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SIERRA-AMD: A Retrospective, Real-World Evidence Study of Patients with Neovascular Age-Related Macular Degeneration in the United States

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Purpose: Characterize real-world baseline visual acuity (VA) and anti-vascular endothelial growth factor (VEGF) treatment patterns in neovascular age-related macular degeneration patients in 2012—2015.

Design: Retrospective, multicenter, noninterventional real-world evidence study.

Participants: A total of 98 821 eyes from 79 885 patients receiving intravitreal anti-VEGF therapy.

Methods: Anonymized patient data routinely collected over 5 years were extracted from 58 United States centers to a central database using an electronic medical records system.

Main Outcome Measures: Baseline VA, VA change from baseline, treatment frequencies, annual anti-VEGF injections, bilateral treatment frequencies, annual total clinic visits, and noninjection clinic visits.

Results: Baseline characteristics were comparable across years. Baseline VAs (Mean±standard deviation [SD] Early Treatment Diabetic Retinopathy Study [ETDRS] letters) were similar for 2012, 2013, and 2014 (53.6±23.3, 53.2±23.4, and 53.1±23.6, respectively), but was lower for 2015 (50.7±24.4). In eyes with 4-year follow-up, VA changes from baseline (ETDRS letters) were least squares means of +1.1 (95% confidence interval [CI], 1.0;1.3), −1.3 (95%CI, −1.5;−1.0), and −3.1 (95%CI, −3.5;−2.7), and −5.2 (95%CI, −6.0;−4.3) for years 1—4. Mean±SD number of injections was 7.5±1.9, 6.7±2.1, 6.6±2.3, and 6.4±2.3 for years 1—4. By year 4, 36.7% of eyes had ≤8-week dosing intervals (q8w) and 21.2% had ≥12-week dosing intervals. Eyes treated q8w increased 40% from Year 1 (32.4%) to Year 4 (45.3%). Baseline bilateral treatment frequency was 6.1%. Of the patients treated bilaterally, 32.0% received the first treatment in the better-seeing eye, and 68.0% received first treatment in an eye with vision the same as or worse than the fellow-eye. This trend was evident across all index years.

Conclusions: This real-world study describes the treatment burden, initiation and monitoring patterns, and VA outcomes at a scale and timeframe that has not been previously reported. In this cohort, baseline VA was similar for the index years 2012—2014, but lower for 2015. In patients with 4-year follow-up, both VA and injection frequency declined, whereas the proportion of eyes treated more frequently than the recommended q8w interval increased. The reduction in dosing intervals may be a consequence of intensification of treatment due to year-on-year VA loss and disease progression. *Ophthalmology Retina 2020;4:122-133 © 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/).*

Supplemental material available at www.ophthalmologyretina.org.

Age-related macular degeneration (AMD) is a chronic degenerative disorder of the retina that causes progressive loss of central vision and is a leading cause of blindness in older adults.[1,2] Approximately 1.8 million Americans 40 years of age or older are estimated to be affected by AMD. Owing to the rapidly aging population, the number of AMD cases is expected to reach 2.95 million in the Unites States by 2020.[3]

Clinically, AMD is classified into the nonexudative dry or atrophic form and the exudative or neovascular form. Although neovascular AMD (nAMD) accounts for only 10% to 20% of all AMD cases, it is responsible for approximately 80% to 90% of vision loss associated with the disease.[2] Neovascular AMD is characterized by the proliferation of abnormal macular blood vessels that can leak fluid and blood, resulting in damage to the photoreceptors and the retinal pigment epithelium, a process known as choroidal neovascularization (CNV). Without early diagnosis and treatment, nAMD can progress rapidly, leading to irreversible visual impairment in the affected eye.[4] Furthermore, patients with unilateral nAMD have a 4% to 12% risk of CNV developing in the

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second eye 1 year after diagnosis, and between 20% and 42% of such patients harbor the risk of CNV developing 2 to 3 years after diagnosis.[5–8]

Currently, no cure for nAMD exists; however, available treatment options maintain or improve vision, or both. The standard of care for the treatment of nAMD involves intravitreal injections of the licensed anti−vascular endothelial growth factor (VEGF) agents ranibizumab or aflibercept.[4] These agents act by inhibiting the growth of abnormal blood vessels, thus reducing the level of exudation in the macula.[9] Ranibizumab was approved for nAMD by the Food and Drug Administration in 2006 and may be administered on a monthly basis or less frequently after 3 consecutive monthly loading injections at the discretion of the treating physician.[10,11] Aflibercept, which was approved by the Food and Drug Administration for nAMD in 2011, is recommended to be administered bimonthly after 3 consecutive monthly loading doses, but may be administered on a monthly basis in some patients. Aflibercept also may be dosed once every 12 weeks after 1 year of therapy, although the 12-week dosing regimen is less effective than bimonthly dosing. Aflibercept also may be dosed at other intervals of between 4 and 12 weeks based on a treat-and-extend paradigm at the discretion of the managing ophthalmologist.[12] In addition, bevacizumab, an anti-VEGF agent developed for the treatment of metastatic colon cancer in 2004, has been used off label for the treatment of nAMD.[13]

The analysis of large, structured, real-world electronic medical record (EMR) databases can generate insights into the evolution of nAMD patient demographics and clinical characteristics, as well as how clinical trial results compare with population-level treatment outcomes and patterns in routine clinical settings.[14–17] In the current study, we analyzed data from a standardized EMR repository to understand better the real-world characteristics, treatment patterns, and outcomes of a large United States nAMD patient cohort initiating anti-VEGF therapy between 2012 and 2015, with a focus on changes in VA and treatment burden in a real-world routine clinical practice over time. The primary objective of this study was to characterize the differences in baseline VA for United States patients starting anti-VEGF therapy for the treatment of nAMD between the index years 2012 and 2015 based on EMR data. Key secondary objectives included characterization of the nAMD population (by index year) with respect to demographic and clinical data; VA change from baseline to years 1, 2, 3, and 4 after treatment initiation; treatment patterns (i.e., treatment regimen, the number of anti-VEGF injections, the number of total clinic visits and noninjection visits, injection intervals); and the frequency of bilateral anti-VEGF treatment in nAMD patients.

Methods

Ethics Statement

This study was designed, conducted, and reported in accordance with the guidelines for good pharmacoepidemiologic practices of the International Society for Pharmacoepidemiology, the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, and the ethical principles stated in the Declaration of Helsinki.[18–20] Consistent with the United States Code of Federal Regulations (45 CFR 164.514(e)), the EMR source used in this study constituted a limited data set; hence, formal ethics approval was not required.

