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# Real-world Outcomes of Anti–Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema in the United States

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***Purpose:*** This study assessed real-world visual acuity (VA) outcomes of anti–vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME).

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

***Participants:*** DME patient eyes that underwent ≥3 monthly anti-VEGF injections within 4 months of the first injection and between January 2011 and March 2017 were eligible if follow-up data were available prior to March 2018.

***Methods:*** The eyes were divided into 3 groups based on choice of initial intravitreal anti-VEGF agent (aflibercept, bevacizumab, or ranibizumab). These eyes were then subdivided into 3 cohorts, depending on length of follow-up (6, 12, or 24 months), with each cohort being mutually exclusive.

***Main Outcome Measures:*** VA outcomes and number of treatments were assessed on each cohort and stratified by baseline VA.

***Results:*** A total of 15,608 DME patient eyes were included in this analysis. In the 12-month cohort, of 1379 eyes initially treated with aflibercept, the mean 12-month improvement was +5.5 letters (95% confidence interval [CI] +4.5 to +6.6 letters, $P < 0.001$) after 7.5 injections on average, with similar outcomes for bevacizumab (3109 eyes, +5.5 letters, 95% CI +4.7 to +6.3 letters, $P < 0.001$, average 7.9 injections), and for ranibizumab (1352 eyes, +4.0 letters, 95% CI +2.9 to +5.2 letters, $P < 0.001$, average 7.7 injections). The mean numbers of corticosteroid, macular, and panretinal laser treatment sessions were similar in each group. In the 12-month cohort, when stratified by baseline VA of 20/201 or worse, 20/71 to 20/200, 20/41 to 20/70, and 20/40 or better, the final mean letters gained or lost were +28.0, +10.2, +2.8, and −2.5 in the aflibercept group, +36.0, +7.8, +2.9, and −2.0 letters in the bevacizumab group, and +30.5, +7.9, +1.6, and −2.7 letters in the ranibizumab group, respectively.

***Conclusions:*** Real-world VA outcomes following anti-VEGF therapy for DME were meaningfully inferior to those noted in randomized, controlled trials. Eyes with better baseline VA experienced fewer letters gained compared with those with worse baseline VA. The initial choice of anti-VEGF agent did not correlate with visual outcomes. *Ophthalmology Retina 2018;■:1–9 © 2018 by the American Academy of Ophthalmology*

Diabetic macular edema (DME) is a leading cause of blindness in the working-age population of most developed countries.[1] Macular laser photocoagulation, which had traditionally been standard treatment for DME based on the Early Treatment Diabetic Retinopathy Study, slows the rate of best-corrected visual acuity (BCVA) loss but has demonstrated only limited ability to restore lost BCVA.[2] Based on more recent randomized, controlled trials (RCTs), it is now well accepted that intravitreal anti–vascular endothelial growth factor (VEGF) agents, with their antiangiogenic and antipermeability properties,[1,3] are more effective than laser therapy for DME.[4–12] In the VISTA (Study of Intravitreal Aflibercept Injection in Patients with DME) and VIVID (Intravitreal Aflibercept Injection in Vision Impairment Due to DME) RCTs, monthly loading followed by bimonthly aflibercept administration (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY) was associated with significantly better mean 1-year BCVA gain than macular laser photocoagulation (+10.7 vs. +0.2 letters for VISTA, and +10.7 vs. +1.2 letters for VIVID).[12] In the RISE and RIDE (Studies of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus) RCTs, monthly ranibizumab administration (Lucentis, Genentech, Roche Group, South San Francisco, CA) was associated with significantly better mean 1-year BCVA gain than sham drug administration with macular laser photocoagulation rescue (+12.5 vs. +2.6 letters for RISE, and +10.9 vs. +2.3 letters for RIDE).[13]



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Consequently, anti-VEGF therapy is now the first-line treatment for DME associated with decreased VA in the United States (US), according to 95% of US retina specialists who responded in a 2016 American Society of Retinal Specialists Preferences and Trends survey.[14] However, few large-scale prospective studies have compared the efficacy of available anti-VEGF agents. The National Institutes of Health–sponsored Diabetic Retinopathy Clinical Research (DRCR) Network compared aflibercept, off-label bevacizumab (Avastin, Genentech, Roche Group), and ranibizumab for the treatment of DME (Protocol T). After 2 years, all 3 therapies, dosed according to a protocol-specific algorithm, demonstrated similar Early Treatment Diabetic Retinopathy Study letter improvement from baseline (+12.8, +10.0, and +12.3 letters for aflibercept, bevacizumab, and ranibizumab, respectively). Compared with this total study population, the subgroup of patients with moderately to severely diminished baseline BCVA (20/50 to 20/320) experienced a greater number of letters gained (+18.3, +13.3, and +16.1 letters for aflibercept, bevacizumab, and ranibizumab, respectively), with aflibercept significantly more effective than bevacizumab in this subgroup.[15]

