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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

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IMPORTANCE Intravitreous injections of antivascular endothelial growth factor agents are effective for treating diabetic macular edema (DME) involving the center of the macula (center-involved DME [CI-DME]) with visual acuity impairment (20/32 or worse). The best approach to treating patients with CI-DME and good visual acuity (20/25 or better) is unknown.

OBJECTIVE To compare vision loss at 2 years among eyes initially managed with aflibercept, laser photocoagulation, or observation.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 91 US and Canadian sites among 702 adults with type 1 or type 2 diabetes. Participants had 1 study eye with CI-DME and visual acuity of 20/25 or better. The first participant was randomized on November 8, 2013, and the final date of follow-up was September 11, 2018.

INTERVENTIONS Eyes were randomly assigned to 2.0 mg of intravitreous aflibercept (n = 226) as frequently as every 4 weeks, focal/grid laser photocoagulation (n = 240), or observation (n = 236). Aflibercept was required for eyes in the laser photocoagulation or observation groups that had decreased visual acuity from baseline by at least 10 letters (≥ 2 lines on an eye chart) at any visit or by 5 to 9 letters (1-2 lines) at 2 consecutive visits.

MAIN OUTCOMES AND MEASURES The primary outcome was at least a 5-letter visual acuity decrease from baseline at 2 years. Antiplatelet Trialists' Collaboration adverse events (defined as myocardial infarction, stroke, or vascular or unknown death) were reported.

RESULTS Among 702 randomized participants (mean age, 59 years; 38% female [n=264]), 625 of 681 (92% excluding deaths) completed the 2-year visit. For eyes with visual acuity that decreased from baseline, aflibercept was initiated in 25% (60/240) and 34% (80/236) in the laser photocoagulation and observation groups, respectively. At 2 years, the percentage of eyes with at least a 5-letter visual acuity decrease was 16% (33/205), 17% (36/212), and 19% (39/208) in the aflibercept, laser photocoagulation, and observation groups, respectively (aflibercept vs laser photocoagulation risk difference, −2% [95% CI, −9% to 5%]; relative risk, 0.88 [95% CI, 0.57-1.35; *P* = .79]; aflibercept vs observation risk difference, −3% [95% CI, −11% to 4%]; relative risk, 0.83 [95% CI, 0.55-1.27; *P* = .79]; laser photocoagulation vs observation risk difference, −1% [95% CI, −9% to 6%]; relative risk, 0.95 [95% CI, 0.64-1.41; *P* = .79]). Antiplatelet Trialists' Collaboration vascular events occurred in 15 (7%), 13 (5%), and 8 (3%) participants in the aflibercept, laser photocoagulation, and observation groups.

CONCLUSIONS AND RELEVANCE Among eyes with CI-DME and good visual acuity, there was no significant difference in vision loss at 2 years whether eyes were initially managed with aflibercept or with laser photocoagulation or observation and given aflibercept only if visual acuity worsened. Observation without treatment unless visual acuity worsens may be a reasonable strategy for CI-DME.

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Diabetic macular edema (DME) involving the center of the macula is a major cause of visual acuity loss worldwide.[1] From 1985 to 2010, laser photocoagulation was the standard of care for treating center-involved DME (CI-DME).[2-4] Beginning in 2010, several large trials demonstrated that injections of antivascular endothelial growth factor (anti-VEGF) agents into the vitreous of the eye (intravitreous injections) were superior to laser photocoagulation in eyes with CI-DME and visual acuity of 20/32 or worse.[3-7] Since then, treatment of CI-DME with reduced visual acuity has largely transitioned from laser photocoagulation to intravitreous anti-VEGF injections, where available.[8]

The presence of good vision in an eye with CI-DME is a common clinical scenario. In a population-based study in the United States, among persons with DME, 84% had best corrected vision of 20/40 or better in the eye with DME.[9] In the Early Treatment Diabetic Retinopathy Study (ETDRS), approximately 40% of eyes with DME had visual acuity of 20/20 or better.[10] The optimal management strategy for these eyes is unknown. Clinicians frequently initiate DME treatment with anti-VEGF agents in eyes with good vision based on positive results from clinical trials that evaluated anti-VEGF in eyes with reduced visual acuity (20/32 or worse).[4,11,12] However, up to 60% of eyes with CI-DME that are left untreated do not experience moderate visual decline (≥3 lines on an eye chart) over 5 years.[13]

It is unknown if intravitreous anti-VEGF treatment of eyes with CI-DME and good visual acuity results in better long-term visual acuity outcomes vs initial observation or laser photocoagulation followed by anti-VEGF therapy only if visual acuity worsens. Therefore, the Diabetic Retinopathy Clinical Research (DRCR) Retina Network conducted a randomized clinical trial ("Protocol V") to compare visual acuity between 3 different management strategies for eyes with good visual acuity and CI-DME.

Key Points

Question For patients with eyes having diabetic macular edema involving the macular center and vision 20/25 or better, what is the effect on vision loss of initial management with aflibercept vs laser photocoagulation vs observation, with aflibercept added to laser photocoagulation and observation if vision worsens?

Findings In this randomized clinical trial of 702 eyes, a 5-letter or more decrease in visual acuity at 2 years was not significantly different between groups initially managed with aflibercept (16%), laser photocoagulation (17%), and observation (19%).

Meaning Among eyes with diabetic macular edema involving the macular center and good visual acuity, there was no significant difference in vision loss at 2 years whether eyes were initially managed with aflibercept, laser photocoagulation, or observation.

Methods

This multicenter trial was conducted at 91 clinical sites in the United States and Canada. The study adhered to the tenets of the Declaration of Helsinki.[14] 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 and statistical analysis plan are available in Supplement 1 and Supplement 2.