Study Design and Data Sources

The study was a retrospective, noncomparative, nonrandomized cohort study of the characteristics of a United States nAMD patient population. This study was conducted using anonymized EMR data collected in a standardized manner and deposited in the Vestrum Health Retina database (www.vestrumhealth.com). For the current study, all data were extracted from a panel of 58 medical retina practices across the United States between the index years 2012 and 2015; it is important to note that the panel of 58 participating centers may not have been identical across all index years. The index date was defined as the date of the first anti-VEGF injection or, if a patient did not receive anti-VEGF, the date of the first nAMD diagnosis for each study eye available in the database during the study period (January 1, 2012, through June 30, 2016). Patient eyes had 1 to 4 years of follow-up. Data generated under ranibizumab, aflibercept, or unlicensed bevacizumab treatment were assessed in a pooled analysis (i.e., without distinguishing among anti-VEGF drugs).

Participants

The unit of analysis for the current study was the patient eye. Patients who were considered treatment naïve (i.e., no anti-VEGF treatment for more than 180 days before the index date), were 50 years of age or older, and were diagnosed with nAMD in at least 1 eye between January 1, 2012, and December 31, 2015, were eligible for inclusion in this study.

Outcome Measures

To evaluate the primary study objective, all VA measurements in the EMR database were converted from logarithm of minimum angle of resolution (logMAR) scores to Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores according to established guidelines.[21] Secondary outcome measures, assessed in patients who had 1 year or more of follow-up data, included the VA changes from baseline to years 1, 2, 3, and 4; the total number of anti-VEGF injections administered annually; and the annual number of total clinic visits and noninjection clinic visits (defined as a clinic visit without a record of anti-VEGF intravitreal administration in the EMR data). We also examined the proportion of eyes receiving a fixed treatment regimen, where a fixed treatment regimen is defined as an eye with at least 80% of all (nonloading) injections for the year that are 4, 8, or 12 weeks (±15 days) after the previous injection. Finally, we assessed the proportion of eyes receiving unilateral and bilateral treatment and the time between first-eye and second-eye anti-VEGF therapy for bilaterally treated patients. In patients receiving bilateral treatment, the initiation of treatment in the better-seeing study eye versus the worse-seeing fellow eye also was evaluated; for this, better- and worse-seeing eyes were defined as per Bressler et al.[22] Because this study was based on secondary data sources, safety monitoring and safety reporting on an individual case level was not applicable and is not reported here.

Statistical Analysis

All analyses were performed by IQVIA (Cambridge, Massachusetts) using SAS software version 9.2 (SAS Institute, Inc, Cary, NC). Descriptive statistics were tabulated for demographic and clinical characteristics and outcome variables. Continuous variables are summarized as the number of observations, means, standard deviations (SDs), and 95% confidence intervals (CIs). Estimates of least square means (LSMs) VA change from baseline at years 1, 2, 3, and 4 and their 95% CIs were based on an analysis

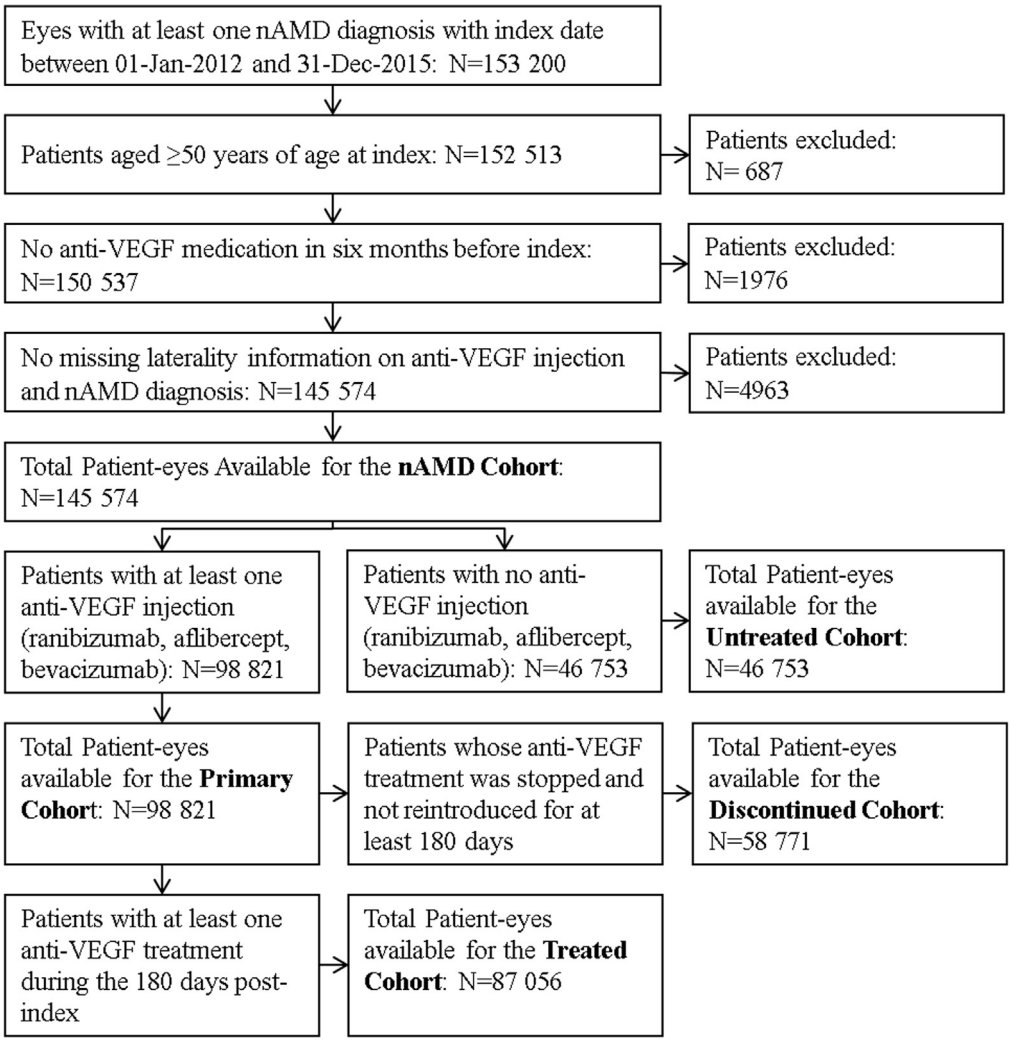

Figure 1. Chart showing selection workflow and patient disposition defining the different study cohorts. The neovascular age-related macular degeneration (nAMD) cohort (n = 145 574) was defined as eyes in adults 50 years of age and older at index with at least 1 record of nAMD diagnosis and with no anti−vascular endothelial growth factor (VEGF) treatment 6 months before the index date. Eyes in the untreated cohort (n = 46 753) did not receive any anti-VEGF injections, whereas eyes in the primary cohort (n = 98 821) received at least 1 anti-VEGF injection. The treated cohort (n = 87 056) was defined as eyes with at least 1 anti-VEGF treatment during the 180 days after index. The discontinued cohort (n = 58 771) was made up of nAMD eyes whose anti-VEGF treatment was stopped and not reintroduced for at least 180 days.

of covariance model adjusted for baseline VA (0−9 ETDRS letters, 10−24 ETDRS letters, 25−39 ETDRS letters, 40−54 ETDRS letters, 55−69 ETDRS letters, 70−84 ETDRS letters, and ≥85 ETDRS letters) and patient age (≤75 years, 76−80 years, 81−85 years, 86−89 years, >89 years) and were calculated overall and for each index year assuming the marginal baseline VA and age distribution of the overall population at each time point. Generalized estimating equations were used to extend the analysis of covariance model by additionally controlling for patient or study eye as a repeated factor. As a sensitivity analysis, mean VA change from baseline was calculated stratifying by years of follow-up rather than by index year. Categorical variables are presented as counts and percentages. Hypothesis testing was not predefined for this study, and hence no statistical tests are reported here.