Few studies have investigated the translatability of Protocol T and similar trials to the realworld, in which patients often do not meet RCT eligibility criteria, because of minimal or extensive systemic or ocular disease severity or both. These studies suggest that patients receive fewer injections on average and have worse visual outcomes compared with participants in RCTs.[16–18] In the current study, we sought to assess real-world DME experience with anti-VEGF therapy in cases recorded in a large database of aggregated, longitudinal electronic medical records (EMRs) from a geographically and demographically diverse sample of patients of US retina specialists. To our knowledge, this is the largest population-based evaluation of anti-VEGF use for DME in the US. Additionally, we sought to assess the potential impact of loss to follow-up on visual outcomes, as loss to follow-up has important implications not only for real-world studies but for all RCTs. In this current study, we specifically assessed DME patients lost to follow-up after 6 and 12 months compared with those patients who were followed for 24 months.

## Methods

### Database

The database, Vestrum Health Retina Database, consisted of aggregated, longitudinal EMRs from a demographically and geographically diverse patient sample that was obtained from a panel of US retina specialists (Vestrum Health, LLC, Naperville, IL). Specifically, the panel included >240 private-practice retina physicians, with 65%, 32%, and 3% of practices located in urban, suburban, and rural settings, respectively. They were 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 >800 000 unique patients and >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 utilization, 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 was generated using an industry-standard 1-way algorithm. The names of treating physicians and practices were removed from the data. The database was refreshed on a weekly basis. Visual acuity (VA) score was reported using an Early Treatment Diabetic Retinopathy Study approximation and calculated as follows: $85 + 50 \times \log$ (Snellen fraction).[19]

### Study Design, Dates for Data Collection, and Inclusion Criteria

This project was considered exempt from institutional review board review, as the research involved only the collection of existing data, which had been de-identified, as noted above. This retrospective, uncontrolled review studied treatment-naïve DME patients who underwent ≥3 monthly anti-VEGF injections during the first 4 months from diagnosis between January 2011 and March 2017; participants were eligible if follow-up data were available prior to March 2018.

To model patient loss to follow-up, mutually exclusive cohorts of patients lost to follow-up after specific time points of 6 and 12 months (no follow-up beyond) were compared with a separate cohort of patients who completed 24 months of follow-up. Age, gender, VA, and number of treatments were extracted from the database. VA measurements were not standardized in this retrospective uncontrolled review. Extracted treatment included anti-VEGF treatments, corticosteroid treatments (triamcinolone with or without preservative and the 0.7-mg dexamethasone implant), as well as macular and panretinal (PRP) laser treatment sessions.

### Analysis

All analyses were performed at the patient-eye level. For bilaterally treated patients, each patient eye was treated independently and results were recorded in the appropriate cohort. The eyes were divided into 3 cohorts: those with records that included VA measurements up to and including 6 months of follow-up but were lost to follow-up beyond (6-month cohort), those with records that included VA measurements up to and including 12 months but were lost to follow-up beyond (12-month cohort), and those with records that included VA measurements up to and including 24 months (24-month cohort), with each cohort being mutually exclusive of the others. Any patient who passed away, relocated, or transferred care would be classified as lost to follow-up for the purposes of this analysis. VA outcomes were assessed on each cohort as a whole and stratified by baseline VA.

Baseline characteristics were summarized with descriptive statistics. Mean values for patient demographics, number of injections, and baseline and final VA (letters) were calculated. Visual acuity outcomes compared with baseline VA were assessed with inferential statistics. Mean change in VA from baseline was calculated, along with 95% CIs and nominal $P$ values, using paired $t$ tests. This analysis was also performed after stratifying the eyes by baseline VA within each of the cohorts.

## Results

### Demographics

From 13,974 patients, 15,608 eyes were included in this analysis, based on the inclusion criteria, with 10.4% of the patients

Table 1. Patient Demographics, Treatments, and Visual Outcomes

| | Overall | 6-month cohort | 12-month cohort | 24-month cohort |
|---|---|---|---|---|
| Eyes, n (%) | 15 608 (100) | 4613 (29.6) | 5840 (37.4) | 5155 (33.0) |
| Patients, n (%) | 13 974 (100) | 4264 (30.5) | 4623 (33.1) | 5087 (36.4) |
| Mean age at initial treatment, y | 62.9 | 62.6 | 62.8 | 63.2 |
| Baseline mean VA, Early Treatment Diabetic Retinopathy Study letters | 57.9 | 56.6 | 57.9 | 59.4 |
| Initial anti-VEGF agent, $n_{eye}$ (%) | | | | |
| Aflibercept | 3329 (21.3) | 1150 (24.9) | 1379 (23.6) | 800 (15.5) |
| Bevacizumab | 8005 (51.3) | 2493 (54.0) | 3109 (53.2) | 2403 (46.6) |
| Ranibizumab | 4274 (27.4) | 970 (21.0) | 1352 (23.2) | 1952 (37.9) |
| Mean number of injections | 8.6 | 5.0 | 7.8 | 12.8 |
| Mean number of focal laser treatments | 0.2 | 0.1 | 0.2 | 0.3 |
| Mean number of panretinal photocoagulation treatments | 0.2 | 0.1 | 0.2 | 0.2 |
| Mean number of corticosteroid injections | 0.2 | 0.1 | 0.1 | 0.3 |

