## Supplementary Online Content

Bressler SB, Liu D, Glassman AR, et al; Diabetic Retinopathy Clinical Research Network. Change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmol*. Published online April 27, 2017. doi:10.1001/jamaophthalmol.2017.0821



This supplementary material has been provided by the authors to give readers additional information about their work.

 

**eAppendix. Institutional Review Boards That Approved the Study**

| Institution | City | State |
|---|---|---|
| Baylor Eye Physicians and Surgeons | Houston | TX |
| Case Western Reserve University | Cleveland | OH |
| Casey Eye Institute | Portland | OR |
| Dean A. McGee Eye Institute | Oklahoma City | OK |
| Emory Eye Center | Atlanta | GA |
| Henry Ford Health System, Dept of Ophthalmology and Eye Care Services | Detroit | MI |
| Jaeb Center for Health Research | Tampa | FL |
| Joslin Diabetes Center | Boston | MA |
| Kittner Eye Center | Chapel Hill | NC |
| Loma Linda University Health Care, Department of Ophthalmology | Loma Linda | CA |
| Mayo Clinic Department of Ophthalmology | Rochester | MN |
| Medical College of Wisconsin | Milwaukee | WI |
| Montefiore Medical Center | Bronx | NY |
| Mount Sinai School of Medicine, Dept. of Ophthalmology | New York | NY |
| Northwestern Medical Faculty Foundation | Chicago | IL |
| OSU Eye Physicians and Surgeons, LLC. | Columbus | OH |
| Retina Associates of Hawaii, Inc. | Honolulu | HI |
| The Institute of Ophthalmology and Visual Science (IOVS) | Newark | NJ |
| The New York Eye and Ear Infirmary/Faculty Eye Practice | New York | NY |
| University of Illinois at Chicago Medical Center | Chicago | IL |
| University of Nebraska Medical Center, Department of Ophthalmology | Omaha | NE |
| University of New Mexico | Albuquerque | NM |

 

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|---|---|---|
| Health Sciences Center | | |
| University of Pennsylvania Scheie Eye Institute | Philadelphia | PA |
| University of Rochester | Rochester | NY |
| University of Washington Medical Center | Seattle | WA |
| University of Wisconsin-Madison, Dept of Ophthalmology/Retina Service | Madison | WI |
| Wake Forest University Eye Center | Winston-Salem | NC |
| Wilmer Eye Institute at Johns Hopkins | Baltimore | MD |

**eTable 1. Visit Completion and Availability of Gradable Photographs for Study Eyes by Baseline Retinopathy Status (Non-Proliferative Diabetic Retinopathy or Proliferative Diabetic Retinopathy) and Drug Assignment**

| | Aflibercept | Bevacizumab | Ranibizumab |
|---|---|---|---|
| ***With NPDR at baseline, N*** | **174** | **153** | **168** |
| **1-year visit*** | | | |
| **Visit not completed**** | 15 (8.6%) | 11 (7.2%) | 8 (4.8%) |
| Died | 3 | 5 | 3 |
| Missed or Dropped | 12 | 6 | 5 |
| **Completed visit (percentage excludes death)**** | 159 (93.0%) | 142 (95.9%) | 160 (97.0%) |
| With gradable photograph‡ | 148 (86.5%) | 136 (91.9%) | 153 (92.7%) |
| Non-gradable photograph† | 5 | 2 | 5 |
| Photograph not collected | 7 | 4 | 2 |
| **2-year visit*** | | | |
| **Visit not completed**** | 20 (11.5%) | 26 (17.0%) | 19 (11.3%) |
| Died | 3 | 9 | 7 |
| Dropped | 17 | 17 | 12 |
| **Completed visit (percentage excludes death)**** | 154 (90.1%) | 127 (88.2%) | 149 (92.5%) |
| With gradable photograph | 140 (81.9%) | 118 (81.9%) | 131 (81.4%) |
| Non-gradable photograph§ | 10 | 6 | 8 |
| Photograph not collected | 4 | 3 | 10 |
| ***With PDR at baseline, N*** | **47** | **59** | **49** |
| **1-year visit*** | | | |
| **Visit not completed**** | 1 (2.1%) | 1 (1.7%) | 4 (8.2%) |
| Died | 1 | 0 | 0 |
| Missed or Dropped | 0 | 1 | 4 |
| **Completed visit (percentage excludes death)**** | 46 (100%) | 58 (98.3%) | 45 (91.8%) |
| With gradable photograph | 44 (95.7%) | 54 (91.5%) | 43 (87.8%) |
| Non-gradable photograph† | 0 | 2 | 0 |
| Photograph not collected | 2 | 2 | 2 |
| **2-year visit*** | | | |
| **Visit not completed**** | 3 (6.4%) | 5 (8.5%) | 7 (14.3%) |
| Died | 1 | 2 | 1 |
| Dropped | 2 | 3 | 6 |
| **Completed visit (percentage excludes death)**** | 44 (95.7%) | 54 (94.7%) | 42 (87.5%) |
| With gradable photograph | 41 (89.1%) | 49 (86.0%) | 38 (79.2%) |
| Non-gradable photograph§ | 3 | 2 | 2 |
| Photograph not collected | 0 | 3 | 2 |

* The protocol specifies 1-year visit as a protocol visit occurring 51 to 53 weeks from randomization, and 2-year visit as one occurring 103 to 105 weeks from randomization.

** For the purpose of the analysis of DR worsening, a visit completed between 44-60 weeks (308-420 days) was defined as “1-year visit”, and a visit completed between 88-120 weeks (616-840 days) was defined as “2-year visit”. If multiple visits fell within the same analysis window, the protocol visit closest to the target date was used.

‡ One NPDR participant in aflibercept group completed an out-of-window 1-year visit thus was considered “missed” (as shown in the table). For the purpose of the analysis, however, the gradable photograph that was collected at that visit was included in the analyses of improvement and worsening outcomes.

† Among 14 eyes that had non-gradable photographs at 1 year, none met the worsening outcome prior to 1 year.

