IRIS database is not confined to referral-based retina practices, the protocol excluded patients with fewer than 3 anti-VEGF injections, and baseline VA was slightly better than the current real-world study). Naturally, compared with RCTs, these real-world studies are prone to worse therapeutic outcomes, given more diverse patient presentations, likely including advanced disease states not consistently eligible for RCTs. This explanation may account for the limited visual outcomes in the current real-world study when controlling for injection frequency.

Another common explanation for less favorable visual outcomes overall is undertreatment. A prior large United States–based retrospective analysis of medical claims from 2006 through 2011 similarly showed that, compared with RCTs, patients in the United States received fewer anti-VEGF treatments and less frequent monitoring.²¹ One reason for fewer injections in the real world compared with

Table 5. Five-Year Trends in Presenting Visual Acuity, Mean Number of Yearly Anti-Vascular Endothelial Growth Factor Injections, and Mean 1-Year Changes in Visual Acuity, Stratified by Initial Anti-Vascular Endothelial Growth Factor Agent

	2012	2013	2014	2015	2016
Mean baseline BCVA (letters)					
Bevacizumab	56.9	53.0	53.3	50.7	51.3
Aflibercept	57.3	57.9	56.6	54.6	56.0
Ranibizumab	57.3	54.0	52.8	50.4	50.5
Mean no. of anti-VEGF injections in the first yr of treatment					
Bevacizumab	6.7	6.9	7.2	7.7	7.8
Aflibercept	7.3	7.4	7.3	7.4	7.3
Ranibizumab	7.2	7.1	7.2	7.3	8.0
Mean VA change at 1 yr (letters)					
Bevacizumab	–1.4	0.8	1.0	2.9	3.5
Aflibercept	–2.0	–1.1	–0.1	2.2	1.7
Ranibizumab	–1.1	–0.4	0.8	2.5	3.8

BCVA = best-corrected visual acuity; VA = visual acuity; VEGF = vascular endothelial growth factor.

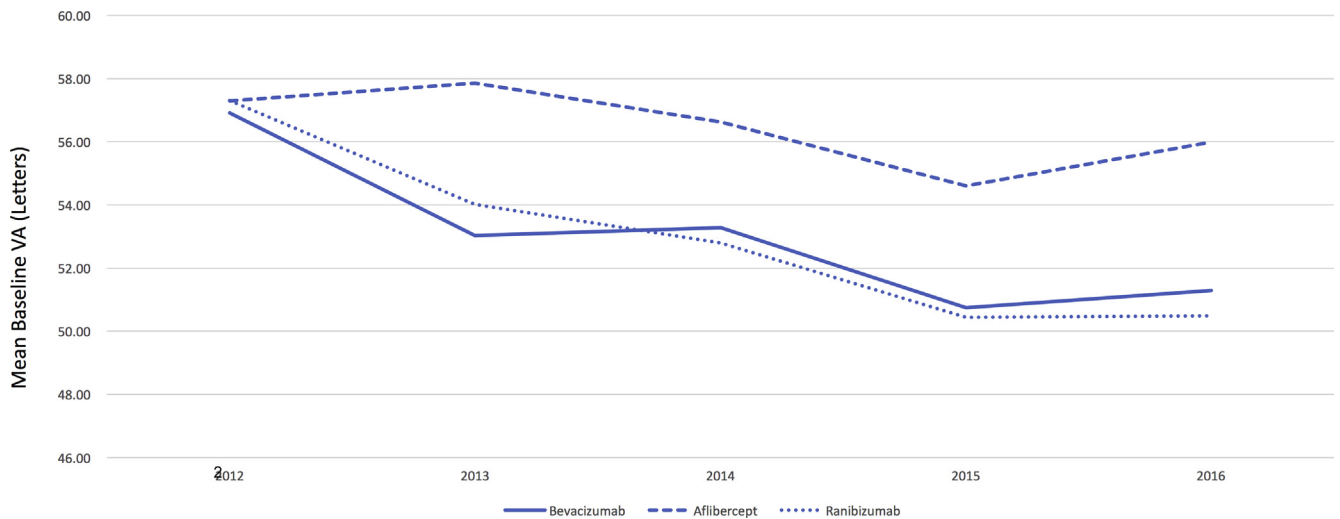


Figure 5. Graph showing mean baseline visual acuity (VA) over time from 2012 through 2016. There were declining trends in presenting VA over this 5-year period that were more prominent in those eyes initially treated with ranibizumab or bevacizumab.

