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Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema

Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial

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Purpose: To provide 2-year results comparing anti−vascular endothelial growth factor (VEGF) agents for center-involved diabetic macular edema (DME) using a standardized follow-up and retreatment regimen.

Design: Randomized clinical trial.

Participants: Six hundred sixty participants with visual acuity (VA) impairment from DME.

Methods: Randomization to 2.0-mg aflibercept, 1.25-mg repackaged (compounded) bevacizumab, or 0.3-mg ranibizumab intravitreous injections performed up to monthly using a protocol-specific follow-up and retreatment regimen. Focal/grid laser photocoagulation was added after 6 months if DME persisted. Visits occurred every 4 weeks during year 1 and were extended up to every 4 months thereafter when VA and macular thickness were stable.

Main Outcome Measures: Change in VA, adverse events, and retreatment frequency.

Results: Median numbers of injections were 5, 6, and 6 in year 2 and 15, 16, and 15 over 2 years in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global $P = 0.08$). Focal/grid laser photocoagulation was administered in 41%, 64%, and 52%, respectively (aflibercept vs. bevacizumab, $P < 0.001$; aflibercept vs. ranibizumab, $P = 0.04$; bevacizumab vs. ranibizumab, $P = 0.01$). At 2 years, mean VA improved by 12.8, 10.0, and 12.3 letters, respectively. Treatment group differences varied by baseline VA ($P = 0.02$ for interaction). With worse baseline VA (20/50 to 20/320), mean improvement was 18.1, 13.3, and 16.1 letters, respectively (aflibercept vs. bevacizumab, $P = 0.02$; aflibercept vs. ranibizumab, $P = 0.18$; ranibizumab vs. bevacizumab, $P = 0.18$). With better baseline VA (20/32 to 20/40), mean improvement was 7.8, 6.8, and 8.6 letters, respectively ($P > 0.10$, for pairwise comparisons). Anti-Platelet Trialists' Collaboration (APTC) events occurred in 5% with aflibercept, 8% with bevacizumab, and 12% with ranibizumab (global $P = 0.047$; aflibercept vs. bevacizumab, $P = 0.34$; aflibercept vs. ranibizumab, $P = 0.047$; ranibizumab vs. bevacizumab, $P = 0.20$; global $P = 0.09$ adjusted for potential confounders).

Conclusions: All 3 anti-VEGF groups showed VA improvement from baseline to 2 years with a decreased number of injections in year 2. Visual acuity outcomes were similar for eyes with better baseline VA. Among eyes with worse baseline VA, aflibercept had superior 2-year VA outcomes compared with bevacizumab, but superiority of aflibercept over ranibizumab, noted at 1 year, was no longer identified. Higher APTC event rates with ranibizumab over 2 years warrants continued evaluation in future trials. *Ophthalmology 2016;123:1351-1359 © 2016 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a comparative effectiveness trial comparing the 3 commonly used anti−vascular endothelial growth factor (VEGF) agents aflibercept (Eylea; Regeneron Pharmaceuticals, Inc [Tarrytown, NY]), bevacizumab (Avastin; Genentech [South San Francisco, CA]), and ranibizumab (Lucentis; Genentech) for center-involved diabetic macular edema (DME) associated with visual impairment. The study used a standardized follow-up and retreatment regimen, including focal/grid laser photocoagulation for persistent DME not improving at 6 months or later. The previously reported 1-year results showed that all

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3 agents improved vision on average, with treatment group differences varying according to initial visual acuity (VA).[1,2] When baseline VA impairment was mild (range, 20/32−20/40), no apparent differences in VA on average were identified among the groups, whereas at worse levels of baseline VA (range, 20/50−20/320), aflibercept on average was more effective at improving vision than the other 2 agents. No statistically significant differences in prespecified ocular or systemic safety events among the 3 anti-VEGF agents were identified.

The 1-year primary outcome time point was chosen in part because previous trials consistently showed that most VA improvement with anti-VEGF agents for DME occurred on average by 1 year.[3−5] Therefore, we anticipated that, if there were treatment group differences, they likely would be apparent by 1 year. However, the secondary and final study end point at 2 years was chosen to determine whether differences in treatment effects identified at 1 year were sustained at 2 years and whether differences in intravitreous injection and laser frequency were identified. The results of the 2-year analyses are reported herein.

Methods

The study procedures and statistical methods were reported previously and are summarized briefly.[2] The protocol is available on the DRCR.net web site (www.drcr.net; accessed: December 22, 2015).

Eighty-nine clinical sites enrolled 660 participants (mean age, 61±10 years; 47% women) with best-corrected VA (approximate Snellen equivalent) of 20/32 to 20/320 (mean baseline VA, approximately 20/50), center-involved DME on clinical examination, and optical coherence tomography (OCT) results based on protocol-defined thresholds (mean baseline central subfield thickness, 412 μm; provided as a Stratus [Carl Zeiss Meditec; Oberkochen, Germany] time-domain equivalent throughout the remainder of this article), and no prior anti-VEGF treatment within 12 months of enrollment. The eyes were assigned randomly 1:1:1 to intravitreous injections of aflibercept (2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg). If the nonstudy eye needed an anti-VEGF injection, the same agent as the study eye was used.

