

# Effect of Intravitreal Aflibercept vs Vitrectomy With Panretinal Photocoagulation on Visual Acuity in Patients With Vitreous Hemorrhage From Proliferative Diabetic Retinopathy

## A Randomized Clinical Trial

Andrew N. Antoszyk, MD; Adam R. Glassman, MS; Wesley T. Beaulieu, PhD; Lee M. Jampol, MD; Chirag D. Jhaveri, MD; Omar S. Punjabi, MD; Hani Salehi-Had, MD; John A. Wells III, MD; Maureen G. Maguire, PhD; Cynthia R. Stockdale, MSPH; Daniel F. Martin, MD; Jennifer K. Sun, MD, MPH; for the DRCR Retina Network

**IMPORTANCE** Vitreous hemorrhage from proliferative diabetic retinopathy can cause loss of vision. The best management approach is unknown.

**OBJECTIVE** To compare initial treatment with intravitreal aflibercept vs vitrectomy with panretinal photocoagulation for vitreous hemorrhage from proliferative diabetic retinopathy.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized clinical trial at 39 DRCR Retina Network sites in the US and Canada including 205 adults with vision loss due to vitreous hemorrhage from proliferative diabetic retinopathy who were enrolled from November 2016 to December 2017. The final follow-up visit was completed in January 2020.

**INTERVENTIONS** Random assignment of eyes (1 per participant) to aflibercept (100 participants) or vitrectomy with panretinal photocoagulation (105 participants). Participants whose eyes were assigned to aflibercept initially received 4 monthly injections. Both groups could receive aflibercept or vitrectomy during follow-up based on protocol criteria.

**MAIN OUTCOMES AND MEASURES** The primary outcome was mean visual acuity letter score (range, 0-100; higher scores indicate better vision) over 24 weeks (area under the curve); the study was powered to detect a difference of 8 letters. Secondary outcomes included mean visual acuity at 4 weeks and 2 years.

**RESULTS** Among 205 participants (205 eyes) who were randomized (mean [SD] age, 57 [11] years; 115 [56%] men; mean visual acuity letter score, 34.5 [Snellen equivalent, 20/200]), 95% (195 of 205) completed the 24-week visit and 90% (177 of 196, excluding 9 deaths) completed the 2-year visit. The mean visual acuity letter score over 24 weeks was 59.3 (Snellen equivalent, 20/63) (95% CI, 54.9 to 63.7) in the aflibercept group vs 63.0 (Snellen equivalent, 20/63) (95% CI, 58.6 to 67.3) in the vitrectomy group (adjusted difference, -5.0 [95% CI, -10.2 to 0.3],  $P = .06$ ). Among 23 secondary outcomes, 15 showed no significant difference. The mean visual acuity letter score was 52.6 (Snellen equivalent, 20/100) in the aflibercept group vs 62.3 (Snellen equivalent, 20/63) in the vitrectomy group at 4 weeks (adjusted difference, -11.2 [95% CI, -18.5 to -3.9],  $P = .003$ ) and 73.7 (Snellen equivalent, 20/40) vs 71.0 (Snellen equivalent, 20/40) at 2 years (adjusted difference, 2.7 [95% CI, -3.1 to 8.4],  $P = .36$ ). Over 2 years, 33 eyes (33%) assigned to aflibercept received vitrectomy and 34 eyes (32%) assigned to vitrectomy received subsequent aflibercept.

**CONCLUSIONS AND RELEVANCE** Among participants whose eyes had vitreous hemorrhage from proliferative diabetic retinopathy, there was no statistically significant difference in the primary outcome of mean visual acuity letter score over 24 weeks following initial treatment with intravitreal aflibercept vs vitrectomy with panretinal photocoagulation. However, the study may have been underpowered, considering the range of the 95% CI, to detect a clinically important benefit in favor of initial vitrectomy with panretinal photocoagulation.

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**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The members of the DRCR Retina Network appear at the end of the article.

**Corresponding Author:** Adam R. Glassman, MS, Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 ([drcrstat2@jaeb.org](mailto:drcrstat2@jaeb.org)).

The global prevalence of proliferative diabetic retinopathy, the most advanced form of diabetic eye disease, is estimated to be approximately 1.4% among all individuals with diabetes.<sup>1</sup> Vitreous hemorrhage from retinal neovascularization is a frequent occurrence of proliferative diabetic retinopathy and can cause acute, severe vision loss.<sup>2</sup> Among eyes with previously untreated proliferative diabetic retinopathy in the DRCR Retina Network Protocol S, vitreous hemorrhage developed in 46% and 48% of eyes over 5 years despite treatment with panretinal photocoagulation and ranibizumab, respectively.<sup>3,4</sup>

Vitrectomy has been the standard treatment for non-clearing vitreous hemorrhage since the 1970s.<sup>5</sup> Removal of the vitreous gel during surgery provides rapid clearance of hemorrhage, elimination of traction on neovascular vessels that contribute to recurrent vitreous hemorrhage, and intraoperative delivery of photocoagulation to treat neovascularization. Although surgical techniques have improved over the last 5 decades,<sup>6,7</sup> the risk of complications remains.<sup>8,9</sup> Thus, clinicians are highly interested in developing nonsurgical approaches.

A more recent method for managing vitreous hemorrhage is in-office intravitreal injection of an antivascular endothelial growth factor (anti-VEGF) agent that stimulates regression of neovascularization.<sup>10</sup> The goal of anti-VEGF treatment for vitreous hemorrhage is not to directly remove the hemorrhage, but to regress neovascularization to prevent rebleeding while the hemorrhage is absorbed.<sup>11,12</sup>

Despite the frequency of this common condition and 2 available treatment approaches, there are not well-established guidelines regarding how to treat vitreous hemorrhage to optimize visual outcomes. The hypothesis of the study was that visual acuity recovery would be faster with vitrectomy because the blood is mechanically cleared during surgery. The objective of this study was to determine the efficacy of initial treatment with aflibercept vs vitrectomy with panretinal photocoagulation for vitreous hemorrhage from proliferative diabetic retinopathy.

## Methods

This DRCR Retina Network study (Protocol AB) adhered to the tenets of the Declaration of Helsinki.<sup>13</sup> The ethics board associated with each site provided approval. Study participants provided written informed consent. An independent data and safety monitoring committee provided oversight. The study protocol appears in [Supplement 1](#) and the statistical analysis plan appears in [Supplement 2](#).

### Study Population

We recruited adults with type 1 or 2 diabetes at 39 sites in the US and Canada. We collected participant-reported race/ethnicity based on fixed categories per the National Institutes of Health policy and consistent with the US Food and Drug Administration guidelines.<sup>14,15</sup> We enrolled 1 eye per participant; eyes had vitreous hemorrhage from proliferative diabetic retinopathy causing vision impairment

## Key Points

**Question** Among patients with vitreous hemorrhage from proliferative diabetic retinopathy, what is the effect of initial treatment with intravitreal aflibercept vs vitrectomy with panretinal photocoagulation on vision?

**Findings** In this randomized trial of 205 eyes among 205 participants, the mean visual acuity letter score over 24 weeks was 59.3 (Snellen equivalent, 20/63) for the aflibercept group vs 63.0 (Snellen equivalent, 20/63) for the vitrectomy with panretinal photocoagulation group, a difference that was not statistically significant.

**Meaning** In participants with vitreous hemorrhage from proliferative diabetic retinopathy, there was no statistically significant difference in visual acuity over 24 weeks following initial treatment with aflibercept vs vitrectomy with panretinal photocoagulation, but the study may have been underpowered to detect a clinically important benefit in favor of initial vitrectomy with panretinal photocoagulation.

(best-corrected visual acuity letter score  $\leq 78$  [Snellen equivalent, 20/32 or worse] with at least light perception) for which the investigator deemed an intervention was indicated. Patients were excluded if their eyes had known center-involved diabetic macular edema, retinal detachments from fibrosis or scar tissue pulling on the retina (ie, traction) that were involving or threatening the macula, rhegmatogenous retinal detachments, neovascular glaucoma, or prior vitrectomy. We permitted patients who had prior panretinal photocoagulation and intravitreal anti-VEGF injection if the injections were administered more than 2 months before hemorrhage onset.

### Study Design

Randomization schedules were stratified by site with a 1:1 assignment ratio for initial treatment with intravitreal injections containing 2 mg of aflibercept (Eylea, Regeneron) or vitrectomy with panretinal photocoagulation (**Figure 1**). A statistician used computer-generated random numbers to create permuted block design randomization schedules (block sizes of 2 and 4). Treatment assignments were obtained by the study coordinator from the study website.

Certified technicians obtained best-corrected visual acuity following protocol-defined refraction using electronic Early Treatment for Diabetic Retinopathy Study visual acuity testing<sup>16</sup> at each visit and optical coherence tomography scans (if not precluded by media opacity from vitreous hemorrhage) at baseline and at weeks 24, 52, and 104. Retinal detachments were clinically assessed at each visit and during vitrectomy and, if needed, B-scan ultrasonography was performed. Visual acuity technicians were masked to treatment allocation; however, the investigators and participants were not.

