Effect of Initial Afibercept, Laser, or Observation on Low-Contrast Visual Acuity in Eyes With Diabetic Macular Edema and Good Vision: Ancillary Study Within a Randomized Clinical Trial

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Purpose: To describe 2.5% low-contrast visual acuity (VA) among eyes with good vision despite center-involved diabetic macular edema and compare changes after initial management with afibercept, laser, or observation.

Methods: This was an ancillary study within a multicenter randomized clinical trial (DRCR Retina Network Protocol V). Participants had diabetes and 1 study eye with center-involved diabetic macular edema and a VA of 20/25 or better randomly assigned to afibercept (n = 112), focal/grid laser (n = 146), or observation (n = 129). Eyes in the laser and observation groups received afibercept if VA met prespecified worsening criteria.

Results: Participants had median age of 60 years, 37% were female and 70% were non-Hispanic White. At baseline, the mean ± standard deviation (SD) high-contrast VA was 85.2 ± 3.6 letters (Snellen equivalent 20/20), mean ± SD 2.5% low-contrast VA was 47.6 ± 18.9 letters (Snellen equivalent 20/125), and low-contrast VA letter score was 2 SDs or more below the age-specific normative values in 23%. At 2 years, the mean change ± SD in low-contrast VA in the afibercept, laser, and observation groups was 2.7 ± 20.1, −2.0 ± 19.6, and −3.1 ± 20.8 letters (adjusted difference, afibercept vs. laser, 5.3 [95% confidence interval, −0.2 to 10.8], P = 0.06; afibercept vs. observation, 5.5 [95% confidence interval −0.2 to 11.2], P = 0.06; and laser vs. observation, 0.2 [95% confidence interval −4.6 to 5.0], P = 0.94).

Conclusions: There was no significant difference between treatment groups in low-contrast VA change from baseline to 2 years. Considering the range of the 95% confidence intervals, however, the study may have been underpowered to detect a clinically meaningful benefit between treatment groups.

Translational Relevance: Low-contrast VA, an important visual function, is decreased in eyes with diabetic macular edema.

Introduction

The DRCR Retina Network Protocol V randomized clinical trial demonstrated no significant difference in the rate of 2-year visual acuity (VA) loss among eyes with center-involved diabetic macular edema (CIDME) and good VA (20/25 or better) when managed initially with afibercept (EYLEA, Regeneron, Tarrytown, NY) vs. focal/grid laser vs. observation. 1 Eyes in
the initial laser and initial observation groups received aflibercept during follow-up if the VA decreased from baseline, which occurred in 25% and 34% of eyes, respectively. However, VA is just one of several components of visual function that is adversely affected by diabetes.2

Contrast sensitivity is decreased among people with diabetes, often before signs of diabetic retinopathy develop, and the mean levels of contrast sensitivity decrease with more severe levels of diabetic retinopathy.3–7 Contrast sensitivity is important for several aspects of visual function important in daily life, including driving,8–10 recognizing faces,11,12 reading,12,13 identifying objects,14 and mobility.12 Although VA and contrast sensitivity are correlated strongly within the eyes of people who do not have systemic or ocular disease, the correlation is weaker among people with diabetes.15

Low-contrast VA was assessed for study eyes in Protocol V in a subset of centers that recruited participants. To our knowledge, contrast sensitivity in eyes with DME and good VA (i.e., 20/25 or better) has been addressed in only 1 study with only 8 eyes having DME.4 The goals of this report are to describe low-contrast VA in eyes with CI-DME and good high-contrast VA and to evaluate differences in low-contrast VA between the management strategies tested in Protocol V over 2 years.

Methods

The full methods for Protocol V (ClinicalTrials.gov Identifier: NCT01909791) have been published elsewhere.1 The study adhered to the tenets of the Declaration of Helsinki. The ethics board associated with each site provided approval. Study participants provided written informed consent. An independent data and safety monitoring committee provided oversight. Briefly, 702 adult participants with type 1 or type 2 diabetes mellitus were enrolled with one study eye having VA 20/25 or better and DME confirmed on optical coherence tomography (OCT) at 2 visits. The sample size was chosen for the primary outcome of at least a 5-letter loss of high-contrast VA at 2 years. Eyes were randomly assigned to initial aflibercept, laser, or observation stratified by clinical site and recent or planned DME treatment in the nonstudy eye. Eyes in the initial laser and initial observation groups received aflibercept if VA decreased from baseline by 10 or more letters at any visit or 5 to 9 letters at 2 consecutive visits. The aflibercept treatment regimen, once initiated, was the same in each group.