Participants underwent follow-up examinations every 4 weeks during the first year and every 4 to 16 weeks during the second year, depending on treatment course. At each visit, study eyes were assessed for retreatment with the anti-VEGF agent based on VA and OCT criteria. Starting at the 6-month visit, focal/grid laser photocoagulation was administered if DME persisted and was not improving. Medical monitoring of all adverse events was completed by a masked physician (R.W.B.) at the DRCR.net Coordinating Center. A secondary review by another masked physician independent of the DRCR.net was performed for all serious adverse events to confirm prespecified safety outcomes.

At annual visits, the VA and OCT technicians were masked to treatment group. Investigators and study coordinators were not masked. Participants were masked until the primary results were published in February 2015, when they were informed of the study's primary results and of their treatment group assignment. At that time, if deemed warranted by the investigator, the study participant could switch anti-VEGF agents after discussion with the protocol chair.

The 2-year analyses methods mirrored the 1-year analyses.[2] The primary analysis consisted of 3 pairwise comparisons of mean VA change from baseline in the 3 treatment groups using an analysis of covariance model, adjusted for baseline VA, with the Hochberg method used to control overall type I error.[6] The primary analysis followed the intention-to-treat principle, including all randomized eyes. Central subfield thickness was analyzed similarly, with additional adjustment for baseline thickness. For VA, multiple imputation was used to impute missing 2-year data, and outlying values were truncated to 3 standard deviations from the mean.[7] Binary VA and central subfield thickness outcomes were analyzed using binomial regression or Poisson regression with robust variance estimation.[8] Observed data are presented for summary statistics unless otherwise specified. For adverse events and number of treatments, global P values for the overall 3-group comparison were calculated; pairwise comparisons were calculated if the global P value was less than 0.05, adjusting for multiple treatment comparisons.[9] All P values are 2 sided. SAS software version 9.4 (SAS Institute) was used for all analyses.

Results

The 2-year visit was completed by 90%, 85%, and 88% of the 660 randomized participants (91%, 90%, and 91% excluding deaths) in the aflibercept, bevacizumab, and ranibizumab groups, respectively (Fig S1, available at www.aaojournal.org). There were no substantial differences identified in the baseline characteristics of those who completed and those who did not complete the 2-year visit (Table S1, available at www.aaojournal.org). For those who completed 2 years of follow-up, the median number of visits during the second year was 10 in all 3 groups (Table S2, available at www.aaojournal.org).

Among participants completing the 2-year visit, the median numbers of intravitreous injections during the 2 years were 15 (interquartile range [IQR], 11−17), 16 (IQR, 12−20), and 15 (IQR, 11−19) injections in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global $P = 0.08$), with 5 (IQR, 2−7), 6 (IQR, 2−9), and 6 (IQR, 2−9) injections, respectively, between the 1- and 2-year visits (global $P = 0.32$; Table S2, available at www.aaojournal.org). Most eyes (84%) received at least 1 injection in the second year, and 98% of the protocol-required injections (based on VA and OCT) were administered over the 2 years (Table S2, available at www.aaojournal.org). The percentages of eyes undergoing at least 1 session of focal/grid laser photocoagulation during the 2 years were 41%, 64%, and 52% in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global $P < 0.001$; pairwise comparisons: $P < 0.001$ for aflibercept vs. bevacizumab, $P = 0.04$ for aflibercept vs. ranibizumab, and $P = 0.01$ for ranibizumab vs. bevacizumab), with 20%, 31%, and 27%, respectively, undergoing at least 1 session of focal/grid laser photocoagulation in the second year (global $P = 0.046$; Table S2, available at www.aaojournal.org). Three eyes in the aflibercept group, 10 in the bevacizumab group, and 1 in the ranibizumab group received 1 or more alternative treatments for DME other than the randomly assigned anti-VEGF or focal/grid laser photocoagulation. For only 1 of the eyes receiving alternative treatment did that treatment occur after the participant had been unmasked to their treatment assignment and informed of the 1-year results (1 eye in the bevacizumab group received aflibercept).

Effect of Treatment on Visual Acuity

Visual acuity at the 2-year visit improved from baseline, on average, by 12.8 letters with aflibercept, 10.0 letters with bevacizumab, and 12.3 letters with ranibizumab (pairwise comparisons: $P = 0.02$ for aflibercept vs. bevacizumab, $P = 0.47$ for aflibercept vs. ranibizumab, and $P = 0.11$ for ranibizumab vs.

bevacizumab; Table S3, available at www.aaojournal.org; Fig 1; Fig S2, available at www.aaojournal.org). However, the relative effect of the treatments varied by initial VA ($P = 0.02$ for interaction, with baseline VA letter score as a continuous variable; and $P = 0.11$ for interaction, with baseline VA as a binary variable; letter score, 69 or better or worse than 69 [approximate Snellen equivalent, 20/50]; Table 1; Fig S3, available at www.aaojournal.org). Specifically, when initial VA letter score was less than 69 (Snellen equivalent, 20/50 or worse; approximately 50% of the cohort), mean VA letter score improvement from baseline to the 2-year visit was +18.1±13.8 letters, +13.3±13.4 letters, and +16.1±12.1 letters, respectively (aflibercept vs. bevacizumab, +4.7 letters [95% confidence interval (CI), +0.5 to +8.8 letters; $P = 0.02$]; aflibercept vs. ranibizumab, +2.3 letters [95% CI, −1.1 to +5.6 letters; $P = 0.18$]; and ranibizumab vs. bevacizumab, +2.4 letters [95% CI, −1.0 to +5.8 letters; $P = 0.18$]; Table 1). When initial VA was 78 to 69 letters (Snellen equivalent, 20/32 or 20/40), mean improvement at the 2-year visit was +7.8±8.4 letters for aflibercept, +6.8±8.8 letters for bevacizumab, and +8.6±7.0 letters for ranibizumab without any statistically significant differences between groups (Table 1). Sensitivity analyses with different approaches for handling missing data and outlier values produced similar results (Table S4, available at www.aaojournal.org).