Results

Patient Disposition

A total of 153 200 eyes with at least 1 nAMD diagnosis and an index date between January 1, 2012, and December 31, 2015, were identified in the EMR database. A total of 145 574 eyes were found to fulfill the inclusion and exclusion criteria; of these, 98 821 eyes received intravitreal anti-VEGF therapy and were defined as the study eye, on which the primary outcome of the study was assessed. Further data refinement identified a total of 87 056 eyes that were classified as having received at least 1 intravitreal anti-VEGF treatment during the 180 days after index; these eyes

Table 1. Baseline Characteristics of the Primary Cohort across All Index Years

Characteristics	Index Year				
	Overall (n = 79 885 Patients; n = 98 821 Eyes)	*2012 (n = 12 340 Patients; n = 14 438 Eyes)*	*2013 (n = 18 929 Patients; n = 23 132 Eyes)*	*2014 (n = 29 056 Patients; n = 36 099 Eyes)*	*2015 (n = 19 560 Patients; n = 25 152 Eyes)*
Age (yrs)					
≤70	7609 (9.5)	819 (6.6)	1575 (8.3)	2773 (9.5)	2442 (12.5)
71–75	7736 (9.7)	1016 (8.2)	1726 (9.1)	2835 (9.8)	2159 (11.0)
76–80	12 094 (15.1)	1641 (13.3)	2901 (15.3)	4291 (14.8)	3261 (16.7)
81–85	16 897 (21.2)	2558 (20.7)	4017 (21.2)	6163 (21.2)	4159 (21.3)
86–89	15 912 (19.9)	2711 (22.0)	3836 (20.3)	5736 (19.7)	3629 (18.6)
≥90	19 637 (24.6)	3595 (29.1)	4874 (25.7)	7258 (25.0)	3910 (20.0)
Mean (SD)	82.6 (8.4)	83.9 (7.8)	83.0 (8.2)	82.7 (8.4)	81.4 (8.8)
Sex					
Male	29 254 (37.0)	4324 (36.3)	6985 (37.7)	10 566 (36.4)	7379 (37.7)
Female	49 777 (63.0)	7582 (63.7)	11 544 (62.3)	18 476 (63.6)	12 175 (62.3)
Missing	854	434	400	14	6
VA study eye (ETDRS letters)	66 394 (67.2)	8665 (60.0)	15 973 (69.1)	24 807 (68.7)	16 949 (67.4)
≥70	17 763 (26.8)	2439 (28.1)	4398 (27.5)	6830 (27.5)	4096 (24.2)
≤35	17 427 (26.2)	2233 (25.8)	4234 (26.5)	6208 (25.0)	4752 (28.0)
Mean (SD)	52.6 (23.8)	53.6 (23.3)	53.2 (23.4)	53.1 (23.6)	50.7 (24.4)

ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
Data are no. (%) unless otherwise indicated. Number of eyes treated indicated the study eye(s) treated for each given patient. Age is recorded as a 5-year range with the midpoint of the range used to calculate mean and 92 years used for the highest category (≥90 years).

comprised the final treated cohort for which secondary outcomes are reported. In the primary and the treated cohorts, 99.6% of all included study eyes were truly treatment naïve (i.e., had never previously received any anti-VEGF therapy); 0.4% of study eyes in the primary (n = 376) and the treated (n = 312 eyes) cohorts had received anti-VEGF therapy more than 180 days before the index date. Figure 1 details the patient disposition for the current study, with further details of the attrition of the study sample in Table S1 (available at www.ophthalmologyretina.org).

Baseline Characteristics for the Primary Patient Cohort

Baseline characteristics for the primary cohort (n = 98 821 eyes; n = 79 885 patients) across all index years (2012–2015) are presented in Table 1. A total of 14 438 eyes (n = 12 340 patients), 23 132 eyes (n = 18 929 patients), 36 099 eyes (n = 29 056 patients), and 25 152 eyes (n = 19 560 patients) initiated treatment in 2012, 2013, 2014, and 2015, respectively. The overall proportion of women was 63% (n = 49 777) and was comparable among all index years. The overall mean patient age in the primary cohort was 82.6 years (standard deviation [SD], 8.4 years), with a trend toward younger mean patient age with each index year (2012, 83.9 years [SD, 7.8 years]; 2013, 83.0 years [SD, 8.2 years]; 2014, 82.7 years [SD, 8.4]; and 2015, 81.4 years [SD, 8.8 years]).

Baseline Visual Acuity of Primary Cohort Eyes over the Index Years

The primary objective of this study was to characterize the baseline VA for eyes in the primary cohort (n = 98 821) that received anti-VEGF treatment during the index years (Table 1). For eyes with available data (n = 66 394), the mean baseline VA was comparable for the index years 2012 (n = 8655 eyes [60.0%]), 2013 (n = 15 973 eyes [69.1%]), and 2014 (n = 24 807 [68.7%]) with values of 53.6 ETDRS letters (SD, 23.3 ETDRS letters), 53.2 ETDRS letters (23.4 ETDRS letters), and 53.1 ETDRS letters (23.6 ETDRS letters), respectively, but was lower for 2015 (n = 16 949 [67.4%]; VA, 50.7 ETDRS letters [SD, 24.4 ETDRS letters]). The overall VA for the patient population across all index years was 52.6 ETDRS letters (SD, 23.8 ETDRS letters).

Among index years, the proportion of eyes with a VA of 35 ETDRS letters or fewer (i.e., legal blindness[23]) at baseline ranged between 25.0% (in 2014) and 28.0% (in 2015), whereas the proportion of eyes with 70 ETDRS letters VA or more (i.e., driving eligibility[24]) at baseline decreased marginally from 28.1% in 2012 to 27.5% in both 2013 and 2014 and to 24.2% in 2015. Overall, the proportion of eyes with VA of 35 ETDRS letters or fewer and 70 ETDRS letters or more was 26.2% and 26.8%, respectively.