anti-VEGF = anti–vascular endothelial growth factor; VA = visual acuity.
From 13 974 patients, 15 608 eyes were included in this analysis, with 10.4% of the patients undergoing bilateral treatment during the study period. Consequently, all analyses were performed at the patient-eye level. For bilaterally treated patients, each patient eye was analyzed independently and results were recorded in the appropriate cohort. The mean number of corticosteroid injections includes intravitreal triamcinolone with or without preservative and a 0.7-mg dexamethasone implant. The breakdown of anti-VEGF agents prescribed in this study is affected by the study inclusion dates (between 2011 and 2018), given that aflibercept was not approved for the treatment of diabetic macular edema until 2014. In particular, the patient eyes that completed the 24-month follow-up period were less likely to have been started on aflibercept than patient eyes in the 12-month and 6-month cohorts. The choice of initial anti-VEGF therapy had no effect on visual outcomes in any of the baseline VA subgroups of any of the follow-up cohorts.

undergoing bilateral treatment during the study period. As noted above, all analyses were performed at the patient-eye level, with each patient eye being treated independently in the appropriate cohort. From the 15 608 DME patient eyes, there were 4613 (29.6%) in the 6-month cohort, 5840 (37.4%) in the 12-month cohort, and 5155 (33.0%) in the 24-month cohort. Baseline demographics are summarized in Table 1. The mean overall age was 62.9 years, which was similar across cohorts. The initial anti-VEGF agent was aflibercept in 21.3% of eyes, bevacizumab in 51.3%, and ranibizumab in 27.4%. The breakdown of anti-VEGF agents prescribed in this study is affected by the study inclusion dates (between 2011 and 2018), given that aflibercept was not approved for the treatment of DME until 2014. In particular, the eyes of patients who completed the 24-month follow-up were less likely to have been started on aflibercept than patient eyes in the 12-month and 6-month cohorts. The baseline mean VA scores of the 6-, 12-, and 24-month cohorts were 56.6, 57.9, and 59.4 letters, respectively. The change in VA from baseline for the 3 follow-up cohorts is depicted in Figure 1; most visual improvement occurred in the first 3 months of treatment.

## Injection Frequency and Visual Outcomes

In the 6-month cohort, of 1150 DME patient eyes initially treated with aflibercept, the mean 6-month improvement was +6.8 letters (95% CI +5.8 to +7.8 letters, $P < 0.001$) after 4.9 injections on average, with similar outcomes for bevacizumab (2493 eyes, +6.4 letters, 95% CI +5.5 to +7.2 letters, $P < 0.001$, 5.1 average injections) and ranibizumab (970 eyes, +4.9 letters, 95% CI +3.8 to +6.0 letters, $P < 0.001$, 5.0 average injections). The mean numbers of macular and PRP laser treatment sessions were similar in each group (≤0.2 macular and ≤0.2 PRP laser treatments). The mean number of corticosteroid treatments was <0.1 in each cohort.

In the 12-month cohort, of 1379 DME patient eyes initially treated with aflibercept, the mean 12-month improvement was +5.5 letters (95% CI +4.5 to +6.6 letters, $P < 0.001$) after 7.5 injections on average, with similar outcomes for bevacizumab (3109 eyes, +5.5 letters, 95% CI +4.7 to +6.3 letters, $P < 0.001$, 7.9 average injections), and for ranibizumab (1352 eyes, +4.0 letters, 95% CI +2.9 to +5.2 letters, $P < 0.001$, 7.7 average injections). The mean numbers of macular and PRP laser treatment sessions were similar in each group (≤0.3 macular and <0.2 PRP laser treatments). The mean number of corticosteroid treatments was <0.2 in each group.

