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Ranibizumab or Aflibercept for Diabetic Macular Edema

Comparison of 1-Year Outcomes from the Fight Retinal Blindness! Registry

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Purpose: Both ranibizumab and aflibercept improved vision and decreased macular thickness in eyes with diabetic macular edema (DME) in clinical trials. This study compared the 12-month treatment outcomes of each drug in routine clinical practice.

Design: Retrospective analysis of data from the prospectively designed observational Fight Retinal Blindness! registry.

Participants: Treatment-naive eyes tracked in the registry that initiated treatment with either ranibizumab (0.5 mg) or aflibercept (2 mg) for DME from December 1, 2013, through June 1, 2018.

Methods: Visual acuity (VA) was analyzed at 12 months in all eyes (completers, noncompleters, and eyes that switched treatment).

Main Outcome Measures: The primary outcome was the mean change in VA from baseline to 12 months.

Results: We identified 383 eyes (ranibizumab, n = 166 eyes; aflibercept, n = 217 eyes) of 291 patients. Eyes receiving aflibercept showed a lower mean VA (mean difference, −3.1 letters) and a thicker maculae (mean difference, +26 μm) at baseline than those receiving ranibizumab, which were not significantly different. Patients receiving ranibizumab were older (mean difference, +2.7 years). The adjusted mean difference in VA change and central subfield thickness (CST) reduction were, respectively, +1 letter (1.4 letters for aflibercept vs. 0.4 letter for ranibizumab; $P = 0.4$) and −30 μm (−85 vs. −55 μm; $P < 0.01$) in eyes with initial VA of 20/40 or better and +3 letters (10.6 vs. 7.6 letters; $P < 0.01$) and −46 μm (−148 vs. −102 μm; $P < 0.02$) in those with VA of 20/50 or worse. Eyes in the aflibercept group received more median injections over 12 months than the ranibizumab group although this difference was not significant (8 vs. 6 injections; $P = 0.13$). Treatment switches, albeit low, were more frequent from ranibizumab to aflibercept than vice versa. Significantly more eyes in the aflibercept group were lost to follow-up within 12 months (21% vs. 9% ranibizumab; $P < 0.01$).

Conclusions: Both drugs were beneficial for DME. Aflibercept-treated eyes, which had borderline worse vision and thicker maculae at baseline, showed larger CST reductions after 12 months of treatment. Larger VA gains were observed with aflibercept treatment when the initial VA was 20/50 or worse. *Ophthalmology 2019;■:1–8 © 2019 by the American Academy of Ophthalmology*

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Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA; Novartis, Basel, Switzerland) and aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY/Bayer) are vascular endothelial growth factor (VEGF) inhibitors used as first-line treatment for diabetic macular edema (DME).[1–4] The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study found that aflibercept (2 mg) was more effective than ranibizumab (0.3 mg) in improving vision at 1 year in eyes with visual acuity (VA) of 68 letters or fewer (Snellen equivalent, 20/50) at presentation, whereas no difference was observed in those with VA of 69 letters or better (Snellen equivalent, 20/40) at presentation.[5] This difference was not observed 2 years after starting treatment.[6] A meta-analysis of 24 clinical trials of anti-VEGF treatments for DME produced "moderate" evidence that aflibercept had an advantage over ranibizumab 1 year after starting treatment in terms of VA and reduction in macular edema.[7]

Clinical trials determine the effects of new treatments in controlled conditions for a selected group of patients who may not be representative of the general population with the disease. The validity of results of clinical trials are

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confirmed ideally in the general population by population-based postmarketing observational studies. Real-world studies have found that ranibizumab and aflibercept treatment significantly improve VA and macular thickness 1 year after starting treatment in eyes with DME.[8,9] A direct comparison of treatment outcomes of the 2 VEGF inhibitors for DME in real-world clinical practice has yet to be performed. This study aimed to compare the visual and anatomic outcomes and frequency of treatments of ranibizumab versus aflibercept in treatment-naive eyes with DME in routine clinical practice.