Percentages of eyes with at least 10-letter or at least 15-letter changes at the 2-year visit are provided in Table 1, Table S3 (available at www.aaojournal.org), and Figure S4 (available at www.aaojournal.org); there were no statistically significant differences between groups for any of the binary VA outcomes, overall, or within VA subgroups. The detailed distribution of VA at 2 years is provided in Table S5 (available at www.aaojournal.org). There was no statistically significant interaction between treatment and any of the 3 other preplanned baseline factors: OCT central subfield thickness, prior anti-VEGF treatment, or lens status (Table S6, available at www.aaojournal.org). Mean change in VA over 2 years stratified in a post hoc analysis by both baseline VA and central subfield thickness is provided in Figure S5 (available at www.aaojournal.org); within the eyes with better baseline vision and with thicker baseline central subfield thickness (400 μm or thicker on time-domain equivalent), there was a suggestion of less VA improvement in the bevacizumab group than in the other 2 groups.

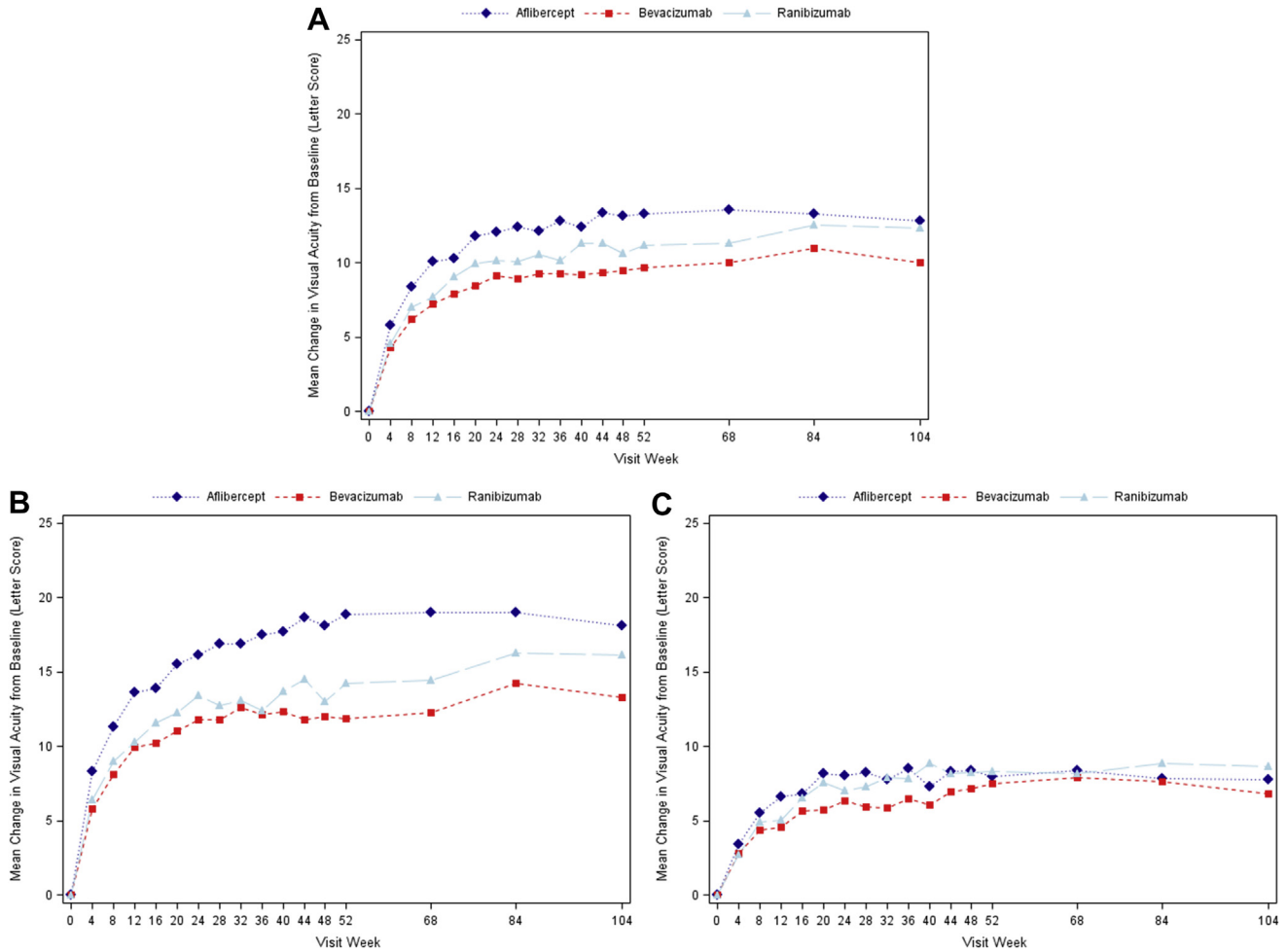

Figure 1. Graphs showing the mean change in visual acuity over time stratified by baseline visual acuity (approximate Snellen equivalent): (**A**) overall, (**B**) 20/50 or worse and (**C**) 20/32 to 20/40. Change in visual acuity was truncated to 3 standard deviations from the mean. The number of eyes at each time point ranged from 195 to 224 in the aflibercept group, 185 to 218 in the bevacizumab group, and 188 to 218 in the ranibizumab group (see Fig S1 in the Supplementary Appendix and Fig S2 in the 1 Year Supplementary Appendix[2] for the number at each time point; available at www.aaojournal.org).

Table 1. Visual Acuity at 2 Years Stratified by Visual Acuity Subgroup

Visual Acuity	Observed Data			Treatment Group Comparisons: Differences in Mean Change or Difference in Proportions (Adjusted 95% Confidence Interval) and Adjusted P Value		
	Aflibercept	*Bevacizumab*	*Ranibizumab*	*Aflibercept vs. Bevacizumab*	*Aflibercept vs. Ranibizumab*	*Ranibizumab vs. Bevacizumab*
Baseline visual acuity 20/50 or worse (letter score, <69)						
No. of patients	98	92	94			