In the 24-month cohort, of 800 DME patient eyes initially treated with aflibercept, the mean 24-month improvement was +4.7 letters (95% CI +3.2 to +6.2 letters, $P < 0.001$) after 12.5 injections on average, with similar outcomes for bevacizumab (2403 eyes, +3.8 letters, 95% CI +2.9 to +4.7 letters, $P < 0.001$, 12.6 average injections) and for ranibizumab (1952 eyes, +2.3 letters, 95% CI +1.5 to +3.2 letters, $P < 0.001$, 13.1 average injections). The mean numbers of macular and PRP laser treatment

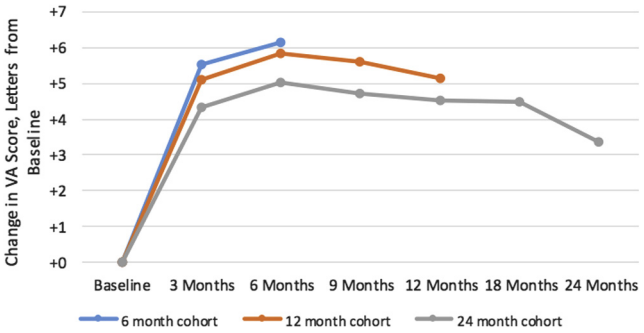


**Figure 1.** Change in mean visual acuity (VA) score from baseline. The change in VA from baseline is depicted for the 6-, 12-, and 24-month cohorts. The change from baseline was not meaningfully different between cohorts. Most improvement in VA occurred during the first 3 months in all follow-up cohorts.

Table 2. Mean Letters Gained or Lost in Each Cohort, Stratified by Baseline Visual Acuity

| 6-Month Cohort | Total | | | |
|---|---|---|---|---|
| Baseline visual acuity score | *Eyes, n* | *6-month change* | P *value* | *95% confidence interval* |
| All eyes | 4613 | 6.15 | <0.001 | 5.58 to 6.72 |
| 20/40 or better | 1435 | −1.31 | <0.001 | −1.85 to −0.77 |
| 20/41 to 20/70 | 1543 | 3.63 | <0.001 | 3.00 to 4.26 |
| 20/71 to 20/200 | 1155 | 8.55 | <0.001 | 7.59 to 9.51 |
| 20/201 or worse | 480 | 30.74 | <0.001 | 27.37 to 34.11 |
| **12-Month Cohort** | **Total** | | | |
| **Baseline visual acuity score** | *Eyes, n* | *12 Month change* | P *value* | *95% confidence interval* |
| All eyes | 5840 | 5.16 | <0.001 | 4.61 to 5.71 |
| 20/40 or better | 1834 | −2.30 | <0.001 | −2.95 to −1.65 |
| 20/41 to 20/70 | 2061 | 2.57 | <0.001 | 1.92 to 3.22 |
| 20/71 to 20/200 | 1429 | 8.45 | <0.001 | 7.42 to 9.48 |
| 20/201 or worse | 516 | 32.84 | <0.001 | 29.53 to 36.15 |
| **24-Month Cohort** | **Total** | | | |
| **Baseline visual acuity score** | *Eyes, n* | *24-month change* | P *value* | *95% confidence interval* |
| All eyes | 5155 | 3.36 | <0.001 | 2.78 to 3.94 |
| 20/40 or better | 1658 | −3.35 | <0.001 | −4.06 to −2.64 |
| 20/41 to 20/70 | 1904 | 1.51 | <0.001 | 0.77 to 2.25 |
| 20/71 to 20/200 | 1214 | 7.47 | <0.001 | 6.31 to 8.63 |
| 20/201 or worse | 379 | 28.88 | <0.001 | 24.95 to 32.81 |

sessions were similar in each group (≤0.4 macular and ≤0.3 PRP laser treatments). The mean number of corticosteroid treatments was <0.4 in each group.

## Baseline VA and Visual Outcomes

Worse baseline VA was associated with greater VA gain in all follow-up cohorts (Table 2, Figures 2–4). In the 12-month cohort, when stratified by baseline VA of 20/201 or worse, 20/71 to 20/200, 20/41 to 20/70, and 20/40 or better, the final mean changes in number of letters gained or lost in the aflibercept group were +28.0, +10.2, +2.8, and −2.5, respectively, in the bevacizumab group were +36.0, +7.8, +2.9, and −2.0 letters, respectively, and in the ranibizumab group were +30.5, +7.9, +1.6, and −2.7 letters, respectively. This result did not correlate with the relative number of injections administered, as this was similar across each baseline VA subgroup (as shown in Figure 5).

Similar VA outcomes were found in the 6- and 24- month cohorts, summarized in Figure 3B and 3C. Similarly, in these cohorts, the trend of greater VA gain in those eyes with worse baseline VA did not correlate with the relative number of