### Treatment Protocol

Eyes assigned to vitrectomy with panretinal photocoagulation underwent surgery within 2 weeks of randomization. Vitrectomy was performed according to the investigator's usual

routine using 23-gauge or smaller instruments with complete panretinal photocoagulation performed intraoperatively. Aflibercept could be given preoperatively but not intraoperatively or within 4 weeks after surgery. Four weeks after the vitrectomy, recurrent vitreous hemorrhage was treated with 2 monthly aflibercept injections and additional injections every 4 weeks at the discretion of the investigators. Repeat vitrectomy could be performed if the vitreous hemorrhage failed to clear after 2 aflibercept injections.

Eyes assigned to aflibercept received injections at baseline and at weeks 4, 8, and 12. At 16 weeks, injections were deferred if the complete fundus could be viewed and neovascularization was absent. At 24 weeks, injections were given unless the eye stabilized (2 consecutive visits with the size and density of the hemorrhage and neovascularization clinically unchanged since the last visit). Starting at 16 weeks, vitrectomy could be performed if there was persistent vitreous hemorrhage causing vision impairment following 2 monthly injections. Care during and following vitrectomy was the same as in the vitrectomy group.

All participants received aflibercept if the eye included in the study developed center-involved diabetic macular edema and visual acuity was 20/32 or worse and central subfield thickness met prespecified thresholds.<sup>17</sup> Once initiated, treatment for macular edema followed the DRCR Retina Network anti-VEGF retreatment protocol.<sup>18</sup> Participants whose contralateral eye, which was not included in the study, required anti-VEGF were treated with study-provided aflibercept.

## Outcomes

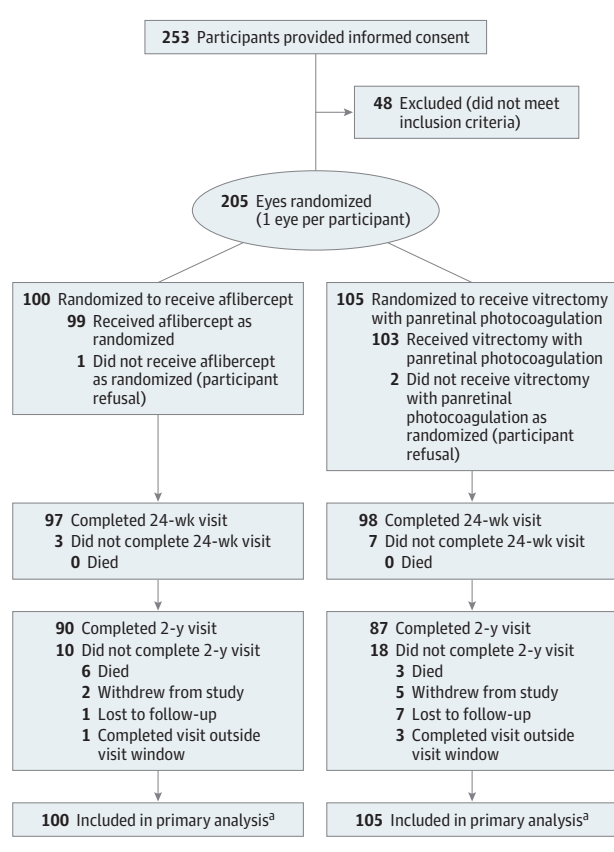
The primary outcome was mean visual acuity letter score over 24 weeks calculated using area under the curve.<sup>19</sup> Visual acuity is measured on a scale from 100 letters (Snellen equivalent, 20/10) to 0 letters (Snellen equivalent, <20/800); higher scores indicate better vision.

The prespecified secondary outcomes included mean visual acuity letter score, percentage of eyes 20/32 or better, and percentage of eyes 20/200 or worse at weeks 4, 12, 24, 52, and 104; mean visual acuity letter score over 104 weeks; and recurrent vitreous hemorrhage, retinal neovascularization, and central subfield thickness at weeks 24, 52, and 104. The percentage of eyes 20/20 or better, 20/40 or better, 20/800 or worse, and gain or loss of at least 30 letters were reported as tabulations without statistical comparison per the statistical analysis plan (Supplement 2). A prespecified secondary analysis of work productivity and activity impairment and an economic analysis are not reported.

The prespecified exploratory outcomes included an increase or decrease of at least 15 visual acuity letters and treatment for center-involved diabetic macular edema. Within-group frequency of aflibercept injections, panretinal photocoagulation, and vitrectomy (including frequency, timing, indication, and surgical details) also are presented.

A medical monitor, who was masked to treatment allocation, coded all adverse events according to the *Medical Dictionary for Regulatory Activities*. Prespecified ocular and systemic adverse events included endophthalmitis, retinal detachment, retinal tear, cataract extraction, visually signifi-

Figure 1. Randomization and Participant Flow in the Trial



<sup>a</sup> Missing data were imputed via multiple imputation for the primary analysis of visual acuity over 24 weeks.

Participants were not formally screened before obtaining informed consent. The reasons for participant ineligibility were not systematically collected. Visit completion at 2 years was prespecified as completion of any study visit from 92 to 116 weeks.

cant cataract (based on investigator judgment without standardized grading), ocular inflammation, elevated intraocular pressure, neovascular glaucoma, iris neovascularization, vascular events defined by Antiplatelet Trialists' Collaboration criteria, death, hospitalization, and any serious systemic adverse event.

## Statistical Methods

A sample size of 162 was calculated, assuming a difference of 8 letters in mean visual acuity over 24 weeks, a standard deviation of 18 letters, 80% power, and an overall 2-sided type I error rate of 0.049. A mean difference of 5 letters has been used as the noninferiority limit for retinal diseases and a greater difference is needed for eyes with worse visual acuity such as those with vitreous hemorrhage.<sup>4,20,21</sup> The sample size was increased to 200 to account for uncertainty in these assumptions.

The prespecified primary analysis was a multiple linear regression model with mean visual acuity over 24 weeks as the dependent variable and baseline visual acuity and lens status as covariates. Missing primary outcome data and secondary

visual acuity outcomes were imputed with Markov chain-Monte Carlo multiple imputation. Prespecified sensitivity analyses for the primary outcome included analyses without imputation for missing outcomes, predictive mean matching imputation, Van der Waerden score transformation, robust regression using M-estimation, adjustment for additional covariates, and tipping point analyses. An analysis controlling for site effects was conducted post hoc. The prespecified subgroups of primary interest included prior panretinal photocoagulation, lens status, and age. The prespecified exploratory subgroups included prior treatment for diabetic macular edema, hemoglobin A<sub>1c</sub> level, vitreous hemorrhage duration, participant sex, and race/ethnicity. Differences in treatment effect between subgroups were evaluated by including an interaction term in the regression model.

Summary statistics were calculated from observed data. Complete case analyses were used for non-visual acuity outcomes. The regression models for the visual acuity outcomes included baseline visual acuity and lens status as covariates. The models for the other outcomes included baseline lens status as a covariate. Continuous outcomes were analyzed with multiple linear regression. Dichotomous outcomes were analyzed via logistic regression, risk differences were estimated by conditional standardization, and 95% CIs were estimated using the delta method.<sup>22</sup> Kaplan-Meier estimates were plotted for time to event outcomes.<sup>23</sup> Cox proportional hazards regression<sup>24</sup> with lens status as a covariate was used for the development of center-involved diabetic macular edema. The proportional hazards assumption was verified using cumulative sums of Martingale residuals.<sup>25</sup>

The *P* values and 95% CIs were 2-sided. In the primary analysis, *P* < .049 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, the findings for the analyses of the secondary end points should be interpreted as exploratory. The analyses were conducted using SAS software version 9.4 (SAS Institute Inc).

## Results

### Study Participants

From November 2016 to December 2017, 205 participants were randomly assigned to treatment with aflibercept (*n* = 100) or vitrectomy with panretinal photocoagulation (*n* = 105) (Figure 1). The final 2-year visit was completed in January 2020. Key baseline demographic and clinical factors were similar between groups (Table 1). Overall, the mean (SD) age was 57 (11) years, 115 (56%) were male, the mean hemoglobin A<sub>1c</sub> level was 8.5%, and the mean visual acuity letter score was 34.5 (Snellen equivalent, 20/200). At 24 weeks, 195 of 205 participants (95%) completed the visit; 177 of 196 participants (90% excluding 9 deaths) completed the 2-year visit.

### Study Treatments

Among participants in the aflibercept group, the mean number of aflibercept injections was 4.6 over 24 weeks and 8.9 over 2 years; 893 of 914 (98%) protocol-required injections were per-

formed at completed visits (Table 2). The cumulative probability of vitrectomy over 2 years was 34% (95% CI, 26% to 45%) (eFigure 1 in Supplement 3). During the first 16 weeks, 6 eyes underwent 7 vitrectomies (6 for retinal detachment and 1 for endophthalmitis) (eTable 1 in Supplement 3). Over 2 years, 33 eyes (33%) assigned to aflibercept received vitrectomy. Participants completed a median of 19 visits.

