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Impact of baseline Diabetic Retinopathy Severity Scale scores on visual outcomes in the VIVID-DME and VISTA-DME studies

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ABSTRACT

Background/aims To evaluate intravitreal aflibercept versus laser in subgroups of patients with baseline Diabetic Retinopathy Severity Scale (DRSS) scores ≤43, 47, and ≥53 in VIVID-DME and VISTA-DME.

Methods Patients with diabetic macular oedema were randomised to receive intravitreal aflibercept 2 mg every 4 weeks (2q4), intravitreal aflibercept 2 mg every 8 weeks after five initial monthly doses (2q8), or macular laser photocoagulation at baseline with sham injections at every visit. These post hoc analyses evaluate outcomes based on baseline DRSS scores in patients in the integrated dataset. The 2q4 and 2q8 treatment groups were also pooled.

Results 748 patients had a baseline DRSS score based on fundus photographs (≤43, n=301; 47, n=153; ≥53, n=294). At week 100, the least squares mean difference between treatment groups (effect of intravitreal aflibercept above that of laser, adjusting for baseline best-corrected visual acuity) was 8.9 (95% CI 5.99 to 11.81), 9.7 (95% CI 5.54 to 13.91), and 11.0 (95% CI 7.96 to 14.1) letters in those with baseline DRSS scores ≤43, 47, and ≥53, respectively. The proportions of patients with ≥2 step DRSS score improvement were greater in the intravitreal aflibercept group versus laser, respectively, for those with baseline DRSS scores of ≤43 (13% vs 5.9%), 47 (25.8% vs 4.5%), and ≥53 (64.5% vs 28.4%).

Conclusions Regardless of baseline DRSS score, functional outcomes were superior in intravitreal aflibercept-treated patients, demonstrating consistent treatment benefit across various baseline levels of retinopathy.

Trial registration numbers NCT01331681 and NCT01363440, Post-results.

INTRODUCTION

Diabetic retinopathy (DR) is the most common microvascular complication in patients with diabetes mellitus (DM), and is the leading cause of blindness in working-age adults.[1 2] Diabetic macular oedema (DME), which can occur at any stage of DR, is a major cause of vision loss in patients with DR.[1]

Based on the results of recent clinical trials, treatment with anti-vascular endothelial growth factor (VEGF) agents has increasingly replaced laser photocoagulation as the standard of care in DME. Several clinical trials have demonstrated the efficacy and safety of intravitreal ranibizumab in the treatment of DME.[3–5] Similar results were obtained in studies of intravitreal bevacizumab[6 7]; however, bevacizumab is not licensed for ophthalmic use. In the VIVID-DME and VISTA-DME studies, patients with DME who were treated with intravitreal aflibercept monotherapy achieved superior visual and anatomical outcomes compared with patients who received laser monotherapy.[8 9] A comparative effectiveness study conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) demonstrated statistical significance of intravitreal aflibercept over ranibizumab or bevacizumab in patients with DME at 12 months, the primary endpoint of the study, particularly in those with a baseline visual acuity of 20/50 or worse.[10] At 2 years, the visual gains achieved with intravitreal aflibercept were statistically superior to bevacizumab but the statistical superiority to ranibizumab was no longer evident.[11] An area under the curve analysis showed that mean change in visual acuity over 2 years was greater with intravitreal aflibercept than with bevacizumab or ranibizumab.[12]

The Early Treatment Diabetic Retinopathy Study (ETDRS) was a clinical trial sponsored by the National Eye Institute in which patients were randomised to treatment with early or deferred photocoagulation, a study design which allowed observation of the natural course of DR in the initially untreated eye. The study found that severity of intraretinal microvascular abnormalities, haemorrhages and/or microaneurysms, and venous beading on fundus photographs were the most important factors in predicting the progression of DR. Based on these findings, the authors developed a Diabetic Retinopathy Severity Scale (DRSS) that divides DR into 13 levels ranging from absence of retinopathy to severe retinopathy including vitreous haemorrhage (table 1). This scale can be used to describe overall retinopathy severity as well as the change in severity over time.[13] According to the American Academy of Ophthalmology, DRSS scores are associated with the risk of developing proliferative DR (PDR). The risk of developing early PDR after 1 year is low (5.4–11.9%) in patients