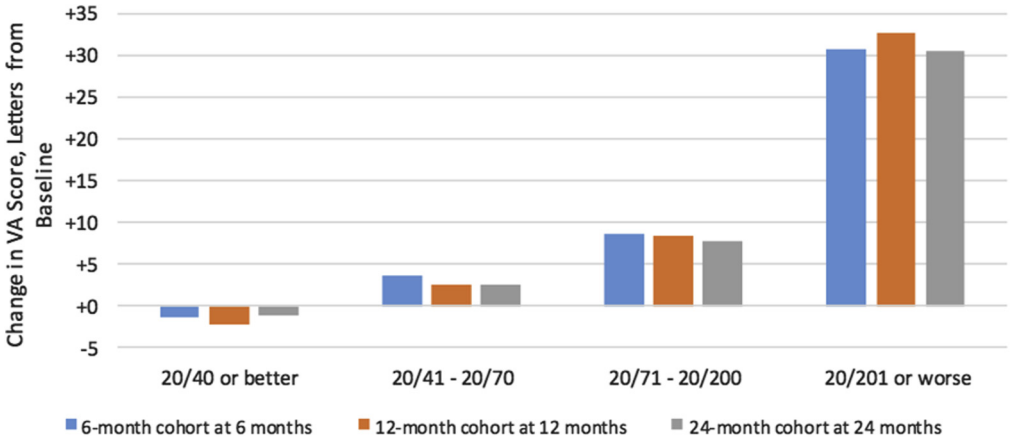


**Figure 2.** Change in mean visual acuity (VA) score from baseline for follow-up groups stratified by baseline VA. The change in VA between baseline and respective final follow-up visit for the 6-, 12-, and 24-month cohorts is depicted, stratified by baseline VA. Eyes with initially good VA (20/40 or better) lost Early Treatment Diabetic Retinopathy Study (ETDRS) letters on average, whereas eyes with the worst VA (20/201 or worse) gained the most letters. No significant difference in VA outcome was observed between follow-up groups, suggesting that poor VA at the final follow-up visit was not a significant factor in loss to follow-up.

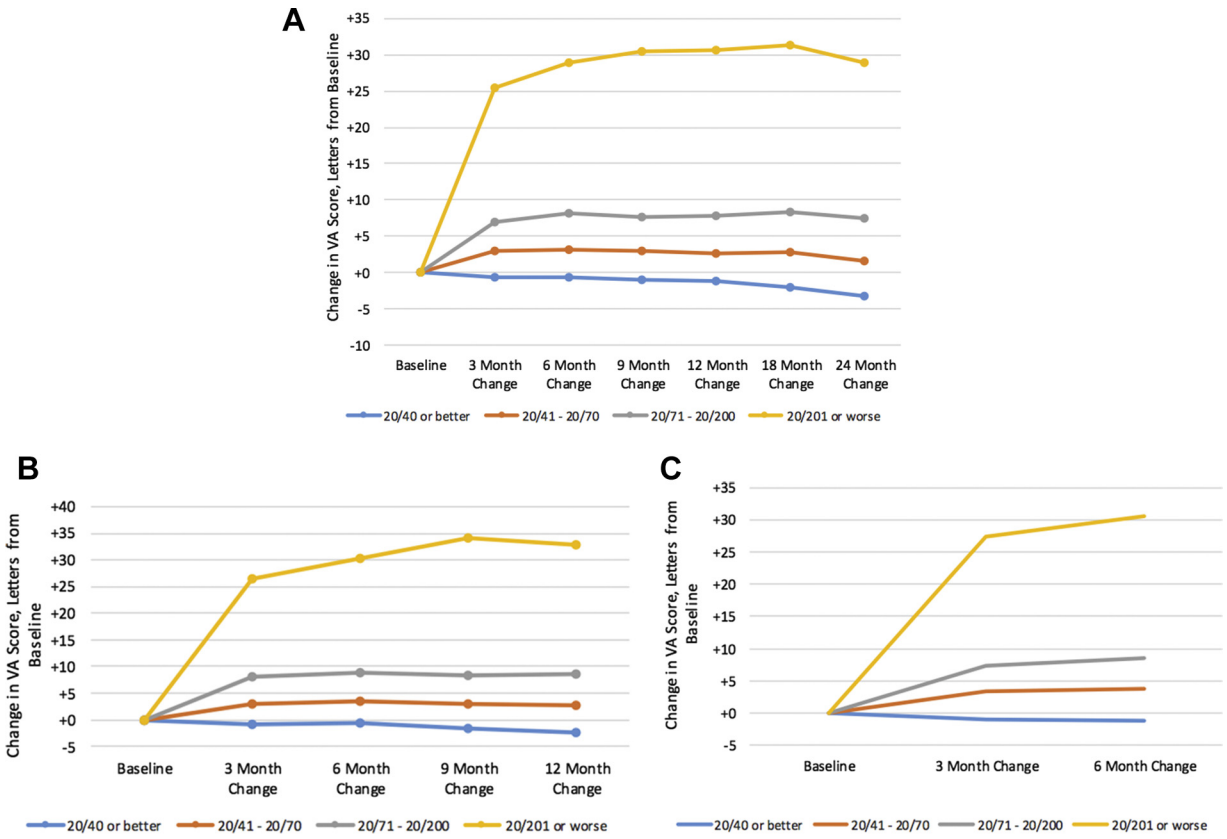


**Figure 3. A,** Change in mean visual acuity (VA) score from baseline in the 24-month cohort based on initial VA stratification. **B,** Change in VA in the 12-month cohort based on initial VA stratification. **C,** Change in VA in the 6-month cohort based on initial VA stratification. The change in VA from baseline for each of the follow-up cohorts is depicted. Eyes with worse baseline VA consistently tended to gain, and then maintain, more Early Treatment Diabetic Retinopathy Study (ETDRS) letters throughout the follow-up period. Eyes with good initial baseline VA maintained a small loss of VA throughout the respective follow-up period.