Among participants in the vitrectomy group, 103 eyes (98%) underwent vitrectomy with panretinal photocoagulation (eTable 2 in Supplement 3) and 44 of 103 eyes (43%) received preoperative aflibercept. Repeat vitrectomy was performed in 8 eyes (8%) (Table 2 and eTable 2 in Supplement 3). Over 2 years, 34 eyes (32%) assigned to vitrectomy received subsequent aflibercept (mean, 2.3 injections over 2 years). There were 21 participants (20%) who received injections for diabetic macular edema and 20 participants (19%) who received injections for complications of proliferative diabetic retinopathy. Participants completed a median of 12 visits.

### Primary Outcome

The primary outcome of mean visual acuity letter score over 24 weeks was 59.3 (Snellen equivalent, 20/63) (95% CI, 54.9 to 63.7) in the aflibercept group vs 63.0 (Snellen equivalent, 20/63) (95% CI, 58.6 to 67.3) in the vitrectomy group (adjusted difference, -5.0 [95% CI, -10.2 to 0.3], *P* = .06) (Table 3). Visual acuity improved faster with vitrectomy, but there was no difference at 24 weeks (Figure 2 and eFigure 2 in Supplement 3). The prespecified and post hoc sensitivity analyses provided estimated treatment effects of 3.9 to 6.3 letters better with vitrectomy and corresponding *P* values of .14 to .007 (eTable 3 in Supplement 3). There were no significant (*P* < .05) interaction effects to indicate that the difference between treatment groups varied in the primary preplanned subgroup analyses (lens status, prior panretinal photocoagulation, age; eTable 4 in Supplement 3).

### Secondary Outcomes

The secondary outcome of mean visual acuity letter score at 4 weeks was 52.6 (Snellen equivalent, 20/100) (95% CI, 46.7 to 58.6) in the aflibercept group vs 62.3 (Snellen equivalent, 20/63) (95% CI, 57.0 to 67.7) in the vitrectomy group (adjusted difference, -11.2 [95% CI, -18.5 to -3.9], *P* = .003) (Table 3). At 24 weeks, the mean visual acuity letter score was 69.4 (Snellen equivalent, 20/40) (95% CI, 64.6 to 74.2) in the aflibercept group vs 69.0 (Snellen equivalent, 20/40) (95% CI, 64.4-73.6) in the vitrectomy group (adjusted difference, -0.5 [95% CI, -6.7 to 5.7], *P* = .88) (Table 3). A good visual acuity letter score of 74 letters or more (Snellen equivalent, 20/32 or better) occurred in 61 of 97 eyes (63%) in the aflibercept group vs 59 of 98 eyes (60%) in the vitrectomy group (adjusted difference, 2% [95% CI, -12% to 16%], *P* = .75). A poor visual acuity letter score of 38 letters or fewer (Snellen equivalent, 20/200 or worse) occurred in 10 eyes (10%) in each group (adjusted difference, 1% [95% CI, -8% to 7%], *P* = .85). Additional secondary and exploratory outcomes appear in eTable 5 and eTable 6 in Supplement 3.

The mean visual acuity letter score over 2 years was 68.7 (Snellen equivalent, 20/50) (95% CI, 65.6 to 71.9) in the

**Table 1. Baseline Characteristics**

	Aflibercept (n = 100)	Vitrectomy with panretinal photocoagulation (n = 105)
<b>Participant characteristics, No. (%)<sup>a</sup></b>		
Sex		
Male	53 (53)	62 (59)
Female	47 (47)	43 (41)
Age, mean (SD), y	56 (12)	57 (11)
Self-reported race/ethnicity		
Hispanic or Latino	43 (43)	41 (39)
Non-Hispanic White	36 (36)	47 (45)
Non-Hispanic Black	16 (16)	11 (10)
Asian	2 (2)	5 (5)
American Indian/Alaska Native	1 (1)	0
>1 race	1 (1)	0
Unknown or not reported	1 (1)	1 (1)
Type of diabetes <sup>b</sup>		
1	17 (17)	19 (18)
2	83 (83)	86 (82)
Duration of diabetes, mean (SD), y <sup>b</sup>	19 (10)	21 (11)
Insulin used	78 (78)	78 (74)
Hemoglobin A <sub>1c</sub> level, mean (SD), %	(n = 96) 8.7 (2.2)	(n = 104) 8.3 (1.9)
Mean arterial pressure, mean (SD), mm Hg <sup>c</sup>	102 (12)	102 (12)
Disease or event <sup>b</sup>		
Myocardial infarction	7 (7)	15 (14)
Stroke	5 (5)	8 (8)
Kidney disease	20 (20)	18 (17)
Body mass index, mean (SD) <sup>d</sup>	(n = 85) 31 (7)	(n = 93) 32 (7)
Daily cigarette smoking		
Never	60 (60)	72 (69)
Prior	27 (27)	25 (24)
Current	13 (13)	8 (8)
<b>Study eye characteristics, No. (%)<sup>a</sup></b>		
Diabetic macular edema		
Prior treatment	29 (29)	37 (35)
Prior treatment with anti-VEGF injection	23 (23)	28 (27)
Prior focal or grid laser photocoagulation	15 (15)	16 (15)
Diabetic retinopathy		
Prior anti-VEGF injection	23 (23)	22 (21)
Prior panretinal photocoagulation	42 (42)	58 (55)
Approximate duration of vitreous hemorrhage, mo		
<1	60 (60)	57 (54)
1-3	27 (27)	27 (26)
4-6	8 (8)	6 (6)
7-12	1 (1)	6 (6)
>12	4 (4)	9 (9)
Lens status at clinical examination		
Phakic (natural lens)	75 (75)	81 (77)
Prosthetic intraocular lens	25 (25)	24 (23)

(continued)



Table 1. Baseline Characteristics (continued)

	Aflibercept (n = 100)	Vitrectomy with panretinal photocoagulation (n = 105)
Visual acuity <sup>e</sup>		
Letter score, mean (SD)	35.6 (28.1)	33.5 (28.8)
Snellen equivalent, mean	20/200	20/250
Letter score, median (IQR)	37.0 (63.0-2.0)	37.0 (62.0-0)
Snellen equivalent, median	20/200	20/200
Snellen equivalent range (letter score range)		
20/32-20/40 (78-69)	17 (17)	15 (14)
20/50-20/80 (68-54)	18 (18)	24 (23)
20/100-20/160 (53-39)	13 (13)	9 (9)
20/200-20/800 (38-4)	26 (26)	24 (23)
Worse than 20/800 (≤3)	26 (26)	33 (31)
Traction retinal detachment <sup>f</sup>		
Yes (macula not threatened)	5 (5)	3 (3)
No	95 (95)	102 (97)
Intraocular pressure, mean (SD), mm Hg <sup>g</sup>	16 (4)	15 (3)
Abbreviations: IQR, interquartile range; VEGF, vascular endothelial growth factor.		
<sup>a</sup> Some of the data are expressed as mean (SD) or median (IQR) as indicated.		
<sup>b</sup> Collected by chart review when possible or was self-reported.		
<sup>c</sup> Calculated as (2/3 × diastolic blood pressure) + (1/3 × systolic blood pressure) at enrollment.		
<sup>d</sup> Calculated as weight in kilograms divided by height in meters squared.		
<sup>e</sup> Measured using electronic Early Treatment for Diabetic Retinopathy Study visual acuity testing on a scale from 100 letters (Snellen equivalent, 20/10) to 0 letters (Snellen equivalent, <20/800); higher scores indicate better vision. The data presented are the best-corrected visual acuity scores in the study eye following protocol-defined refraction.		
<sup>f</sup> Caused by the presence of retinal fibrosis or scarring that pulls on the retina.		
<sup>g</sup> Measured using a Goldmann Applanation tonometer (when available) or a Tono-Pen tonometer.		

Table 2. Study Treatment During Follow-up

	Aflibercept (n = 100)	Vitrectomy with panretinal photocoagulation (n = 105)
Had ≥1 vitrectomy, No. (%) <sup>a</sup>	33 (33)	8 (8)
Timing of first vitrectomy, No. (%) <sup>a</sup>		
Between 0 and <24 wk	14 (14)	5 (5)
Between 24 and <52 wk	9 (9)	3 (3)
Between 52 and 104 wk	10 (10)	0
Panretinal photocoagulation, No. (%) <sup>a</sup>		
During follow-up vitrectomy	32 (32)	4 (4)
Outside follow-up vitrectomy	0	1 (<1)
Had ≥1 intravitreal aflibercept injection, No. (%) <sup>b</sup>	99 (99) <sup>c</sup>	34 (32) <sup>d</sup>
No. of intravitreal aflibercept injections, mean (SD), wk <sup>b</sup>		
Between 0 and <24 wk	4.6 (1.3)	0.3 (0.8)
Between 0 and 104 wk	8.9 (4.6)	2.3 (4.3)
No. of intravitreal aflibercept injections through 104 wk, No. (%) <sup>b</sup>		
0	1 (1) <sup>c</sup>	71 (68)
1-4	12 (12)	11 (10)
5-8	39 (39)	12 (11)
9-12	28 (28)	6 (6)
≥13	20 (20)	5 (5)

<sup>a</sup> Excludes the initial vitrectomy and any procedures performed before or during the initial vitrectomy.