Methods

Design and Setting

This was a retrospective analysis of data tracked in a prospectively designed observational database, The Fight Retinal Blindness! Registry of real-world treatment outcomes of macular diseases.[10] The registry has modules to collect data for age-related macular degeneration, retinal vein occlusion, and DME. The DME module was implemented in Australia, New Zealand, and Switzerland in April 2015. This has now expanded to other countries in Europe and Asia. Eyes receiving treatment for clinically significant diabetic macular edema (CSME) in routine clinical practice are eligible in the DME module. Investigators undertook to enter all eyes starting treatment for DME in their practices from when they started data entry. Australian practitioners undertake to track at least 85% of their eligible patients to satisfy the mandatory self-audit requirement for annual registration. This analysis included treatment-naive eyes that started ranibizumab or aflibercept for DME. Participants in this analysis were patients from practices in Australia, France, Italy, Switzerland, and the United Kingdom. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the South Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (Société Française d'Ophtalmologie Institutional Review Board), the Ethics Committee of the University of Milan, the Cantonal Ethics Committee Zurich, and the Caldicott Guardian at the Royal Free London National Health Service Foundation Trust. Informed consent (opt-in consent) was sought from patients in France, Italy, and Switzerland. Ethics committees in Australia approved the use of opt-out patient consent. Data in the registry are anonymized and compliant with the UK Policy Framework for Health and Social Care Research. This study adhered to the tenets of the Declaration of Helsinki.

Data Sources and Measurements

The Fight Retinal Blindness! Registry has a module that collects data from eyes being treated for DME. The data recorded at each clinical visit include the number of letters read on a logarithm of the minimum angle of resolution VA chart (best of uncorrected, corrected, or pinhole), treatment administered, central subfield thickness (CST; in micrometers) measured using spectral-domain OCT, the activity of DME (center-involving CSME, non−center-involving CSME, or no CSME), procedures, and ocular adverse events.[11] Duration and type of diabetes, grading of diabetic retinopathy (DR), and previous treatment for DME were recorded at the baseline visit. All treatment decisions, including choice of treatment and frequency of visits, were based on VA and OCT at the discretion of the practitioner in consultation with the patient, thereby reflecting real-world practice.

Patient Selection

Treatment-naive eyes that started DME treatment with either ranibizumab (0.5 mg; Lucentis) or aflibercept (2 mg; Eylea) from December 1, 2013, through June 1, 2018, were studied, thereby allowing the possibility of having at least 12 months of observation after the initial treatment. Eyes that did not receive the initial 2 injections of the same drug were excluded from the analysis. Eyes that completed at least 12 months of visits were defined as completers. Switchers were defined as eyes that received 2 or more injections of the other drug during this period. Visits occurring after the switch to the other drug were censored for analysis. Eyes that did not complete 12 months of observation were defined as noncompleters.

Outcomes

The main outcome was the mean change in VA in the ranibizumab and the aflibercept treatment groups at 12 months. Secondary outcomes were the mean change in CST, frequency of treatments and visits, the proportions of eyes with VA of 70 letters or more (Snellen equivalent, 20/40) and 35 letters or fewer (Snellen equivalent, 20/200), and the proportions of eyes that gained 10 letters or more and those that lost 10 letters or more at 12 months. Outcomes also were analyzed in eyes stratified by baseline VA into 2 groups, 69 letters or more (Snellen equivalent, 20/40) and 68 letters or fewer (Snellen equivalent, 20/50), to study the relationship of baseline VA on the VA change. Other outcomes of interest were the proportion of eyes that switched treatment and the rate of noncompletion in each of the groups at 12 months.

Statistical Analysis

Descriptive data included the mean (standard deviation), median (interquartile range), and percentages where appropriate. Eyes were considered to have been observed from the first treatment visit up to their 12-month (365±30 days) visit. Wilcoxon rank-sum tests, *t* tests, chi-square tests, and Fisher exact tests were used as appropriate to compare baseline characteristics between ranibizumab- and aflibercept-treated eyes. Locally weighted scatterplot smoothing regression curves were used to visualize VA results in eyes throughout the follow-up. Calculation of crude visual outcomes at 12 months used the last observation carried forward for switchers and noncompleters.

We compared VA and CST outcomes between treatments at 12 months using mixed-effects longitudinal generalized additive models with the interaction between initial injection and time as the main predictor variable. Longitudinal models included all visits from completers, switchers (until the time of switch), and noncompleters (last observation before the dropout) and were adjusted for age, baseline VA, baseline CST (fixed effects), and practice and intrapatient correlation for bilateral cases (random effects). We used predictions from this model to plot VA and the difference in the mean VA and CST change over 12 months in all eyes. Quasi-Poisson regression models adjusted for age, baseline VA, baseline CST (fixed effects), and practice and intrapatient correlation (random effects) with log days of follow-up included as an offset variable were used to compare the number of injections and visits. Cox proportional hazards regression models adjusted for age, VA and CST at baseline (fixed effects), and practice and intrapatient correlation (random effects) were used to compare the median time to noncompletion and switching over 12 months. Kaplan-Meier survival analysis was used to plot survival curves for time to noncompletion and switching.