Low-contrast VA was collected at all sites that had testing capabilities (51 of 91 sites comprising 387 of 702 participants [55%]) and measured at 2.5% contrast using an Electronic-Early Treatment Diabetic Retinopathy Study VA tester by technicians masked to treatment group. The contrast level of 2.5% was chosen based on unpublished pilot data that suggested very few eyes in this cohort would be unable to read any letters at 2.5% contrast. The monitors used for testing had luminance of 95 cd/m² and were calibrated before each test. Testing was performed in a room where the only light source was the monitor (i.e., the door was shut and overhead lights were off). Low-contrast VA was assessed at baseline, 1 year, and 2 years using the refraction obtained for high-contrast VA.

Statistical Analyses

A 10-letter change in low-contrast VA has been shown to be associated with a 4-point change in the National Eye Institute Visual Functioning Questionnaire and is considered a meaningful change on an individual basis.16–18 Similarly, a 10-letter change in high-contrast VA is considered to be a clinically meaningful change for an individual and is beyond measurement error.16,19,20 Mean changes of high-contrast VA of 5 to 10 letters are considered clinically significant for a group.20

Changes in low-contrast VA from baseline were analyzed using a general linear model with the robust sandwich covariance estimator. An increase in the low-contrast VA letter score by 10 or more letters was analyzed with Poisson regression and the robust sandwich covariance estimator. An increase in the low-contrast VA letter score by 10 or more letters was analyzed with Poisson regression and the robust sandwich covariance estimator to estimate a relative risk.21 Baseline low-contrast VA and recent or planned DME treatment in the study eye were included as covariates in all analyses. Missing follow-up data were imputed via multiple imputation (100 imputations). The imputation model included the treatment group, recent or planned DME treatment in the nonstudy eye, baseline low-contrast VA, and changes in low-contrast VA from baseline at 1 and 2 years, which is analogous to how missing data were imputed in the primary analysis of the trial.1 Low-contrast VA, high-contrast VA, and OCT central subfield thickness (CST) at follow-up and change from baseline were truncated at 3 standard deviations (SDs) from the mean based on available 104-week data. The percentage of eyes with deficits in low-contrast VA was calculated as at least 2 SDs below age-specific normative values; the normal mean ± SD values of low-contrast (2.5%) VA are approximately 62 ± 8 letters (20/63) for ages 40 to 49 years, 59 ± 7 letters (20/63) for ages 50 to 59 years, and 49 ± 10 letters (20/100) for age 60 years and older.22
### Table 1. Baseline Characteristics of Participants and Study Eyes