<sup>b</sup> Includes the initial injection of aflibercept.

<sup>c</sup> One participant refused treatment.

<sup>d</sup> Twenty-one eyes (20%) received at least 1 aflibercept injection for center-involved diabetic macular edema; 20 eyes (19%) received at least 1 aflibercept injection for complications of proliferative diabetic retinopathy, which included vitreous hemorrhage.

aflibercept group vs 70.0 (Snellen equivalent, 20/40) (95% CI, 66.0 to 74.0) in the vitrectomy group (adjusted difference, -2.2 [95% CI, -6.7 to 2.3], *P* = .34) (Table 3). At 2 years,

the mean visual acuity letter score was 73.7 (Snellen equivalent, 20/40) (95% CI, 70.2 to 77.1) in the aflibercept group vs 71.0 (Snellen equivalent, 20/40) (95% CI, 65.9 to 76.1) in the

Table 3. Primary and Secondary Visual Acuity Outcomes

	Aflibercept	Vitrectomy with panretinal photocoagulation	Difference (95% CI) <sup>a,b</sup>		P value <sup>a,c</sup>
			Unadjusted	Adjusted <sup>c</sup>	
<b>Primary outcome<sup>d</sup></b>					
No. of participants over 24 wk	97	98			
Visual acuity letter score (area under the curve), mean (SD)	59.3 (21.9)	63.0 (21.7)	-4.3 (-10.0 to 1.4)	-5.0 (-10.2 to 0.3)	.06
Snellen equivalent, mean	20/63	20/63			
Visual acuity letter score (area under the curve), median (IQR)	65.0 (75.5 to 49.5)	71.3 (77.5 to 57.4)			
Snellen equivalent, median	20/50	20/40			
<b>Secondary outcomes<sup>d</sup></b>					
No. of participants at 4 wk	95	99			
Visual acuity letter score, mean (SD)	52.6 (29.4)	62.3 (26.8)	-10.3 (-18.2 to -2.4)	-11.2 (-18.5 to -3.9)	.003
Snellen equivalent, mean	20/100	20/63			
Visual acuity letter score, median (IQR)	63.0 (74.0 to 23.0)	73.0 (81.0 to 56.0)			
Snellen equivalent, median	20/63	20/40			
Snellen equivalent range (visual acuity score), No. (%)					
20/32 or better (≥74)	24 (25)	49 (49)	-24 (-37 to -11)	-28 (-42 to -14)	<.001
20/200 or worse (≤38)	26 (27)	18 (18)	10 (-2 to 22)	11 (-0 to 23)	.05
No. of participants at 24 wk	97	98			
Visual acuity letter score, mean (SD)	69.4 (23.8)	69.0 (23.1)	0.1 (-6.3 to 6.6)	-0.5 (-6.7 to 5.7)	.88
Snellen equivalent, mean	20/40	20/40			
Visual acuity letter score, median (IQR)	76.0 (85.0 to 67.0)	76.0 (83.0 to 66.0)			
Snellen equivalent, median	20/32	20/32			
Snellen equivalent range (visual acuity score), No. (%)					
20/32 or better (≥74)	61 (63)	59 (60)	3 (-11 to 17)	2 (-12 to 16)	.75
20/200 or worse (≤38)	10 (10)	10 (10)	0 (-8 to 9)	1 (-7 to 8)	.85
No. of participants over 2 y	90	87			
Visual acuity letter score (area under the curve), mean (SD)	68.7 (15.0)	70.0 (18.8)	-1.8 (-6.5 to 3.0)	-2.2 (-6.7 to 2.3)	.34
Snellen equivalent, mean	20/50	20/40			
Visual acuity letter score (area under the curve), median (IQR)	70.5 (79.4 to 64.2)	75.4 (82.1 to 65.8)			
Snellen equivalent, median	20/40	20/32			
No. of participants at 2 y	90	87			
Visual acuity letter score, mean (SD)	73.7 (16.4)	71.0 (24.0)	2.9 (-2.9 to 8.7)	2.7 (-3.1 to 8.4)	.36
Snellen equivalent, mean	20/40	20/40			
Visual acuity letter score, median (IQR)	78.0 (85.0 to 65.0)	78.0 (85.0 to 69.0)			
Snellen equivalent, median	20/32	20/32			
Snellen equivalent range (visual acuity score), No. (%)					
20/32 or better (≥74)	56 (62)	59 (68)	-2 (-17 to 12)	-3 (-17 to 11)	.68
20/200 or worse (≤38)	3 (3)	10 (11)	-7 (-14 to 0)	-6 (-13 to 1)	.08

Abbreviation: IQR, interquartile range.

<sup>a</sup> Missing data were imputed with Markov chain-Monte Carlo multiple imputation. The imputation model included treatment group, lens status, baseline visual acuity score, and visual acuity score at common follow-up visits.

<sup>b</sup> The mean differences were estimated via multiple linear regression for continuous outcomes (positive values indicate better visual acuity scores with aflibercept; ie, aflibercept minus vitrectomy) and the risk differences were estimated via logistic regression and the delta method for binary outcomes

(positive values indicate greater risk with aflibercept; ie, aflibercept minus vitrectomy).

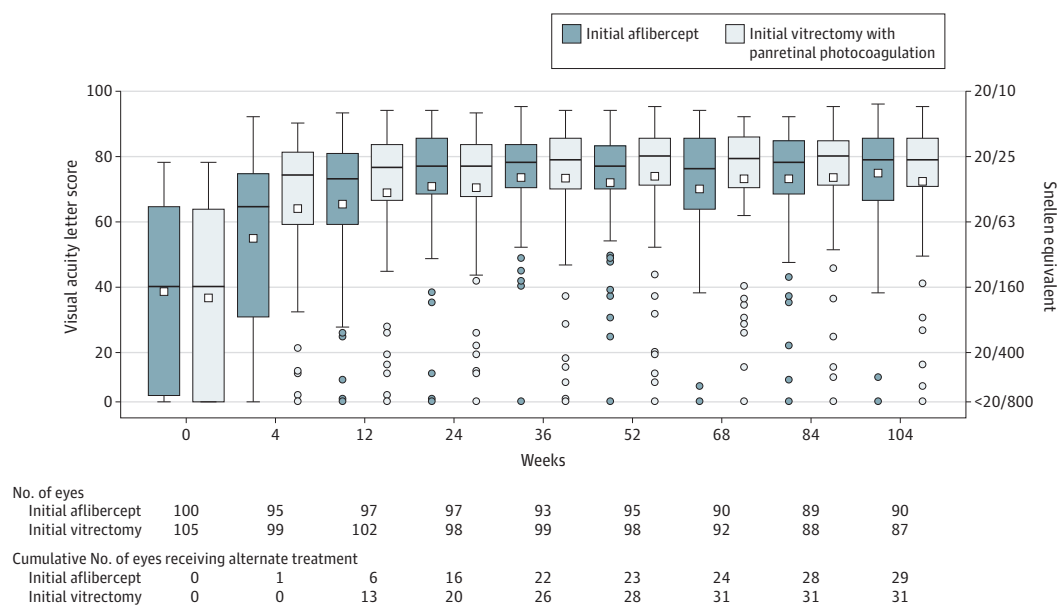
<sup>c</sup> Adjusted for baseline visual acuity and lens status.

<sup>d</sup> Scores indicate best-corrected visual acuity in the study eye following protocol-defined refraction. Visual acuity was measured using electronic Early Treatment for Diabetic Retinopathy Study visual acuity testing on a scale from 100 letters (Snellen equivalent, 20/10) to 0 letters (Snellen equivalent, <20/800); higher scores indicate better vision.

vitrectomy group (adjusted difference, 2.7 [95% CI, -3.1 to 8.4], *P* = .36). A good visual acuity letter score of 74 or more (Snellen equivalent, 20/32 or better) occurred in 56 of 90

eyes (62%) in the aflibercept group vs 59 of 87 eyes (68%) in the vitrectomy group (adjusted difference, -3% [95% CI, -17 to 11%], *P* = .68). A poor visual acuity letter score of 38

Figure 2. Visual Acuity Letter Score Through 2 Years



Within each box and whisker plot, the horizontal bar represents the median and the white square represents the mean. The top of the box is the third quartile (75th percentile) and the bottom of the box is the first quartile (25th percentile). Whiskers extend from the nearest quartile to the most extreme data point within 1.5 times the interquartile range; values beyond these limits are plotted as circles. The number of eyes completing each visit and the cumulative number of eyes that received alternative treatment through the visit

(eg, aflibercept in the vitrectomy group or vitrectomy in the aflibercept group) appear below the plot. The best-corrected visual acuity was collected after protocol-defined refraction. Visual acuity was measured using electronic Early Treatment for Diabetic Retinopathy Study visual acuity testing on a scale from 100 letters (Snellen equivalent, 20/10) to 0 letters (Snellen equivalent, <20/800); higher scores indicate better vision.

letters or fewer (Snellen equivalent, 20/200 or worse) occurred in 3 eyes (3%) in the aflibercept group vs 10 eyes (11%) in the vitrectomy group (adjusted difference, -6% [95% CI, -13% to 1%],  $P = .08$ ).