Study Population

Participants were at least 18 years old with type 1 or 2 diabetes (eTable 1 in Supplement 3). Participant-reported race/ethnicity was collected per National Institutes of Health policy and consistent with recent US Food and Drug Administration guidelines based on fixed categories.[15,16] Study eyes had CI-DME involving the center of the macula on ophthalmoscopic examination and confirmed on optical coherence tomography (OCT) as central subfield thickening at 2 consecutive visits 1 to 28 days apart (screening and randomization). Best-corrected electronic ETDRS visual acuity letter score was at least 79 (Snellen equivalent of 20/25 or better) at screening and randomization. Eyes receiving laser photocoagulation or intravitreous treatment for DME in the past 12 months or more than 1 laser photocoagulation or 4 intraocular injections at any time were excluded. Only 1 eye per participant was included. If both eyes were eligible, the investigator and participant selected the eye to be enrolled.

Study Design

Randomization was performed on the study website using a permuted block design (random block sizes of 3 and 6) stratified by site and recent or planned CI-DME treatment in the nonstudy eye using computer-generated random numbers. Study eyes were randomly assigned 1:1:1 to 2.0 mg of aflibercept, focal/grid laser photocoagulation, or observation. In the laser photocoagulation and observation groups, aflibercept injections were initiated during follow-up if visual acuity met prespecified worsening criteria (see below).

Certified technicians obtained visual acuity with refraction and OCT scans at each visit and fundus photographs annually. Technicians were masked to treatment assignment at annual visits. Investigators and participants were not masked. Spectral-domain OCT values were converted to time-domain (Zeiss Stratus) equivalents for reporting (≥250 µm is considered CI-DME on time-domain OCT).[17]

Treatment Protocol

Eyes in the aflibercept group received an injection at baseline and were evaluated for repeat injections up to every 4 weeks as needed (eFigure 1 in Supplement 3). Eyes continued to receive injections if visual acuity or OCT central subfield thickness (CST) was improving or worsening (defined as ≥5-letter visual acuity or ≥10% CST change) from either of the last two 4-week visits. Injections were deferred if the eye met sustained stability criteria by not improving or worsening over 2 visits and either (1) CST was below the screening visit threshold and visual acuity was 20/20 or better or (2) at least 24 weeks had passed since injections were initiated. If deferral occurred at 3 consecutive visits after 24 weeks, the follow-up interval was extended to 8 weeks and then 16 weeks provided that deferral

criteria were still met. Injections were resumed if visual acuity or CST worsened. After 24 weeks, laser photocoagulation could be added at the discretion of the investigator if CST was above the screening visit threshold or there was edema threatening the fovea and visual acuity and CST had not improved from the last 2 injections (eFigure 2 in Supplement 3).

No treatment was given to eyes in the observation group initially. Eyes in the laser photocoagulation group received laser photocoagulation treatment at baseline, with retreatment at 13-week intervals if indicated (eFigure 3 in Supplement 3). In the laser photocoagulation and observation groups, follow-up occurred at 8 and 16 weeks and then every 16 weeks unless visual acuity or CST worsened. Aflibercept injections were initiated for eyes in the laser photocoagulation and observation groups if visual acuity decreased from baseline by at least 10 letters (≥2 lines on an eye chart) at any visit or by 5 to 9 letters (1-2 lines) at 2 consecutive visits. Retreatment followed the same regimen as the aflibercept group.

Outcomes

The primary outcome was a decrease from baseline of at least 5 letters of visual acuity (at least 1 line on an eye chart) at 2 years. Baseline visual acuity (and CST) were the average of the screening and randomization measurements. A loss of at least 5 letters was considered a clinically important change for eyes with good visual acuity. Visual acuity is measured on a scale from 100 letters (Snellen equivalent of 20/12) to 0 letters (Snellen equivalent of <20/800).

Prespecified secondary outcomes included mean change in visual acuity from baseline, visual acuity of at least 84 letters (Snellen equivalent of 20/20), loss of at least 10 and at least 15 letters of visual acuity, gain of at least 5 letters of visual acuity, mean change in CST from baseline, proportion of eyes with at least 10% CST change from baseline (considered a clinically important change), proportion of eyes with at least a 10% decrease in CST from baseline with CST below thresholds for DME defined by central subfield thickness according to OCT machine and sex (Heidelberg Spectralis ≥305 µm in women and ≥320 µm in men; Zeiss Cirrus ≥290 µm in women and ≥305 µm in men), 1 and 2 log-step worsening and improvement in CST, and mean change in OCT retinal volume from baseline.

Prespecified exploratory outcomes included change in visual acuity over 2 years (area under the curve analysis of common visits at 8, 52, and 104 weeks), at least 2-step worsening and improvement in diabetic retinopathy severity level on color fundus photographs graded by a central reading center.[18] Change in low-contrast visual acuity, an additional prespecified secondary outcome, and the proportion of eyes with leakage on fluorescein angiography, a prespecified exploratory outcome, as well as development of vitreous hemorrhage or receipt of panretinal photocoagulation, anti-VEGF for proliferative diabetic retinopathy (PDR), or vitrectomy for PDR (among eyes with PDR at randomization) are not reported herein.

Receipt of aflibercept in the laser photocoagulation and observation groups were prespecified within-group outcomes. The time to receipt of first aflibercept injection in the laser photocoagulation and observation groups was evaluated post hoc. A medical monitor reviewed all reported adverse events and coded the events according to the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical Analysis

Sample size was set at 702 eyes, which provided 93% power to reject any of 3 pairwise comparisons assuming 10% loss to follow-up and outcome rates of 5% for aflibercept, 10% for laser photocoagulation, and 17% for observation. The laser photocoagulation and observation rates were based on publicly available data from the ETDRS, specifically eyes with DME and visual acuity of 20/25 or better at baseline, and adjusted to be lower based on clinical judgment to account for anti-VEGF treatment not being available during the ETDRS. The aflibercept rate was based on publicly available data (https://public.jaeb.org/drcrnet/stdy) from DRCR Retina Network Protocol I eyes that had DME, had visual acuity of 20/32 at baseline, and were randomly assigned to anti-VEGF injections.