injections administered. Furthermore, within the 24-month cohort, although eyes with baseline VA of 20/200 or worse showed the greatest gain in VA, they received slightly fewer treatments on average than eyes with better baseline VA. The choice of initial anti-VEGF therapy had no effect on visual outcomes in any of the baseline VA subgroups of any of the follow-up cohorts.

### Loss to Follow-up and Outcomes

Eyes of DME patients lost to follow-up at earlier time points (i.e., 6- and 12-month cohorts) experienced similar visual outcomes compared with eyes treated for a longer duration. At month 6, the mean changes in VA were +6.2, +5.9, and +5.0 letters for the 6-, 12-, and 24-month cohorts, respectively. At month 12, the mean changes in VA were +5.2 and +3.6 letters for the 12- and 24-month cohorts, respectively. For eyes with the worst baseline visual acuity, the 3 follow-up cohorts had similar mean response to treatment, improving by >25 letters in the first 3 months of treatment (Figure 4).

## Discussion

This study assessed visual real-world outcomes of anti-VEGF–treated DME patient eyes in the US. The real-world sample was derived from a database of aggregated, longitudinal EMRs representing a geographically and demographically diverse group of patients examined by retina specialists in the US.

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 real-world study is limited by its retrospective nature, utilization of aggregated data, and nonstandardized VA assessment from the sites, as well as the possibility of prior treatment for DME in a practice that does not report to the database. Another limitation of this study is the classification of DME patient eyes based on initial anti-VEGF agent, without accounting for switching between agents. Thus, this methodology limits the ability to assess for relationships between visual outcomes and anti-VEGF therapy, except for that used initially; given this and the other noted limitations, it is not surprising that no differences among therapeutic agents were noted. In addition, inferential testing in retrospective studies is inherently limited by selection bias, and consequently, the resulting *P* values are only nominal in nature. Furthermore, the patient sample may not have entirely resembled real-world patients given the eligibility requirement of ≥3 monthly anti-VEGF injections in the first 4 months from diagnosis, although many retina specialists in the US do include a series of initial monthly injections as part of an "induction" regimen.

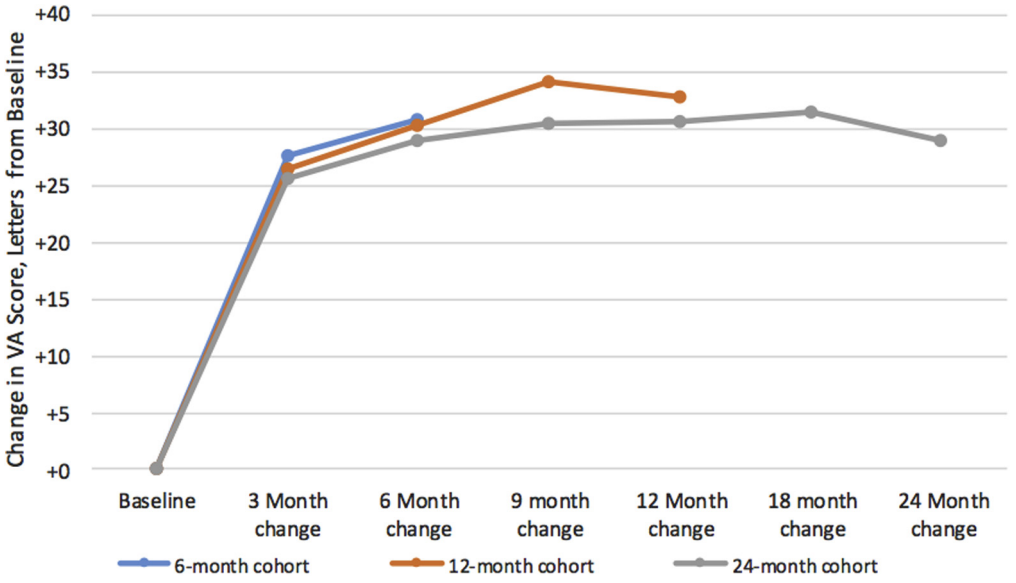


**Figure 4.** Change in mean visual acuity (VA) score from baseline of follow-up cohorts in eyes with poor baseline VA. The VA change from baseline, compared between follow-up cohorts, in eyes with poor baseline VA (20/201 or worse) is depicted. VA improved by >25 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the first 3 months following initiation of therapy in all 3 groups.