| Characteristic                                      | Aflibercept (n = 112) | Initial Laser (n = 146) | Initial Observation (n = 129) |
|-----------------------------------------------------|-----------------------|-------------------------|-------------------------------|
| **Participant characteristics**                     |                       |                         |                               |
| **Sex**                                             |                       |                         |                               |
| Female                                              | 50 (45)               | 46 (32)                 | 48 (37)                       |
| Male                                                | 62 (55)               | 100 (68)                | 81 (63)                       |
| **Age, median (IQR), y**                            | 59 (52–64)            | 60 (53–65)              | 62 (54–68)                    |
| **Race/ethnicity**                                  |                       |                         |                               |
| Non-Hispanic White                                  | 75 (67)               | 99 (68)                 | 97 (75)                       |
| Non-Hispanic Black/African American                 | 14 (13)               | 16 (11)                 | 13 (10)                       |
| Hispanic or Latino                                  | 21 (19)               | 26 (18)                 | 16 (12)                       |
| Asian                                               | 1 (<1)                | 0                       | 1 (<1)                        |
| American Indian or Alaskan Native                   | 0                     | 1 (<1)                  | 0                             |
| Native Hawaiian or other Pacific Islander           | 0                     | 1 (<1)                  | 1 (<1)                        |
| More than 1 race                                    | 1 (<1)                | 2 (1)                   | 0                             |
| Unknown or not reported                              | 0                     | 1 (<1)                  | 1 (<1)                        |
| **Diabetes type**                                   |                       |                         |                               |
| 2                                                   | 103 (92)              | 133 (91)                | 118 (91)                      |
| 1                                                   | 8 (7)                 | 13 (9)                  | 8 (6)                         |
| Uncertain                                           | 1 (<1)                | 0                       | 3 (2)                         |
| **Duration of diabetes, median (IQR), y**           | 15 (9–20)             | 15 (10–20)              | 17 (10–25)                    |
| **Hemoglobin A1c, median (IQR), %**                 | 7.6 (6.7–9.3) [n = 112] | 7.7 (6.8–8.8) [n = 141] | 7.5 (6.8–8.6) [n = 126] |
| **Recent or planned DME treatment in the nonstudy eye** | 42 (38)               | 60 (41)                 | 53 (41)                       |
| **Study eye ocular characteristics**                |                       |                         |                               |
| Prior treatment for DME                             | 18 (16)               | 19 (13)                 | 20 (16)                       |
| **Lens status at clinical examination**             |                       |                         |                               |
| Phakic (natural lens)                               | 89 (79)               | 114 (78)                | 97 (75)                       |
| Posterior chamber intraocular lens                   | 23 (21)               | 32 (22)                 | 32 (25)                       |
| **VA, letter score**                                | Mean ± SD             |                         |                               |
| 85.2 ± 3.3                                          |                       |                         |                               |
| ≥89 (20/16 or better)                               | 21 (19)               | 30 (21)                 | 31 (24)                       |
| 88–84 (20/20)                                       | 59 (53)               | 64 (44)                 | 51 (40)                       |
| 83–79 (20/25)                                       | 32 (29)               | 52 (36)                 | 47 (36)                       |

*a* Participants with data missing have been excluded.
| Characteristic                                      | Aflibercept (n = 112) | Initial Laser (n = 146) | Initial Observation (n = 129) |
|----------------------------------------------------|----------------------|-------------------------|-------------------------------|
| **Low-contrast VA, letter score**                   |                      |                         |                               |
| Mean ± SD                                          | 45.4 ± 19.4          | 48.7 ± 19.2             | 48.4 ± 17.9                   |
| Snellen equivalent of mean                         | 20/125               | 20/125                  | 20/125                        |
| Zero letters read                                  | 8 (7)                | 11 (8)                  | 6 (5)                         |
| ≥2 SD below age-specific normative value           | 34 (30)              | 33 (23)                 | 22 (17)                       |
| **Low-contrast deficit, mean ± SD**                | 39.8 ± 18.5          | 36.5 ± 18.2             | 36.9 ± 17.1                   |
| **Intraocular pressure, median (IQR), mm Hg**      | 15 (13–18)           | 16 (14–18)              | 16 (14–18)                    |
| CST (Zeiss Stratus equivalent), µm<d               | 317 ± 58             | 316 ± 57                | 312 ± 60                      |
| -250                                              | 3 (5)                | 5 (3)                   | 4 (3)                         |
| 250–300                                           | 51 (46)              | 67 (46)                 | 65 (50)                       |
| 301–399                                           | 41 (37)              | 60 (41)                 | 49 (38)                       |
| 400–499                                           | 16 (14)              | 10 (7)                  | 9 (7)                         |
| ≥500                                              | 1 (<1)               | 4 (3)                   | 2 (2)                         |
| **Diabetic retinopathy severity level<sup>e</sup>** | [n=105]              | [n=139]                 | [n=127]                       |
| Diabetic retinopathy absent or questionable (levels 10, 12, 14, and 15) | 0                    | 2 (1)                   | 1 (<1)                        |
| Microaneurysms only (level 20)                     | 7 (7)                | 5 (4)                   | 2 (2)                         |
| Mild to moderate NPDR (levels 35 and 43)           | 59 (56)              | 75 (54)                 | 81 (64)                       |
| Moderately severe to severe NPDR (levels 47 and 53) | 27 (26)              | 43 (31)                 | 33 (26)                       |
| Inactive PDR (level 60)                            | 3 (3)                | 6 (4)                   | 5 (4)                         |
| Mild to moderate PDR (levels 61 and 65)            | 6 (6)                | 8 (6)                   | 4 (3)                         |
| High-risk PDR (levels 71 and 75)                   | 3 (3)                | 0                      | 1 (<1)                        |

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

<sup>a</sup>Data are expressed as No. (%) unless otherwise indicated.