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Table 1 ETDRS final retinopathy severity scale (for individual eyes)

Level	Severity	Definition
10	DR absent	Microaneurysms and other characteristics absent
20	Microaneurysms only	Microaneurysms definite; other characteristics absent
35	Mild NPDR	One or more of the following: • Venous loops ≥D/1 • SE, IRMA, or VB=Q • Retinal haemorrhages present • HE ≥D/1 • SE ≥D/1
43	Moderate NPDR	H/Ma=M/4–5 — S/1 or IRMA=D/1–3 (not both)
47	Moderately severe NPDR	Both L43 characteristics and/or 1 (only) of the following: • IRMA=D4–5 • H/Ma=S/2–3 • VB=D/1
53	Severe NPDR	One or more of the following: • ≥2 of the 3 L47 characteristics • H/Ma ≥S/4–5 • IRMA ≥M/1 • VB ≥D/2–3
61	Mild PDR	FPD or FPE present with NVD and NVE absent; or NVE=D
65	Moderate PDR	Either of the following: • NVE ≥M/1 or NVD=D and VH or PRH=A or Q •VH or PRH=D and NVE <M/1 and NVD absent
71	High-risk PDR	Any of the following: • VH or PRH ≥M/1 • NVE ≥M/1 and VH or PRH ≥D/1 • NVD=2 and VH or PRH ≥D/1 • NVD ≥M
75	High-risk PDR	NVD ≥M and VH or PRH ≥D/1
81	Advanced PDR: fundus partially obscured, centre of macula attached	NVD=cannot grade, or NVD <D and NVE=cannot grade in ≥1 field and absent in all others; and retinal detachment at centre of macula <D
85	Advanced PDR: posterior fundus obscured, or centre of macula detached	VH=VS in fields 1 and 2; or retinal detachment at centre of macula=D
90	Cannot grade, even sufficiently for level 81 or 85	

Severity categories for characteristics graded in multiple fields are of the form 'maximum severity/extent', where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of fields at that severity level. For example, M/2–3 means that there are two or three fields from fields 3 to 7 with moderate severity, and none with higher severity.
ETDRS, Early Treatment Diabetic Retinopathy Study; DR, diabetic retinopathy; FPD, fibrous proliferations disc; FPE, fibrous proliferations elsewhere; HE, hard exudates; H/Ma, haemorrhages/microaneurysms; IRMA, intraretinal microvascular abnormalities; NPDR, non-proliferative DR; NVD, new vessels disc (within one disc diameter of disc margin); NVE, new vessels elsewhere (>1 disc diameter from disc); PDR, proliferative DR; SE, soft exudates; VB, venous beading; VH, vitreous haemorrhage; PRH, preretinal haemorrhage.

with a DRSS score ≤43, moderate (26.3%) in patients with a DRSS score of 47, and high (50.2%) in patients with a DRSS score ≥53.[14]

To the best of our knowledge, no studies have examined the relationship between baseline DRSS scores and outcomes in patients with DME treated with anti-VEGF agents. Here, we report on the impact of baseline DRSS scores on functional and anatomical outcomes in patients enrolled in the VIVID-DME and VISTA-DME studies.

Table 2 Baseline demographics and disease characteristics by baseline DRSS score

	Low risk (≤43) n=301		Moderate risk (47) n=153		High risk (≥53) n=294	
	Laser	Intravitreal aflibercept	Laser	Intravitreal aflibercept	Laser	Intravitreal aflibercept
Age, years	64.9 (7.7)	64.9 (9.2)	63.7 (8.3)	63.8 (8.9)	59.4 (9.2)	60.0 (9.6)
Duration of diabetes, years	18.5 (9.7)	18.3 (11.2)	16.5 (10.0)	16.3 (9.4)	14.3 (9.2)	13.5 (8.9)
HbA1c, %	7.40 (1.2)	7.86 (1.5)	7.71 (1.4)	7.75 (1.7)	7.83 (1.9)	7.83 (1.5)
BCVA, ETDRS letters	60.6 (10.8)	60.5 (9.7)	62.3 (9.6)	62.4 (9.6)	58.5 (11.7)	57.2 (11.5)
CRT, µm	487 (141.2)	472.3 (136.1)	488.6 (149.5)	469.3 (122.0)	541.4 (168.3)	535.2 (177.3)