§ Among 31 eyes that had non-gradable photographs at 2 years, 1 NPDR eye met the worsening outcome during first year, 2 NPDR eyes and 1 PDR eye met the worsening outcome prior to 2 years by manifesting complications of PDR.

**eTable 2. Baseline Characteristics for Eyes Within Each Treatment Group That Completed the 1-Year and 2-Year Visit by Baseline Retinopathy Subgroup**

| | Aflibercept | | Bevacizumab | | Ranibizumab | |
|---|---|---|---|---|---|---|
| | 1-year completers | 2-year completers | 1-year completers | 2-year completers | 1-year completers | 2-year completers |
| ***With Non-Proliferative Diabetic Retinopathy at Baseline, N*** | **159** | **154** | **142** | **127** | **160** | **149** |
| **Female**, N (%) | 75 (47.2%) | 71 (46.1%) | 72 (50.7%) | 66 (52.0%) | 71 (44.4%) | 69 (46.3%) |
| **Age** (yrs.), Median ($25^{th}$, $75^{th}$ percentile) | 61 (55, 67) | 61 (55, 67) | 64 (57, 70) | 64 (57, 69) | 59 (54, 68) | 59 (54, 68) |
| **Race/ethnicity**, N (%) | | | | | | |
| White | 107 (67.3%) | 105 (68.2%) | 95 (66.9%) | 86 (67.7%) | 110 (68.8%) | 102 (68.5%) |
| African-American | 20 (12.6%) | 19 (12.3%) | 21 (14.8%) | 20 (15.7%) | 28 (17.5%) | 27 (18.1%) |
| Hispanic or Latino | 23 (14.5%) | 22 (14.3%) | 23 (16.2%) | 20 (15.7%) | 20 (12.5%) | 18 (12.1%) |
| Asian | 2 (1.3%) | 2 (1.3%) | 0 | 0 | 0 | 0 |
| Native Hawaiian/ Other Pacific Islander | 2 (1.3%) | 1 (<1%) | 1 (<1%) | 0 | 0 | 0 |
| American Indian/ Alaskan Native | 1 (<1%) | 1 (<1%) | 0 | 0 | 0 | 0 |
| More than one race | 4 (2.5%) | 4 (2.6%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) |
| Unknown/not reported | 0 | 0 | 1 (<1%) | 0 | 1 (<1%) | 1 (<1%) |
| **Diabetes type**, N (%) | | | | | | |
| Type 1 | 13 (8.2%) | 13 (8.4%) | 4 (2.8%) | 3 (2.4%) | 8 (5.0%) | 8 (5.4%) |
| Type 2 | 141 (88.7%) | 136 (88.3%) | 137 (96.5%) | 123 (96.9%) | 149 (93.1%) | 139 (93.3%) |
| Uncertain | 5 (3.1%) | 5 (3.2%) | 1 (<1%) | 1 (<1%) | 3 (1.9%) | 2 (1.3%) |
| **Duration of diabetes** (yrs.), Median ($25^{th}$, $75^{th}$ percentile) | 15 (8, 21) | 15 (8, 21) | 16 (10, 23) | 16 (10, 23) | 17 (11, 23) | 16 (11, 23) |
| **HbA1c** (%), Median ($25^{th}$, $75^{th}$ percentile)* | 7.6 (6.7, 9.0) | 7.6 (6.7, 8.9) | 7.7 (6.6, 8.8) | 7.6 (6.6, 8.7) | 7.9 (7.0, 9.3) | 8.0 (6.9, 9.3) |
| **Prior PRP**[†], N (%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) |
| **Prior DME Treatment**, N (%) | 58 (36.5%) | 57 (37.0%) | 53 (37.3%) | 47 (37.0%) | 57 (35.6%) | 52 (34.9%) |
| **Visual acuity**, Median ($25^{th}$, $75^{th}$ percentile) | | | | | | |

| | Aflibercept | | Bevacizumab | | Ranibizumab | |
|---|---|---|---|---|---|---|
| | 1-year completers | 2-year completers | 1-year completers | 2-year completers | 1-year completers | 2-year completers |
| Letter score | 69 (62, 74) | 70 (60, 74) | 69 (61, 73) | 69 (61, 73) | 69 (60, 73) | 69 (60, 73) |
| Snellen equivalent | 20/40 (20/63, 20/32) | 20/40 (20/63, 20/32) | 20/40 (20/63, 20/40) | 20/40 (20/63, 20/40) | 20/40 (20/63, 20/40) | 20/40 (20/63, 20/40) |
| Baseline VA subgroups | | | | | | |
| 20/32 – 20/40, N (%) | 85 (53.5%) | 83 (53.9%) | 74 (52.1%) | 68 (53.5%) | 82 (51.3%) | 78 (52.3%) |
| 20/50 or worse, N (%) | 74 (46.5%) | 71 (46.1%) | 68 (47.9%) | 59 (46.5%) | 78 (48.8%) | 71 (47.7%) |
| **Central Subfield Thickness (microns) on OCT**, Median ($25^{th}$, $75^{th}$ percentile) § | 426 (358,484) | 425 (358,481) | 433 (357,507) | 434 (361,508) | 434 (359,531) | 434 (358,533) |
| **ETDRS Retinopathy severity level (ETDRS description)**, N (%) | | | | | | |
| Level 10, 12 (diabetic retinopathy absent) | 0 | 0 | 1 (<1%) | 1 (<1%) | 2 (1.3%) | 2 (1.3%) |
| Level 14, 15, 20 (minimal NPDR) | 7 (4.4%) | 7 (4.5%) | 4 (2.8%) | 4 (3.1%) | 2 (1.3%) | 2 (1.3%) |
| Level 35 (mild NPDR) | 49 (30.8%) | 48 (31.2%) | 55 (38.7%) | 50 (39.4%) | 44 (27.5%) | 41 (27.5%) |
| Level 43 (moderate NPDR) | 41 (25.8%) | 40 (26.0%) | 26 (18.3%) | 23 (18.1%) | 32 (20.0%) | 29 (19.5%) |
| Level 47 (moderately severe NPDR) | 48 (30.2%) | 45 (29.2%) | 42 (29.6%) | 38 (29.9%) | 64 (40.0%) | 59 (39.6%) |
| Level 53 (severe or very severe NPDR) | 14 (8.8%) | 14 (9.1%) | 14 (9.9%) | 11 (8.7%) | 16 (10.0%) | 16 (10.7%) |
| ***With Proliferative Diabetic Retinopathy at Baseline, N*** | **46** | **44** | **58** | **54** | **45** | **42** |
| **Female**, N (%) | 22 (47.8%) | 21 (47.7%) | 23 (39.7%) | 22 (40.7%) | 18 (40.0%) | 16 (38.1%) |
| **Age** (yrs.), Median ($25^{th}$, $75^{th}$ percentile) | 58 (49, 64) | 58 (50, 64) | 61 (54, 66) | 60 (54, 65) | 59 (51, 64) | 60 (49, 64) |
| **Race/ethnicity**, N (%) | | | | | | |
| White | 29 (63.0%) | 27 (61.4%) | 34 (58.6%) | 32 (59.3%) | 29 (64.4%) | 27 (64.3%) |
| African-American | 7 (15.2%) | 7 (15.9%) | 11 (19.0%) | 10 (18.5%) | 5 (11.1%) | 5 (11.9%) |
| Hispanic or Latino | 9 (19.6%) | 9 (20.5%) | 11 (19.0%) | 10 (18.5%) | 8 (17.8%) | 8 (19.0%) |
| Asian | 0 | 0 | 1 (1.7%) | 1 (1.9%) | 3 (6.7%) | 2 (4.8%) |