All analyses were conducted using R software version 3.5.3 (R Project for Statistical COmputing, Vienna, Austria; R Foundation

for Statistical Computing; 2019, Available at: https://cran.r-project.org) with the lme4 package (version 1.1-21) for mixed-effects regression analysis, the mgcv package (version 1.8-24) for generalized additive (mixed) model computation, the emmeans package (version 1.3.3) for pairwise comparison of adjusted means, the coxme package (version 2.2-10) to calculate the median time to noncompletion and switching, and the survival package (version 2.38) for dropout analysis.[12–16]

Results

Study Participants

A total of 383 treatment-naive eyes (166 ranibizumab and 217 aflibercept) from 291 patients who started DME treatment with either ranibizumab or aflibercept from December 1, 2013, through June 1, 2018, were identified. Table 1 summarizes the baseline characteristics of the eyes in each of the groups. Patients receiving ranibizumab were significantly older than those receiving aflibercept (mean, 65.4 vs. 62.7 years; $P = 0.04$) and had diabetes for a longer duration (mean, 16 vs. 15 years; $P = 0.04$). Eyes with severe DR grades (severe nonproliferative DR and proliferative DR) were more likely to receive aflibercept. Eyes receiving ranibizumab tended to have better mean vision (67.8 vs. 64.7 letters; $P = 0.05$) and somewhat lower mean CST (407 vs. 433 μm; $P = 0.05$) at baseline. Most eyes demonstrated center-involving CSME (92% for both ranibizumab and aflibercept; Table 1).

Table 1. Baseline Characteristics of Eyes Treated with Ranibizumab and Aflibercept

Characteristic	Ranibizumab	Aflibercept	*P* Value
No. of eyes	166	217	
No. of patients	134	158	
Female gender, no. (%)	55 (41)	58 (37)	0.39
Diabetes duration (yrs), mean (SD)	16 (18)	15 (19)	0.04
Diabetes type, %			0.56
1	7	9	
2	93	91	
Diabetic retinopathy grade, %			
Mild NPDR	19	8	<0.01
Moderate NPDR	44	41	
Severe NPDR	28	32	
PDR, low risk	5	9	
PDR, high risk	4	10	
Baseline age (yrs), mean (SD)	65.4 (12.4)	62.7 (12.3)	0.04
Baseline VA (letters), mean (SD)	67.8 (14.3)	64.7 (16)	0.05
VA ≥ 70 letters, %	51	49	0.72
VA ≤ 35 letters, %	3	5	0.46
CST (μm), mean (SD)	407 (108)	433 (138)	0.05
DME activity, %			
Center-involving CSME	92	92	0.22
Non–center-involving CSME	8	7	
No CSME	0	2	

CSME = clinically significant macular edema; CST = central subfield thickness; DME = diabetic macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation; VA = visual acuity (logarithm of the minimum angle of resolution letters).

Visual Outcomes at 12 Months

The crude mean (95% confidence interval [CI]) VA change at 12 months for all eyes, using the last observation carried forward for switchers and dropouts, was higher for aflibercept (mean, 6.1 letters [95% CI, 4.5–7.7 letters] vs. 3.3 letters [95% CI, 1.6–5.1 letters] for ranibizumab; $P = 0.02$; Table S1, available at www.aaojournal.org). The mean adjusted VA change, using longitudinal models adjusted for age, baseline VA, and baseline CST, also was greater in the aflibercept group (mean, 5.4 letters [95% CI, 4.1–6.7 letters] vs. 3.3 letters [95% CI, 1.9–4.7 letters] for ranibizumab; $P < 0.01$; Table S1). The adjusted mean VA over 12 months for all eyes is shown in Figure 1A. The adjusted mean difference in the VA change was significantly in favor of aflibercept for most of the 12 months after starting treatment (Fig 1B). The proportion of all eyes with VA of 70 letters or more and those with VA of 35 letters or fewer at 12 months in both the groups were similar. More eyes in the aflibercept group gained 10 letters or more at 12 months, whereas similar proportions of each group lost 10 letters or more.