Recurrent vitreous hemorrhage occurred at least once in 48 of 97 participants (49%) in the aflibercept group and 16 of 104 participants (15%) in the vitrectomy group (adjusted difference, 34% [95% CI, 22% to 46%],  $P < .001$ ; eTable 7 in Supplement 3). The proportion of eyes with retinal neovascularization on clinical examination was significantly greater among participants in the aflibercept group vs participants in the vitrectomy group at 24 weeks (25 of 85 [29%] vs 3 of 92 [3%], respectively; adjusted difference, 25% [95% CI, 15% to 36%],  $P < .001$ ) and at 2 years (20 of 88 [23%] vs 2 of 83 [2%]; adjusted difference, 20% [95% CI, 11% to 30%],  $P < .001$ ).

### Exploratory Outcomes

The proportion with center-involved diabetic macular edema at 24 weeks was 8% (7 of 87) in the aflibercept group vs 31% (28 of 90) in the vitrectomy group (difference, -23% [95% CI, -34% to -12%],  $P < .001$ ) and was 17% (15 of 88) vs 21% (17 of 80), respectively, at 2 years (difference, -4% [95% CI, -16% to 8%],  $P = .48$ ; eTable 8 in Supplement 3). The cumulative probability of receiving anti-VEGF injections for center-involved diabetic macular edema through 2 years was 18% in the aflibercept group vs 22% in the vitrectomy group (adjusted hazard ratio, 0.77 [95% CI, 0.41 to 1.46],  $P = .42$ ; eFigure 3 in Supplement 3).

### Adverse Events

Endophthalmitis occurred in 1 eye (1%) in the aflibercept group (related to aflibercept injection) and in 2 eyes (2%) in the vitrectomy group (related to vitrectomy) (Table 4). In the aflibercept group, traction retinal detachment was identified at or before the first visit when vitreous hemorrhage subsided sufficiently to allow the investigator a clear view of the retina or the first vitrectomy (whichever occurred first) in 13 eyes (13%) and after that time in 9 eyes (9%). In the vitrectomy group, traction retinal detachment was first identified during the initial vitrectomy in 13 eyes (12%) and after the initial vitrectomy in 1 eye (<1%) (additional details appear in eTable 9 in Supplement 3). New or worsened rhegmatogenous retinal detachment was identified in 4 eyes (4%) assigned to aflibercept and in 5 eyes (5%) assigned to vitrectomy. Among phakic eyes, cataract extraction or visually significant cataract (per the investigator) occurred in 37 of 75 eyes (49%) in the aflibercept group and in 36 of 81 eyes (44%) in the vitrectomy group; cataract extraction was performed in 23 eyes (31%) and 22 eyes (27%), respectively.

At least 1 serious systemic adverse event occurred in 42 participants (42%) in the aflibercept group and in 43 participants (41%) in the vitrectomy group. Myocardial infarction, stroke, and death of vascular or unknown cause occurred in 8 participants (8%) in the aflibercept group and in 7 participants (7%) in the vitrectomy group. All adverse events appear in eTables 10 through 12 in Supplement 3.



Table 4. Adverse Events Through 2 Years

	No. (%)	
	Aflibercept (n = 100)	Vitrectomy and panretinal photocoagulation (n = 105)
<b>Ocular adverse events occurring in study eyes: participants with ≥1 event</b>		
Cataract extraction or visually significant cataract on clinical examination (eyes with natural lens only)	(n = 75) 37 (49)	(n = 81) 36 (44)
Visually significant cataract	(n = 75) 34 (45)	(n = 81) 35 (43)
Cataract extraction	(n = 75) <sup>a</sup> 23 (31)	(n = 81) 22 (27)
Adverse intraocular pressure event	23 (23)	25 (24)
Increase in intraocular pressure ≥10 mm Hg from baseline	16 (16)	17 (16)
Intraocular pressure ≥30 mm Hg at any visit	8 (8)	10 (10)
Initiation of medication not in use at baseline to lower intraocular pressure	14 (14)	16 (15)
Glaucoma procedure	0	2 (2)
Retinal detachment	23 (23)	15 (14)
Traction retinal detachment	22 (22)	14 (13)
Rhegmatogenous retinal detachment	4 (4)	5 (5)
Ocular inflammation	6 (6)	4 (4)
Neovascularization of the iris	2 (2)	5 (5)
Retinal tear (without detachment)	3 (3)	2 (2)
Endophthalmitis	1 (1)	2 (2)
Neovascular glaucoma	1 (1)	2 (2)
<b>Systemic adverse events: participants with ≥1 event</b>		
Serious adverse event	42 (42)	43 (41)
Hospitalization	39 (39)	41 (39)
Death	6 (6)	3 (3)
Vascular events defined by Antiplatelet Trialists' Collaboration criteria		
Any event	8 (8)	7 (7)
Death due to vascular or unknown cause	5 (5)	3 (3)
Nonfatal stroke	2 (2)	2 (2)
Nonfatal myocardial infarction	1 (1)	2 (2)

<sup>a</sup> Among the 75 eyes with natural lens (ie, phakic eyes) in the initial aflibercept group at baseline, 27 underwent vitrectomy during follow-up. Of the 23 eyes that underwent cataract extraction, 9 had cataract extraction and no vitrectomy during follow-up, 3 had cataract extraction before undergoing vitrectomy (ie, these eyes were phakic at baseline but pseudophakic at time of first vitrectomy), and 11 had cataract extraction after their first vitrectomy.

## Discussion

In this multicenter randomized clinical trial among participants whose eyes had vitreous hemorrhage from proliferative diabetic retinopathy, there was no statistically significant difference in the primary outcome of mean visual acuity letter score over 24 weeks between eyes initially treated with intravitreal aflibercept injections vs those treated with vitrectomy with panretinal photocoagulation, but the 95% CI was wide, and the study may have been underpowered to detect a clinically important benefit in favor of initial vitrectomy with panretinal photocoagulation. Nonetheless, mean visual acuity was not significantly different between the groups at 12 weeks or at any visit thereafter through 2 years.

Most previous studies of vitrectomy for vitreous hemorrhage have been retrospective and involved a limited number of sites and surgeons.<sup>26-28</sup> This study, however, was a multicenter randomized trial involving 87 investigators across 39 clinical sites. Surgeons could use their routine technique with prior specifications regarding only instrumentation gauge, pan-

retinal photocoagulation, and perioperative anti-VEGF injection, which enabled collection of surgical data across a diversity of practices and enhanced the generalizability of these results. Importantly, because the protocol (Supplement 1) allowed crossover treatment for prespecified criteria, 1 in 3 eyes from each group received the alternate treatment (aflibercept or vitrectomy with panretinal photocoagulation) over 2 years. Thus, when following treatment approaches developed by the DRCR Retina Network investigators, many participants receive both therapies.

During vitrectomy, visible vitreoretinal traction is generally removed along with vitreous scaffolding. Therefore, most surgeries relieve retinal detachments with macular-threatening traction and help prevent subsequent traction retinal detachments. Only 1 eye developed traction retinal detachment after initial surgery in the vitrectomy group. Eyes starting treatment with aflibercept remained at risk for persistence, progression, or development of a traction retinal detachment. Some of the 22 traction retinal detachments noted after baseline were likely present at baseline but not visible because the vitreous hemorrhage precluded complete retinal

viewing. Regardless of when the traction retinal detachments developed, 12 eyes (12%) in the aflibercept group underwent vitrectomy for traction retinal detachment, and the final visual acuity scores for eyes in the aflibercept group with traction retinal detachment were similar to eyes without traction retinal detachment (median, 20/32 for both).

Although visual outcomes were not significantly different between treatment groups from 12 weeks through 2 years, additional findings from this study may help clinicians guide therapeutic decisions for individuals with vitreous hemorrhage. The benefits of vitrectomy in this study included faster restoration of vision, reduced likelihood of recurrent vitreous hemorrhage, and greater resolution of neovascularization. In contrast, the aflibercept group experienced less frequent center-involved diabetic macular edema and avoided vitrectomy in two-thirds of participants. Based on prior results, panretinal photocoagulation may result in more peripheral visual field deficits than anti-VEGF agents injected in the eyes of patients with proliferative diabetic retinopathy.<sup>3,29</sup> The decision to initiate treatment using anti-VEGF injections vs vitrectomy with panretinal photocoagulation is influenced by many factors, including anticipated likelihood of patient adherence with follow-up visits, medical comorbidities, access to specialized treatments or medications, and the need or desire to hasten visual recovery, particularly for patients whose fellow eye also does not have good vision.

### Limitations

This study has several limitations. First, even though retention through 24 weeks and 1 year was excellent in both groups

(93%-97%), retention was lower in the vitrectomy group vs the aflibercept group at 2 years (85% vs 96%, respectively), which could bias comparisons of 2-year outcomes if loss to follow-up was related to treatment efficacy.