For the primary, secondary, and exploratory analyses, all randomized eyes were included in statistical analyses and analyzed according to their randomization group. Point estimates are reported using observed data. For statistical analyses, missing visual acuity and CST values were imputed using the Markov chain Monte Carlo method (100 imputations). Sensitivity analyses were conducted using only observed data from participants completing the 2-year visit (ie, complete case analysis), adjusting for potential confounding factors and clinical site. Subgroup analyses were conducted by testing a treatment × subgroup factor interaction using observed data.[19] Baseline CST, diabetic retinopathy severity, and presence of epiretinal membrane were prespecified subgroup factors.

To limit the influence of potential outliers, changes in visual acuity and CST from baseline were truncated at ±3 SDs. Continuous outcomes were analyzed using a general linear model; binary outcomes were analyzed with Poisson regression with a log link (estimating relative risk [RR]) and binomial regression with an identity link (estimating risk difference); time-to-event outcomes were analyzed with Cox proportional hazards regression (the proportional hazards assumption was verified using Martingale residuals).[20] If the binomial regression model did not converge, then the continuous baseline covariate (eg, visual acuity) was excluded and the model was rerun to achieve convergence. Confidence intervals and *P* values were calculated with robust variance estimation. Analyses included adjustment for recent or planned CI-DME treatment in the nonstudy eye and baseline visual acuity, CST, or diabetic retinopathy severity, per the outcome. The family-wise type I error rate for treatment group comparisons was controlled at 5% with the Hochberg procedure.[21,22]

For adverse event analyses, Fisher exact test compared all 3 groups simultaneously and included all randomized participants. If the global test had $P \leq .05$, pairwise comparisons were conducted. Note that the study was not powered to detect differences in rates of adverse events.

All *P* values are 2-sided. Analyses were completed using SAS version 9.4 (SAS Institute Inc). Because of the potential for type I error due to multiple comparisons, analyses of secondary outcomes and adverse events should be interpreted as exploratory.

Results

Study Participants

From November 8, 2013, to September 26, 2016, 702 participants were randomly assigned to initial management with aflibercept (n=226), laser photocoagulation (n=240), or observation (n=236) (**Table 1** and **Figure 1**). Follow-up concluded when the final 2-year visit was completed on September 11, 2018. Mean age was 59 (SD, 10) years, 264 (38%) were female, and 466 (66%) were white. Mean baseline visual acuity letter score was 85.2 (SD, 3.7) (Snellen equivalent of 20/20); mean CST was 311 (SD, 57) µm. Baseline characteristics appeared similar among groups. Excluding deaths, the 2-year completion rate was 92% (625/681). The median number of visits over 2 years was 18, 11, and 12 in the aflibercept, laser photocoagulation, and observation groups, respectively.

Treatment of Diabetic Macular Edema

In the aflibercept group, 225 of 226 eyes received at least 1 intravitreous aflibercept injection. The median number of aflibercept injections over 2 years was 8 (interquartile range, 6-11), with 98% of protocol-required injections performed. Laser photocoagulation was performed in 13 (6%) aflibercept-group eyes (eTable 2 in Supplement 3).

Aflibercept was initiated in 25% (60/240) and 34% (80/236) of eyes in the laser photocoagulation and observation groups, respectively. Using the Kaplan-Meier method to account for participants lost to follow-up, the cumulative probability of receiving aflibercept by 2 years was 26% (95% CI, 21%-33%) in the laser photocoagulation group and 36% (95% CI, 30%-43%) in the observation group (post hoc analysis: hazard ratio, 0.66; 95% CI, 0.47-0.92; $P = .01$) (**Figure 2**). Among eyes receiving at least 1 injection, the median number of injections over 2 years was 7 (interquartile range, 5-9) in the laser photocoagulation group and 9 (interquartile range, 6-11) in the observation group. In the laser photocoagulation and observation groups, 4 (2%) and 2 (<1%) eyes initiated aflibercept without meeting prespecified criteria for visual acuity loss, respectively. Overall, 98% of protocol-required injections were performed in each group. In the laser photocoagulation group, 77 (32%) eyes received additional laser photocoagulation during follow-up; in the observation group, 5 (2%) eyes received laser photocoagulation.

Effect of Treatment on Visual Acuity

The percentage of eyes with at least a 5-letter visual acuity decrease at 2 years (primary outcome) was 16% with aflibercept, 17% with laser photocoagulation, and 19% with observation (aflibercept vs laser photocoagulation risk difference, −2% [95% CI −9% to 5%]; RR, 0.88 [95% CI, 0.57-1.35; $P = .79$]; aflibercept vs observation risk difference, −3% [95% CI, −11% to 4%]; RR, 0.83 [95% CI, 0.55-1.27; $P = .79$]; laser photocoagulation vs observation risk difference, −1% [95% CI, −9% to 6%]; RR, 0.95 [95% CI, 0.64-1.41; $P = .79$]) (**Table 2** and eFigure 4 in Supplement 3). Sensitivity analyses produced similar results (eTable 3 in Supplement 3). None of the preplanned subgroup analyses (baseline CST, diabetic retinopathy severity, and presence of central epiretinal membrane or vitreomacular traction) indicated a significant subgroup effect (eTable 4 in Supplement 3).

Mean change in visual acuity letter score from baseline at 2 years (secondary outcome) was 0.9 (SD, 6.4) with aflibercept, 0.1 (SD, 6.3) with laser photocoagulation, and −0.4 (SD, 6.4) with observation (aflibercept vs laser photocoagulation mean difference, 1.0 [95% CI, −0.4 to 2.5; $P = .21$]; aflibercept vs observation mean difference, 1.3 [95% CI, −0.3 to 2.8; $P = .14$]; laser photocoagulation vs observation mean difference, 0.2 [95% CI, −1.0 to 1.5; $P = .70$]) (eFigure 5 in Supplement 3). At 1 and 2 years, the mean visual acuity Snellen equivalent was 20/20 in each group (**Figure 3**A). The percentage of eyes with visual acuity of 20/20 or better at 2 years (secondary outcome) was 77% with aflibercept, 71% with laser photocoagulation, and 66% with observation (aflibercept vs laser photocoagulation RR, 1.11 [95% CI, 0.97-1.27; $P = .15$]; aflibercept vs observation RR, 1.18 [95% CI, 1.01-1.37; $P = .03$]; laser photocoagulation vs observation RR, 1.06 [95% CI, 0.93-1.20; $P = .40$]).