Visual Acuity Changes from Baseline in the Treated Patient Cohort

A key secondary outcome of this study was the overall change in VA from baseline to years 1, 2, 3, and 4 for eyes in the treated cohort (i.e., eyes receiving at least 1 anti-VEGF injection in the 180 days after index; Table 2). In total, 58 794 of 87 056 eyes (67.5%) in the treated cohort had baseline VA data available for this analysis. For this cohort, comparable baseline LSM (±95% CI) VA was observed for index years 2012 (53.4 ETDRS letters [95% CI, 53.3–53.5 ETDRS letters]; n = 7878), 2013 (53.3 ETDRS letters [95% CI, 53.3–53.4 ETDRS letters]; n = 14 111), 2014 (53.0 ETDRS letters [95% CI, 53.0–53.1 ETDRS letters]; n = 21 784), and 2015 (52.9 ETDRS letters [95% CI, 52.9–53.0 ETDRS letters]; n = 15 021). Analysis of the VA

Table 2. Mean Change in Visual Acuity from Baseline for the Treated Patient Cohort

Characteristics	Overall	Index Years			
		2012	2013	2014	2015
Baseline, no. of eyes (%)	58 794 (100)	7878 (100)	14 111 (100)	21 784 (100)	15 021 (100)
Mean VA, ETDRS letters (SD)	53.1 (23.3)	54.2 (22.9)	53.9 (22.8)	53.6 (23.2)	51.1 (24.0)
Mean VA (ETDRS letters), LSM (95% CI)	53.1 (53.1–53.1)	53.4 (53.3–53.4)	53.3 (53.3–53.4)	53.0 (53.0–53.1)	52.9 (52.9–53.0)
Year 1 follow-up, no. of eyes (%)	32 840 (55.9)	5009 (63.6)	8143 (57.7)	12 875 (59.1)	6813 (45.4)
Mean change in VA from baseline, ETDRS letters (SD)	1.1 (15.3)	−0.4 (13.5)	0.5 (14.7)	1.2 (15.4)	2.9 (16.6)
Mean VA (ETDRS letters), LSM (95% CI)	1.1 (1.0–1.3)	−0.1 (−0.5 to 0.3)	0.7 (0.4–1.0)	1.3 (1.1–1.5)	2.1 (1.8–2.5)
Year 2 follow-up, no. of eyes (%)	17 171 (29.2)	3682 (46.7)	5521 (39.1)	7968 (36.6)	
Mean change in VA from baseline, ETDRS letters (SD)	−1.3 (16.3)	−1.9 (15.0)	−1.2 (16.4)	−1.0 (16.9)	
Mean VA (ETDRS letters), LSM (95% CI)	−1.3 (−1.5 to −1.0)	−1.7 (−2.2 to −1.2)	−1.3 (−1.7 to −0.9)	−1.1 (−1.4 to −0.7)	
Year 3 follow-up, no. of eyes (%)	6118 (10.4)	2884 (36.6)	3234 (22.9)		
Mean change in VA from baseline, ETDRS letters (SD)	−3.1 (17.2)	−3.6 (16.2)	−2.6 (18.0)		
Mean VA (ETDRS letters), LSM (95% CI)	−3.1 (−3.5 to −2.7)	−3.4 (−4.0 to −2.8)	−2.8 (−3.3 to −2.2)		
Year 4 follow-up, no. of eyes (%)	1649 (2.8)	1649 (20.9)			
Mean change in VA from baseline, ETDRS letters (SD)	−5.2 (18.2)	−5.2 (18.2)			
Mean VA (ETDRS letters), LSM (95% CI)	−5.2 (−6.0 to −4.3)	−5.2 (−6.0 to −4.3)			

CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LSM = least square mean; SD = standard deviation; VA = visual acuity. Excludes eyes with baseline VA missing or not convertible to letter score.

change (±95% CI) from baseline at year 1 for each index year revealed greater visual gains in 2015 (+2.1 ETDRS letters [95% CI, 1.8–2.5 ETDRS letters]) compared with the other index years (2012, −0.1 ETDRS letters [95% CI, −0.5 to 0.3 ETDRS letters]; 2013, +0.7 ETDRS letters [95% CI, 0.4–1.0 ETDRS letters]; 2014, +1.3 ETDRS letters [95% CI, 1.1–1.5 ETDRS letters]; Table 2).

We further assessed overall visual changes from baseline in the treated cohort for all eyes with a total of 1 year (n = 32 840), 2 years (n = 17 171), 3 years (n = 6118), and 4 years (n = 1649) of follow-up. Of the 21.7% of patient eyes with baseline VA of more than 70 ETDRS letters, approximately half (50.9%) of those with available VA at year 1 maintained VA of more than 70 ETDRS letters during the first year of treatment. At the end of years 2 and 3, 33.3% and 24.7% maintained VA of more than 70 ETDRS letters, respectively. Visual acuity (LSM) improved marginally from baseline after 1 year of follow-up (+1.1 ETDRS letters [95% CI, 1.0–1.3 ETDRS letters]), but declined over longer-term follow-up periods (2 years of follow-up: −1.3 ETDRS letters [95% CI, −1.5 to −1.0 ETDRS letters]; 3 years of follow-up: −3.1 ETDRS letters [95% CI, −3.5 to −2.7 ETDRS letters]; 4 years of follow-up: −5.2 ETDRS letters [95% CI, −6.0 to −4.3 ETDRS letters]; Table 2). The rates of VA decline were similar for eyes with the 4 index years (2012–2015; Fig 2A) and for eyes with 1 to 4 years of follow-up (Fig 2B).

Anti–Vascular Endothelial Growth Factor Injection and Clinic Visit Frequency over Time in the Treated Cohort

In total, 51 300 of 87 056 eyes (58.9%) in the treated cohort had at least 1 year of follow-up injection frequency data available for analysis. The overall mean number of injections for eyes with 1 year of follow-up was 7.6 (SD, 2.1), and this was comparable across each index year (2012, 7.2 [SD, 2.0]; 2013, 7.7 [SD, 2.1]; 2014, 7.6 [SD, 2.2]; 2015, 7.7 [SD, 2.1]; Table 3). The mean annual total number of clinic visits for the treated cohort in the first year of follow-up was comparable for each index year (2012, 8.9 [SD, 3.3]; 2013, 9.5 [SD, 3.4]; 2014, 9.0 [SD, 3.2]; 2015, 9.2 [SD, 3.1]; Table 4). In eyes with 4 years of follow-up, the overall mean number of injections was 7.5 (SD, 1.9), 6.7 (SD, 2.1), 6.6 (SD, 2.3), and 6.4 (SD, 2.3) for first, second, third, and fourth year, respectively (Table 3). The mean number of noninjection visits was 1.8 (SD, 2.9), 1.9 (SD, 2.9), 1.9 (SD, 3.0), and 1.9 (SD, 3.0) for years 1, 2, 3, and 4 (Table 5). Consequently, the mean total number of clinic visits decreased yearly from 9.3 (SD, 3.5) in the first year of follow-up to 8.2 (SD, 4.0) in the fourth year of follow-up, with