| | Aflibercept | | Bevacizumab | | Ranibizumab | |
|---|---|---|---|---|---|---|
| | 1-year completers | 2-year completers | 1-year completers | 2-year completers | 1-year completers | 2-year completers |
| Native Hawaiian/ Other Pacific Islander | 0 | 0 | 1 (1.7%) | 1 (1.9%) | 0 | 0 |
| American Indian/ Alaskan Native | 0 | 0 | 0 | 0 | 0 | 0 |
| More than one race | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown/not reported | 1 (2.2%) | 1 (2.3%) | 0 | 0 | 0 | 0 |
| **Diabetes type**, N (%) | | | | | | |
| Type 1 | 9 (19.6%) | 8 (18.2%) | 7 (12.1%) | 7 (13.0%) | 7 (15.6%) | 7 (16.7%) |
| Type 2 | 36 (78.3%) | 35 (79.5%) | 51 (87.9%) | 47 (87.0%) | 35 (77.8%) | 33 (78.6%) |
| Uncertain | 1 (2.2%) | 1 (2.3%) | 0 | 0 | 3 (6.7%) | 2 (4.8%) |
| **Duration of diabetes** (yrs.), Median (25th, 75th percentile) | 18 (11, 24) | 18 (11, 23) | 21 (14, 29) | 22 (14, 29) | 16 (13, 24) | 16 (13, 25) |
| **HbA1c** (%), Median (25th, 75th percentile)* | 8.1 (7.2, 9.7) | 7.8 (7.1, 9.6) | 7.8 (6.9, 9.0) | 7.8 (6.9, 9.0) | 7.7 (6.7, 8.4) | 7.8 (6.8, 8.8) |
| **Prior PRP**, N (%) | 27 (58.7%) | 26 (59.1%) | 37 (63.8%) | 35 (64.8%) | 32 (71.1%) | 30 (71.4%) |
| **Prior DME Treatment**, N (%) | 23 (50.0%) | 22 (50.0%) | 38 (65.5%) | 35 (64.8%) | 26 (57.8%) | 24 (57.1%) |
| **Visual acuity levels**, Median (25th, 75th percentile) | | | | | | |
| Letter score | 67 (51, 72) | 66 (51, 72) | 67 (60, 71) | 66 (60, 71) | 68 (59, 72) | 67 (58, 72) |
| Snellen equivalent | 20/50 (20/100, 20/40) | 20/50 (20/100, 20/40) | 20/50 (20/63, 20/40) | 20/50 (20/63, 20/40) | 20/50 (20/63, 20/40) | 20/50 (20/80, 20/40) |
| Baseline VA subgroups | | | | | | |
| 20/32 – 20/40, N (%) | 21 (45.7%) | 20 (45.5%) | 27 (46.6%) | 24 (44.4%) | 22 (48.9%) | 19 (45.2%) |
| 20/50 or worse, N (%) | 25 (54.3%) | 24 (54.5%) | 31 (53.4%) | 30 (55.6%) | 23 (51.1%) | 23 (54.8%) |
| **Central Subfield Thickness (microns) on OCT**, Median (25th, 75th percentile) § | 451 (376, 557) | 455 (382, 568) | 420 (360, 578) | 413 (360, 555) | 421 (365, 520) | 418 (368, 516) |
| **ETDRS Retinopathy severity level (ETDRS description)**, N (%) | | | | | | |
| *Without Prior PRP* | | | | | | |
| Level 60 (inactive PDR) | 0 | 0 | 3 (5.2%) | 2 (3.7%) | 1 (2.2%) | 1 (2.4%) |

| | Aflibercept | | Bevacizumab | | Ranibizumab | |
|---|---|---|---|---|---|---|
| | 1-year completers | 2-year completers | 1-year completers | 2-year completers | 1-year completers | 2-year completers |
| Level 61 (mild PDR) | 10 (21.7%) | 9 (20.5%) | 7 (12.1%) | 6 (11.1%) | 8 (17.8%) | 7 (16.7%) |
| Level 65 (moderate PDR) | 7 (15.2%) | 7 (15.9%) | 7 (12.1%) | 7 (13.0%) | 1 (2.2%) | 1 (2.4%) |
| Level 71, 75 (high-risk PDR) | 2 (4.3%) | 2 (4.5%) | 4 (6.9%) | 4 (7.4%) | 3 (6.7%) | 3 (7.1%) |
| *With Prior PRP* | | | | | | |
| Level 60 (inactive PDR) | 16 (34.8%) | 16 (36.4%) | 18 (31.0%) | 16 (29.6%) | 15 (33.3%) | 14 (33.3%) |
| Level 61 (mild PDR) | 4 (8.7%) | 3 (6.8%) | 12 (20.7%) | 12 (22.2%) | 10 (22.2%) | 9 (21.4%) |
| Level 65 (moderate PDR) | 7 (15.2%) | 7 (15.9%) | 4 (6.9%) | 4 (7.4%) | 2 (4.4%) | 2 (4.8%) |
| Level 71,75 (high-risk PDR) | 0 | 0 | 3 (5.2%) | 3 (5.6%) | 5 (11.1%) | 5 (11.9%) |

Abbreviation: HbA1c = hemoglobin A1C; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor; OCT = optical coherence tomography; NPDR = non-proliferative diabetic retinopathy; PRP = panretinal photocoagulation; PDR = proliferative diabetic retinopathy.