Baseline						
Mean ± SD	55.8±11.1	56.9±10.5	56.1±10.1			
~Snellen equivalent	20/80	20/80	20/80			
1 year (in 2-yr cohort)						
Mean ± SD	75.4±10.4	69.6±12.0	70.8±12.0			
~Snellen equivalent	20/32	20/40	20/40			
Mean change ±SD	19.4±11.1	12.6±11.8	14.7±10.2			
2 year						
Mean ± SD	74.3±13.3	69.8±15.7	71.9±14.6			
~Snellen equivalent	20/32	20/40	20/40			
Change from baseline (letter score)						
Mean ± SD	+18.1±13.8	+13.3±13.4	+16.1±12.1	+4.7 (+0.5 to +8.8) P = 0.02	+2.3 (−1.1 to +5.6) P = 0.18	+2.4 (−1.0 to +5.8) P = 0.18
≥10-letter improvement, no. (%)	74 (76)	61 (66)	67 (71)	+10 (−6 to +26) P = 0.35	+3 (−9 to +15) P = 0.57	+7 (−6 to +20) P = 0.57
≥10-letter decline, no. (%)	5 (5)	8 (9)	2 (2)	−3 (−10 to +3) P = 0.49	+2 (−3 to +7) P = 0.49	−5 (−13 to +3) P = 0.33
≥15-letter improvement, no. (%)	57 (58)	48 (52)	52 (55)	+8 (−9 to +25) P = 0.74	+2 (−11 to +15) P = 0.75	+6 (−8 to +20) P = 0.75
≥15-letter decline, no. (%)	2 (2)	4 (4)	2 (2)	−2 (−7 to +3) P = 0.86	0 (−4 to +4) P = 0.86	−2 (−6 to +3) P = 0.86
Baseline visual acuity 20/32−20/40 (letter score, 78−69)						
No. of patients	103	93	97			
Baseline						
Mean ± SD	73.5±2.6	73.0±2.9	73.4±2.7			
~Snellen equivalent	20/32	20/40	20/40			
1 year (in 2-yr cohort)						
Mean ± SD	81.3±8.3	79.8±10.5	81.8±6.8			
~Snellen equivalent	20/25	20/25	20/25			
Mean change±SD	7.9±7.7	7.3±7.3	8.4±6.8			
2 year						
Mean ± SD	81.2±8.3	79.3±11.4	82.0±6.8			
~Snellen equivalent	20/25	20/25	20/25			
Change from baseline (letter score)						
Mean ± SD	+7.8±8.4	+6.8±8.8	+8.6±7.0	+1.1 (−1.1 to +3.4) P = 0.51	−0.7 (−2.9 to +1.5) P = 0.51	+1.9 (−0.9 to +4.7) P = 0.31
≥10-letter improvement, no. (%)	51 (50)	38 (41)	45 (46)	+9 (−7 to +25) P = 0.52	+4 (−10 to +17) P = 0.59	+5 (−8 to +19) P = 0.59
≥10-letter decline, no. (%)	4 (4)	4 (4)	1 (1)	0 (−6 to +5) P = 0.96	+3 (−3 to +8) P = 0.55	−3 (−8 to +3) P = 0.55
≥15-letter improvement, no. (%)	21 (20)	16 (17)	18 (19)	+1 (−10 to +11) P = 0.89	+2 (−8 to +11) P = 0.89	−1 (−11 to +10) P = 0.89
≥15-letter decline, no. (%)	3 (3)	2 (2)	1 (1)	+1 (−3 to +5) P = 0.69	+2 (−2 to +5) P = 0.69	−1 (−4 to +3) P = 0.69

SD = standard deviation.
See Table S3 (available at www.aaojournal.org) for detailed footnote.