<sup>b</sup>This sample size applies to all characteristics unless otherwise noted. Eyes in the initial laser and initial observation groups were given aflibercept if VA decreased from baseline (see Methods for full details).

<sup>c</sup>Average of screening and randomization values.

<sup>d</sup>Difference between high-contrast VA and low-contrast VA.

<sup>e</sup>Graded by a central reading center. Levels are based on the Early Treatment Diabetic Retinopathy Study definitions. 31
The Hochberg procedure was used to control the familywise type I error rate at 5% by adjusting confidence intervals and $P$ values within each outcome. All $P$ values are 2-sided. Changes in low-contrast VA from baseline at 1 and 2 years were prespecified outcomes. Improvement of low-contrast VA by at least 10 letters and correlation analyses are considered exploratory. Correlations are described using the language of Evans: $0$ to $0.19 = \text{very weak}$, $0.20$ to $0.39 = \text{weak}$, $0.40$ to $0.59 = \text{moderate}$, $0.60$ to $0.79 = \text{strong}$, and $0.80$ to $0.99 = \text{very strong}$. Analyses were conducted using SAS 9.4 with SAS/STAT 15.1 (SAS Institute, Cary, NC).

## Results

### Analysis Cohort

Among 387 participants included in this ancillary study, baseline characteristics were similar to the full cohort. The median age was 60 years, 37% were female, 70% were non-Hispanic White, 91% had type 2 diabetes, and the median hemoglobin A1c was 7.6%. Baseline characteristics by treatment group are shown in Table 1. Most eyes had mild to moderate nonproliferative diabetic retinopathy (58%). The mean ± SD
high-contrast VA letter score was 85.2 ± 3.6 (Snellen equivalent 20/20). Excluding deaths, 2-year data were available for 83% of eyes (314/380) with low-contrast VA baseline testing.

Within the subgroup of eyes with low-contrast VA, key outcomes were similar to those of the full cohort:1 Aflibercept was initiated in 28% (41/146) and 33% (42/129) of eyes in the initial laser and initial observation groups, respectively. At 2 years, the percentage of eyes with at least a 5-letter VA decrease was 13% (13/103), 19% (25/131), and 18% (21/120) in the aflibercept, laser, and observation groups, respectively. The mean ± SD change in VA letter score from baseline at 2 years was 1.6 ± 5.9, −0.5 ± 6.9, and −0.4 ± 6.2. The mean ± SD change in OCT CST from baseline at 2 years was −60 ± 61 μm, −39 ± 79 μm, and −37 ± 81 μm.

**Low-Contrast VA at Baseline**

At baseline, the mean ± SD low-contrast VA letter score was 47.6 ± 18.9 (Snellen equivalent 20/125) (Fig. 1A); 25 eyes (6%) were unable to read any low-contrast VA letters and 89 (23%) were at least 2 SDs below the age-specific normative values.22 The correlation between low-contrast VA and OCT CST was weak at 0.34 (95% confidence interval, 0.25–0.42) and the correlation between low-contrast VA and OCT CST was weak at −0.20 (95% confidence interval, −0.29 to −0.10).

**Change in Low-Contrast VA from Baseline by Treatment Group**

The mean ± SD change in low-contrast VA in the aflibercept, laser, and observation groups at 1 year was 6.0 ± 20.1, 0.7 ± 20.1, and 0.3 ± 19.8 (adjusted differences: aflibercept vs. laser, 3.2 [95% confidence interval, −2.0 to 8.4], P = 0.34; aflibercept vs. observation, 4.0 [95% confidence interval, −1.8 to 9.7], P = 0.29; laser vs. observation, 0.8 [95% confidence interval, −3.7 to 5.3], P = 0.74). At 2 years, the mean changes were 2.7 ± 20.1, −2.0 ± 19.6, and −3.1 ± 20.8 (adjusted differences: aflibercept vs. laser, 5.3 [95% confidence interval, −0.2 to 10.8], P = 0.06; aflibercept vs. observation, 5.5 [95% confidence interval, −0.2 to 11.2], P = 0.06; laser vs. observation, 0.2 [95% confidence interval, −4.6 to 5.0], P = 0.94) (Fig. 1 and Table 2).