Although mining EMRs has numerous limitations, the resulting data can yield important longitudinal insights to better understand patient outcomes in clinical practice. Most importantly, this study reveals pertinent insights. First, in the US, real-world DME patient eyes experience worse visual outcomes and receive slightly fewer anti-VEGF injections compared with eyes receiving protocol-specified or fixed, frequent therapy in RCTs. Second, eyes with better VA at presentation tend to be particularly vulnerable to vision loss compared with eyes with worse VA at presentation. Last, compared with other eyes, those ultimately lost to follow-up tend to demonstrate similar visual outcomes at, or prior to, their final visit, suggesting that an evolving poor outcome may not have precipitated loss to follow-up.

## Real-World DME Patient Eyes Experience Worse Outcomes Compared with Participants in RCTs

Real-world DME patient eyes in our US-based study experienced worse visual outcomes and received slightly fewer anti-VEGF injections when compared with eyes receiving fixed, frequent therapy or protocol-based therapy in RCTs (Tables 1 and 2). In the DRCR Protocol T trial, the average VA letter improvements at 12 months were +13.3, +9.7, and +11.2 for aflibercept, bevacizumab, and ranibizumab, respectively.[27] In contrast, the 12-month VA improvements in this real-world analysis were +5.5, +5.5, and +4.0 letters gained in the 12-month cohort for eyes started on aflibercept, bevacizumab, and ranibizumab, respectively. The difference in 12-month VA outcomes between DRCR Protocol T and this current real-world analysis approximates 1 line of vision.

A previous real-world analysis of patients with neovascular age-related macular degeneration that employed the same database suggested inferior visual outcomes in neovascular age-related macular degeneration may be related to undertreatment.[20] Our data suggest only a minor potential role of undertreatment to account for in the limited VA outcomes of this DME population. For example, in this real-world analysis, the mean numbers of injections at 12 months were 7.5, 7.9, and 7.7 for those started on aflibercept, bevacizumab, and ranibizumab, respectively. In the DRCR Protocol T trial, the mean number of injections at 12 months were 9.2, 9.7, and 9.4 for aflibercept, bevacizumab, and ranibizumab, respectively. Whereas RISE and RIDE employed monthly ranibizumab treatment[13] and VISTA and VIVID employed bimonthly

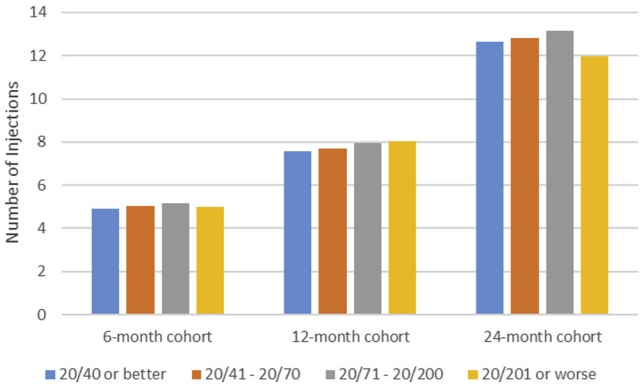


**Figure 5.** Number of injections, stratified by follow-up and baseline visual acuity (VA). The mean number of intravitreal treatments for each cohort, stratified by baseline VA, is depicted. Inclusion required eyes with diabetic macular edema (DME) to have received 3 monthly injections of anti–vascular endothelial growth factor in the first 4 months from diagnosis. Within the 6- and 12-month cohorts, there were no differences in the mean number of treatments when results were stratified by baseline VA. Within the 24-month cohort, although those eyes with baseline VA of 20/200 or worse showed the greatest gain in VA, they received slightly fewer treatments on average than eyes with better baseline VA.

aflibercept treatment after 5 monthly treatments,[12] DRCR Protocol T employed a protocol-specific algorithm.[15] In DRCR Protocol T, the eyes received monthly treatment, unless the BCVA was 20/20 or better, the central subfield thickness (CSFT) was less than the eligibility threshold, and there was no improvement or worsening after 2 monthly injections. (Improvement was defined as an increase in BCVA of ≥5 letters or decrease in CSFT of ≥10%. Worsening was defined as a decrease in BCVA of ≥5 letters or an increase in in CSFT of ≥10%.) Starting at week 24, treatment was withheld if there was no improvement or worsening after 2 injections, and treatment was reinitiated if the BCVA or the CSFT worsened. The slight decrease in injection frequency in this real-world analysis compared with that of DRCR Protocol T suggests that physicians are not using frequent, fixed dosing regimens but are employing as-needed or treat-and-extend regimens.