We divided the cohort into 2 groups according to the VA at baseline, eyes with VA of 69 letters or more (191 eyes [53%]) and those with VA of 68 letters or fewer (192 eyes [47%]), to study the relationship of initial vision on VA gain with treatments. The mean VA change at 12 months of treatment in eyes with good vision at baseline (VA, ≥69 letters) was similar for both aflibercept and ranibizumab, although more eyes receiving aflibercept gained 10 letters or more at 12 months (19% vs. 4%; $P < 0.01$; Table S2, available at www.aaojournal.org). However, the mean VA gain at 12 months in eyes with initial vision of 68 letters or fewer was significantly higher in eyes receiving aflibercept (mean, 10.6 letters; 95% CI, 7.9–13.2 letters) than in those receiving ranibizumab (mean, 7.6 letters; 95% CI, 4.4–10.8 letters; $P = 0.01$).

Figure 2 shows the mean VA over 12 months of 303 eyes (79%) that completed 12 months of monotherapy (aflibercept, n = 167 [77%] eyes; ranibizumab, n = 136 [82%] eyes; Table S1). The mean VA of these eyes in the ranibizumab and the aflibercept groups at baseline and 12 months was similar. The crude mean VA change was similar for the 2 groups at 12 months, but the adjusted mean VA change was significantly higher for the aflibercept group (Table S1). The proportion of eyes with VA of 70 letters or more and those with VA of 35 letters or fewer at 12 months was similar in both groups, as was the proportion of eyes that gained 10 letters or more and those that lost 10 letters or more at 12 months.

Macular Thickness

Both drugs were effective in reducing macular thickness (Fig 1). Eyes in the aflibercept group showed a significantly greater reduction in mean adjusted CST at 12 months than those in the ranibizumab group (mean, −126 μm [95% CI, −144 to −98 μm] vs. −89 μm [95% CI, −109 to −69 μm]; $P < 0.01$; Table S1). The difference in the mean CST change between the 2 anti-VEGF agents at 12 months significantly favored aflibercept (Fig 1C). The advantage of aflibercept over ranibizumab in reducing macular thickness was observed regardless of whether the initial VA was 69 letters or more or 68 letters or fewer (Table S2). Figure 2 illustrates the mean CST over 12 months in eyes that completed 12 months in both groups.

Treatments and Visits

The median number of anti-VEGF injections and visits in eyes that completed 12 months of continuous treatment in the 2 groups were as follows: 8 injections (interquartile range [IQR], 6–9 injections)