At 1 year, improvement in low-contrast VA by at least 10 letters occurred in 39% (38/97), 27% (33/123), and 20% (22/108) of eyes in the aflibercept, laser, and observation groups, respectively (adjusted relative risk: aflibercept vs. laser, 1.34 [95% confidence interval, 0.91–1.98], P = 0.18; aflibercept vs. observation, 1.53 [95% confidence interval, 0.96–2.45], P = 0.09; laser vs. observation, 1.14 [95% confidence interval, 0.77–1.70], P = 0.51); worsening by at least 10 letters (among eyes with baseline low-contrast VA of ≥10 letters) occurred in 17% (15/87), 23% (26/112), and 23% (23/98) of eyes (Table 2). At 2 years, improvement of low-contrast VA by at least 10 letters occurred in 34% (32/93), 23% (27/117), and 24% (25/104) of eyes (adjusted relative risk: aflibercept vs. laser, 1.46 [95% confidence interval, 0.91–2.35], P = 0.17; aflibercept vs. observation, 1.31 [95% confidence interval, 0.84–2.05], P = 0.35; laser vs. observation, 0.90 [95% confidence interval, 0.58–1.39], P = 0.63); worsening by at least 10 letters (among eyes with a baseline low-contrast VA of ≥10 letters) occurred in 24% (21/87), 28% (30/107), and 32% (30/94) of eyes.

At 1 year, the percentage of eyes with low-contrast VA at least 2 SDs below age-specific normative values was 18% (17/97), 20% (25/123), and 22% (24/108) in the aflibercept, laser, and observation groups, respectively. At 2 years, the percentages were 17% (16/93), 27% (32/117), and 24% (25/104).

**Correlations of Low-Contrast VA with High-Contrast VA and CST During Follow-up**

At 1 year, the correlation between low-contrast VA and high-contrast VA was moderate at 0.53 (95% confidence interval, 0.45–0.61); at 2 years, the correlation was moderate at 0.58 (95% confidence interval, 0.51–0.65) (Fig. 2). The correlation between change in low-contrast VA and change in high-contrast VA at 1 year was moderate at 0.44 (95% confidence interval, 0.35–0.53); at 2 years, the correlation was moderate at 0.47 (95% confidence interval, 0.38–0.55) (Fig. 3).

At 1 year, the correlation between low-contrast VA and OCT CST was weak at −0.23 (95% confidence interval, −0.33 to −0.13); at 2 years, there was no significant correlation (r = −0.07 [95% confidence interval, −0.18 to 0.04]) (Fig. 2). The correlation between change in low-contrast VA and change in OCT CST at 1 year was moderate at −0.40 (95% confidence interval, −0.48 to −0.30); at 2 years, the correlation was weak at −0.20 (95% confidence interval, −0.30 to −0.09) (Fig. 3).

**Discussion**

In this ancillary study from Protocol V, a randomized clinical trial of initial management with aflibercept, laser, or observation for CI-DME in eyes with good high-contrast VA, there was no statistically
### Table 2. Change in Low-Contrast VA at 1 and 2 Years

| Low-Contrast VA                     | Observed Data       | Adjusted Treatment Group Comparisons<sup>a</sup>       |
|------------------------------------|---------------------|--------------------------------------------------------|
|                                    | Aflibercept         | Initial Laser                                         | Initial Observation |
| 1-Year Visit                       | n = 97              | n = 123                                               | n = 108             |
| Baseline letterscore, mean ± SD    | 44.7 ± 19.1         | 48.4 ± 19.3                                           | 47.8 ± 19.0         |
| 1-year letterscore, mean ± SD      | 50.7 ± 18.9         | 49.1 ± 20.8                                           | 48.2 ± 21.7         |
| ≥ 2 SD below age-specific normative value, no. (%) | 17 (18)           | 25 (20)                                               | 24 (22)             |
| Change from baseline, mean ± SD    | 6.0 ± 20.1          | 0.7 ± 20.1                                            | 0.3 ± 19.8          |
| ≥ 10-letter increase, no. (%)      | 38 (39)             | 33 (27)                                               | 22 (20)             |
| 2-Year visit                       | n = 93              | n = 117                                               | n = 104             |
| Baseline letterscore, mean ± SD    | 47.6 ± 17.2         | 48.5 ± 19.2                                           | 47.3 ± 19.1         |
| 2-year letterscore, mean ± SD      | 50.4 ± 20.6         | 46.5 ± 22.7                                           | 44.3 ± 22.1         |
| ≥ 2 SD below age-specific normative value, no. (%) | 16 (17)            | 32 (27)                                               | 25 (24)             |
| Change from baseline, mean ± SD    | 2.7 ± 20.1          | −2.0 ± 19.6                                           | −3.1 ± 20.8         |
| ≥ 10-letter increase, no. (%)      | 32 (34)             | 27 (23)                                               | 25 (24)             |
| ≥10-letter decrease, no. (%)<sup>b</sup> | 21 (24)           | 30 (28)                                               | 30 (32)             |