Effect of Treatment on Macular Edema

At the 2-year visit, central subfield thickness decreased on average by 171±141 μm with aflibercept, 126±143 μm with bevacizumab, and 149±141 μm with ranibizumab (aflibercept vs. bevacizumab, −48.5 μm [95% CI, −70.0 to −27.0 μm; $P < 0.001$]; aflibercept vs. ranibizumab, −15.5 μm [95% CI, −33.0 to +2.0 μm; $P = 0.08$]; and ranibizumab vs. bevacizumab, −33.0 μm [95% CI, −53.4 to −12.6 μm; $P < 0.001$]; Table S7, available at www.aaojournal.org). The number of eyes achieving central subfield thickness of less than 250 μm (based on Zeiss Stratus equivalent) was 141 eyes (71%), 75 eyes (41%), and 121 eyes (65%), respectively. The relative treatment effect on central subfield thickness varied based on initial VA ($P < 0.001$ for interaction; Table 2; Fig 2). When initial VA was 20/50 or worse, central subfield thickness at 2 years decreased on average by 211±155 μm, 185±158 μm, and 174±159 μm with aflibercept, bevacizumab, and ranibizumab, respectively; in eyes with initial VA of 20/32 or 20/40, it decreased 133±115 μm, 68±98 μm, and 125±118 μm, respectively. Change in retinal

volume from baseline to 2 years is reported in Table S8 (available at www.aaojournal.org).

Safety

Ocular adverse events over 2 years are summarized in Table 3 and in Table S9 and S10 (available at www.aaojournal.org). One injection-related case of infectious endophthalmitis occurred in each group. Systemic adverse events over 2 years are provided in Table 3 and in Tables S11-S15 (available at www.aaojournal.org). Across the 3 treatment groups, the percentages of serious adverse events reported (37%–39%) and of participants hospitalized (33%–34%) within 2 years were similar (global $P = 0.90$ and $P = 0.93$, respectively). In the aflibercept, bevacizumab, and ranibizumab groups, respectively, there were 2%, 6%, and 5% deaths (global $P = 0.12$) and 5%, 8%, and 12% in prespecified analysis using the Anti-Platelet Trialists Collaboration definition of events (global $P = 0.047$; pairwise comparisons: $P = 0.34$ for aflibercept vs. bevacizumab, $P = 0.047$ for aflibercept vs. ranibizumab, and $P = 0.20$ for ranibizumab vs. bevacizumab; global $P = 0.09$, adjusted for 12 potential baseline confounders [listed in a footnote to Table 3]; global $P = 0.06$, adjusted for prior myocardial infarction or prior stroke). The higher rate of Anti-Platelet Trialists' Collaboration (APTC) events for ranibizumab included more nonfatal strokes (2 for aflibercept, 6 for bevacizumab, and 11 for ranibizumab) and vascular deaths (3 for aflibercept, 8 for bevacizumab, and 9 for ranibizumab). In a post hoc analysis among the aflibercept, bevacizumab, and ranibizumab participants, respectively, without a history of stroke or myocardial infarction before study entry, 5% (10/203), 6% (12/193), and 9% (17/193) experienced an APTC event, whereas among those with a history of a prior stroke or myocardial infarction, 10% (2/21), 20% (5/25), and 36% (9/25) experienced an APTC event (Table S10, available at www.aaojournal.org).

In a post hoc analysis, among treatment group comparisons in 24 Medical Dictionary for Regulatory Activities (MedDRA) system organ classes, 1 treatment group difference was associated with a P value less than 0.05 (ear and labyrinth disorders), presumably a chance finding resulting from the large number of comparisons (Table S11, available at www.aaojournal.org). When combining the systems of cardiac and vascular disorders, 31%, 32%, and 38% (global $P = 0.26$) of participants had at least 1 event in the aflibercept, bevacizumab, and ranibizumab groups, respectively (Table S12, available at www.aaojournal.org).

Discussion

This randomized trial of eyes with vision-impairing center-involved DME compared treatment with intravitreous aflibercept, bevacizumab, or ranibizumab. Focal/grid laser photocoagulation was added per protocol after 6 months when DME persisted and no longer was improving. All 3 regimens, on average, produced substantial VA improvement through 2 years. However, as in year 1, the relative treatment effect differed by baseline VA. At 2 years in eyes with better baseline VA, there were still no meaningful differences identified in mean VA change among the treatment groups. In eyes with baseline VA of 20/50 or worse,

Table 2. Optical Coherence Tomography Central Subfield Thickness at 2 Years Stratified by Visual Acuity Subgroup