In a prespecified, exploratory, longitudinal analysis, the mean change in visual acuity letter score over 2 years (area under the curve) was 1.5 (SD, 4.0) with aflibercept, 0.0 (SD, 3.9) with laser photocoagulation, and −0.4 (SD, 4.2) with observation (aflibercept vs laser photocoagulation mean difference, 1.9 [95% CI, 1.0-2.8; $P < .001$]; aflibercept vs observation mean difference, 2.1 [95% CI, 1.1-3.1; $P < .001$]; laser photocoagulation vs observation mean difference, 0.2 [95% CI, −0.7 to 1.0; $P = .73$]) (eFigure 6 in Supplement 3). eTable 5 in Supplement 3 shows 1-year visual acuity outcomes.

Effect of Treatment on Retinal Thickening

Mean change in CST from baseline at 2 years (secondary outcome) was −48 (SD, 65) µm, −41 (SD, 75) µm, and −42 (SD, 75) µm in the aflibercept, laser photocoagulation, and observation groups, respectively (aflibercept vs laser photocoagulation mean difference, −12 µm [95% CI, −24 to 1 µm; $P = .07$]; aflibercept vs observation mean difference, −13 µm [95% CI, −27 to 1 µm; $P = .07$]; laser photocoagulation vs observation mean difference, −1 µm [95% CI, −13 to 11 µm; $P = .82$]) (Figure 3B and Table 2). eTable 6 in Supplement 3 shows additional outcomes at 1 and 2 years.

Effect of Treatment on Diabetic Retinopathy

At 2 years, the percentage of eyes with at least 2-step improvement of diabetic retinopathy severity level on color photographs (exploratory outcome) was 14%, 12%, and 10% in the aflibercept, laser photocoagulation, and observation groups, respectively (aflibercept vs laser photocoagulation RR, 0.90 [95% CI, 0.52-1.54; $P = .69$]; aflibercept vs observation RR, 1.16 [95% CI, 0.65-2.07; $P = .69$]; laser photocoagulation vs observation RR, 1.29 [95% CI, 0.75-2.24; $P = .69$]). At 2 years, the percentage of eyes with at least 2-step worsening (exploratory outcome) was 4%, 10%, and 11%, respectively (aflibercept vs laser photocoagulation RR, 0.39 [95% CI, 0.15-1.04; $P = .06$]; aflibercept vs observation RR, 0.36 [95% CI, 0.13-0.99; $P = .05$]; laser photocoagulation vs observation RR, 0.90 [95% CI, 0.49-1.65; $P = .74$]). eTable 7 in Supplement 3 shows outcomes at 1 year.

Table 1. Baseline Participant and Ocular Characteristics

Characteristics	No. (%) of Participants[a]		
	Aflibercept (n = 226)	Laser Photocoagulation (n = 240)	Observation (n = 236)
Sex			
Male	131 (58)	158 (66)	149 (63)
Female	95 (42)	82 (34)	87 (37)
Age, median (IQR), y	59 (52-65)	60 (53-66)	60 (53-67)
Race/ethnicity			
Non-Hispanic white	145 (64)	160 (67)	161 (68)
Non-Hispanic black/ African American	37 (16)	36 (15)	41 (17)
Hispanic or Latino	31 (14)	35 (15)	25 (11)
Asian	6 (3)	1 (<1)	5 (2)
American Indian or Alaskan Native	1 (<1)	1 (<1)	0
Native Hawaiian or other Pacific Islander	0	3 (1)	1 (<1)
≥1 Race	4 (2)	2 (<1)	1 (<1)
Unknown or not reported	2 (<1)	2 (<1)	2 (<1)
Diabetes type			
Type 2	211 (93)	221 (92)	210 (89)
Type 1	13 (6)	18 (8)	18 (8)
Uncertain	2 (<1)	1 (<1)	8 (3)
Duration of diabetes, median (IQR), y	15 (10-21)	15 (10-20)	16 (10-24)
Insulin used	141 (62)	145 (60)	160 (68)
Hemoglobin A_{1c}, median (IQR), %	7.6 (6.8-9.1) [n=217]	7.6 (6.6-8.6) [n=232]	7.6 (6.8-8.7) [n=226]
Arterial blood pressure, median (IQR), mm Hg	99 (91-107)	98 (89-105)	98 (91-105)
Prior myocardial infarction	11 (5)	21 (9)	19 (8)
Prior stroke	16 (7)	6 (3)	9 (4)
Body mass index, median (IQR)[b]	32.3 (27.6-37.0) [n=184]	32.1 (28.2-37.4) [n=207]	32.3 (28.0-37.5) [n=199]
Daily cigarette smoking			
Never	165 (73)	157 (65)	141 (60)
Prior	46 (20)	67 (28)	75 (32)
Current	15 (7)	16 (7)	20 (8)
Recent or planned DME treatment in nonstudy eye (randomization stratification factor)	86 (38)	90 (38)	92 (39)
Study Eye Ocular Characteristics			
Prior treatment for DME	34 (15)	31 (13)	34 (14)
Prior anti-VEGF therapy for DME	11 (5)	14 (6)	13 (6)
Prior focal/grid laser photocoagulation for DME	26 (12)	24 (10)	24 (10)
Prior panretinal photocoagulation	15 (7)	12 (5)	9 (4)
Lens status at clinical examination			
Phakic (natural lens)	180 (80)	188 (78)	182 (77)
Prosthetic intraocular lens	46 (20)	52 (22)	54 (23)
Visual acuity[c,d]			
Letter score, mean (SD)	85.2 (3.5)	85.2 (3.8)	85.2 (3.8)
Snellen equivalent, mean	20/20	20/20	20/20
20/16 or better (≥89)	45 (20)	57 (24)	53 (22)
20/20 (88-84)	105 (46)	92 (38)	99 (42)
20/25 (83-79)	76 (34)	91 (38)	84 (36)