Second, neither the investigators nor the participants could be masked to treatment allocation owing to the nature of the treatments; however, visual acuity technicians were masked to treatment allocation, which limits bias in the primary analysis.

Third, aflibercept was the only anti-VEGF agent used in this study; therefore, it is unknown whether similar results would be obtained with an alternative such as bevacizumab or ranibizumab.

Fourth, although the long-term effects of treatments in the population with diabetes are important, this trial did not address visual outcomes or durability of neovascularization bx regression beyond 2 years.

### Conclusions

Among participants whose eyes had vitreous hemorrhage from proliferative diabetic retinopathy, there was no statistically significant difference in the primary outcome of mean visual acuity letter score over 24 weeks following initial treatment with intravitreal aflibercept vs vitrectomy with panretinal photocoagulation. However, the study may have been underpowered, considering the range of the 95% CI, to detect a clinically important benefit in favor of initial vitrectomy with panretinal photocoagulation.

### ARTICLE INFORMATION

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**Author Affiliations:** Charlotte Eye, Ear, Nose & Throat Associates, Charlotte, North Carolina (Antoszyk, Punjabi); Jaeb Center for Health Research, Tampa, Florida (Glassman, Beaulieu, Stockdale); Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Jampol); Retina Research Center, Austin, Texas (Jhaveri); Dell Medical School, University of Texas, Austin (Jhaveri); Retina Associates of Southern California, Huntington Beach (Salehi-Had); Palmetto Retina Center, Columbia, South Carolina (Wells); Department of Ophthalmology, University of Pennsylvania, Philadelphia (Maguire); Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio (Martin); Joslin Diabetes Center, Beetham Eye Institute, Department of Ophthalmology, Harvard University, Boston, Massachusetts (Sun).

**Author Contributions:** Dr 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.

**Concept and design:** Antoszyk, Glassman, Jampol, Jhaveri, Punjabi, Wells, Stockdale, Sun.

**Acquisition, analysis, or interpretation of data:** Antoszyk, Glassman, Beaulieu, Jampol, Jhaveri, Punjabi, Salehi-Had, Wells, Maguire, Martin, Sun.

**Drafting of the manuscript:** Antoszyk, Glassman, Beaulieu, Jampol, Punjabi, Wells, Martin, Sun.

**Critical revision of the manuscript for important intellectual content:** Antoszyk, Beaulieu, Jampol,

Jhaveri, Punjabi, Salehi-Had, Wells, Maguire, Stockdale, Martin, Sun.

**Statistical analysis:** Glassman, Beaulieu, Punjabi, Maguire.

**Obtained funding:** Glassman, Jampol, Martin, Sun.

**Administrative, technical, or material support:** Antoszyk, Glassman, Jampol, Punjabi, Salehi-Had, Stockdale.

**Supervision:** Antoszyk, Glassman, Punjabi, Wells, Martin, Sun.

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Dr Beaulieu reported receiving grants and nonfinancial support from Genentech, Regeneron, and Allergan. Dr Jampol reported receiving personal fees from Sanofi. Dr Jhaveri reported receiving personal fees from Genentech, Allergan, and Novartis. Dr Wells reported receiving grants and personal fees from Genentech and Adverum; and participating in clinical research with Emmes, Genentech, Kodiak, Lpach Incorporated, Neurotech, Ophthotech, Opthea, Regeneron, and Thrombogenics. Dr Maguire reported receiving personal fees from Genentech; and receiving payment from the Jaeb Center for Health Research paid to her institution. Ms Stockdale reported receiving grants and nonfinancial support from Genentech, Regeneron, and Allergan. Dr Sun

reported receiving grants from the Jaeb Center for Health Research, Roche Genentech, the Juvenile Diabetes Research Foundation, and Kalvista; receiving personal fees from *Current Diabetes Reports*, *JAMA Ophthalmology*, and Merck; receiving nonfinancial support from Optovue (equipment loaned for research), Boston Micromachines, Adaptive Sensory Technologies, Roche Genentech (food/beverage), Novartis, and Kalvista (travel support); and receiving grants and nonfinancial support from Novo Nordisk, Boehringer Ingelheim, and Roche. No other disclosures were reported.

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management, analysis, or interpretation of the data, or in the preparation of the manuscript.

**The DRCR Retina Network: Coordinating Center Staff at Jaeb Center for Health Research:**

Adam R. Glassman, MS (director and principal investigator), Roy W. Beck, MD, PhD (executive director), Alyssa Baptista, BS, Wesley T. Beaulieu, PhD, Claire T. Boyle, MS, Sharon R. Constantine, BS, Brian B. Dale, Simone S. Dupre, BS, Sandra Galusic, MSPH, Meagan Huggins, BA, Paula A. Johnson, MPH, Kristen Josic, PhD, Brittany Kelly, MS, Danni Liu, MSPH, Brenda L. Loggins, BS, Maureen G. Maguire, PhD, Michele Melia, ScM, Ilona Nemeth, MA, Carin M. Preston, MPH, Cynthia R. Stockdale, MSPH, and Katie Stutz, BS. **Duke Reading Center Staff:** Katrina Postell Winter, BS (lead reader), Garrett Thompson, MD (reader), Dee Busian, BA (reader), Glenn J. Jaffe, MD (director of grading), Adiel Mora, BA (project manager), Lucia Foster, MA (assistant project manager), and John Keifer McGugan, BS (assistant project manager). **DRCR Retina Network Chairs:** Jennifer K. Sun, MD, MPH (Joslin Diabetes Center, Beetham Eye Institute, Harvard Department of Ophthalmology; 2018-present), Daniel F. Martin, MD (Cole Eye Institute at Cleveland Clinic; 2018-present), Lee M. Jampol, MD (Feinberg School of Medicine, Northwestern University; 2013-2017), and Neil M. Bressler, MD (Department of Ophthalmology, Johns Hopkins University School of Medicine; 2006-2012). **DRCR Retina Network Vice Chairs:** Carl W. Baker, MD (Paducah Retinal Center; 2011-2013 and 2017-2019), Chirag Jhaveri, MD (Retina Consultants of Austin; 2016-2018), Mathew MacCumber, MD, PhD (Rush University Medical Center; 2018-present), Andrew Antoszyk, MD (Charlotte Eye, Ear, Nose & Throat Associates; 2013-2016 and 2020-present), Susan B. Bressler, MD (Wilmer Eye Institute; 2009-2011), Scott Friedman, MD (Florida Retina Consultants; 2009-2012), Judy Kim, MD (Medical College of Wisconsin; 2015-2017), Ingrid U. Scott, MD, MPH (Penn State College of Medicine; 2009-2010), Jennifer K. Sun, MD, MPH (Joslin Diabetes Center, Beetham Eye Institute, Harvard Department of Ophthalmology; 2012-2014), and John A. Wells III, MD (Palmetto Retina Center; 2013-2015). **National Eye Institute:** Sangeeta Bhargava, PhD (2016-current), and Eleanor Schron, PhD (2009-2015). **Executive Committee:** Andrew N. Antoszyk, MD (Charlotte Eye, Ear, Nose & Throat Associates; 2009 and 2013-present), Roy W. Beck, MD, PhD (Jaeb Center for Health Research; 2002-present), Sangeeta Bhargava, PhD (National Eye Institute, National Institutes of Health; 2016-present), Barbra Blodi, MD (University of Wisconsin, Madison; 2014-present), Frederick L. Ferris III, MD (Ophthalmic Research Consultants; 2002-present), Adam R. Glassman, MS (Jaeb Center for Health Research; 2005-present), Glenn J. Jaffe, MD (Duke Reading Center; 2012-present), Lee M. Jampol, MD (Feinberg School of Medicine, Northwestern University; 2012-present), Chirag D. Jhaveri, MD (Retina Consultants of Austin; 2016-present), Judy E. Kim, MD (Medical College of Wisconsin; 2015-2017 and 2020-present), Brandon Lujan, MD (Casey Eye Center; 2017-present), Mathew MacCumber, MD, PhD (Rush University Medical Center; 2018-present), Dennis M. Marcus, MD (Southeast Retina Center, PC; 2011-2012 and 2018-present), Daniel F. Martin, MD (Cole Eye Institute at Cleveland Clinic; 2017-present), Raj K. Maturi, MD (private practice of Raj K. Maturi, MD; 2009-2011 and 2013-present), Jennifer K. Sun, MD,