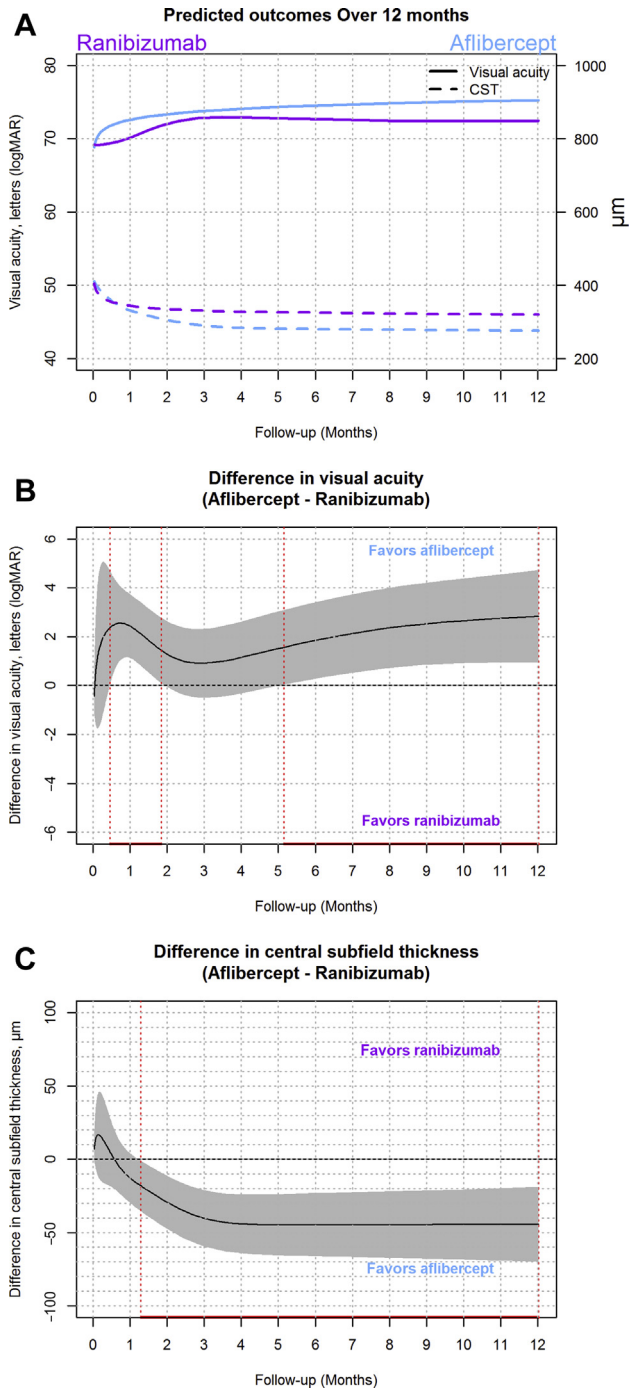

Figure 1. Line graphs showing (**A**) the mean predicted visual acuity (VA; solid lines) in logarithm of the minimum angle of resolution (logMAR) letters (y-axis) and central subfield thickness (CST; dashed lines) in microns (z-axis) and (**B**) the difference in the mean change in VA and (**C**) CST between ranibizumab-treated (purple) and aflibercept-treated (blue) eyes over 12 months in all eyes regardless of whether they completed, switched (visits at the time of switch), or did not complete 12 months of observations from starting treatment. The grey shaded areas in (**B**) and (**C**) represent the 95% confidence interval. Red dashed lines in (**B**) and (**C**) indicate areas where the 95% confidence interval does not intersect with 0. Predictions were made from a generalized additive model considering adjustments for age, VA, and CST at baseline (fixed effects) and the practice and intrapatient correlation for bilateral cases (random effects).

for aflibercept versus 6 injections (IQR, 4−8 injections; $P = 0.13$) for ranibizumab and a mean of 10 visits (IQR, 8−12 visits) versus 10 visits (IQR, 7−12 visits; $P = 0.11$; Table S1). The number of additional treatments, macular laser sessions, and intravitreal steroid injections (triamcinolone and Ozurdex [Allergan Inc., Irvine, CA]) in each of the groups during the 12 months also were similar (Table S1). No difference was found in the median number of treatments (including additional macular laser therapy and steroids) and visits between ranibizumab and aflibercept groups when eyes were stratified based on the initial VA (Table S2).

Treatment Switch

Treatment switches occurring within 12 months were uncommon (19 eyes [5%]) and were more frequent from ranibizumab to aflibercept than vice versa (9% vs. 2%; $P < 0.01$; Fig 3A). The median time to switching from ranibizumab to aflibercept was 231 days (IQR, 117−296 days) and from aflibercept to ranibizumab was 196 days (IQR, 113−264 days). The mean VA in eyes at baseline and at the time of switching in each of the groups that switched treatment, the mean changes in VA and CST from the start of treatment to the switch, and the number of anti-VEGF injections and visits from the start of treatment to the time of switching are shown in Table S1 (available at www.aaojournal.org).

Noncompletion Rate at 12 Months

Sixty-one eyes (16%) discontinued treatment before completing 12 months of follow-up. The noncompletion rate was higher in the aflibercept group (21% vs. 9% in eyes receiving ranibizumab; $P < 0.01$; Fig 3B). The median time to dropout was 223 days (IQR, 121.5−278 days) for aflibercept and 196 days (IQR, 112.5−264 days) for ranibizumab. Eyes that discontinued treatment in both groups showed a similar mean VA at baseline and at the last visit before discontinuing treatment. The mean VA change was +7.7 letters (95% CI, 4.8−10.7 letters) for aflibercept and 3.0 letters (95% CI, −1.2 to 7.2 letters) for ranibizumab ($P = 0.06$) from the start of treatment to the last visit (Table S1). The maculae of the aflibercept group were significantly thicker than those of eyes in the ranibizumab group when they started treatment. The mean drop in CST at the time of treatment discontinuation also was significantly greater in eyes receiving aflibercept treatment than those receiving ranibizumab treatment. The median number of anti-VEGF injections (median, 6 injections [IQR, 3−7 injections] of aflibercept vs. 4 injections [IQR, 3−5.5 injections; $P = 0.51$] of ranibizumab) and visits (median, 7 visits [IQR, 4.2−8 visits] vs. 5 visits [IQR, 3−7.5 visits], respectively; $P = 0.22$) in the 2 groups from the start of treatment to the last visit were similar.