Data presented as mean (SD).
Only those with gradable baseline DRSS score are included.
BCVA, best-corrected visual acuity; CRT, central retinal thickness; DRSS, Diabetic Retinopathy Severity Scale; ETRDS, Early Treatment Diabetic Retinopathy Study; HbA1c, glycated haemoglobin A1c.

METHODS

Design

The study design and methods have been published previously.[8 9] Key details are summarised here. VIVID-DME (NCT01331681) and VISTA-DME (NCT01363440) were phase 3, randomised, double-masked, active-controlled, 148 week trials comparing two dosing regimens of intravitreal aflibercept with laser for the treatment of DME. The studies were conducted at 127 sites in the USA, Europe, Japan, and Australia, and were conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation.

Participants

Adult patients with type 1 or type 2 diabetes mellitus who presented with central-involved DME (defined as retinal thickening involving the 1 mm central subfield thickness) were included if best-corrected visual acuity (BCVA) was between 73 and 24 letters (20/40–20/320 Snellen equivalent) in the study eye. Only one eye per patient was included.

Randomisation and treatment

Patients were randomised 1:1:1 to treatment with intravitreal aflibercept 2 mg every 4 weeks (2q4), intravitreal aflibercept 2 mg every 8 weeks after five initial monthly doses (2q8), or macular laser photocoagulation at baseline with sham injections at every visit. Eyes in the 2q8 group received sham injections on non-treatment visits. From week 24, additional active treatment (laser in the intravitreal aflibercept groups and intravitreal aflibercept in the laser group) was allowed in the case of disease recurrence/worsening based on prespecified criteria.

Outcomes

The primary efficacy endpoint for the VIVID-DME and VISTA-DME studies was the change from baseline in BCVA in ETDRS letters at week 52.

Table 3 Unadjusted mean (SD) change in BCVA by baseline DRSS score at week 52 and week 100

	Week 52		Week 100	
	Laser (n=249)	Intravitreal aflibercept (n=499)	Laser (n=249)	Intravitreal aflibercept (n=499)
Low risk (DRSS ≤43)	1.3 (11.2)	10.3 (8.7)	1.3 (11.6)	10.2 (10.7)
Moderate risk (DRSS =47)	0.0 (12.7)	10.0 (6.7)	0.5 (14.5)	10.2 (10.5)
High risk (DRSS ≥53)	0.5 (11.3)	12.8 (9.5)	0.9 (12.9)	12.1 (12.7)

Only those with gradable baseline DRSS scores are included.
BCVA, best-corrected visual acuity; DRSS, Diabetic Retinopathy Severity Scale.

Here we report on the impact of baseline DRSS score (low risk (≤43), moderate risk (47), and high risk (≥53)) on outcomes for patients enrolled in VIVID-DME and VISTA-DME. Colour fundus photography was performed at baseline, week 24, week 52, week 72 (VISTA-DME) or week 76 (VIVID-DME), and week 100. Images were evaluated by masked graders at independent reading centres. Fundus images were evaluated by the Vienna Reading Centre, Vienna, Austria (VIVID-DME) and the Digital Angiography Reading Centre, Great Neck, New York, USA (VISTA-DME). Images for 114 patients were categorised as 'ungradable.' The remaining patients were stratified into three subgroups based on baseline DRSS score: low risk (≤43), moderate risk (47), and high risk (≥53).

For these post hoc analyses, data from VIVID-DME and VISTA-DME have been integrated. Results of statistical analyses are presented for pooled intravitreal aflibercept and laser treatment arms.