* Missing HbA1C data for 4 NPDR completers and 1 PDR completer in the aflibercept group.

§ Missing central subfield thickness data for 2 NPDR completers in the aflibercept group, 2 NPDR completers in the bevacizumab group, and 1 NPDR completer and 2 PDR completers in the ranibizumab group.

† The baseline DR severity levels of NPDR eyes labelled as prior PRP by investigator are 43 (aflibercept), 43 (bevacizumab), and 47 (ranibizumab) at the reading center.

**eTable 3. Sensitivity Analysis of Retinopathy Improvement or Worsening at 2 Years by Anti-VEGF Treatment Group and Baseline Diabetic Retinopathy Status**

| | Aflibercept | Bevacizumab | Ranibizumab | Pairwise Treatment Group Comparisons: difference in percentage with improvement or hazard ratio of worsening (adjusted 95% CI) and adjusted P-values*, ** A vs. B | A vs. R | R vs. B |
|---|---|---|---|---|---|---|
| ***Improvement at 2 years***[§] | | | | | | |
| **With NPDR at baseline** | | | | | | |
| No. of eyes improved (No. of eyes with gradable photographs) | 37 (148) | 31 (134) | 48 (152) | 2.7% (-3.6%, 9.0%) | 1.6% (-4.8%, 8.0%) | 1.1% (-4.7%, 6.9%) |
| Percentage with improvement (95% CI) | 25.0% (18.3%, 32.8%) | 23.1% (16.3%, 31.2%) | 31.6% (24.3%, 39.6%) | P=0.71 | P=0.71 | P=0.71 |
| **With PDR at baseline** | | | | | | |
| No. of eyes improved (No. of eyes with gradable photographs) | 21 (30) | 12 (36) | 13 (29) | 31.7% (3.4%, 60.0%) | 23.5% (-5.6%, 52.7%) | 8.1% (-15.5%, 31.8%) |
| Percentage with improvement (95% CI) | 70.0% (50.6%, 85.3%) | 33.3% (18.6%, 51.0%) | 44.8% (26.4%, 64.3%) | P=0.022 | P=0.14 | P=0.50 |
| ***Worsening by 2 years***[§§] | | | | | | |
| **With NPDR at baseline** | | | | | | |
| No. of eyes worsened (No. of eyes with gradable photographs) | 14 (133) | 11 (115) | 8 (129) | 1.10 (0.50, 2.43) | 1.91 (0.66, 5.57) | 0.58 (0.20, 1.64) |
| Cumulative probability of worsening (95% CI) | 10.5% (6.4%, 17.1%) | 9.6% (5.4%, 16.6%) | 6.2% (3.2%, 12.0%) | P=0.81 | P=0.44 | P=0.48 |
| **With PDR at baseline** | | | | | | |
| No. of eyes worsened (No. of eyes with gradable photograph | 7 (39) | 15 (47) | 6 (37) | 0.54 (0.18, 1.57) | 1.17 (0.37, 3.71) | 0.46 (0.14, 1.47) |

| | | | | Pairwise Treatment Group Comparisons: difference in percentage with improvement or hazard ratio of worsening (adjusted 95% CI) and adjusted P-values*, ** | | |
|---|---|---|---|---|---|---|
| | Aflibercept | Bevacizumab | Ranibizumab | A vs. B | A vs. R | R vs. B |
| s) | | | | | | |
| Cumulative probability of worsening (95% CI) | 17.9% (9.0%, 34.0%) | 31.9% (20.6%, 47.3%) | 16.2% (7.6%, 32.6%) | P=0.39 | P=0.79 | P=0.32 |

§ Eyes that were evaluable for improvement at baseline and had gradable photos at the 1- and/or 2-year visit were included in the improvement analysis. Last-observation-carried-forward were applied to eyes with only 1-year photos. 95% confidence intervals for the binomial proportions of improvement were obtained using Clopper-Pearson exact method.

* Pairwise comparisons of percentage with retinopathy improvement were performed using binomial regression with adjustment for categorical baseline DR severity (see detailed footnote under Table 2) and multiple treatment group comparisons. Reported P-values and 95% confidence intervals were adjusted using Hochberg method to account for an overall type I error of 0.05.

§§ Eyes that had gradable photos at both 1- and 2-year visits were included in the worsening analysis. Cumulative probabilities of retinopathy worsening were obtained from life-table estimates.

** Pairwise comparisons of retinopathy worsening were performed using a proportional hazards model with adjustment for baseline retinopathy severity category and multiple treatment group comparisons. See detailed footnote under Table 3. Reported P-values and 95% confidence intervals were adjusted using Hochberg method to account for an overall type I error of 0.05.