	Observed Data			Treatment Group Comparisons: Differences in Mean Change or Difference in Proportions (Adjusted 95% Confidence Interval), and Adjusted P Value		
Visual Acuity	*Aflibercept*	*Bevacizumab*	*Ranibizumab*	*Aflibercept vs. Bevacizumab*	*Aflibercept vs. Ranibizumab*	*Ranibizumab vs. Bevacizumab*
Baseline visual acuity 20/50 or worse (letter score, <69)						
No. of patients	97	89	91			
Baseline CSF, mean ± SD	450±142	471±153	430±135			
1 year (in 2-year cohort)						
Mean ± SD	236 ± 74	325±150	249±95			
Mean change ± SD	−212±152	−143±155	−177±149			
2 year						
Mean ± SD	236±82	282±108	253±115			
Mean change ± SD	−211±155	−185±158	−174±159	−42.1 (−77.2 to −7.0) $P = 0.01$	−19.3 (−47.8 to +9.3) $P = 0.19$	−22.8 (−52.2 to +6.6) $P = 0.19$
CSF <250 μm, no. (%)	73 (75)	41 (46)	60 (66)	+31 (+14 to +47) $P < 0.001$	+12 (−1 to +25) $P = 0.08$	+19 (+2 to +35) $P = 0.02$
Baseline visual acuity 20/32–20/40 (letter score, 78–69)						
No. of patients	101	93	95			
Baseline CSF, mean ± SD	373±108	360±82	377±97			
1 year (in 2-year cohort)						
Mean ± SD	243±57	296±83	259±83			
Mean change ± SD	−127±111	−62±61	−117±111			
2 year						
Mean ± SD	237±50	291±95	250±81			
Mean change ± SD	−133±115	−68±98	−125±118	−57.3 (−82.7 to −31.9) $P < 0.001$	−11.8 (−32.4 to +8.8) $P = 0.26$	−45.4 (−69.6 to −21.3) $P < 0.001$
CSF <250 μm, no. (%)	68 (67)	34 (37)	61 (64)	+33 (+17 to +49) $P < 0.001$	+2 (−12 to +15) $P = 0.81$	+32 (+16 to +47) $P < 0.001$

CSF = central subfield; SD = standard deviation.
See Table S7 (available at www.aaojournal.org) for detailed footnote.

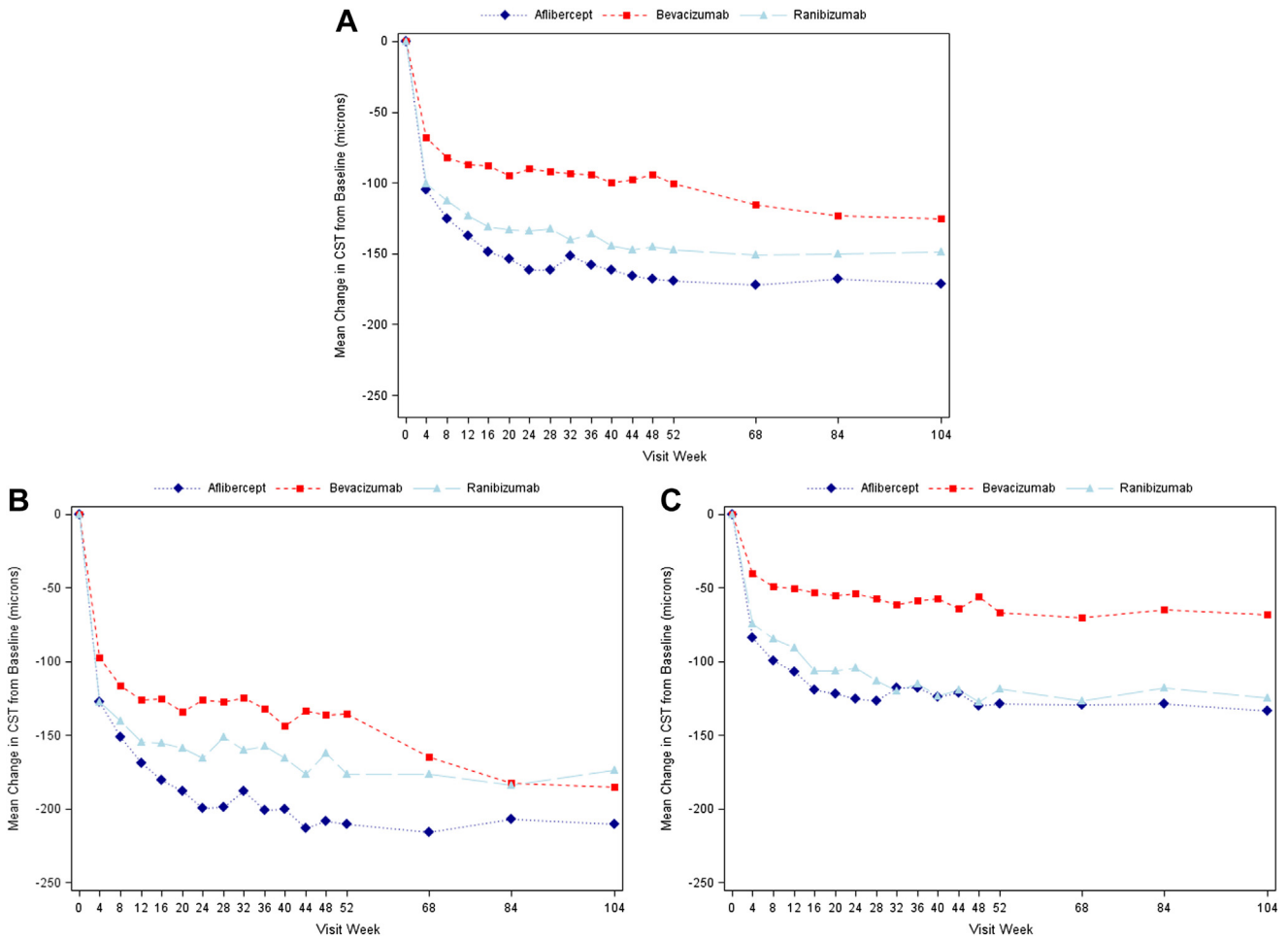

Figure 2. Graphs showing the mean improvement in optical coherence tomography central subfield thickness over time stratified by baseline visual acuity (approximate Snellen equivalent): (**A**) overall; (**B**) 20/50 or worse, and (**C**) 20/32 to 20/40. The number of eyes at each time point ranged from 192 to 221 in the aflibercept group, 181 to 216 in the bevacizumab group, and 185 to 215 in the ranibizumab group (see Fig S1 in the Supplementary Appendix and Fig S2 in the 1 Year Supplementary Appendix[2] for the number at each time point) available at www.aaojournal.org). CST = central subfield thickness.