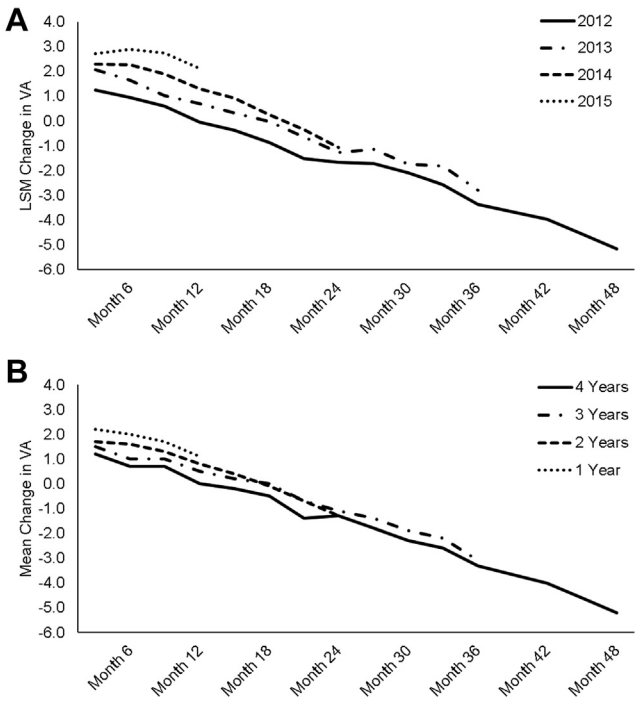

Figure 2. Graphs showing change in visual acuity (VA) by index year and by follow-up duration. **A**, Least square mean (LSM) change in VA in eyes with index years 2012 through 2015. **B**, Mean change in VA for study eyes with 1 to 4 years of follow-up.

8.5 (SD, 3.7) and 8.5 (SD, 3.9) mean clinic visits in the second and third year of follow-up, respectively, because of the reduction in injection visits (Table 4).

Anti–Vascular Endothelial Growth Factor Dose Regimens in the Treated Cohort

The overall proportion of eyes on a fixed regimen for patients with 1 year of follow-up (n = 51 300) was 55.4%, and this proportion was consistent among index years (52.8% in 2012, 54.5% in 2013, 58.0% in 2014, and 53.9% in 2015). For eyes with 4 years of follow-up (n = 2926), 59.0% (n = 1726), 64.5% (n = 1887), 66.5% (n = 1946), and 68.0% (n = 1991) were treated according to a fixed treatment regimen in years 1, 2, 3, and 4, respectively (Table 6). Further analysis of these patients revealed that 36.7% (n = 1076) received an injection more frequently than every 8 weeks, whereas 21.2% (n = 621) had achieved a treatment interval of every 12 weeks or more by the end of the fourth year of treatment (Table 7). The proportion of eyes treated more frequently than every 8 weeks increased by more than 40% from years 1 to 4 of follow-up (year 1, 32.4%; year 2, 31.3%; year 3, 29.3%; and year 4, 45.3%; Fig 3).

The Frequency of Bilateral Treatment in the Primary Cohort

The overall proportion of patients receiving bilateral treatment at baseline or during follow-up was 6.1% (n = 4907) and 23.7% (n = 18 936), respectively. For patients with 1 year of follow-up in the first-treated eye (n = 41 303 patients), 22.5% (n = 9298) received treatment in the second eye in year 1 of follow-up (Table 8). In patients with 4 years of follow-up (n = 2456), 6.1% (n = 151) were treated bilaterally at baseline, with 27.6% (n = 679), 30.4% (n = 746), 32.2% (n = 792), and 32.8% (n = 805) receiving bilateral treatment in the first, second, third, and fourth year of follow-up, respectively. Of patients with both eyes treated with different treatment initiation dates and with a VA record at treatment initiation (n = 10 978), 32.0% (n = 3514) received first treatment in the better-seeing eye, whereas in 68.0% of patients (n = 7464), the VA of the first-treated eye was the same as or worse than that in the second-treated eye (Table 8). This trend was evident across all index years.

Discussion

This study is among the largest EMR database analyses to date to assess both real-world treatment patterns and long-term visual outcomes in a United States nAMD patient

Table 3. Number of Injections by Index Year and Years of Follow-up in the Treated Cohort

Characteristic	Overall	Index Years			
		2012	2013	2014	2015
Eyes, no. (%)	87 056 (100)	13 024 (100)	20 349 (100)	31 562 (100)	22 121 (100)
Eyes with 1 year of follow-up, no. (%)	51 300 (58.9)	8501 (65.3)	12 098 (59.5)	19 650 (62.3)	11 051 (50.0)
Mean no. of injections in year 1 (SD)	7.6 (2.1)	7.2 (2.0)	7.7 (2.1)	7.6 (2.2)	7.7 (2.1)
Eyes with 2 years of follow-up, no. (%)	26 883 (30.9)	6021 (46.2)	8314 (40.9)	12 548 (39.8)	
Mean no. of injections in year 1 (SD)	7.7 (2.1)	7.4 (2.0)	7.9 (2.1)	7.7 (2.2)	
Mean no. of injections in year 2 (SD)	6.6 (2.3)	6.5 (2.1)	6.9 (2.3)	6.6 (2.3)	
Eyes with 3 years of follow-up, no. (%)	9813 (11.3)	4725 (36.3)	5088 (25.0)		
Mean no. of injections in year 1 (SD)	7.7 (2.1)	7.4 (2.0)	8.0 (2.1)		
Mean no. of injections in year 2 (SD)	6.9 (2.3)	6.6 (2.1)	7.1 (2.3)		
Mean no. of injections in year 3 (SD)	6.7 (2.4)	6.5 (2.3)	6.9 (2.5)		
Eyes with 4 years of follow-up, no. (%)	2926 (3.4)	2926 (22.5)			
Mean no. of injections in year 1 (SD)	7.5 (1.9)	7.5 (1.9)			
Mean no. of injections in year 2 (SD)	6.7 (2.1)	6.7 (2.1)			
Mean no. of injections in year 3 (SD)	6.6 (2.3)	6.6 (2.3)			
Mean no. of injections in year 4 (SD)	6.4 (2.3)	6.4 (2.3)			

SD = standard deviation.