RCTs involves the adoption of variable frequency anti-VEGF treatment regimens that aim to decrease treatment burden for nAMD patients. The 2015 American Society of Retina Specialists Preferences and Trends Survey of more than 2700 retina specialists in 60 countries revealed that more than 90% of retina specialists, both in the United States and internationally, use OCT-guided variable frequency anti-VEGF treatment protocols for nAMD. In the current real-world study, patients received a mean number of anti-VEGF injections similar to that in the prior United States claims analysis,²¹ similar to that in the IRIS registry real-world study,¹⁹ and similar to that in the as-needed treatment arms of CATT.^{2,22} These findings are consistent with variable frequency treatment regimens for nAMD among United States retina physicians in the Vestrum Health Retina Database.

This current real-world study also showed nearly identical mean 1-year change in VA when stratified by anti-VEGF agent, which is not surprising, because RCTs have shown bevacizumab to be noninferior to ranibizumab^{2,22,23} and various regimens of aflibercept to be noninferior to monthly ranibizumab.^{3,24} Furthermore, in this study, comparison of mean 1-year VA change is limited by the higher mean baseline VA for patients treated with aflibercept versus other agents by approximately 4 letters. Nevertheless, the IRIS registry real-world study, which did not allow for switching between anti-VEGF agents, also showed similar visual outcomes among the anti-VEGF agents.¹⁹

Mean Change in Visual Acuity Correlates with Treatment Intensity at 1 Year, Whereas Older Patients and Those with Poor Baseline Visual Acuity May Be Prone to Undertreatment; Patients with Better Visual Acuity at Presentation Tend to Be Particularly Vulnerable to Vision Loss

This study showed a linear relationship between mean letters gained and mean number of anti-VEGF injections,

between 4 and 10 injections in the first year of treatment, with 4 or fewer injections or 10 or more injections associated with loss of vision or a plateau, respectively. Furthermore, regardless of treatment intensity, nAMD patients with good baseline VA tend to be particularly vulnerable to vision loss. Nevertheless, these patients also showed better final VA compared with those patients with worse baseline VA, who gained more letters at 1 year.

Multiple reports have suggested a relationship between the number of anti-VEGF injections and letters gained, with fewer injections associated with worse outcomes.^{6–8,12,15,25,26} Consequently, attempts to limit treatment burden through the adoption of variable frequency anti-VEGF treatment regimens must be approached cautiously. Multiple prospective RCTs have demonstrated that variable frequency anti-VEGF therapy for nAMD results in a less favorable visual outcome compared with fixed, frequent anti-VEGF suppression.^{22,23,27–30} In CATT, for example, patients assigned to monthly treatment regimens of ranibizumab or bevacizumab experienced a statistically significantly greater benefit in VA gain compared with those receiving as-needed therapy (difference of 2.4 Early Treatment Diabetic Retinopathy Study letters at 2 years; $P = 0.046$).²²

Another variable frequency regimen, treat and extend, seems to perform relatively well in practice based mainly on retrospective studies, a randomized study of 441 patients (the Lucentis Compared to Avastin Study)³¹ and a randomized trial of 60 patients (the Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration).³² However, the mean number of treatments over the first year in these latter two randomized trials exceeded the mean number of treatments in the current study. This further supports relative undertreatment in the real world, as well as real-world patient presentations that are prone to worse therapeutic outcomes.

In this study, patients who were undertreated, receiving 4 or fewer injections in 1 year, showed lower mean baseline