**eTable 4. Diabetic Retinopathy Improvement: Percentage With 2 or More Steps Improvement on Photos at Annual Visits by Anti-VEGF Treatment Group and Baseline Retinopathy Status**

| | Aflibercept | Bevacizumab | Ranibizumab | Pairwise Treatment Group Comparisons: difference in percentage with improvement (adjusted 95% CI) and adjusted P-values*,† A vs. B | A vs. R | R vs. B |
|---|---|---|---|---|---|---|
| ***With Non-Proliferative Diabetic Retinopathy at Baseline*** §§,* | | | | | | |
| **No. of eyes, N**§ | 167 | 147 | 163 | | | |
| **Improvement at 1 year** | | | | | | |
| No. of eyes improved (No. of eyes with gradable photographs) | 44 (141) | 29 (131) | 57 (151) | 11.7% (2.9%, 20.6%) | 2.9% (-5.7%, 11.4%) | 8.9% (1.7%, 16.1%) |
| Percentage with improvement (95% CI) | 31.2% (23.7%, 39.5%) | 22.1% (15.4%, 30.2%) | 37.7% (30.0%, 46.0%) | P=0.004 | P=0.51 | P=0.012 |
| **Improvement at 2 years** | | | | | | |
| No. of eyes improved (No. of eyes with gradable photographs) | 34 (133) | 25 (113) | 40 (129) | 3.3% (-3.1%, 9.7%) | 1.0% (-6.1%, 8.0%) | 2.3% (-4.1%, 8.7%) |
| Percentage with improvement (95% CI) | 25.6% (18.4%, 33.8%) | 22.1% (14.9%, 30.9%) | 31.0% (23.2%, 39.7%) | P=0.79 | P=0.79 | P=0.79 |
| ***With Proliferative Diabetic Retinopathy at Baseline*** §§,† | | | | | | |
| **No. of eyes, N**§ | 30 | 38 | 32 | | | |
| **Improvement at 1 year** | | | | | | |
| No. of eyes improved (No. of eyes with gradable photographs) | 23 (29) | 12 (35) | 16 (29) | 54.0% (28.6%, 79.3%) | 34.5% (5.6%, 63.4%) | 19.4% (-4.7%, 43.6%) |
| Percentage with improvement (95% CI) | 79.3% (60.3%, 92.0%) | 34.3% (19.1%, 52.2%) | 55.2% (35.7%, 73.6%) | P<0.001 | P=0.015 | P=0.11 |
| **Improvement at 2 years** | | | | | | |
| No. of eyes improved (No. of eyes with | 21 (27) | 16 (33) | 12 (24) | 39.1% (10.3%, 67.8%) | 34.5% (1.8%, 67.2%) | 4.5% (-22.4%, 31.4%) |

| | Aflibercept | Bevacizumab | Ranibizumab | Pairwise Treatment Group Comparisons: difference in percentage with improvement (adjusted 95% CI) and adjusted P-values*,† A vs. B | A vs. R | R vs. B |
|---|---|---|---|---|---|---|
| gradable photographs[§§]) | | | | | | |
| Percentage with improvement (95% CI) | 77.8% (57.7%, 91.4%) | 48.5% (30.8%, 66.5%) | 50.0% (29.1%, 70.9%) | P=0.003 | P=0.036 | P=0.74 |

[§] Only including eyes that were evaluable for improvement at baseline (i.e., excluding eyes with baseline DR severity level of 20 or below, or level 60).

[§§] Eyes that were evaluable for improvement at baseline and had gradable photos at the corresponding annual visit were included in the analysis. 95% confidence intervals for the binomial proportions of improvement were obtained using Clopper-Pearson exact method.

* Pairwise comparisons of retinopathy improvement (NPDR eyes only) were performed using binomial regression with adjustment for categorical baseline DR severity (see detailed footnote under Table 2) and multiple treatment group comparisons. Reported P-values and 95% confidence intervals were adjusted using Hochberg method to account for an overall type I error of 0.05.

† Pairwise comparisons of retinopathy improvement (PDR eyes only) were performed using Poisson regression with adjustment for categorical baseline DR severity (see detailed footnote under Table 2) and multiple treatment group comparisons. Reported P-values and 95% confidence intervals were adjusted using Hochberg method to account for an overall type I error of 0.05.

**eTable 5. Diabetic Retinopathy Improvement or Worsening by Anti-VEGF Treatment Group Combining NPDR and PDR Subgroups**

| | | | | Pairwise Treatment Group Comparisons: difference in percentage with improvement or hazard ratio for worsening (adjusted 95% CI) and adjusted P-values [**] | | |
|---|---|---|---|---|---|---|
| | Aflibercept | Bevacizumab | Ranibizumab | A vs. B | A vs. R | R vs. B |
| ***Diabetic Retinopathy Improvement*** [§§] | | | | | | |
| **No. of eyes, N**[§] | 197 | 185 | 195 | | | |
| **Improvement at 1 year** | | | | | | |
| No. of eyes improved (No. of eyes with gradable photographs) | 66 (170) | 40 (166) | 73 (180) | 14.5% (6.1%, 22.9%) | 5.4% (-2.7%, 13.5%) | 9.1% (2.1%, 16.1%) |
| Percentage with improvement (95% CI) | 38.8% (31.5%, 46.6%) | 24.1% (17.8%, 31.3%) | 40.6% (33.3%, 48.1%) | P<0.001 | P=0.19 | P=0.007 |
| **Improvement at 2 years** | | | | | | |
| No. of eyes improved (No. of eyes with gradable photographs) | 52 (160) | 35 (146) | 49 (153) | 5.0% (-2.6%, 12.6%) | 2.5% (-4.3%, 9.4%) | 2.5% (-3.7%, 8.6%) |
| Percentage with improvement (95% CI) | 32.5% (25.3%, 40.3%) | 24.0% (17.3%, 31.7%) | 32.0% (24.7%, 40.0%) | P=0.35 | P=0.47 | P=0.47 |
| ***Diabetic Retinopathy Worsening*** [*] | | | | | | |
| **No. of eyes, N** | 221 | 212 | 217 | | | |
| **Worsened by 1 year**[†] | | | | | | |
| No. of eyes worsened | 6 | 15 | 12 | | | |
| Cumulative probability of worsening (95% | 2.9% (1.3%, 6.3%) | 7.3% (4.5%, 11.9%) | 5.8% (3.3%, 10.0%) | | | |

| | | | | Pairwise Treatment Group Comparisons: difference in percentage with improvement or hazard ratio for worsening (adjusted 95% CI) and adjusted P-values ** | | |
|---|---|---|---|---|---|---|
| | Aflibercept | Bevacizumab | Ranibizumab | A vs. B | A vs. R | R vs. B |
| CI) | | | | | | |
| **Worsened by 2 years** | | | | | | |
| No. of eyes worsened | 24 | 29 | 19 | 0.86 (0.50, 1.49) | 1.42 (0.70, 2.88) | 0.61 (0.30, 1.24) |
| Cumulative probability of worsening (95% CI) | 11.8% (8.1%, 17.1%) | 14.8% (10.6%, 20.7%) | 9.4% (6.1%, 14.4%) | P=0.60 | P=0.52 | P=0.28 |

§ Only including eyes that were evaluable for improvement at baseline (i.e., excluding eyes with baseline DR severity level of 20 or below, or level 60).