Statistics

Patients included in the efficacy analyses are those from the full analysis set (FAS) in both studies (VIVID-DME and VISTA-DME), which includes all randomised patients who received any study medication and had at least one baseline and one postbaseline assessment. The FAS was analysed as randomised. Baseline DRSS scores were stratified into three subgroups: low risk (≤43), moderate risk (47), and high risk (≥53). Patients without baseline DRSS scores (missing or 'ungradable' cases as mentioned above) were not included in the analyses. For continuous endpoints such as change from baseline BCVA, an analysis of covariance model was fitted with baseline BCVA, baseline DRSS subgroup, treatment group, study, and the interaction between baseline DRSS subgroup and treatment as the fixed effect. Nominal p values were presented in these ad hoc analyses without further multiplicity adjustment. For binary endpoints, such as proportion of patients who gained or lost ≥15 letters, the counts and percentages were calculated for each treatment group.

Missing values in the outcomes were imputed using the last observation carried forward method, and for eyes that received additional treatment, the last value before additional treatment was used for analyses.

Patients included in the safety analyses are those from the safety population in both studies, which includes all randomised patients who received any study treatment.

RESULTS

At baseline, among those with baseline DRSS scores (n=748), the proportions of patients with DRSS scores of low risk (≤43), moderate risk (47), and high risk (≥53) were 38.7%, 20.6%, and 40.7%, respectively, in the pooled intravitreal aflibercept group and 43.4%, 20.1%, and 36.5% in the laser group. Baseline demographics and disease characteristics based on baseline DRSS scores are reported in table 2. On average, patients in the high-risk group were younger, with a shorter duration of diabetes, and had worse BCVA and thicker retinas at baseline. Haemoglobin A1c levels at baseline were similar across the three risk groups.

At both week 52 and week 100, unadjusted mean gains in BCVA were greater in patients in all baseline DRSS score subgroups treated with intravitreal aflibercept compared with laser-treated patients (table 3). An analysis of the least squares mean difference between treatment groups (adjusting for baseline BCVA) showed that, at both time points, the difference in treatment effect between intravitreal aflibercept and laser had some numerical increasing trend as baseline DRSS score increased, from 8.9 (95% CI 5.99 to 11.81), 9.7 (95% CI 5.54 to 13.91), and 11.0 (95% CI 7.96 to 14.1) letters in those with baseline DRSS scores ≤43, 47, and ≥53, respectively(figure 1). .

At both week 52 and week 100, a greater proportion of patients in all baseline DRSS score subgroups treated with intravitreal aflibercept achieved a ≥2 step improvement in