Table 4. Mean Number of Total Visits by Index Year and Years of Follow-up in the Treated Cohort

Characteristic	Overall	Index Year			
		2012	2013	2014	2015
Baseline	87 056 (100)	13 024 (100)	20 349 (100)	31 562 (100)	22 121 (100)
Eyes with 1 year of follow-up, no. (%)	51 300 (58.9)	8501 (65.3)	12 098 (59.5)	19 650 (62.3)	11 051 (50.0)
Mean no. of total visits in year 1 of follow-up (SD)	9.2 (3.3)	8.9 (3.3)	9.5 (3.4)	9.0 (3.2)	9.2 (3.1)
Eyes with 2 years of follow-up, no. (%)	26 883 (30.9)	6021 (46.2)	8314 (40.9)	12 548 (39.8)	
Mean no. of total visits in year 1 of follow-up (SD)	9.3 (3.4)	9.1 (3.4)	9.7 (3.5)	9.1 (3.3)	
Mean no. of total visits in year 2 of follow-up (SD)	8.2 (3.5)	8.3 (3.6)	8.6 (3.6)	7.9 (3.4)	
Eyes with 3 years of follow-up, no. (%)	9813 (11.3)	4725 (36.3)	5088 (25.0)		
Mean no. of non-injection visits in year 1 (SD)	9.6 (3.6)	9.3 (3.5)	10.0 (3.6)		
Mean no. of noninjection visits in year 2 (SD)	8.7 (3.7)	8.4 (3.6)	8.9 (3.7)		
Mean no. of noninjection visits in year 3 (SD)	8.5 (3.8)	8.4 (3.9)	8.6 (3.7)		
Eyes with 4 years of follow-up, no. (%)	2 926 (3.4)	2 926 (3.4)			
Mean no. of noninjection visits in year 1 (SD)	9.3 (3.5)	9.3 (3.5)			
Mean no. of noninjection visits in year 2 (SD)	8.5 (3.7)	8.5 (3.7)			
Mean no. of noninjection visits in year 3 (SD)	8.5 (3.9)	8.5 (3.9)			
Mean no. of noninjection visits in year 4 (SD)	8.2 (4.0)	8.2 (4.0)			

SD = standard deviation.

population. Our results show that United States patients with nAMD receiving anti-VEGF therapy between 2012 and 2015 were broadly comparable in terms of demographics, baseline characteristics, and VA. Furthermore, this study highlights the wealth of data contained in EMR databases for evaluating longitudinal treatment patterns and outcomes in patients with nAMD after anti-VEGF therapy.

The primary objective of this study was to characterize differences in baseline VA for patients who started anti-VEGF treatment (primary cohort) during the index years (2012–2015). A lower baseline VA was observed in 2015 (51.1 ETDRS letters) compared with 2012 through 2014 (53.6–54.2 ETDRS letters). A reduction in the proportion of patients with baseline vision of 70 ETDRS letters or more was also observed from 2012 (28.1%) to 2015 (24.2%), with the highest proportion of patients with baseline vision of 35 ETDRS letters of fewer also recorded in 2015 (28.0%). A greater proportion of worse-seeing eyes were treated in 2015, and this is reflected in the lower baseline VA observed in this index year compared with earlier index years.[25] It is also conceivable that the EMR data submitted by different medical retina practices among the index years may have contributed to the variation in baseline VA scores. In addition, when assessing real-world evidence (RWE) from clinical practice, it is likely in that there may be concomitant pathologic characteristics for some patients that can have an impact on vision.

Further analysis of the primary patient cohort revealed that most first-treated eyes at baseline in each index year showed the same or worse VA than the second-treated eye (range, 65.8%–69.1%). These results suggest that United States physicians preferentially treat to maintain or improve

Table 5. Mean Number of Noninjection Visits by Index Year and Years of Follow-up in the Treated Cohort

Characteristic	Overall	Index Year			
		2012	2013	2014	2015
Baseline	87 056 (100)	13 024 (100)	20 349 (100)	31 562 (100)	22 121 (100)
Eyes with 1 year of follow-up, no. (%)	51 300 (58.9)	8501 (65.3)	12 098 (59.5)	19 650 (62.3)	11 051 (50.0)
Mean no. of noninjection visits in year 1 (SD)	1.6 (2.5)	1.7 (2.7)	1.8 (2.7)	1.4 (2.4)	1.5 (2.5)
Eyes with 2 years of follow-up, no. (%)	26 883 (30.9)	6021 (46.2)	8314 (40.9)	12 548 (39.8)	
Mean no. of noninjection visits in year 1 (SD)	1.6 (2.7)	1.8 (2.8)	1.9 (2.8)	1.4 (2.5)	
Mean no. of noninjection visits in year 2 (SD)	1.6 (2.6)	1.8 (2.8)	1.8 (2.8)	1.3 (2.4)	
Eyes with 3 years of follow-up, no. (%)	9813 (11.3)	4725 (36.3)	5088 (25.0)		
Mean no. of noninjection visits in year 1 (SD)	1.9 (2.9)	1.8 (2.9)	2.0 (2.9)		
Mean no. of noninjection visits in year 2 (SD)	1.8 (2.9)	1.8 (2.9)	1.8 (2.9)		
Mean no. of noninjection visits in year 3 (SD)	1.8 (2.9)	1.9 (3.0)	1.7 (2.8)		
Eyes with 4 years of follow-up, no. (%)	2926 (3.4)	2926 (3.4)			
Mean no. of noninjection visits in year 1 (SD)	1.8 (2.9)	1.8 (2.9)			
Mean no. of noninjection visits in year 2 (SD)	1.9 (2.9)	1.9 (2.9)			
Mean no. of noninjection visits in year 3 (SD)	1.9 (3.0)	1.9 (3.0)			
Mean no. of noninjection visits in year 4 (SD)	1.9 (3.0)	1.9 (3.0)			

SD = standard deviation.

Table 6. Proportion of Eyes with Fixed Treatment Regimen by Year and Duration of Follow-up in the Treated Cohort

Characteristics	Index Year			
	2012	*2013*	*2014*	*2015*
No. of eyes	13 024	20 349	31 562	22 121
Eyes with 1 year of follow-up, no. (%)	8501 (65.3)	12 098 (59.5)	19 650 (62.3)	11 051 (50.0)
Year 1	4487 (52.8)	6596 (54.5)	11 398 (58.0)	5959 (53.9)
Eyes with 2 years of follow-up, no. (%)	6021 (46.2)	8314 (40.9)	12 548 (39.8)	
Year 1	3447 (57.2)	4760 (57.3)	7691 (61.3)	
Year 2	3669 (60.9)	5066 (60.9)	7954 (63.4)	
Eyes with 3 years of follow-up, no. (%)	4725 (36.3)	5088 (25.0)		
Year 1	2813 (59.5)	2928 (57.5)		
Year 2	3005 (63.6)	3210 (63.1)		
Year 3	3123 (66.1)	3266 (64.2)		
Eyes with 4 years of follow-up, no. (%)	2926 (22.5)			
Year 1	1726 (59.0)			
Year 2	1887 (64.5)			
Year 3	1946 (66.5)			
Year 4	1991 (68.0)			