§§ Eyes that were evaluable for improvement at baseline and had gradable photos at the corresponding annual visit were included in the analysis. 95% confidence intervals for the binomial proportions of improvement were obtained using Clopper-Pearson exact method. Pairwise comparisons of retinopathy improvement were performed using binomial regression with adjustment for categorical baseline DR severity (see detailed footnote under Table 2) and multiple treatment group comparisons.

* Cumulative probabilities of retinopathy worsening were obtained from life-table estimates. Pairwise comparisons of retinopathy worsening were performed using a proportional hazards model with adjustment for baseline retinopathy severity category and multiple treatment group comparisons. See detailed footnote under Table 3.

† Under the proportional hazards assumption, the hazard ratio for worsening from each pairwise comparison is considered constant at any time point throughout 2 years of follow-up.

** Reported P-values and 95% confidence intervals were adjusted using Hochberg method to account for an overall type I error of 0.05**.**

**eTable 6. Distribution of the First Event Which Triggered Categorization as Worsening of Diabetic Retinopathy by Baseline Diabetic Retinopathy Status**

| | Aflibercept | Bevacizumab | Ranibizumab |
|---|---|---|---|
| ***With Non-Proliferative Diabetic Retinopathy at Baseline*** | **N = 174** | **N = 153** | **N = 168** |
| **Worsened between baseline to 1 year, N** | **4** | **7** | **6** |
| PRP | 1 | 2 | 2 |
| Vitreous Hemorrhage | 1 | 2 | 1 |
| Two or more steps worsening on photo from baseline at 1 year | 2 | 3 | 3 |
| **Worsened between baseline to 2 years, N** | **16** | **14** | **11** |
| PRP | 1 | 2 | 2 |
| Vitreous Hemorrhage | 9 | 4 | 3 |
| Retinal Detachment | 1 | 1 | 0 |
| Anti-VEGF injection to manage PDR | 0 | 2 | 0 |
| Two or more steps worsening on photo from baseline at 1 year | 2 | 3 | 3 |
| Two or more steps worsening on photo from baseline at 2 years[†] | 3 | 2 | 3 |
| ***With Proliferative Diabetic Retinopathy at Baseline*** | **N = 47** | **N = 59** | **N = 49** |
| **Worsened between baseline to 1 year, N** | **2** | **8** | **6** |
| PRP | 0 | 2 | 0 |
| Vitreous Hemorrhage | 2 | 6 | 6 |
| **Worsened between baseline to 2 years, N** | **8** | **15** | **8** |
| PRP | 3 | 3 | 1 |
| Vitreous Hemorrhage | 5 | 11 | 7 |
| Retinal Detachment | 0 | 1 | 0 |

[†] Counting eyes that worsened on photo at 2 years as the first occurrence of retinopathy worsening (i.e., these eyes did not worsen on 1-year photographs)

**eTable 7. Diabetic Retinopathy Worsening: Percentage With 2 or More Steps Worsening on Photos at Annual Visits by Anti-VEGF Treatment Group and Retinopathy Status**

| | | | | Pairwise Treatment Group Comparisons: difference in percentage with worsening (adjusted 95% CI) and adjusted P-values | | |
|---|---|---|---|---|---|---|
| | **Aflibercept** | **Bevacizumab** | **Ranibizumab** | **A vs. B** | **A vs. R** | **R vs. B** |
| ***With Non-Proliferative Diabetic Retinopathy at Baseline*** * | | | | | | |
| **No. of eyes, N** | 174 | 153 | 168 | | | |
| **Worsening at 1 year** | | | | | | |
| No. of eyes worsened (No. of eyes with gradable photographs[§]) | 4 (148) | 5 (136) | 5 (153) | -1.2% (-4.8%, 2.5%) | -1.1% (-5.1%, 2.8%) | 0.0% (-4.4%, 4.3%) |
| Percentage with worsening (95% CI) | 2.7% (0.7%, 6.8%) | 3.7% (1.2%, 8.4%) | 3.3% (1.1%, 7.5%) | P=0.98 | P=0.98 | P=0.98 |
| **Worsening at 2 years** | | | | | | |
| No. of eyes worsened (No. of eyes with gradable photographs[§]) | 10 (140) | 9 (118) | 7 (131) | -0.6% (-6.7%, 5.4%) | 2.1% (-3.3%, 7.4%) | -2.7% (-8.5%, 3.1%) |
| Percentage with worsening (95% CI) | 7.1% (3.5%, 12.7%) | 7.6% (3.5%, 14.0%) | 5.3% (2.2%, 10.7%) | P=0.84 | P=0.84 | P=0.84 |
| ***With Proliferative Diabetic Retinopathy at Baseline*** ** | | | | | | |
| **No. of eyes, N** | 47 | 59 | 49 | | | |
| **Worsening at 1 year** | | | | | | |
| No. of eyes worsened (No. of eyes with gradable photographs[§]) | 0 (44) | 1 (54) | 0 (43) | -1.9% (-10.1%, 6.9%) | 0% (-8.3%, 8.0%) | -1.9% (-10.5%, 6.7%) |
| Percentage with worsening | 0% (0%, 8.0%) | 1.9% (0%, 9.9%) | 0% (0%, 8.2%) | P=1.00 | P=1.00 | P=1.00 |

| | | | | | | |
|---|---|---|---|---|---|---|
| (95% CI) | | | | | | |
| **Worsening at 2 years** | | | | | | |
| No. of eyes worsened (No. of eyes with gradable photographs[§]) | 1 (41) | 2 (49) | 1 (38) | -1.6% (-12.4%, 9.3%) | -0.2% (-12.2%, 10.6%) | -1.5% (-11.8%, 10.7%) |
| Percentage with worsening (95% CI) | 2.4% (0.1%, 12.9%) | 4.1% (0.5%, 14.0%) | 2.6% (0.1%, 13.8%) | P=1.00 | P=1.00 | P=1.00 |

[§] Eyes that had gradable photos at the corresponding annual visit were included in the analysis. 95% confidence intervals for the binomial proportions of worsening were obtained using Clopper-Pearson exact method.