<sup>a</sup> Missing data were imputed via multiple imputation for statistical modeling. Pairwise comparisons between the 3 groups were performed using the Hochberg procedure to control the overall type 1 error for multiple comparisons by adjusting the confidence intervals and \( P \) values. Mean difference estimated for continuous outcomes and relative risk estimated for dichotomous outcomes with adjustment for recent or planned DME treatment in the nonstudy eye and baseline low-contrast VA in both.

<sup>b</sup> Excludes eyes with baseline low-contrast VA of <10 letters because they are ineligible for the outcome.
significant difference in the mean change in low-contrast VA between any of the groups at 1 or 2 years. This finding is congruent with the primary result of Protocol V, which did not identify a statistically significant difference in the proportion with 1-line high-contrast VA loss at 2 years.

We found that 23% of eyes had deficits in low-contrast VA at baseline despite having a high-contrast VA of 20/25 or better. Consistent with prior research on eyes without DME, we found weak to moderate correlations of low-contrast VA with high-contrast VA at both baseline and follow-up.\textsuperscript{15} We found mostly weak negative correlations between low-contrast VA and OCT CST at both baseline and follow-up and between changes in these measures during follow-up, a finding that has not been documented in other publications.

There has been limited research of contrast sensitivity in eyes with CI-DME and VA impairment. A small randomized trial (41 eyes) of bevacizumab vs. sham for CI-DME with VA impairment (20/40 to 20/200) showed a strong correlation of contrast sensitivity with VA at baseline ($r = 0.7$) and suggested greater improvement in contrast sensitivity with bevacizumab.\textsuperscript{25} In the RIDE/RISE trials of ranibizumab vs. sham injection for CI-DME with VA impairment (20/40 to 20/320), eyes treated with ranibizumab had improved contrast sensitivity at 2 years and those with a greater

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**Figure 2.** Correlations of low-contrast VA with high-contrast VA and OCT CST at 1 and 2 years. Scatterplot of low-contrast VA letter score vs. high-contrast VA letter score (A, C) and OCT CST (B, D) at 1 year (A, B) and 2 years (C, D). The Pearson correlation coefficient and 95% confidence interval are shown on each plot. VA was measured on a scale from 100 (Snellen equivalent 20/10) to 0 (Snellen equivalent <20/800).
improvement in retinopathy severity had a greater improvement in contrast sensitivity. Contrast sensitivity data from eyes treated with sham were not reported for the RIDE/RISE trials, preventing a comparison of the effect of anti-vascular endothelial growth factor treatment vs. sham on contrast sensitivity. In the current study, only the aflibercept group had an increase in average low-contrast VA from baseline to 2 years. These results are consistent with a possible beneficial effect of intravitreous anti-vascular endothelial growth factor treatment on contrast sensitivity in eyes with CI-DME, which this study was not powered to detect.

There are limitations to this analysis. First, this study was conducted at a subset of Protocol V sites, which limited the sample size. Second, this study was not specifically powered to detect differences in low-contrast VA. Although our data show that the mean change in low-contrast acuity over 2 years was not significantly different between the 3 treatment approaches, the confidence intervals for comparisons involving aflibercept range from a less than 1-letter difference favoring laser or observation to greater than a 10-letter difference favoring aflibercept over each of the other 2 initial management strategies. Thus, the confidence intervals do not rule out clinically

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**Figure 3.** Correlations of change in low-contrast VA with change in high-contrast VA and change in OCT CST at 1 and 2 years. Scatterplot of low-contrast VA change from baseline vs. high-contrast visual change from baseline (A, C) and OCT CST change from baseline (B, D) at 1 year (A, B) and 2 years (C, D). The Pearson correlation coefficient and 95% confidence interval are shown on each plot. A change of 10 letters is equal to approximately 2 lines on an Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
meaningful differences in favor of aflibercept. Third, 17% of the 2-year data were missing and had to be imputed with methods that are described in the Methods section. Despite these limitations, the data were collected in the context of a large randomized clinical trial by masked technicians, which should limit bias in treatment-group comparisons.