(continued)

Table 1. Baseline Participant and Ocular Characteristics (continued)

Characteristics	No. (%) of Participants[a] Aflibercept (n = 226)	Laser Photocoagulation (n = 240)	Observation (n = 236)
Intraocular pressure, median (IQR), mm Hg	15 (13-18)	15 (13-18)	15 (13-18)
Patient-reported visual problems presumed due to DME	99 (44)	116 (48)	118 (50)
Optical coherence tomography machine			
Heidelberg Spectralis	148 (65)	151 (63)	151 (64)
Zeiss Cirrus	78 (35)	89 (37)	85 (36)
Central subfield thickness (time-domain equivalent), μm[c]			
Mean (SD)	306 (55)	314 (52)	314 (64)
<250	13 (6)	8 (3)	14 (6)
250-300	117 (52)	109 (45)	111 (47)
301-399	75 (33)	104 (43)	89 (38)
400-499	19 (8)	15 (6)	17 (7)
≥500	2 (<1)	4 (2)	5 (2)
Macular volume (time-domain equivalent), mean (SD), mm^3[c]	7.9 (1.1) [n=226]	8.0 (1.2) [n=240]	8.0 (1.1) [n=235]
Diabetic retinopathy severity[e]	n=216	n=227	n=229
Absent or questionable (levels 10, 12, 14, 15)	2 (<1)	4 (2)	1 (<1)
Microaneurysms only (level 20)	13 (6)	8 (4)	6 (3)
Mild to moderate NPDR (levels 35, 43)	119 (55)	132 (58)	142 (62)
Moderately severe to severe NPDR (levels 47, 53)	58 (27)	64 (28)	62 (27)
Inactive PDR (level 60)	6 (3)	7 (3)	7 (3)
Mild to moderate PDR (levels 61, 65)	14 (6)	12 (5)	9 (4)
High-risk PDR (levels 71, 75)	4 (2)	0	2 (<1)

Abbreviations: DME, diabetic macular edema; IQR, interquartile range; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.

[a] Data are expressed as No. (%) unless otherwise indicated.

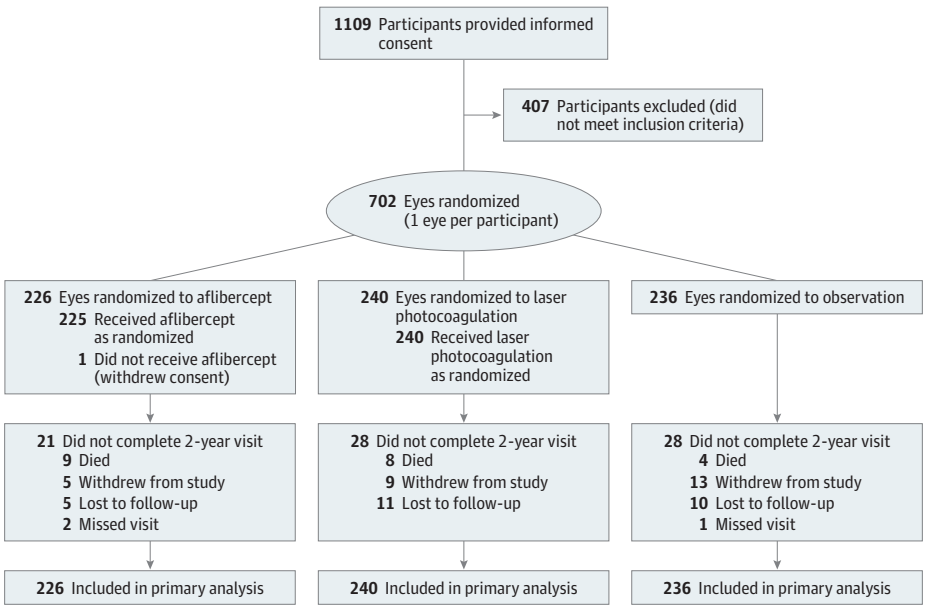
[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Average of screening and randomization values.

[d] Best-corrected visual acuity following protocol-defined refraction. Visual acuity was measured with the electronic Early Treatment Study visual acuity test on a scale from 100 letters (Snellen equivalent of 20/12) to 0 letters (Snellen equivalent of <20/800).

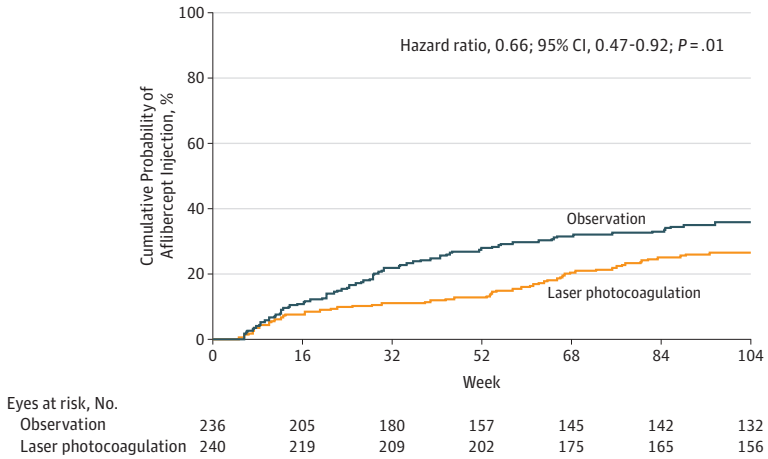
[e] Graded at a central reading center. Levels are based on Early Treatment Diabetic Retinopathy Study definitions.[23]

Figure 1. Participant Flow From Screening to Final 2-Year Visit



Participants were not formally screened before obtaining informed consent. Reasons for participant ineligibility were not collected. Visit completion at 2 years was prespecified as completion of any study visit from 92 to 116 weeks. Deaths exclude 1 participant from each group who completed a visit in this window but died before completing the designated 2-year study visit. For eyes not completing the 2-year visit, multiple imputation was used to impute missing data in the primary analysis. There were 77 eyes that had values imputed: 21 in the aflibercept group; 28 in the laser photocoagulation group; and 28 in the observation group.