* Pairwise comparisons of retinopathy worsening (NPDR eyes only) were performed using binomial regression with adjustment for categorical baseline DR severity and multiple treatment group comparisons. NPDR eyes were categorized into 2 subgroups: 1) moderate NPDR or better (level 43 or less), or 2) moderately severe or very severe NPDR (level 47 or 53). Reported P-values and 95% confidence intervals were adjusted using Hochberg method to account for an overall type I error of 0.05

** Pairwise comparisons of retinopathy worsening (PDR eyes only) were performed using Barnard's exact test with adjustment for multiple treatment group comparisons. Reported P-values and 95% confidence intervals were adjusted using Hochberg method to account for an overall type I error of 0.05.

**eTable 8. Number of Anti-VEGF Injections Administered to Manage Center-Involved DME by Baseline Diabetic Retinopathy Status and Diabetic Retinopathy Improvement Outcome**

| | Aflibercept | | Bevacizumab | | Ranibizumab | | Global *P*-value for effect of numbers of injections[†] |
|---|---|---|---|---|---|---|---|
| | Improved | Not improved | Improved | Not improved | Improved | Not improved | |
| ***With Non-Proliferative Diabetic Retinopathy at Baseline*** | | | | | | | |
| **1-year cohort**[§] | | | | | | | |
| *No. of participants* | 44 | 97 | 29 | 102 | 57 | 94 | |
| ***Injections in 1st year*** | | | | | | | |
| Mean ± SD | 10.1 ± 2 | 8.4 ± 2 | 9.7 ± 2 | 9.6 ± 2 | 10.2 ± 2 | 8.9 ± 2 | *N/A*[*] |
| P-value[†] | P < 0.001 | | P = 0.79 | | P = 0.009 | | |
| **2-year cohort**[§] | | | | | | | |
| *No. of participants* | 33 | 100 | 25 | 88 | 40 | 89 | |
| ***Injections in 1st year*** | | | | | | | |
| Mean ± SD | 9.2 ± 2 | 8.8 ± 2 | 10.2 ± 2 | 9.5 ± 2 | 10.3 ± 2 | 9.1 ± 2 | 0.029 |
| ***Injections in 2nd year*** | | | | | | | |
| Mean ± SD | 5.1 ± 3 | 4.1 ± 3 | 7.1 ± 4 | 4.9 ± 4 | 7.1 ± 4 | 4.3 ± 4 | < 0.001 |
| ***Injections over 2 years*** | | | | | | | |
| Mean ± SD | 14.3 ± 4 | 12.9 ± 4 | 17.2 ± 5 | 14.4 ± 6 | 17.3 ± 5 | 13.4 ± 5 | < 0.001 |
| ***With Proliferative Diabetic Retinopathy at Baseline*** | | | | | | | |
| **1-year cohort**[§] | | | | | | | |
| *No. of participants* | 22 | 7 | 11 | 24 | 16 | 13 | |
| ***Injections in 1st year*** | | | | | | | |
| Mean ± SD | 9.0 ± 2 | 9.0 ± 1 | 10.1 ± 2 | 9.5 ± 3 | 10.3 ± 1 | 8.5 ± 3 | *N/A*[*] |
| *P*-value[†] | P = 0.67 | | P = 0.64 | | P = 0.037 | | |
| **2-year cohort**[§] | | | | | | | |
| *No. of participants* | 19 | 8 | 10 | 23 | 9 | 15 | |
| ***Injections in 1st year*** | | | | | | | |
| Mean ± SD | 9.1 ± 2 | 9.3 ± 2 | 9.9 ± 2 | 9.6 ± 3 | 9.1 ± 2 | 9.0 ± 2 | 0.69 |
| ***Injections in 2nd year*** | | | | | | | |
| Mean ± SD | 5.5 ± 3 | 6.1 ± 3 | 6.8 ± 3 | 5.2 ± 3 | 6.4 ± 2 | 4.3 ± 4 | 0.16 |
| ***Injections over 2 years*** | | | | | | | |
| Mean ± SD | 14.6 ± 4 | 15.4 ± 5 | 16.7 ± 3 | 14.8 ± 6 | 15.6 ± 3 | 13.3 ± 4 | 0.21 |

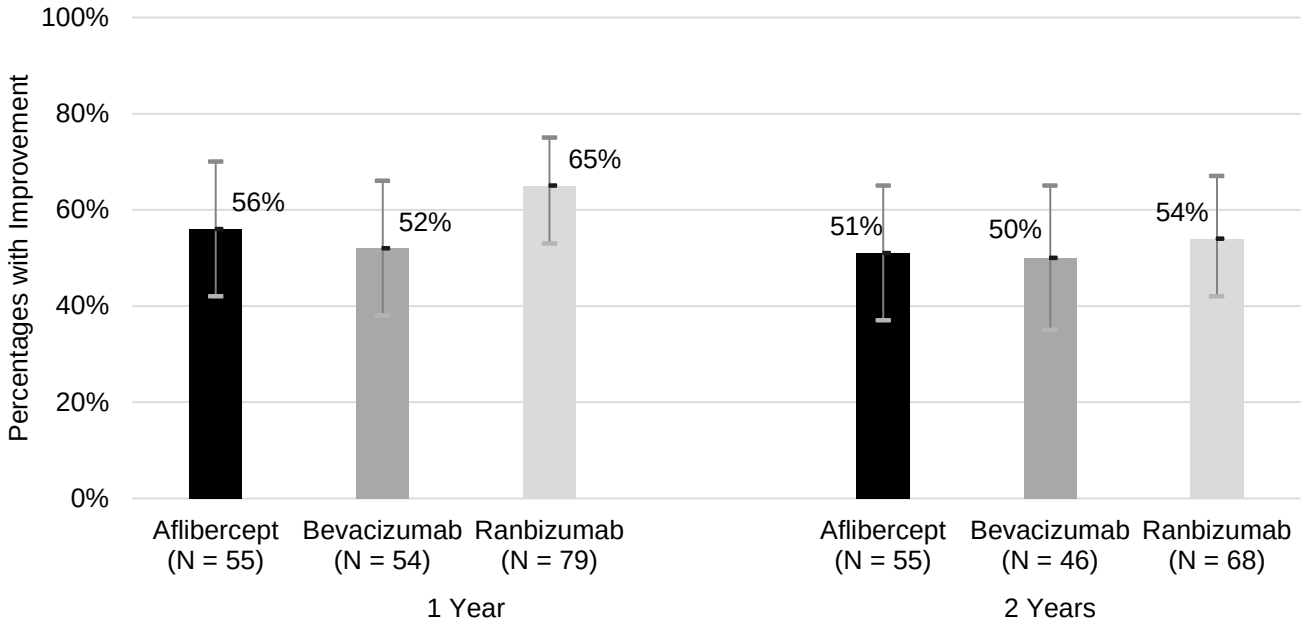
[§] Including eyes that were eligible for improvement and had gradable photograph at the corresponding annual visit only.