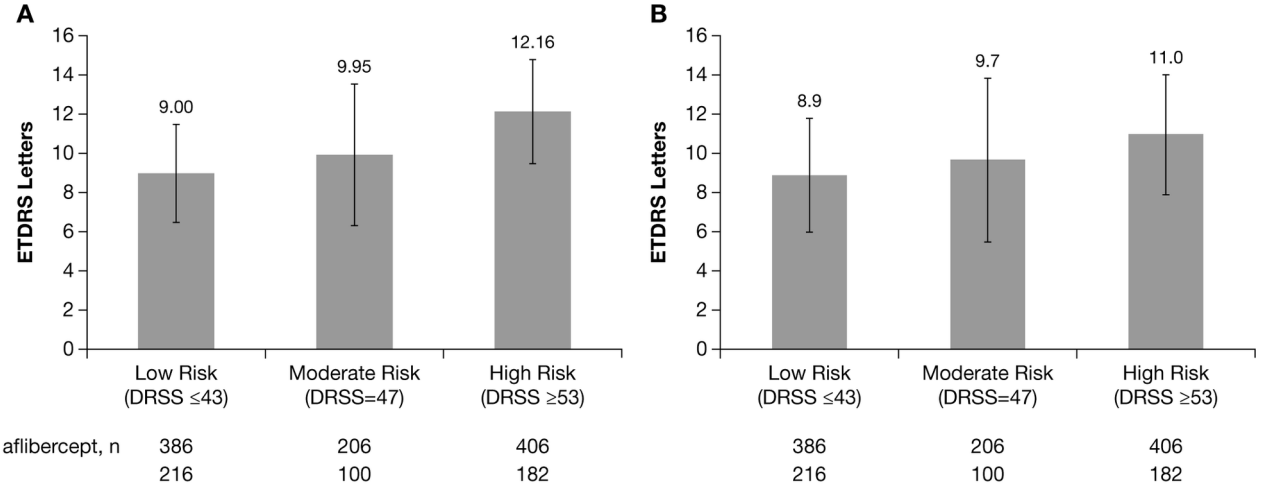

Figure 1 Difference in treatment effect between intravitreal aflibercept and laser (ETDRS letters), adjusting for baseline BCVA at (A) week 52 and (B) week 100. BCVA, best-corrected visual acuity; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study.