Based on the primary results from Protocol V, which showed no difference in 1-line loss of high-contrast VA, many clinicians may choose observation with deferred aflibercept for eyes with DME and good high-contrast VA.27 However, further work is needed to determine whether there is any benefit to initial anti-vascular endothelial growth factor treatment in eyes with good high-contrast VA.

Selecting the contrast level is a balance between making the test challenging enough to discriminate between participants on the basis of contrast sensitivity and making the test so challenging that participants are not testable. In this study, only 6% of participants had a baseline 2.5% low-contrast VA of 0 letters and were, therefore, untestable. A higher contrast level (e.g., 5%) would likely have decreased the proportion of participants who were untestable and the SDs, which were large.28

Data from this ancillary study can be used to develop future studies of low-contrast VA in eyes with CI-DME. We observed a high degree of variability in the change in low-contrast VA between baseline and year 1 or year 2, with an SD of approximately 20 letters for the distribution of change (Table 2). In a recent study of 49 participants (65% with a high-contrast VA ≥20/25; 35% with 20/30 to 20/100), the SD for the difference in low-contrast VA (2.5%) measurements taken 1 week apart was 6 letters.29 Although the eyes of Protocol V participants measured 1 and 2 years after baseline may have had true changes in function over these longer time spans, the much larger SD of change in letter score (approximately 20 letters vs. 6 letters) suggests that the measurement error was higher than in the recent study. Greater effort in training examiners on the testing procedure may be necessary to decrease the measurement error, such as continuing to prompt the participant to guess when they are unsure of the letter displayed on the screen. In addition, a newer technology, the AST Platform, which uses the quick contrast sensitivity function method, allows an estimation of the area under the contrast sensitivity function curve across a broad range of spatial frequencies.3,30 This approach provides a more complete characterization of the contrast sensitivity function and may provide lower test-retest variability than the contrast acuity method used in this study, which measures acuity at a single fixed contrast level, or testing with Pelli–Robson charts, which measures contrast sensitivity at fixed spatial frequencies. The DRCR Retina Network is planning to use the AST Platform with a detailed training program in an upcoming study.

In conclusion, among eyes with CI-DME and a high-contrast VA of 20/25 or better, approximately 1 in 4 eyes had low-contrast VA letter scores below normal limits at baseline. There were no significant differences between initial management with aflibercept, laser, or observation with respect to change in low-contrast VA from baseline to 2 years. Considering the range of the 95% confidence intervals, however, the study may have been underpowered to detect a clinically meaningful difference between treatment groups.

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Adam Glassman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs. laser photocoagulation vs. observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*. 2019;321(19):1880–1894.

2. Ewing FM, Deary IJ, Strachan MW, Frier BM. Seeing beyond retinopathy in diabetes: electrophysiological and psychophysical abnormalities and alterations in vision. *Endocr Rev.* 1998;19(4):462–476.

3. Joltikov KA, de Castro VM, Davila JR, et al. Multidimensional functional and structural evaluation reveals neuroretinal impairment in early diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 2017;58(6):BIO277–BIO290.

4. Stavrou EP, Wood JM. Letter contrast sensitivity changes in early diabetic retinopathy. *Clin Exp Optom.* 2003;86(3):152–156.

5. Regan D, Neima D. Low-contrast letter charts in early diabetic retinopathy, ocular hypertension, glaucoma, and Parkinson’s disease. *Br J Ophthalmol.* 1984;68(12):885–889.

6. Sokol S, Moskowitz A, Skarf B, Evans R, Molitch M, Senior B. Contrast sensitivity in diabetics with and without background retinopathy. *Arch Ophthalmol.* 1985;103(1):51–54.

7. Sukha AY, Rubin A. High, medium, and low contrast visual acuities in diabetic retinal disease. *Optom Vis Sci.* 2009;86(9):1086–1095.

8. McGwin G, Jr., Chapman V, Owsley C. Visual risk factors for driving difficulty among older drivers. *Accid Anal Prev.* 2000;32(6):735–744.