The reasons for treatment discontinuation were tracked in 25 of the 61 eyes (41%). The main reason was transfer of care to another physician (52%; ranibizumab, n = 6 eyes; aflibercept, n = 7 eyes). Other reasons were patient declined further treatment (24%; ranibizumab, n = 0 eyes; aflibercept, n = 6 eyes), patient death (16%; ranibizumab, n = 3 eyes; aflibercept, n = 1 eyes), lack of response to treatment (4%; ranibizumab, n = 1 eyes; aflibercept, n = 0 eyes), and successful treatment (4%; ranibizumab, n = 1 eyes; aflibercept, n = 0 eyes).

Discussion

This analysis in real-world clinical practice from a prospectively designed observational registry found that both

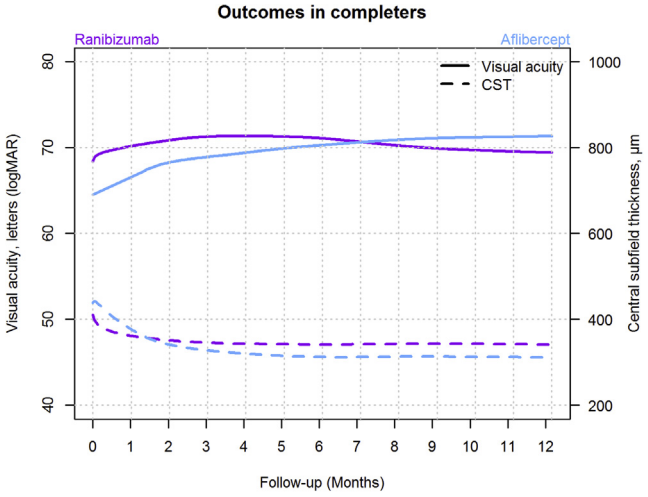

Figure 2. Locally weighted scatterplot smoothing regression curves showing the mean visual acuity (solid lines) in logarithm of the minimum angle of resolution letters (y-axis) and central subfield thickness (CST; dashed lines) in micrometers (z-axis) in ranibizumab-treated (purple) and aflibercept-treated (blue) eyes completing 12 months of observations from the start of treatment (x-axis).

aflibercept and ranibizumab improved vision and reduced macular thickness in eyes with DME after 1 year of treatment. Changes in VA for the 2 treatment groups, +1.4 letters for aflibercept versus 0.4 letters for ranibizumab ($P = 0.4$), were similar (adjusted mean difference, 1 letter) in eyes with initial VA of 69 letters or more (Snellen equivalent, 20/40), and a greater improvement with aflibercept, 10.6 letters versus 7.6 letters ($P < 0.01$), was observed in eyes with initial VA of 68 letters of fewer (Snellen equivalent, 20/50). Aflibercept-treated eyes showed significantly greater reductions in macular thickness (mean CST change, −128 µm vs. −80 µm; $P < 0.01$). Some of this difference may be related to differences in baseline characteristics and injection numbers. Eyes in the aflibercept group received more injections over 12 months (median, 8 injections [IQR, 6−9 injections]) than the ranibizumab group (median, 6 injections; [IQR, 4−8 injections]), although this difference was not significant ($P = 0.13$). Patients had the same number of visits in both groups. A few treatment switches occurred during the 12 months, more from ranibizumab to aflibercept than vice versa. The proportion of patients who did not complete 12 months follow-up was higher in the aflibercept group. Eyes that dropped out in both groups had similar outcomes to the overall group in terms of visit and treatment frequencies and mean VA change from the start of treatment to the last visit.