the advantage of aflibercept over ranibizumab, noted at 1 year, had decreased and was no longer statistically significant at 2 years, whereas aflibercept remained superior to bevacizumab. Few eyes in any group lost substantial amounts of vision, regardless of the baseline VA.

In eyes with baseline VA of 20/50 or worse, the VA differences between aflibercept and the other 2 agents were clinically relevant at 1 year; the relative difference in percentage of eyes in the aflibercept group that gained 15 letters or more at 1 year was 63% greater than in the bevacizumab group (67% vs. 41%) and 34% greater than in the ranibizumab group (67% vs. 50%).[2] However, at 2 years, these relative differences were only 12% (58% vs. 52%) and 5% (58% vs. 55%), respectively. Similar small relative differences were seen for a 10-letter or more improvement at 2 years (15% and 7% respectively), raising the question of whether differences observed at 2 years are clinically relevant.

At year 1, bevacizumab was less effective at reducing retinal thickness than the other 2 agents. This difference persisted in year 2 among the eyes with better initial VA. If this finding was coupled with VA benefits, it could be judged relevant; however, because a difference in VA was not identified with better initial VA, this observation may not be of clinical importance.

Over 2 years, the cumulative numbers of injections were similar across the 3 treatment arms, with the number in year 2 being approximately half that in year 1. Through 2 years, laser treatment was required less frequently in aflibercept-treated eyes than with the other 2 agents. Because laser was a protocol-defined part of the treatment regimen, it is not possible to separate the effect of macular laser from the anti-VEGF treatment on the VA and thickness outcomes.

Rates of ocular adverse events, including endophthalmitis and postinjection inflammation, remained low through 2 years with all 3 agents. Systemic APTC rates were higher in the ranibizumab group, with a greater number of nonfatal strokes and vascular deaths in the ranibizumab group. Although the *P* values increased slightly after adjusting for a history of prior stroke or myocardial infarction and other potential confounders, this did not substantially alter the results. These findings have not been

Table 3. Prespecified Adverse Events of Interest Occurring over 2 Years

	Aflibercept (n = 224)	Bevacizumab (n = 218)	Ranibizumab (n = 218)	*P* Value*
Study eye ocular adverse events				
No. of study eye injections	2998	3115	3066[†]	
Prespecified ocular events occurring at least once, no. of eyes (%)				
Endophthalmitis	0	1 (<1)	0	0.66
Inflammation	6 (3)	3 (1)	4 (2)	0.69
Retinal detachment (traction, rhegmatogenous, or unspecified)	2 (<1)	2 (<1)	1 (<1)	1.0
Retinal tear	1 (<1)	1 (<1)	1 (<1)	1.0
Vitreous hemorrhage	15 (7)	17 (8)	10 (5)	0.37
Injection-related cataract	3 (1)	2 (<1)	0	0.38
Intraocular pressure elevation[‡]	39 (17)	27 (12)	35 (16)	0.31
Nonstudy eye ocular adverse events (eyes receiving study treatment)				
No. of nonstudy eyes treated	144	134	132	
No. of injections	1180	1316	1225[§]	
Prespecified ocular events occurring at least once from the first injection, no. of eyes (%)				
Endophthalmitis	1 (<1)	0	1 (<1)	0.77
Inflammation	3 (2)	1 (<1)	2 (2)	0.79
Retinal detachment (traction, rhegmatogenous, or unspecified)	0	0	0	
Retinal tear	0	0	2 (2)	0.10
Vitreous hemorrhage	11 (8)	12 (9)	9 (7)	0.83
Injection-related cataract	2 (1)	1 (<1)	0	0.78
Intraocular pressure elevation[‡]	18 (13)	15 (11)	18 (14)	0.85
Systemic adverse events				
Vascular events according to Antiplatelet Trialists' Collaboration[14] occurring at least once, no. of participants (%)				
Nonfatal myocardial infarction	7 (3)	3 (1)	6 (3)	
Nonfatal stroke	2 (<1)	6 (3)	11 (5)	
Vascular death (from any potential vascular or unknown cause)	3 (1)	8 (4)	9 (4)	
Any Antiplatelet Trialists' Collaboration Event	12 (5)	17 (8)	26 (12)	0.047[‖]
Prespecified systemic events occurring at least once, no. of participants (%)				
Death (any cause)	5 (2)	13 (6)	11 (5)	0.12
Hospitalization	77 (34)	71 (33)	73 (33)	0.93
Serious adverse event	88 (39)	81 (37)	82 (38)	0.90
Gastrointestinal[¶]	67 (30)	64 (29)	60 (28)	0.85
Kidney[#]	50 (22)	46 (21)	35 (16)	0.22
Hypertension	39 (17)	27 (12)	44 (20)	0.08