Figure 2. Time to First Aflibercept Injection in the Laser Photocoagulation and Observation Groups



Eyes at risk, No.							
Observation	236	205	180	157	145	142	132
Laser photocoagulation	240	219	209	202	175	165	156

Post hoc analysis of prespecified within-group outcomes. Hazard ratio and *P* value are from Cox proportional hazards regression with robust variance estimation and adjustment for recent or planned diabetic macular edema treatment in the nonstudy eye. The median follow-up time was 719 (interquartile range, 703-736) days and 721 (interquartile range, 707-735) days in the laser photocoagulation and observation groups, respectively.

Adverse Events

There were no cases of endophthalmitis in study or nonstudy eyes among 4872 injections (eTable 8 in Supplement 3). Intraocular pressure elevation was reported more frequently with aflibercept (8%) than observation (3%) but not laser photocoagulation (6%) (global *P* = .02). The rate of any Antiplatelet Trialists' Collaboration adverse event (defined as myocardial infarction, stroke, or vascular or unknown death) was not significantly different among the treatment groups (7% with aflibercept, 5% with laser photocoagulation, and 3% with observation; *P* = .28), nor were the frequencies of at least 1 serious adverse event (28%, 32%, and 29%, respectively; *P* = .66) and hospitalization (24%, 30%, and 27%, respectively; *P* = .45). The frequency of all-cause mortality was 4% with aflibercept, 4% with laser photocoagulation, and 2% with observation (*P* = .37). eTables 9, 10, and 11 in Supplement 3 provide all systemic, ocular, and nonstudy eye ocular (after the first study-provided aflibercept injection) adverse events.

Discussion

In this randomized clinical trial of patients with eyes having CI-DME and good visual acuity, rates of visual acuity loss of 5 or more ETDRS letters at 2 years were not significantly different among eyes initially managed with intravitreous aflibercept, laser photocoagulation, or observation, with eyes in the laser photocoagulation and observation groups receiving aflibercept only if visual acuity worsened.

All 3 management strategies resulted in mean vision of 20/20 and mean changes in visual acuity and CST that were not significantly different at 2 years. The proportion of eyes with visual acuity of 20/20 or better was significantly greater with aflibercept than observation but not laser photocoagulation (1 of 5 secondary visual acuity outcomes at 2 years and the only significant difference). The approximately 2-letter differences in mean visual acuity change over the course of 2 years (area under the curve) in the aflibercept vs the laser photocoagulation and observation groups are of questionable clinical relevance because these differences occurred within a range that constitutes a mean visual acuity of 20/20. The majority of eyes in the laser photocoagulation group (75%) and observation group (66%) did not receive aflibercept during 2 years of follow-up. No systemic adverse event concerns were identified.

To our knowledge, this is the first large, randomized trial since the US Food and Drug Administration approved anti-VEGF injections for intravitreous use that was designed to evaluate management strategies for CI-DME in eyes with good visual acuity, which is a commonly encountered clinical scenario.[9] Despite a lack of supporting evidence, many clinicians initiate anti-VEGF treatment in eyes with CI-DME, even when visual acuity is only minimally affected or unaffected because of concern that visual outcomes will be worse if anti-VEGF therapy is deferred. On the contrary, results from this protocol demonstrate that mean visual acuity in eyes with CI-DME and good vision remains 20/20 at 2 years with all 3 management strategies.

Approximately two-thirds to three-fourths of the eyes in the observation and laser photocoagulation groups never received aflibercept. Each aflibercept injection has an average Medicare cost of $1850, and all intravitreal injections carry a small risk of endophthalmitis (<0.1%).[24] Thus, reducing anti-VEGF treatment in these eyes while maintaining good vision has clinical and economic advantages for patients and public health.

This study did not compare monotherapy with aflibercept, laser photocoagulation, or observation alone. Instead, it compared 3 different strategies for managing eyes with CI-DME and good vision. Eyes were followed up carefully, and aflibercept was initiated in the laser photocoagulation and observation groups if vision decreased by 1 line of visual acuity at 2 consecutive visits or by 2 or more lines at 1 visit. Of note, an increase in CST alone (ie, worsening edema) did not trigger anti-VEGF initiation in the laser photocoagulation or observation groups. The primary outcome was loss of at least 5 letters (1 line) on an eye chart. This outcome can be clinically relevant in eyes with good vision and is unlikely due to chance