A more likely explanation for the difference in outcomes is the difference in population characteristics. RCTs have strict exclusion criteria that exclude DME patient eyes with well-preserved or extremely poor baseline VA.[12,13,15] Eyes with well-preserved baseline VA exhibit a ceiling effect, limiting improvement in VA, whereas those with extremely poor baseline VA could harbor advanced DME with ischemia or atrophy that could limit recovery. No visual exclusion criteria were included in this real-world analysis. Other possibly pertinent exclusion criteria in the RCTs not present in real-world analyses include the presence of epiretinal membranes and vitreomacular traction. The presence of vitreomacular traction and epiretinal membranes has been correlated with worse visual and anatomic outcomes with anti-VEGF therapy.[21] Furthermore, real-world patients may have more severely uncontrolled diabetes, uncontrolled hypertension, and chronic renal insufficiency. In addition, patients with diabetes who enter clinical trials may assume better control of their diabetes and other systemic disorders because of better compliance reinforced by frequent study visits.

### DME Patient Eyes with Better VA at Presentation Tend to be Particularly Vulnerable to Vision Loss

Naturally, a ceiling effect may limit improvement in eyes with better baseline BCVA; conversely, these eyes also have a relatively higher chance of vision loss. In this current study, DME patient eyes with baseline VA of 20/40 or better, on average, lost vision by month 12 despite treatment. For example, in the 12-month cohort, the mean VA changes were −2.5, −2.0, and −2.7 for the aflibercept-, bevacizumab-, and ranibizumab–started groups, respectively. In contrast, in the DRCR Protocol T trial, those eyes with baseline VA of 20/40 or better improved by a mean of +7.4, +6.0, and +6.1 letters at 12 months for aflibercept, bevacizumab, and ranibizumab, respectively.[15] Although the populations are not completely analogous, this difference in 12-month VA outcomes between DRCR Protocol T and this current real-world analysis approximates 2 lines of vision for those DME patient eyes with VA of 20/40 or better.

In this current study, the reason for vision loss in DME patient eyes with better baseline VA is not clear. Undertreatment, relatively more advanced diabetic macular disease, and more advanced systemic disease could partially account for this outcome, as noted above. Another possible factor could be progression in cataracts, as this real-world analysis did not screen for cataract severity at baseline, and patients with underlying diabetes are at increased risk of development and progression of both nuclear sclerotic and posterior subcapsular cataracts.[22] The visual outcomes of DME patient eyes with excellent baseline VA is currently being further evaluated by the DRCR network in Protocol V, with the conclusion of the study anticipated to be August 2018.

### DME Patient Eyes Lost to Follow-up

DME patient eyes were divided into mutually exclusive cohorts: those who were followed for ≤6 months, those followed for ≤12 months, and those followed for 24 months. Patients who did not show in the EMR after 6 or 12 months were presumed to be lost to follow-up. Limitations of this loss to follow-up estimation are the untracked variables such as patient death, relocation, or transferred care. Patients with evolving poor visual outcomes might be expected to have a greater frequency of loss to follow-up compared with other patients, and this has been demonstrated in the literature in neovascular age-related macular degeneration.[20,23–26] However, this analysis of DME patient eyes did not reveal a significant difference in visual outcomes between those lost to follow-up at 6 or 12 months, compared with those of patients followed for 24 months. The reasons for this outcome are unclear, but factors leading to patient nonadherence may be different between disease processes, as has previously been described.[26]

## Conclusions

Overall, this study demonstrates that the visual outcomes of DME patient eyes treated with anti-VEGF in the real world are inferior to those of participants in the RCTs by approximately 1 line of VA at 1 year. Undertreatment, however, may play only a limited role in this outcome. Real-world DME patient eyes may have well-preserved baseline VA, leading to a ceiling effect, limiting improvement in VA. Real-world DME patient eyes can also have extremely poor baseline VA, due to advanced DME with ischemia or atrophy, which could limit recovery. Population characteristics such as more advanced ocular disease or uncontrolled systemic comorbidities are found in this real-world patient population but excluded from RCTs. Additionally, this study demonstrates that real-world DME patient eyes with well-preserved baseline VA (better than 20/40) lost vision on average at 1 year, with a difference of nearly 2 lines of vision compared with outcomes in those DME patient eyes with well-preserved VA in DRCR Protocol T. This result highlights the need for proper patient counselling based on baseline characteristics.

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## Footnotes and Financial Disclosures

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No animal subjects were used in this study.

Abbreviations and Acronyms:
**anti-VEGF** = antievascular endothelial growth factor; **B** = bevacizumab; **BCVA** = best-corrected visual acuity; **DRCR** = Diabetic Retinopathy Clinical Research Network; **ERM** = epiretinal membrane; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **OCT** = optical coherence tomography; **PDR** = proliferative diabetic retinopathy; **R** = ranibizumab; **RIDE** = A Study of Ranibizumab Injection in Participants with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus; **RISE** = A Study of Ranibizumab Injection in Participants with Clinical Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VISTA** = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema; **VIVID** = Intravitreal Aflibercept Injection in Vision Impairment Due to Diabetic Macular Edema; **VMT** = vitreomacular traction.

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