*Global (overall 3 group comparison) *P* value from Fisher exact test.
[†]Seven study eyes received 1 injection and 2 eyes received 2 injections of 0.5 mg ranibizumab before the Food and Drug Administration approved a 0.3-mg dose of ranibizumab for diabetic macular edema treatment.
[‡]Includes intraocular pressure increase ≥10 mmHg from baseline at any visit, intraocular pressure ≥30 mmHg at any visit, initiation of intraocular pressure-lowering medications not in use at baseline, or glaucoma surgery.
[§]Nonstudy eyes receiving 0.5 mg dose of ranibizumab: 8 received 1 injection, 2 received 2 injections, 1 received 4 injections, 1 received 5 injections, 1 received 9 injections, and 1 received 11 injections.
[‖]Pairwise comparisons from the Fisher exact test (adjusted for multiple comparisons by taking the maximum of the global and pairwise comparison *P* values): aflibercept vs. bevacizumab, $P = 0.34$; aflibercept vs. ranibizumab, $P = 0.047$; and bevacizumab vs. ranibizumab, $P = 0.20$. Global *P* value from Poisson model with robust variance estimation using the log link,[8] adjusting for gender, age at baseline, hemoglobin A1c level at baseline, diabetes type, diabetes duration at baseline, insulin use, prior coronary artery disease, prior myocardial infarction, prior stroke, prior transient ischemic attack, prior hypertension, and smoking status: $P = 0.09$.
[¶]Includes events with a Medical Dictionary for Regulatory Activities system organ class of gastrointestinal disorders.
[#]Includes a subset of Medical Dictionary for Regulatory Activities system organ class of renal and urinary disorder events indicating intrinsic kidney disease, plus increased or abnormal blood creatinine or renal transplant from other system organ classes.

demonstrated consistently in previously reported clinical trials. Table S16 and Figure S6 (available at www.aaojournal.org) summarize 2-year APTC events from prior anti-VEGF studies for DME and choroidal neovascularization in age-related macular degeneration. In the RISE and RIDE trials comparing ranibizumab and sham injections in eyes with DME, a higher percentage of participants in the pooled 0.5-mg ranibizumab group (7.2%) had an APTC event than in the 0.3-mg ranibizumab group (5.6%) or the control group (5.2%).[5] In RISE, 0.3 mg ranibizumab had the lowest rate of participants with an APTC event among the 3 treatment groups, and in RIDE, it had the highest. In DRCR.net protocol I, fewer participants experienced an APTC event over 2 years in the 0.5-mg ranibizumab group (7%) than in the laser group (13%).[3] In previous trials of age-related macular degeneration, 2-year percentages of participants with an APTC event were similar between 0.5-mg ranibizumab and bevacizumab groups and between aflibercept and 0.5-mg ranibizumab groups.[10–12] Across multiple retinal diseases, a meta-analysis from Thulliez et al[13] did not identify an increased risk of major cardiovascular or hemorrhagic

events with ranibizumab compared with control. It is noteworthy that the 12% frequency of ranibizumab-managed participants with 1 or more APTC events in the current study seems to be larger relative to the other trials, including DRCR.net protocol I, where the percentage was 7% with high overlap in DRCR.net clinical centers. The inconsistencies in the totality of the evidence create uncertainty as to whether there is a true increased risk of APTC events with ranibizumab at this time.

Strengths of the study include excellent compliance with the standardized retreatment regimen (98%), making it unlikely that a potential limitation of bias to treat or not to treat on the part of the unmasked ophthalmologist influenced the outcomes. Furthermore, good retention among the living participants, with approximately 90% of all enrolled eyes across all 3 groups completing the 2-year visit, makes it unlikely that losses to follow-up biased the results. Another potential limitation is that participants were unmasked to treatment group after the 1-year results were published; however, only 1 study participant switched to an alternative anti-VEGF treatment after the unmasking. Because the eligibility criteria were relatively broad with participants enrolled among 89 community- and university-based sites across the United States, the results likely are generalizable to similarly characterized patients treated in a similar manner. The absence of other similarly designed comparative effectiveness trials across these 3 anti-VEGF agents precludes comparing these results with those of other studies.

In summary, this DRCR.net comparative effectiveness study for center-involved DME showed vision gains in all 3 drugs at the 2-year visit, with an average of almost half the number of injections, slightly decreased frequency of visits, and decreased amounts of focal/grid laser photocoagulation treatment in all 3 groups in the second year. Among eyes with better VA at baseline, no difference was identified in vision outcomes through the 2-year visit. For the eyes with worse VA at baseline, the advantage of aflibercept over bevacizumab for mean VA gain persisted through 2 years, although the difference at 2-years was diminished. The VA difference between aflibercept and ranibizumab for eyes with worse VA at baseline that was noted at 1 year had decreased at 2 years. The implications of the increased rate of APTC events with ranibizumab found in the current study is uncertain because of inconsistency with prior trials. The results from this randomized clinical trial provide strong evidence for ophthalmologists to consider when applying this information to individual patients with DME.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
APTC = Anti-Platelet Trialists' Collaboration; **CI** = confidence interval; **DRCR.net** = Diabetic Retinopathy Clinical Research Network; **DME** = diabetic macular edema; **IQR** = interquartile range; **OCT** = optical coherence tomography; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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