Table 2. Efficacy Outcomes at 2 Years

Outcomes	Observed Data			Adjusted Treatment Group Comparisons[a]					
				Relative Risk or Mean Difference (95% CI)			Risk Difference (95% CI)		
	Initiation With Aflibercept (n=205)	Initiation With Laser Photocoagulation (n=212)	Initiation With Observation (n=208)	Aflibercept vs Laser	Aflibercept vs Observation	Laser vs Observation	Aflibercept vs Laser	Aflibercept vs Observation	Laser vs Observation
Primary Outcome									
≥5-Letter visual acuity decrease, No. (%)	33 (16)	36 (17)	39 (19)	0.88 (0.57 to 1.35)	0.83 (0.55 to 1.27)	0.95 (0.64 to 1.41)	−2 (−9 to 5)	−3 (−11 to 4)	−1 (−9 to 6)
P value				.79	.79	.79	.77	.77	.77
Prespecified Secondary Outcomes									
Baseline visual acuity									
Letter score, mean (SD)[b]	85.2 (3.5)	85.4 (3.7)	85.2 (3.8)						
Snellen equivalent, mean	20/20	20/20	20/20						
Letter score, median (IQR)	85.0 (87.0 to 83.0)	85.0 (88.0 to 82.0)	85.0 (87.0 to 82.0)						
Snellen equivalent, median	20/20	20/20	20/20						
Change from baseline, mean (SD)	0.9 (6.4)	0.1 (6.3)	−0.4 (6.4)	1.0 (−0.4 to 2.5)[c]	1.3 (−0.3 to 2.8)[c]	0.2 (−1.0 to 1.5)[c]			
P value				.21	.14	.70			
Change from baseline, median (IQR)	2.0 (−1.0 to 5.0)	1.0 (−2.0 to 4.5)	0.5 (−3.0 to 4.0)						
≥5-Letter increase, No. (%)	55 (27)	53 (25)	43 (21)	1.13 (0.82 to 1.55)	1.30 (0.86 to 1.98)	1.15 (0.81 to 1.64)	3 (−6 to 11)	6 (−4 to 16)	3 (−5 to 11)
P value				.46	.40	.46	.54	.46	.54
≥10-Letter decrease, No. (%)	18 (9)	14 (7)	14 (7)	1.13 (0.59 to 2.17)	1.21 (0.62 to 2.36)	1.08 (0.54 to 2.13)	1 (−4 to 6)	2 (−3 to 7)	1 (−4 to 6)
P value				.83	.83	.83	.79	.79	.79
≥15-Letter decrease, No. (%)	5 (2)	8 (4)	8 (4)	0.55 (0.19 to 1.62)	0.63 (0.21 to 1.88)	1.13 (0.45 to 2.86)	−2 (−6 to 2)	−1 (−5 to 2)	0 (−3 to 4)
P value				.79	.79	.79	.71	.71	.79
Visual acuity at 2 years									
Letter score, mean (SD)	86.0 (7.4)	85.3 (7.4)	84.2 (10.1)						
Snellen equivalent, mean	20/20	20/20	20/20						
Letter score, median (IQR)	87.0 (90.0 to 84.0)	87.0 (90.0 to 82.0)	86.0 (89.0 to 81.0)						
Snellen equivalent, median	20/20	20/20	20/20						
20/20 or better (≥84)	158 (77)	151 (71)	137 (66)	1.11 (0.97 to 1.27)	1.18 (1.01 to 1.37)	1.06 (0.93 to 1.20)	7 (−2 to 17)	11 (0 to 22)	3 (−6 to 12)
P value				.15	.03	.40	.18	.05	.45
20/25 (83-79)	19 (9)	28 (13)	42 (20)						
20/32 (78-74)	12 (6)	22 (10)	17 (8)						
20/40 (73-69)	13 (6)	4 (2)	5 (2)						
20/50 to 20/80 (68-54)	1 (<1)	6 (3)	1 (<1)						
20/100 to 20/160 (53-39)	2 (<1)	1 (<1)	5 (2)						
20/200 or worse (38-0)	0	0	1 (<1)						

(continued)

Table 2. Efficacy Outcomes at 2 Years (continued)

Outcomes	Observed Data			Adjusted Treatment Group Comparisons[a]					
				Relative Risk or Mean Difference (95% CI)			Risk Difference (95% CI)		
	Initiation With Aflibercept (n=205)	Initiation With Laser Photocoagulation (n=212)	Initiation With Observation (n=208)	Aflibercept vs Laser	Aflibercept vs Observation	Laser vs Observation	Aflibercept vs Laser	Aflibercept vs Observation	Laser vs Observation
Central subfield thickness, μm[d]	n=205	n=212	n=207						
Baseline									
Mean (SD)[b]	307 (57)	313 (52)	316 (64)						
Median (IQR)	290 (271 to 318)	299 (277 to 335)	301 (275 to 333)						
2 Years									
Mean (SD)	257 (53)	271 (66)	273 (72)						
Median (IQR)	246 (224 to 283)	255 (227 to 312)	261 (227 to 307)						
Change from baseline, mean (SD)	−48 (65)	−41 (75)	−42 (75)	−12 (−24 to 1)[c]	−13 (−27 to 1)[c]	−1 (−13 to 11)[c]			
P value				.07	.07	.82			
Change from baseline, median (IQR)	−47 (−74 to −16)	−42 (−78 to −2)	−37 (−75 to −2)						
No center-involved diabetic macular edema and ≥10% central subfield thickness decrease, No. (%)[e]	95 (46)	90 (42)	74 (36)	1.09 (0.88 to 1.35)	1.31 (0.98 to 1.74)	1.20 (0.91 to 1.58)	4 (−6 to 13)	11 (−1 to 22)	7 (−3 to 18)
P value				.43	.08	.28	.44	.07	.26
Prespecified Exploratory Outcome									
Change in visual acuity letter score from baseline to 2 years (area under the curve)									
Mean (SD)	1.5 (4.0)	0.0 (3.9)	−0.4 (4.2)	1.9 (1.0 to 2.8)[c]	2.1 (1.1 to 3.1)[c]	0.2 (−0.7 to 1.0)[c]			
P value				<.001	<.001	.73			
Median (IQR)	1.8 (−0.3 to 4.0)	0.2 (−1.8 to 2.5)	0.0 (−2.3 to 2.3)						

Abbreviation: IQR, interquartile range.

[a] Missing data were imputed via multiple imputation for eyes not completing the 2-year visit (n=21 in the aflibercept group; n=28 in the laser photocoagulation group; and n=28 in the observation group) or where data are otherwise noted as missing. For each outcome, pairwise comparisons among the 3 groups were performed using the Hochberg procedure to control the overall type I error for multiple comparisons. When there are 3 pairwise comparisons, if the largest (unadjusted) *P* value is greater the 2 times the middle (unadjusted) *P* value AND 3 times the smallest (unadjusted) *P* value, then all 3 comparisons have adjusted *P* values equal to the highest of the unadjusted *P* values. The *P* values are assigned as follows: (1) For the comparison with the largest *P* value, the adjusted *P* value is equal to the observed *P* value. (2) For the comparison with the middle *P* value, the adjusted *P* value is equal to minimum (*P* value from step 1; 2 times middle of observed *P* values). (3) For the comparison with the smallest *P* value, the adjusted *P* value is equal to minimum (*P* value from step 2; 3 times smallest of observed *P* values).