An eye with a fixed treatment regimen was defined as an eye with at least 80% of all (nonloading) injections for the year that are 4, 8, or 12 weeks (±15 days) after the previous injection. That is, the weeks between injections (4, 8, or 12) could vary by patient or follow-up year, but must have remained the same for 80% of injections for a given patient-year combination. A loading injection was 1 of the first 3 injections not later than 90 days after index.

binocular patient vision; this observation is supported by recent real-world evidence from Denmark.[25]

We further posit that because second-treated eyes are more likely to have better baseline visual acuity,[26] a reduction in bilateral treatment frequency at baseline may be the result of earlier diagnosis of disease in the first eye and absence of disease in the second eye. Vigilant monitoring of second eyes, relative to the recent diagnosis of nAMD in the first-treated eye, may account for most second-eye treatment initiations in the first year of follow-up to reduce the risk of undetected CNV development in the second eye 1 year after diagnosis.[5,6,25]

Assessment of the 1-year mean VA changes from baseline for eyes in the treated cohort revealed greater LSM VA improvements from 2013 through 2015 (+0.7 to +2.1 ETDRS letters), with marginal reductions in vision in 2012 (−0.1 ETDRS letters). An inverse relationship between baseline VA and 1-year VA gains across the index years was observed, with the lowest baseline VA and highest VA gains reported in 2015, and the highest baseline VA and lowest VA gain reported in 2012. This is consistent with previous real-world anti-VEGF studies describing a ceiling effect in VA gains.[17,27] These results also show that early diagnosis and treatment of nAMD are key to maintaining and achieving optimal visual outcomes in real-world clinical practice.

Observational studies report preservation of vision in treatment-naïve patients with nAMD in real-world settings during the first year of anti-VEGF treatment,[17,28–32] which is consistent with VA outcomes of patients followed up for up to 4 years in our study. As the length of follow-up increased, patients showed an average decline in VA, which is in agreement with outcomes reported in previous observational studies of anti-VEGF therapy for nAMD.[33–35] Loss of vision in treated eyes may be explained by the distribution of baseline VA scores within the cohort. For example, 26.8% of treated eyes showed a baseline VA of 70 ETDRS letters or more and therefore were less likely to demonstrate VA improvements because of the ceiling effect in VA gains.[17,27,36]

It is also possible that the adoption of less stringent re-treatment criteria or missed clinic visits in real-world settings contribute to the observed decline in long-term vision in this patient cohort. Although a relaxing of re-treatment criteria may play a substantial role in decreased vision, the effect cannot be demonstrated, because this information is not captured typically in real-world data sources. Furthermore, given that this observation study did not distinguish between anti-VEGF therapies, it is not clear if the study included outcomes from eyes that did not receive the

Table 7. Extension Intervals Achieved at Year 4 of Follow-up in the Treated Cohort

Interval	Overall (n = 87 056 Eyes)
Eyes with 4 years of follow-up, no. (%)	2926 (3.4)
Attained 6-wk treatment interval at year 4 of follow-up, no. (%)	504 (17.2)
Mean no. of intervals in year 4 (SD)	12.3 (11.0)
Attained 8-wk treatment interval at year 4 of follow-up, no. (%)	572 (19.5)
Mean no. of intervals in year 4 (SD)	7.9 (7.7)
Attained 10-wk treatment interval at year 4 of follow-up, no. (%)	407 (13.9)
Mean no. of intervals in year 4 (SD)	4.0 (4.3)
Attained 12-wk treatment interval at year 4 of follow-up, no. (%)	621 (21.2)
Mean no. of intervals in year 4 (SD)	5.7 (4.7)

SD = standard deviation.
Prespecified treatment extension intervals were 6, 8, 10, and 12 weeks (±7 days). Intervals longer than 12 weeks were considered equivalent to 12 weeks. Attainment of 10-week intervals at year 4 was defined as whether a treatment interval of 10 weeks (±1 week) covers the year 4 time point. Duration of the interval was calculated by counting this interval and all prior intervals until an interval of less than 10 weeks was found. Similar logic was used for 6-week, 8-week, and 12-week intervals.

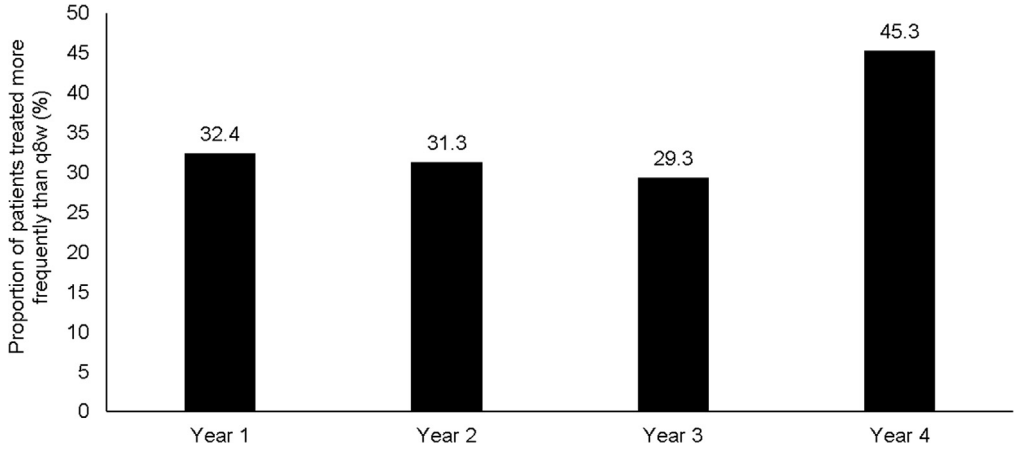

Figure 3. Graph showing the proportion of eyes at years 1 through 4 of follow-up receiving anti–vascular endothelial growth factor (VEGF) treatment more frequently than every 8 weeks.

optimal care needed to prevent vision loss (e.g., eye receiving the complete, label-recommended loading dose), which previously was reported to influence anti-VEGF treatment VA outcomes.[33] Finally, as with all real-world studies, this study had wide inclusion criteria that did not impose restrictions on baseline VA; baseline lesion size and type; baseline disease activity; presence of subretinal scarring, hemorrhage, or photoreceptor damage; or prior medical history. Each of these may have influenced the final study outcomes.