MPH (Joslin Diabetes Center, Beetham Eye Institute, Harvard Department of Ophthalmology; 2009-present). **Previously on Executive Committee:** Lloyd Paul Aiello, MD, PhD (Beetham Eye Institute, Joslin Diabetes Center, Harvard Medical School; 2002-2018 and chair for 2002-2005), Carl W. Baker, MD (Paducah Retinal Center; 2009-2019), Abdhish Bhavsar, MD (Retina Center of Minnesota; 2007-2008 and 2010-2012), Neil M. Bressler, MD (Department of Ophthalmology, Johns Hopkins University School of Medicine; 2006-2019 and chair for 2006-2008), Susan B. Bressler, MD (Wilmer Eye Institute; 2009-2019), Alexander J. Brucker, MD (Scheie Eye Institute; 2009-2011), Kakarla V. Chalam, MD, PhD, MBA (Loma Linda University Eye Institute; 2009-2011), Ronald P. Danis, MD (University of Wisconsin, Madison; 2004-2015), Matthew D. Davis, MD (Medical College of Wisconsin; 2002-2017), Michael J. Elman, MD (Elman Retina Group, PA; 2006-2018 and chair for 2009 and 2012), Donald F. Everett, MA (National Eye Institute, National Institutes of Health; 2002-2009), Joan Fish, RN (Wake Forest University Eye Center; 2008-2009), Scott Friedman, MD (Florida Retina Consultants; 2007-2013), Joseph Google Jr, MD (Southeastern Retina Associates, PC; 2009-2011), Jeffrey G. Gross, MD (Carolina Retina Center, PA; 2012-2017), Diana M. Holcomb (Retina Associates of Kentucky; 2011-2012), Andreas K. Lauer, MD (Casey Eye Center; 2007-2008), Ashley A. McClain, BS (Charlotte Eye, Ear, Nose & Throat Associates; 2013), Brandi J. Perez (Loma Linda University Eye Institute; 2013), Eleanor Schron, PhD (National Eye Institute, National Institutes of Health; 2009-2015), Ingrid U. Scott, MD, MPH (Penn State College of Medicine; 2009-2010), JoAnn Starr, BS (Elman Retina Group, PA; 2009-2011), and John A. Wells III, MD (Palmetto Retina Center; 2012-2015). **Clinical Sites:** (ordered by No. of participants enrolled) *Huntington Beach, CA (Atlantis Eye Care; n=20):* Hani Salehi-Had, MD (study investigator), Evelyn Ceja and Sara Ahmed, BS (coordinators); Stephanie Ramirez (coordinator, photographer, and visual acuity technician); Mailan Tran, OD, Mary Ma, OD, and Scott F. Lee, OD (visual acuity technicians); and Nikki Nguyen, BS, Lily Castillo, and Janet Reyes (photographers). *Austin, TX (Retina Research Center; n=19):* Chirag D. Jhaveri, MD, Gowtham Jonna, MD, and Saradha Chexal, MD (study investigators); Daniela Mariel Wilson, Tina A. Seidu, and Cori Renfro (coordinators); Ivana Gunderson, Valerie Gatavaski, and Abba M. Harara (visual acuity technicians); Ryan M. Reid (coordinator and photographer); Boris Corak, BS (photographer and visual acuity technician); and Yong Ren (photographer). *Charlotte, NC (Charlotte Eye, Ear, Nose & Throat Associates; n=19):* Andrew N. Antoszyk, MD, Omar S. Punjabi, MD, and David Browning, MD, PhD (study investigators); Angela K. Price, MPH, Christina J. Fleming, BS, Taylor S. Jones, Sherry L. Fredenberg, and Brittany A. Murphy, BA (coordinators and visual acuity technicians); Sarah A. Ennis, Kayla A. Bratcher, Christina Mutch, Angella K. Gentile, and Erica Breglio (visual acuity technicians); and Lisa A. Jackson, Loraine M. Clark, Lynn Watson, Donna McClain, Carol A. Shore, Uma M. Balasubramaniam, and Shannon Stobbe (photographers). *Indianapolis, IN (private practice of Raj K. Maturi, MD; n=15):* Raj K. Maturi, MD, David A. Lightman, MD, and Stephen J. Saxe (study investigators); Ashley M. Harless and Lorraine

White (coordinators, photographers, and visual acuity technicians); Myra K. Retrum and Carolee K. Novak (visual acuity technicians); and Yesenia Sarmiento (photographer). *McAllen, TX (Valley Retina Institute; n=12):* Victor Hugo Gonzalez, MD, and Nehal R. Patel, MD (study investigators); Elyssa Navarro, Nancy L. Salinas, Angelina Garza, BS, Amber B. Ibarra, BS, and Ana L. Pina, BA (coordinators); Monica R. Cantu, Brenda Velasquez, Christina Villegas, Enrique Chavez, Isaac Cabrera, Yvonne Diaz, Jennifer Moreno, Rebecca R. Flores, and Janette Arredondo (visual acuity technicians); and Monique Montemayor, Georgia L. Villarreal, Stephanie Tamez, Samuel Alonso, and Santos Garza (photographers). *West Columbia, SC (Palmetto Retina Center; n=12):* John A. Wells III, MD, and John F. Payne, MD (study investigators); Cassandra L. Garrison, BS, and Kristin R. Stokes (coordinators); Tiffany R. Swinford (coordinator and visual acuity technician); Ashley Floyd and Tiffany N. Ogbuewu (visual acuity technicians); and Robbin Spivey and Ashley Studebaker (photographers). *Campbell, CA (Retinal Diagnostic Center; n=11):* Clement Chow, MD, Amr Dessouki, MD, and Lingmin He, MD (study investigators); Joel M. Barra, BSBM, Thanh T. Nguyen, and Carla Trujillo (coordinators); Whitney Kuang, Danielle Dinh, and Lynise Cummins (coordinators and visual acuity technicians); Kelly To, Hienmy Dang, and Dao Tran (visual acuity technicians); and Pete Donovan Fernandez, Kenny Trang, Tim Kelley, and Juan Hernandez (photographers). *Baltimore, MD (Elman Retina Group, PA; n=9):* Michael J. Elman, MD (study investigator); JoAnn Starr, Jennifer L. Belz, and Twyla J. Robinson (coordinators); Pamela V. Singleary, Christine Ringrose, Alesia K. McCalla, Amy Thompson, Katherine L. Wentz, Peggy R. Orr, MPH, BSN, RN, and Teresa Coffey (visual acuity technicians); and Peter Sotirakos, Terri Cain, and Ashley M. Metzger (photographers). *Edmond, OK (Retina Vitreous Center; n=8):* Sandeep N. Shah, MD, and Brian S. Phelps, MD (study investigators); Amy L. West, BS (coordinator and photographer); Romesh Babaria, MS (coordinator, visual acuity technician, and photographer); and Jeannette Rodriguez, Mayra Viruet-Nieves, Kellie Meiwes, and Lisa Holley (photographers). *San Antonio, TX (Retinal Consultants of San Antonio; n=8):* Calvin E. Mein, MD, Richard Gary Lane, MD, Darrell E. Baskin, MD, and Moises A. Chica, MD (study investigators); Lydia Adams, Lita Kirschbaum, Sara L. Cloudt, Stacy Rodriguez, Vanessa D. Martinez, and Jenny M. Bermea (coordinators); Victoria Lopez (visual acuity technician); and Samantha Bankston, Christopher Sean Wienecke, Jorge Castellanos, and Brenda Nakoski (photographers). *Paducah, KY (Paducah Retinal Center; n=7):* Carl W. Baker, MD, and Ron H. Tilford, MD (study investigators); Tracey M. Caldwell and Jill D. Baker (coordinators); Lynnette F. Lambert, Mary J. Sharp, and Margaret J. Orr (visual acuity technicians); and Sonya L. Alcaraz, Samantha Kettler, Alecia B. Camp, and Kylie S. Sedberry (photographers). *Loma Linda, CA (Loma Linda University Health Care, Department of Ophthalmology; n=6):* Joseph T. Fan, MD, Samuel C. Kim, MD, David Isaiah Sierpina, MD, Michael E. Rauser, MD, and Kakarla V. Chalam, MD (study investigators); Raquel Hernandez, Vivian L. Garcia, Jayson S. Paw, and Tina L. Ramirez (coordinators); Anthoni Tampubolon (coordinator, visual acuity technician, and photographer); and Moises Tellez, Adel E. Alset, and Marcia Easterly (photographers). *Amarillo, TX (Southwest Retina Specialists; n=5):*