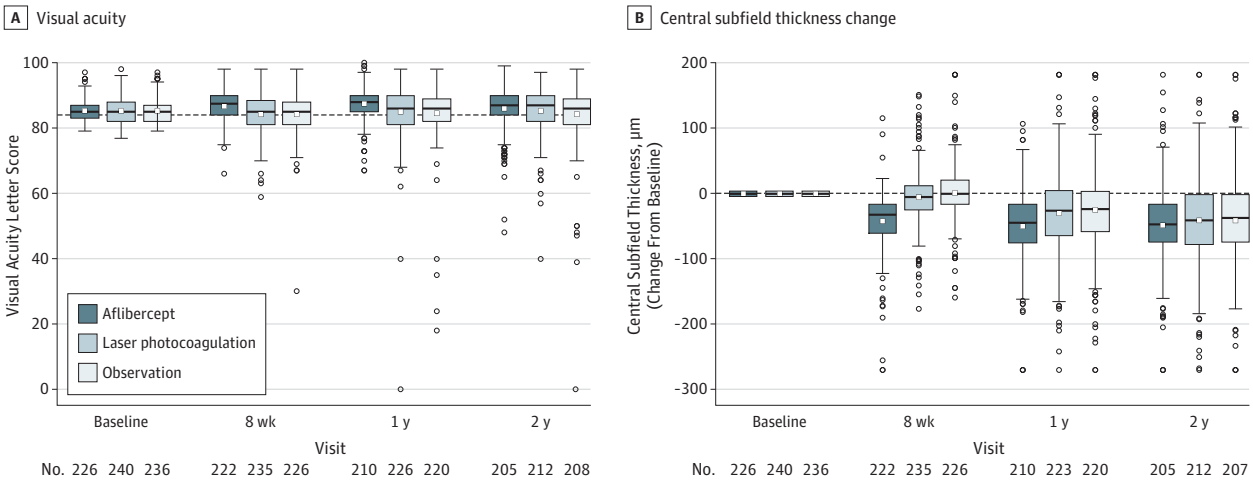
[b] Average of screening and randomization values.

[c] Mean difference.

[d] Values are Zeiss Stratus (time-domain) equivalents.

[e] Defined as follows by central subfield thickness according to optical coherence tomography machine and sex: Heidelberg Spectralis ≥305 μm in women and ≥320 μm in men; Zeiss Cirrus ≥290 μm in women and ≥305 μm in men. As prespecified in the statistical analysis plan, this analysis was conducted without multiple imputation (ie, complete case analysis).

Figure 3. Mean Visual Acuity and Central Subfield Thickness Change From Baseline to 2 Years



For each box-and-whisker plot, the horizontal bar within the box represents median; top and bottom of box, interquartile range; white square, mean. Upper whisker extends from the upper quartile to the closest observed data point below the upper quartile plus 1.5 times the interquartile range; lower whisker extends from the lower quartile to the closest observed data point above the lower quartile minus 1.5 times the interquartile range. Outlying values are plotted as circles. Values in panel A at or above the horizontal dashed line (84 letters) represent visual acuity of 20/20 or better. Numbers of participant eyes shown are observed data only.

variation.[25,26] In the study, visual acuity eligibility was assessed by a standardized method that included a clinical trial protocol refraction performed twice. It is likely that the results from this trial would apply to some eyes assessed in clinical practice at worse levels of visual acuity when measured without optimal refraction.[27]

The subgroup of eyes in the laser photocoagulation and observation groups receiving injections had a similar median number of injections over 2 years compared with the aflibercept group. However, eyes in the laser photocoagulation group had a 10% less absolute likelihood or 34% less relative likelihood of receiving aflibercept injections compared with eyes in the observation group. This difference is consistent with a possible benefit of laser photocoagulation in reducing the need for anti-VEGF. This study cannot determine how a strategy of initial observation followed by laser photocoagulation for vision decline followed by intravitreous anti-VEGF for subsequent decline would compare with initial observation followed by anti-VEGF treatment.

Aflibercept, bevacizumab, and ranibizumab are three anti-VEGF agents commonly used to treat CI-DME. A previous study showed that aflibercept was superior to bevacizumab and ranibizumab at 1 year for eyes with moderate to severe visual impairment (20/50 to 20/320), but no significant difference in eyes with mild visual acuity impairment (20/32 to 20/40) was determined.[28] At 2 years, aflibercept was still superior to bevacizumab for eyes with moderate to severe visual acuity impairment, but there was no significant difference compared with ranibizumab.[29] Given the even better vision (20/25 or better) for eyes in this study, use of bevacizumab or ranibizumab would likely yield similar results.

This study had several strengths, including high participant retention, outcome assessors who were masked to treatment assignment, treatment regimens that were strictly defined by the protocol, and high rates of adherence to treatment.

Limitations

This study has several limitations. First, visit schedules varied by treatment group and clinical course. This limited the ability to compare treatment group trajectories between annual visits and could introduce ascertainment bias because participants in the aflibercept group were seen more frequently. For example, the finding of a greater rate of intraocular pressure elevation in the aflibercept group could be due to intraocular pressure being measured more frequently. However, the trial was designed to compare regimens as intended to be applied in clinical practice, and all participants had visits at 1 and 2 years and at least quarterly in between. Second, clinicians and participants were not masked because of the nature of the treatments. However, visual acuity and OCT testers were masked to participant treatment group at annual visits. Third, the effects of other anti-VEGF agents and treatment regimens cannot be determined from this study. Fourth, because this study cohort had relatively good glycemic control and excellent visit adherence, outcomes might differ among patients in clinical care with worse glycemic control or inconsistent follow-up.

Conclusions

Among eyes with CI-DME and good visual acuity, there was no significant difference in vision loss at 2 years whether eyes were initially managed with aflibercept or with laser photocoagulation or observation and given aflibercept only if visual acuity worsened. Observation without treatment unless visual acuity worsens may be a reasonable strategy for these eyes.

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Data Sharing Statement: See Supplement 4.

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