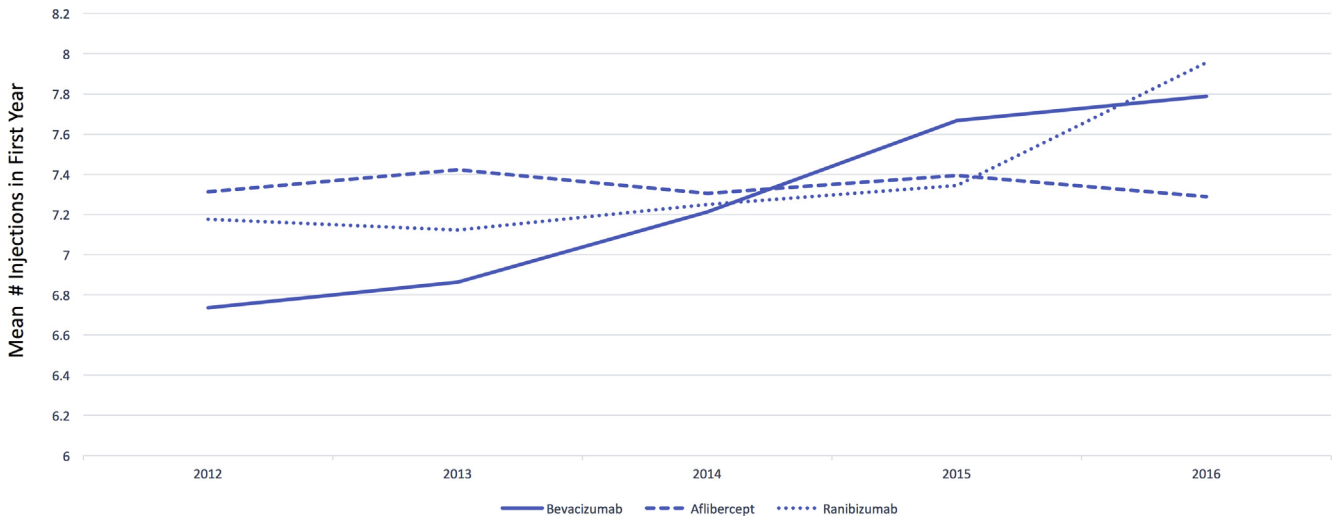


Figure 6. Graph showing mean number of anti-vascular endothelial growth factor (VEGF) injections in the first year of treatment, from 2012 through 2016. Over the 5-year period, there were rising trends in mean numbers of first-year anti-VEGF injections, which were more prominent in those eyes initially treated with ranibizumab or bevacizumab.

VA and greater mean baseline age. Paradoxically, these patients with poor baseline VA could have the most to gain from anti-VEGF therapy, because patients with poor baseline VA generally gain more vision than those patients with better baseline VA. It is unclear if these patients received fewer injections because of the advanced nature of the disease and/or advanced age associated with comorbidities precluding frequent visits and more intense therapy.

For those patients receiving 4 or fewer anti-VEGF injections at 1 year, the apparent floor of approximately 2 letters lost may seem counterintuitive, as one may expect progressively worse outcomes with less treatment, given that registration trials have shown losses averaging 10 letters in control arms without anti-VEGF treatment at 1 year.^{1,4} However, the real-world nAMD patient eyes receiving 4

or fewer anti-VEGF injections also showed lower mean baseline VA, and it is possible that some received fewer injections because of advanced disease and were not expected to improve or worsen meaningfully. In addition, this real-world analysis specifically assessed one-year outcomes and, by design, did not assess patients who failed to follow up at one year, while our previous smaller real-world nAMD study demonstrated that nAMD patients lost to follow-up tend to be experiencing worse outcomes.¹⁸ Consequently, the current analysis could overestimate the mean 1-year change in VA, particularly in those patient eyes that received 4 or fewer anti-VEGF injections.

Patients who received more intense therapy, 10 or more anti-VEGF injections in 1 year, showed greater mean baseline VA and lower mean baseline age. Patients with