Eyes receiving aflibercept tended to have more advanced disease with somewhat lower mean VA and thicker maculae when they started treatment. Patients receiving ranibizumab treatment were, on average, 2 years older than those receiving aflibercept, which is consistent with a previous observation in eyes receiving anti-VEGF treatment for neovascular age-related macular degeneration.[17] This could have resulted from the physicians' concerns regarding the risk of stroke with aflibercept treatment in older patients, which was mentioned in a report from Europe.[18] We compared treatment outcomes between the 2 groups after adjusting for age, baseline VA and CST, and nesting within practices and patients for bilateral cases.[19]

Consistent with pivotal clinical trials and a recent Cochrane meta-analysis, aflibercept and ranibizumab both improved vision in eyes with DME in clinical practice.[1,2,5,7] We found eyes in the aflibercept group achieved larger vision gains than those in the ranibizumab group at 12 months from the start of treatment, although baseline characteristics were not ideally matched. A Cochrane meta-analysis identified a visual advantage of aflibercept over ranibizumab 1 year after starting treatment.[7] Herein, we found that aflibercept also seems to be more effective than 0.5-mg ranibizumab in improving vision at 1 year in eyes with VA of 68 letters or fewer at the start of treatment, as was reported by the DRCR.net Protocol T for 0.3-mg ranibizumab.[5] The visual gains in both the treatment groups were similar in eyes with initial VA of 69 letters or more, perhaps because of the ceiling effect when treating patients with good vision at baseline.

Vision improvements in the present study in both groups were lower than the mean VA gains of 6.8 to 13.1 letters reported after 1 year of treatment in the major clinical trials of anti-VEGF for DME.[5,20−22] Visual acuity improvements in observational studies usually have been lower than those reported by clinical trials.[8,9,23] This may be because of different inclusion or exclusion criteria, because they receive inadequate treatment, or both.[24] Adherence to treatment regimens, which may be onerous, may be higher for participants in clinical trials than in routine clinical practice. Eyes in the present study received a median of 6 ranibizumab or 8 aflibercept injections over 12 months compared with 10 ranibizumab injections (50% of eyes received additional laser treatment) or 9 aflibercept injections (35% eyes received additional macular laser treatment) in the DRCR.net study.[5] However, the mean final VA of approximately 71 letters observed 1 year after the start of treatment was similar to those reported in the DRCR.net study, suggesting the lower gains in the present study may be the result, in part, of the better starting VA.[5] The mean VA change in the present study was approximately 9 letters worse in eyes with initial vision of 68 letters or fewer and 4 letters better in eyes with initial VA of 69 letters or more than those of the DRCR.net study.

Both ranibizumab and aflibercept also reduced macular thickness to an extent similar to that reported by Wells et al,[5] with a significantly greater mean reduction in eyes receiving aflibercept, which was observed in both strata of VA at the initiation of treatment. Eyes in the aflibercept group in the present study showed somewhat thicker maculae at presentation and received somewhat more treatments than eyes in the ranibizumab group, both of which could have contributed to the higher mean drop in macular thickness.

Studies that evaluate treatment outcomes may be biased by eyes that switch treatment or are lost to follow-up because these events may be related to a poor outcome. The rate of switching, although low in the present study (5%), was significantly higher from ranibizumab to aflibercept than vice versa. The noncompletion rate at 12