In eyes treated with anti-VEGF, the overall mean number of injections during the first year of follow-up was 7.6 and was consistent across index years (range, 7.2–7.7). This estimate is notably higher than in previous anti-VEGF real-world studies by 2 to 3 injections and could be the result of a number of factors, the most likely one being the use of unlicensed bevacizumab in this study.[17,29–31] A previous RWE study, using the same EMR data set with the same inclusion and exclusion criteria, but reporting ranibizumab- and aflibercept-treated patients only, demonstrated 1 anti-VEGF injection less in the first year of treatment.[37]

For eyes with at least 4 years of follow-up, the number of injection clinic visits decreased from 7.5 in year 1 to 6.4 in year 4 and was accompanied by a VA increase from baseline of +1.1 ETDRS letters in year 1 to −5.2 ETDRS letters in year 4. Long-term RWE from the Fight Retinal Blindness! outcome registry reported the median number of anti-VEGF injections remained the same during the first 7 years of treatment (range, 5–6 injections),[15] with similar findings reported in a RWE study in the United States with 3 years of follow-up.[37] The number of total clinic visits also decreased between years 1 and 2 of follow-up (9.3 vs. 8.5 visits) and stabilized in the third and fourth year of follow-up (8.5 and 8.2 visits, respectively). Similar decrease and stabilization injection and clinic visit patterns have been observed in previous real-world long-term studies.[33–35] However, based on published studies, an annual mean number of 6 injections or more in the second or third year usually maintains the visual gains from year 1. This was not the case in our study, which showed relatively small initial mean visual gains at the end of year 1 and a relatively quick loss of VA in year 2 and beyond. A recent study using Intelligent Research in Sight Registry data from 13 859 patients demonstrated a VA change of approximately 2.5 ETDRS letters from baseline (0.57 logMAR [56.5 ETDRS letters]) at the end of the first year after treatment with either bevacizumab, aflibercept, or ranibizumab (0.52 logMAR [59 ETDRS letters]).[38] This is comparable with the 1.1 ETDRS letters detected in the current RWE study, which was based on 32 840 nAMD patients' eyes. Real-world VA outcomes from a large United States data set also were comparable with those of the current study after 1 year of treatment.[32]

It is conceivable that the reductions in injection frequency between year 1 and subsequent years are associated with the gradual decline in VA reported here. The potential link between the burden of repeated intravitreal anti-VEGF injections and VA outcomes underscores the importance of sustained anti-VEGF therapy to improve or preserve long-term vision and improve treatment compliance in patients with nAMD in routine clinical practice.[15,39]

Our analysis revealed that 36.7% of patients with 4 years of follow-up had 6- or 8-week dosing intervals and extension of treatment intervals beyond 12 weeks occurred in a minority (21.2%) of nAMD patients receiving prolonged anti-VEGF treatment. Although it is possible that extended injection intervals may accommodate patient and physician needs to reduce treatment burden, frequent treatment was administered to one third of nAMD patients. Although extended treatment intervals may improve anti-VEGF treatment compliance,[40] it is important to balance this reduction in treatment burden against the risk of undertreatment and suboptimal preservation of VA.[41,42]

The current study has some strengths and limitations. Among the study's strengths are its large sample size and the evaluation of the long-term effectiveness of anti-VEGF therapy in a real-world heterogeneous patient population. RWE EMR studies have well-known limitations, including the routine collection of study end points from EMRs used by retina practices in a real-world clinical setting, the conversion of raw VA data from

Table 8. Frequency of Bilateral Treatment in the Primary Cohort

Characteristics	Overall (n = 79 885 Patients; n = 98 821 Eyes)	2012 (n = 12 340 Patients; n = 14 438 Eyes)	2013 (n = 18 929 Patients; n = 23 132 Eyes)	2014 (n = 29 056 Patients; n = 36 099 Eyes)	2015 (n = 19 560 Patients; n = 25 152 Eyes)
Patients with eyes treated uni- or bilaterally (patient), no. (%)					
Unilateral	60 949 (76.3)	8346 (67.6)	13 594 (71.8)	22 194 (76.4)	16 815 (86.0)
Bilateral	18 936 (23.7)	3994 (32.4)	5335 (28.2)	6862 (23.6)	2745 (14.0)
Patients with eyes treated at baseline (patient), no. (%)					
Unilateral	74 978 (93.9)	11 676 (94.6)	17 761 (93.8)	26 944 (92.7)	18 597 (95.1)
Bilateral	4907 (6.1)	664 (5.4)	1168 (6.2)	2112 (7.3)	963 (4.9)
No. of patients with 1 year of follow-up in first-treated eye	41 303	7187	9831	15 724	8561
Patients who received treatment in second eye in year 1 of follow-up	9298 (22.5)	1803 (25.1)	2397 (24.4)	3654 (23.2)	1444 (16.9)
Treated eye status at index (patient), no. (%)					
No. of patients with both eyes treated, one earlier than the other, VA recorded in both eyes at first treatment and no treatment in either eye from January through June 2011	10 978	2056	3161	3902	1859
First-treated eye strictly better than second-treated eye	3514 (32.0)	703 (34.2)	993 (31.4)	1243 (31.9)	575 (30.9)
First-treated eye at least as good as second-treated eye	4386 (40.0)	873 (42.5)	1279 (40.5)	1525 (39.1)	709 (38.1)
First-treated eye the same as or worse than the second-treated eye	7464 (68.0)	1353 (65.8)	2168 (68.6)	2659 (68.1)	1284 (69.1)

VA = visual acuity.

logMAR to ETDRS letters, and the absence of imaging data.[43–45] With real-world data, we can never be certain that a patient is treatment naïve or if the patient was treated previously in a different clinic or hospital. However, we do believe that such cases are limited and do not influence the findings and conclusions. Another limitation with real-world data studies is that proxy definitions are used to define fixed treatment regimens in real-world data studies, because this information is not captured in the EMR. One-year outcomes also were analyzed for each index year as well as outcomes for patients with 4 years of follow-up and whose baseline index year was 2012. Therefore, any conclusions made on the 4-year cohort may not hold in other cohorts with fewer than 4 years of follow-up. Also, patients with fewer than 1 year of follow-up were excluded, which may have introduced a bias toward patients who were younger and more adherent, with potentially less disease progression.

In conclusion, this study is among the largest EMR database analyses to evaluate the treatment patterns and long-term visual outcomes in a United States nAMD patient population and offers insight into the treatment trends in clinical practice year on year, adding to the growing body of real-world evidence regarding nAMD. Baseline VA was similar for the index years 2012, 2013, and 2014, but lower for 2015, and after 1 year of follow-up, mean VA improved by 1.1 ETDRS letters. In patients with 4 years of follow-up, both VA and injection frequency declined, which may be linked to the current anti-VEGF treatment burden. Our results showed that in the United States, most patients received their first treatment in an eye with equivalent or worse VA compared with the fellow-eye. Close monitoring of the study eye may contribute to earlier treatment of fellow eyes, and clinical practice associated with treating the worse-seeing eye first may be related to the decline in baseline VA observed over time resulting from the increased number of unilateral eyes treated in later years.

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Conception and design: Skelly, Bezlyak, Griner, Rodriguez Torres, Sagkriotis

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CI** = confidence interval; **CNV** = choroidal neovascularization; **EMR** = electronic medical record; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **logMAR** = logarithm of minimum angle of resolution; **LSM** = least square mean; **nAMD** = neovascular age-related macular degeneration; **q8w** = every 8 weeks; **RWE** = real-world evidence; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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