[†] Global *P*-value for effect of injection number on DR improvement with adjustment for treatment group and baseline DR severity category. If the interaction between treatment group and number of injections was not significant, it is assumed that the injection effect was similar for each within-treatment group comparison thus only the global p-value was provided. If the interaction was significant, *P*-values from each within-group comparison (with adjustment for baseline DR severity category) were reported instead.

[*] P-value for interaction between number of study treatment injection and treatment group assignment was 0.003 for NPDR 1-year cohort, and 0.046 for PDR 1-year cohort.

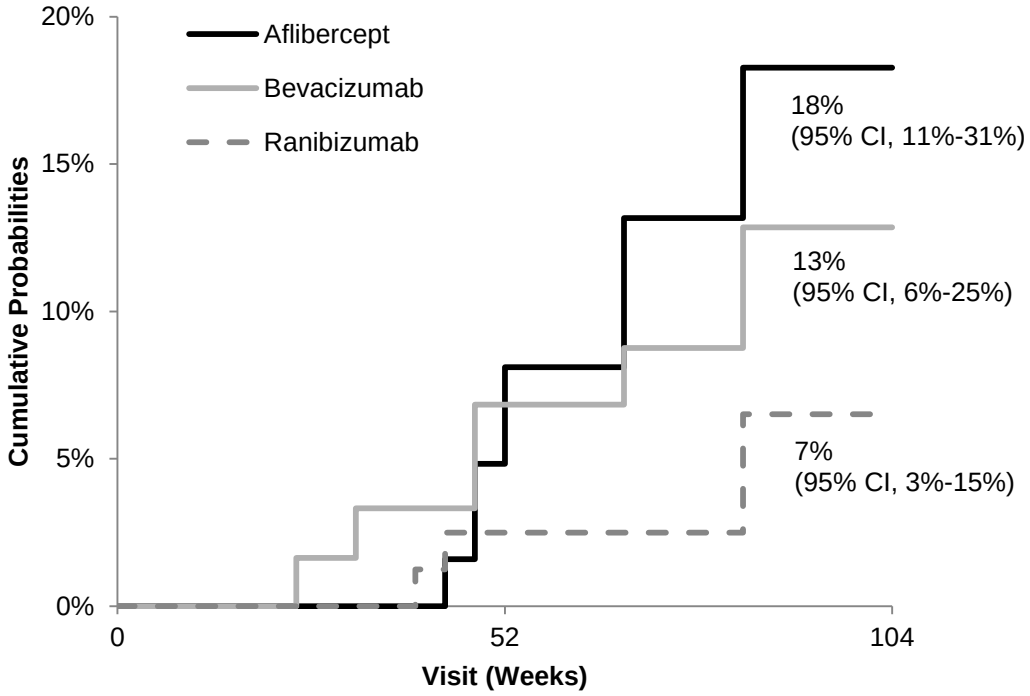
**eFigure 1. Percentage With Improvement of Retinopathy Among Eyes With Moderately Severe or Severe Non-Proliferative Diabetic Retinopathy at Baseline**




Error bars represent the 95% confidence intervals. *P*-values for the pairwise comparisons at 1-year/2-year visit were aflibercept-bevacizumab 0.62/0.97, aflibercept-ranibizumab 0.62/0.97, ranibizumab-bevacizumab 0.53/0.97.

**eFigure 2. Cumulative Probability of Retinopathy Worsening Among Eyes With Moderately Severe or Severe Non-Proliferative Diabetic Retinopathy at Baseline**




| Weeks | 0 | 16 | 32 | 52 | 68 | 84 | 104 |
|---|---|---|---|---|---|---|---|
| **Aflibercept** | | | | | | | |
| **# eyes at risk** | 71 | 65 | 65 | 59 | 55 | 51 | 48 |
| **# events** | 0 | 0 | 3 | 2 | 3 | 3 | 0 |
| **Bevacizumab** | | | | | | | |
| **# eyes at risk** | 62 | 61 | 57 | 53 | 51 | 45 | 42 |
| **# events** | 0 | 2 | 2 | 0 | 1 | 2 | 0 |
| **Ranibizumab** | | | | | | | |
| **# eyes at risk** | 85 | 83 | 81 | 78 | 74 | 73 | 70 |
| **# events** | 0 | 0 | 2 | 0 | 0 | 3 | 0 |

Error bars represent the 95% confidence intervals. *P*-values for the pairwise comparisons through 2-year visit in Figure 3b were aflibercept-bevacizumab 0.47, aflibercept-ranibizumab 0.13, ranibizumab-bevacizumab 0.42. For the purpose of analysis, each visit week included visits that were ±14 days except the 52-week (1-year), 60-week, and 84-week visits, that were ±8 weeks; and the 104-week (2-year) visit that was ±16 weeks.