J. Edward Ysasaga, MD (study investigator); Kasey L. Dalrymple (coordinator); Johnathan R. Hawkins (visual acuity technician); and Ben Ysasaga (photographer). *Augusta, GA (Southeast Retina Center PC; n=5)*: Dennis M. Marcus, MD (study investigator); Siobhan O. Ortiz (coordinator); Thomas Bailey and Michele Woodward (visual acuity technicians); and Ken Ivey (photographer). *Lubbock, TX (Texas Retina Associates; n=4)*: Michel Shami, MD (study investigator); Yolanda Saldivar (coordinator); Ashaki Meeks (visual acuity technician); and Glenn R. Gardner and Ginger K. Rhymes (photographers). *Oklahoma City, OK (Dean A. McGee Eye Institute; n=4)*: Ronald M. Kingsley, MD, Robert E. Leonard, MD, and Vinay A. Shah, MD (study investigators); Alisha N. Brewer, BA, and Shannon R. Almeida (coordinators); Sonny Icks (coordinator and visual acuity technician); Amy L. Ford and Ashley Hughes (visual acuity technicians); and Markeisha Cheadle, Rachel Sohl, Russ Burris, and JoAnn T. Booth (photographers). *San Antonio, TX (Medical Center Ophthalmology Associates; n=4)*: Michael A. Singer, MD, and Darren J. Bell, MD (study investigators); Catherine Ellis, BS, and Rafael L. Wong (coordinators); Connie Bermea and Roxanne Gomez (visual acuity technicians); and Felicia Huron and Rosa Escobar (photographers). *Marietta, GA (Marietta Eye Clinic; n=3)*: Annal Dhanu Meleth, MD, MS, and Lakshmana Murthy Kooragayala, MD (study investigators); Chigozie Nkemka and Shakirah J. Sewell (coordinators); Minuette S. Jackson, BA (coordinator and visual acuity technician); Chenavia Lewis, MS (coordinator and photographer); and Adam Goff and Kenneth Thompson (photographers). *Overland Park, KS (Mid-America Retina Consultants PA; n=3)*: William N. Rosenthal, MD (study investigator); Sarah N. Lamaster, RN, BSN (coordinator and visual acuity technician); and R. Scott Varner and Mary C. Stewart, RN (photographers). *Shawnee Mission, KS (Retina Associates PA; n=3)*: Gregory M. Fox, MD, Ravi S. J. Singh, MD, Blake A. Cooper, MD, and Ivan R. Batlle, MD (study investigators); Lexie R. Ainley and Karla A. Batlle, BS (coordinators); Amber R. VandeVelde, RN, and Holly Wyrick (visual acuity technicians); and Katherine Pippin and Frank T. Yeager (photographers). *St Louis, MO (The Retina Institute; n=3)*: Kevin J. Blinder, MD, and Sabin Dang, MD (study investigators); Rhonda F. Weeks, Ginny S. Nobel, and Erika A. Hoehn, BS (coordinators); Kelly E. Pepple, Diana Reardon, Maria A. Stuart, Brook G. Pulliam, and Lynda K. Boyd (visual acuity technicians); and Steve A. Schremp, Timothy L. Wright, Dana L. Gabel, and Jarrod Wehmeier (photographers). *Sarasota, FL (Retina Associates of Sarasota; n=3)*: Elizabeth R. Richter, MD, PhD, and John H. Niffenegger, MD (study investigators); Arysol Niffenegger, MD (coordinator); Marianne Cottrill (coordinator and photographer); Donna Scully (visual acuity technician); and Marisol Lopez (photographer). *Chattanooga, TN (Southeastern Retina Associates; n=2)*: Richard I. Breazeale, MD, Rohan J. Shah, MD, Francis C. DeCroos, MD, and Devon Ghodasra, MD (study investigators); Steve W. McBee Jr (coordinator); Elizabeth Lisa McDonald (coordinator and photographer); Kate Menefee and Courtney Duncan (visual acuity technicians); and David Woods and Roger P. Melendrez (photographers). *Lakeland, FL (Florida Retina Consultants; n=2)*: Nader Moifar, MD, MPH, and Scott M. Friedman, MD (study investigators); Shannon M. Rehling (coordinator and visual acuity

technician); Ceara L. Wendel and Damanda F. Fagan (coordinators); Karen Seyez and Jacqueline Andrews (visual acuity technicians); and Brenda J. Bobbitt, Allen McKinney, and Shana E. Williams (photographers). *Monroeville, PA (Retina Vitreous Consultants; n=2)*: Karl R. Olsen, MD, Jared E. Knickebein, MD, PhD, and P. William Conrad, MD, PhD (study investigators); Lori A. Merlotti (coordinator); Lois Stepansky and Julie Walter (visual acuity technicians); and Dawn Diperna and Phyllis P. Ostroska (photographers). *Spokane, WA (Spokane Eye Clinic; n=2)*: Robert S. Wirthlin, MD, Andrew G. Cheek, MD, and Loren S. Jack, MD (study investigators); Eileen A. Dittman, RN (coordinator and visual acuity technician); and Jillian N. Erstad, Brian G. Skea, and Dylan C. Waidehlich (coordinators, photographers, and visual acuity technicians). *Tampa, FL (Retina Associates of Florida LLC; n=2)*: Ivan J. Suner, MD, and Marc C. Peden, MD (study investigators); Stephanie Munoz and Rochelle DenBoer, LPN (coordinators); Janet R. Traynom (coordinator and photographer); Susan Ramsey and Heidi Vargo (visual acuity technicians); and Anita Kim Malzahn and Lonie Bree Noel, LPN (photographers). *Ann Arbor, MI (Kellogg Eye Center, University of Michigan; n=1)*: Anjali R. Shah, MD, Thomas W. Gardner, MD, MS, and Grant M. Comer, MD, MS (study investigators); Pamela S. Campbell and Lindsay M. Godsey, MS (coordinators); and Laura A. Rozek, Laura B. Trebesh, and Timothy Sean Costello, BA (photographers). *Ayer, MA (Valley Eye Physicians and Surgeons; n=1)*: Gisela Velez, MD, MPH, MA (study investigator); Oksana Mykhaylyk, Elizabeth I. Johnson, MS, and Maa Ahema Parry, OD, MEd (coordinators); and Jhan Carlos Caro and Chandapilla C. Pallipeedikayil (photographers). *Baltimore, MD (Wilmer Eye Institute at Johns Hopkins; n=1)*: Sharon D. Solomon, MD (study investigator); Lisa K. Levin and Kemi Adeyemo (coordinators); Deborah Donohue (coordinator and visual acuity technician); Mary Frey, BSc, and Brandon S. Gardner (visual acuity technicians); and Dennis Cain, David Emmert, BA, Jacquelyn McDonald, Russ Distle, and Nick Rhoton, AA (photographers). *Boston, MA (Joslin Diabetes Center; n=1)*: Jennifer K. Sun, MD, MPH (study investigator); Tor Ekstrom (coordinator); Margaret E. Stockman and Emily Degan (coordinators and visual acuity technicians); Mina Sehzadeh, OD, and Jerry D. Cavallerano, OD, PhD (visual acuity technicians); and Kylie M. Madigan (photographer). *Chicago, IL (Northwestern Medical Faculty Foundation; n=1)*: Alice T. Lyon, MD, and Rukhsana G. Mirza (study investigators); Evan C. Davies, Priya M. Thakkar, BS, and Nicole M. Seddon (coordinators); Carmen Ramirez (coordinator and visual acuity technician); Julie Pecht and Anson Moore (visual acuity technicians); and Cason Moore, Maritza Barragan, and Evica Simjanoski, BFA (photographers). *Cleveland, OH (University Hospitals Cleveland Medical Center; n=1)*: Shree K. Kurup, MD, Georgios Trichonas, MD, and Yu Hyon Kim, MD (study investigators); Tatiana M. Riedel, BA, Jasmeen K. Randhawa, and Sangeetha P. Raghupathy, BS (coordinators); Peggy Allchin, Margaret N. Petrosky, and Claudia Clow (visual acuity technicians); and Ahmad Al Moshmoh, Geraldo R. Miranda, Ashley Y. Howard, and Irit Baum-Rawraway (photographers). *Knoxville, TN (Southeastern Retina Associates PC; n=1)*: Joseph M. Googe, MD, R. Keith Shuler, MD, and Nicholas G. Anderson, MD (study investigators); Kristina Oliver and Steve Morris (coordinators); Julie Asher

(coordinator and visual acuity technician); Jeff Wheeler (visual acuity technician); and Justin Walsh, Sarah M. Oelrich, Raul E. Lince, and Hodge A. Griffone (photographers). *Milwaukee, WI (Medical College of Wisconsin; n=1)*: Judy E. Kim, MD, and Thomas B. Connor, MD (study investigators); Eleanor Dorsey, BS (coordinator); Shay Bourgeois (coordinator and visual acuity technician); Amber N. Roberts and Vicki Barwick, BS (visual acuity technicians); and Brittany Rego and Hannah Sheppard (photographers). *Minneapolis, MN (Retina Center PA; n=1)*: Abdhish R. Bhavsar, MD (study investigator); Andrea Gilchrist (coordinator); Celeste Moreno (coordinator and photographer); Matt D. Peloquin, AA, and Jason R. Sweet (visual acuity technicians); and Alanna C. Evans and Erin C. Kinney (photographers). *New York, NY (New York Eye and Ear Infirmary/Faculty Eye Practice; n=1)*: Meenakashi Gupta, MD, and Ronald C. Gentile, MD (study investigators); and Melissa Rivas and John Bo Soo Choi (coordinators and visual acuity technicians). *Sandy Springs, GA (Thomas Eye Group; n=1)*: Paul L. Kaufman, MD (study investigator); Kathy T. Wynne, BS (coordinator and visual acuity technician); Cynthia Weaver (visual acuity technician); and Sarah Matloff (photographer). *Urbana, IL (Carle Foundation Hospital; n=1)*: Michael S. Tsipursky, MD (study investigator); Sarah Berlatsky and Elida Iniguez (coordinators); Alexandra Y. Almasov (coordinator and visual acuity technician); Daniel A. Nielsen, OD, and Tina M. Gore (visual acuity technicians); and Zach Dupureur (photographer).

**Data Sharing Statement:** See Supplement 4.

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