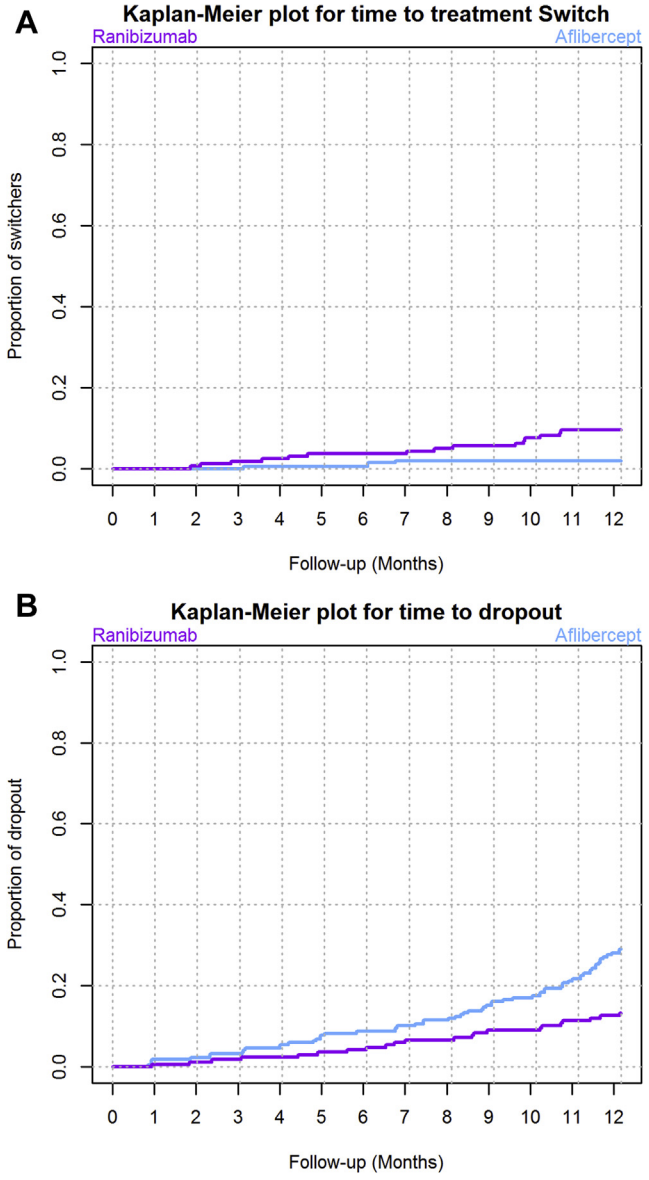

Figure 3. Kaplan-Meier plots showing time from starting treatment to (**A**) treatment switch and (**B**) dropout in eyes treated with ranibizumab (purple) and aflibercept (blue) over 12 months.

months in the present study was higher in the aflibercept group. The primary outcome of the present study included data from all eyes, regardless of whether they completed, switched, or discontinued treatment, to address the potential bias that could arise from asymmetric switching or loss to follow-up. However, the true 12-month outcomes of monotherapy in switchers and noncompleters cannot be known, and our comparison relies on the assumptions of the model, most notably, that the data are missing at random. Thus, we assume that the 12-month outcomes for these eyes can be inferred reasonably based on their observed response and that they did not experience an unobserved deviation from their observed trajectory.

A discontinuation or switching rate of 21%, as we found after 12 months, is typical of observational studies. Reasons for discontinuation, which were recorded in 41% of eyes that did so, were unrelated to poor outcomes in most cases and included transfers to another physician and death (72% of all those who discontinued treatment). Almost a quarter declined further treatment; this may have been due to a poor response or a good response. The similar outcomes achieved between the 12-month completers and noncompleters suggests that a significant number of the latter group had a good result. The remainder were likely related to poor outcomes, including "further treatment considered futile."

This study has limitations that are inherent in real-world studies. Treatment decisions in routine clinical practice, in contrast to the randomized clinical trials, are made without reference from a reading center and are not guided by study protocols. Selection of cases and treatment regimen also may differ from clinical trials and among physicians. The data presented here do not provide reasons for the choice of a particular VEGF inhibitor for each eye or for any treatment switch. Nevertheless, we have compared the 2 VEGF inhibitors for DME treatment because they are actually being used in routine clinical practice. A carefully designed observational study, such as the present study, is unlikely to overestimate the therapeutic effectiveness of an agent.[25] A lack of prospective randomization to treatment groups was observed, but we partially offset this with statistical analysis that was adjusted for baseline factors with potential impact such as VA, age, CST, and nesting of outcomes within practice.

The apparent stronger effect of aflibercept over ranibizumab for DME contrasts with similar observational and clinical studies that have reported no discernible difference in the efficacy of the 2 drugs when they are used for neovascular age-related macular degeneration.[26-28] Perhaps this is because greater levels of aflibercept, which is a much larger molecule than ranibizumab, reach the retinal circulation rather than the subretinal space because of barriers to diffusion of the larger molecule, including the outer limiting membrane and the retinal pigment epithelium for type 1 neovascularization.[29]

This study found that both aflibercept and ranibizumab were effective for DME over 12 months, with aflibercept having somewhat better anatomic outcomes. Larger VA gains were observed in eyes receiving aflibercept treatment when the initial VA was 68 letters or fewer (Snellen equivalent, 20/50), which is consistent with the data from the DRCR.net Protocol T clinical trial. Longer-term observational studies of intravitreal therapy for DME are warranted to ensure that our patients continue to achieve the best possible outcomes.

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Abbreviations and Acronyms:
CI = confidence interval; **CST** = central subfield thickness; **CSME** = clinically significant macular edema; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRCR.net** = Diabetic Retinopathy Clinical Research Network; **IQR** = interquartile range; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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