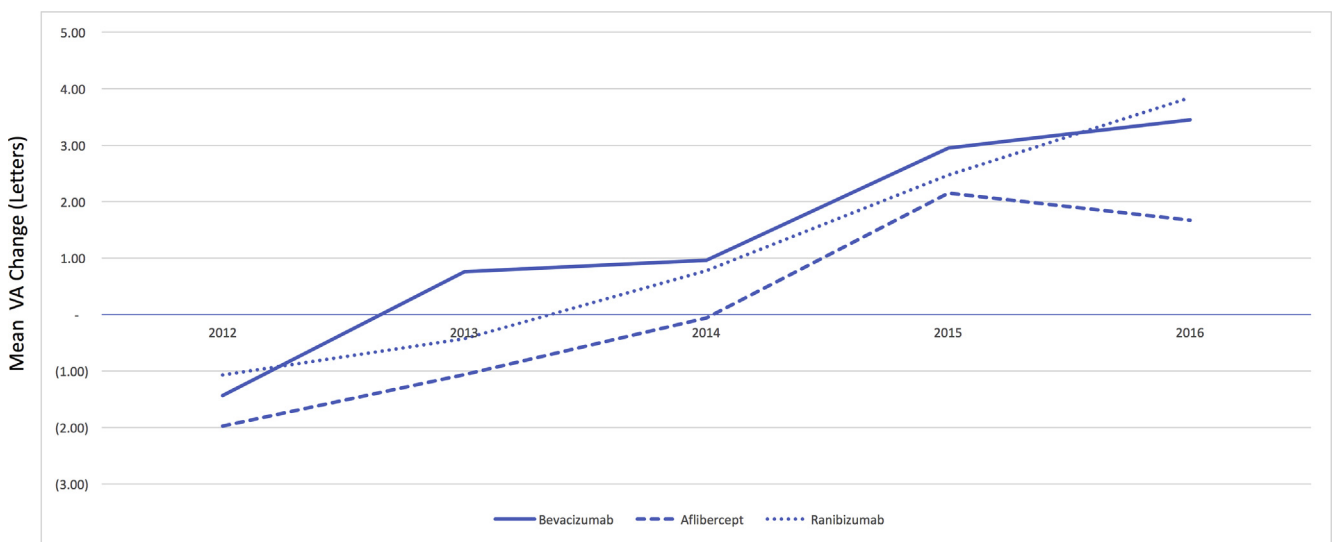


Figure 7. Graph showing mean 1-year change in visual acuity (VA) demonstrating a positive trend from 2012 through 2016 for all 3 anti-vascular endothelial growth factor (VEGF) treatment groups, generally mirroring the trend of increased anti-VEGF frequency over the same period.

greater baseline VA are at greater risk of vision loss, and more intense therapy may prevent significant vision loss, although there is a relative ceiling effect in VA gains. This ceiling effect highlights a limitation of anti-VEGF therapy. Frequent injections of anti-VEGF agents such as anti-VEGF therapy may control exudation but do not address other causes of vision loss in age-related macular degeneration, such as geographic atrophy and subretinal fibrosis.

Five-Year Trends in Presenting Visual Acuity, Mean Number of First-Year Anti-Vascular Endothelial Growth Factor Injections, and Mean 1-Year Change in Visual Acuity

In this study, over a recent 5-year period, declining trends in presenting VA for nAMD patients were found. It is possible that referring physicians and retina practices may view nAMD with less urgency than it once held, as anti-VEGF therapy for nAMD becomes a more routine part of retina practice, and consequently patients wait longer for initial consultation with a retina specialist. In addition, over the past 5 years, there have been rising trends in both first-year treatment intensity and mean 1-year change in VA. Practitioners may be increasingly aware of the implications of undertreatment, with resulting progressively greater treatment intensity and better visual outcomes.

In summary, real-world nAMD patients receive fewer anti-VEGF injections and experience worse visual outcomes compared with patients receiving fixed, frequent therapy in RCTs. When stratified by anti-VEGF agent, the mean 1-year changes in VA were nearly identical. Older patients and those with poor baseline VA may be particularly prone to undertreatment. Mean 1-year change in VA tended to increase in patients with both increased anti-VEGF injection frequency and decreased baseline VA, although ceiling effects are related to both parameters. The rising trends in both treatment intensity and mean 1-year change in VA over the previous 5 years is reassuring.

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Footnotes and Financial Disclosures

Originally received: April 22, 2019.

Final revision: May 20, 2019.

Accepted: May 20, 2019.

Available online: May 25, 2019. Manuscript no. ORET_2019_214.

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Financial Disclosure(s):

The author(s) have made the following disclosure(s): T.A.C.: Employee and Equity owner — Clearside Bio.

J.S.P.: Board member and Equity owner — Notal Vision; Consultant — Genentech, Allegro, Dutch Ophthalmic, Notal Vision, Novartis, Regenxbio; Financial support — Genentech; Co-founder — Vestrum Health.

D.F.W.: Co-founder — Vestrum Health.

HUMAN SUBJECTS: No human subjects were included in this study. This project was considered exempt from institutional review board review because the research involved only the collection of existing data, which

had been de-identified. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Ciulla

Analysis and interpretation: Ciulla, Hussain, Pollack, Williams

Data collection: Ciulla

Obtained funding: N/A

Overall responsibility: Ciulla, Hussain, Pollack, Williams

Abbreviations and Acronyms:

CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; **CI** = confidence interval; **EMR** = electronic medical record; **IRIS** = Intelligent Research in Sight; **nAMD** = neovascular age-related macular degeneration; **RCT** = randomized controlled trial; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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