9. Freeman EE, Munoz B, Turano KA, West SK. Measures of visual function and their association with driving modification in older adults. *Invest Ophthalmol Vis Sci.* 2006;47(2):514–520.

10. Huisingh C, Levitan EB, Irvin MR, MacLennan P, Wadley V, Owsley C. Visual sensory and visual-cognitive function and rate of crash and near-crash involvement among older drivers using naturalistic driving data. *Invest Ophthalmol Vis Sci.* 2017;58(7):2959–2967.

11. Owsley C, Sekuler R, Boldt C. Aging and low-contrast vision: face perception. *Invest Ophthalmol Vis Sci.* 1981;21(2):362–365.

12. West SK, Rubin GS, Broman AT, Munoz B, Bandeen-Roche K, Turano K. How does visual impairment affect performance on tasks of everyday life? The SEE Project. Salisbury Eye Evaluation. *Arch Ophthalmol.* 2002;120(6):774–780.

13. Leat SJ, Woo GC. The validity of current clinical tests of contrast sensitivity and their ability to predict reading speed in low vision. *Eye (Lond).* 1997;11(Pt 6):893–899.

14. Owsley C, Sloane ME. Contrast sensitivity, acuity, and the perception of “real-world” targets. *Br J Ophthalmol.* 1987;71(10):791–796.

15. Misra S, Saxena S, Kishore P, Bhasker SK, Misra A, Meyer CH. Association of contrast sensitivity with LogMAR visual acuity and glycosylated hemoglobin in non-insulin dependent diabetes mellitus. *J Ocul Biol Dis Infor.* 2010;3(2):60–63.

16. Submacular Surgery Trials Research Group. Evaluation of minimum clinically meaningful changes in scores on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) SST report number 19. *Ophthalmic Epidemiol.* 2007;14(4):205–215.

17. Movry EM, Loguidice MJ, Daniels AB, et al. Vision related quality of life in multiple sclerosis: correlation with new measures of low and high contrast letter acuity. *J Neurol Neurosurg Psychiatry.* 2009;80(7):767–772.

18. Suñer IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci.* 2009;50(8):3629–3635.

19. Csaky KG, Richman EA, Ferris FL, 3rd. Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium. *Invest Ophthalmol Vis Sci.* 2008;49(2):479–489.

20. Beck RW, Maguire MG, Bressler NM, Glassman AR, Lindblad AS, Ferris FL. Visual acuity as an outcome measure in clinical trials of retinal diseases. *Ophthalmology.* 2007;114(10):1804–1809.
21. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol.* 2005;162(3):199–200.
22. Pineles SL, Velez FG, Yu F, Demer JL, Birch E. Normative reference ranges for binocular summation as a function of age for low contrast letter charts. *Strabismus.* 2014;22(4):167–175.
23. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika.* 1988;75(4):800–802.
24. Evans JD. *Straightforward Statistics for the Behavioral Sciences.* Pacific Grove, CA: Brooks/Cole Publishing; 1996.
25. Motta AAL, Bonanomi M, Ferraz DA, et al. Short-term effects of intravitreal bevacizumab in contrast sensitivity of patients with diabetic macular edema and optimizing glycemic control. *Diabetes Res Clin Pract.* 2019;149:170–178.
26. Ip MS, Zhang J, Ehrlich JS. The clinical importance of changes in diabetic retinopathy severity score. *Ophthalmology.* 2017;124(5):596–603.
27. Glassman AR, Baker CW, Beaulieu WT, et al. Assessment of the DRCR retina network approach to management with initial observation for eyes with center-involved diabetic macular edema and good visual acuity: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol.* 2020;138(4):341–349.
28. Balcer LJ, Raynowska J, Nolan R, et al. Validity of low-contrast letter acuity as a visual performance outcome measure for multiple sclerosis. *Mult Scler.* 2017;23(5):734–747.
29. Pang Y, Sparschu L, Nylin E, Wang J. Validation of an automated early treatment diabetic retinopathy study low-contrast letter acuity test. *Optom Vis Sci.* 2020;97:370–376.
30. Hou F, Lesmes LA, Kim W, et al. Evaluating the performance of the quick CSF method in detecting contrast sensitivity function changes. *J Vis.* 2016;16(6):18.
31. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology.* 1991;98:823–833.