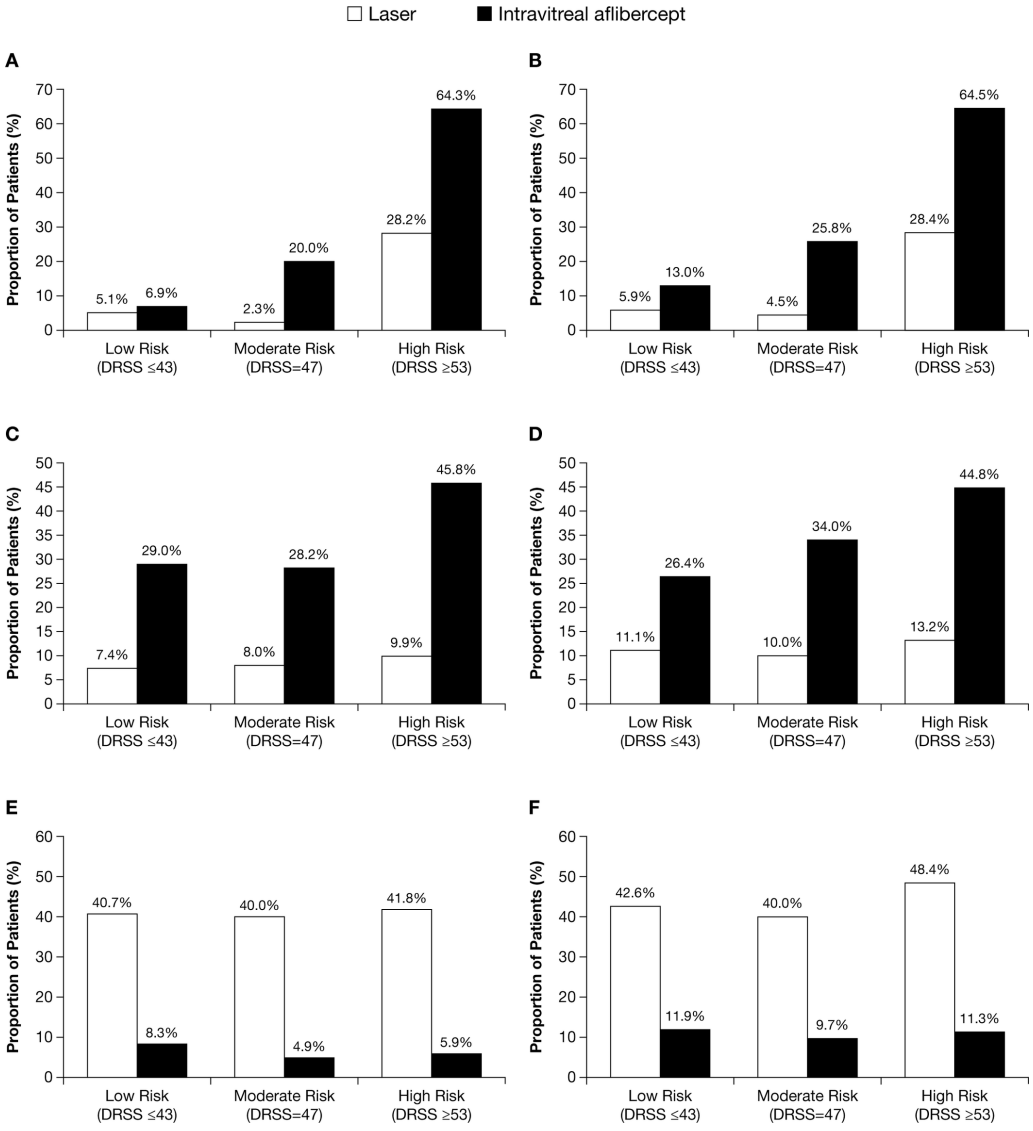

Figure 2 Proportion of patients (A) with ≥2 step improvement in DRSS score by baseline DRSS score at week 52, (B) with ≥2 step improvement in DRSS score by baseline DRSS score at week 100, (C) who gained ≥15 letters in BCVA by baseline DRSS score at week 52, (D) who gained ≥15 letters in BCVA by baseline DRSS score at week 100, (E) who lost >0 letters in BCVA by baseline DRSS score at week 52, and (F) who lost >0 letters in BCVA by baseline DRSS score at week 100. BCVA, best-corrected visual acuity; DRSS, Diabetic Retinopathy Severity Scale.

DRSS score compared with laser-treated patients. Regardless of the treatment group, a greater proportion of patients in the high-risk group had a ≥2 step improvement compared with patients in the medium-risk and low-risk groups (figure 2A and B).

Similarly, at both week 52 and week 100, a greater proportion of patients in all baseline DRSS score subgroups treated with intravitreal aflibercept gained ≥15 letters in BCVA compared with laser-treated patients. Regardless of treatment group, a greater proportion of patients in the high-risk group gained ≥15 letters compared with patients in the medium-risk and low-risk groups (figure 2C and D).

At both week 52 and week 100, the proportion of patients in all baseline DRSS score subgroups who lost >0 letters in BCVA was greater in laser-treated patients compared with those treated with intravitreal aflibercept. There was no discernible pattern based on baseline DRSS score regarding loss of >0 letters in BCVA (figure 2E and F).

DISCUSSION

In this analysis, we evaluated the impact of baseline DRSS scores in patients enrolled in the VIVID-DME and VISTA-DME studies. Patients from these studies were grouped according to baseline DRSS score (which is associated with low, medium, or high risk of developing PDR), and mean changes in BCVA were evaluated for each of the subgroups. Previous studies have examined the impact of baseline characteristics such as central retinal thickness[15 16] and BCVA[17] on visual outcomes in patients with DME treated with anti-VEGF therapy. To the best of our knowledge, the role of baseline DRSS score on visual outcomes in such patients has not been evaluated.

The week 52 and week 100 results showed that, compared with laser, visual outcomes were superior in the intravitreal aflibercept groups, regardless of baseline DRSS score. In all subgroups, the mean change in BCVA at both time points was greater in intravitreal aflibercept-treated eyes compared

with laser-treated eyes. Irrespective of baseline DRSS score (and, therefore, risk of developing PDR), the proportion of patients who gained ≥15 letters in BCVA was greater for those treated with intravitreal aflibercept than with laser, while the proportion of patients who lost >0 letters in BCVA was greater in those treated with laser. These findings suggest that among patients with DME, even those with more advanced DR at baseline and a greater risk of developing PDR within 1 year, greater visual benefits were observed with intravitreal aflibercept compared with laser.

The magnitude of functional improvement with intravitreal aflibercept treatment was similar across baseline DRSS risk groups; however, there was a numerical increasing trend in treatment difference compared with laser as baseline DRSS score increased from low to high. There is a substantial amount of evidence showing that worse baseline visual acuity results in greater improvements in patients treated with anti-VEGF therapy[17–19]; however, in the current study, the numerical increasing trend was still observed after adjustments for baseline visual acuity. This finding suggests a real difference in treatment effect based on baseline DRSS score, although this analysis was not sufficiently powered to show this definitively.

Anatomical outcomes were also superior with intravitreal aflibercept, with ≥2 step improvements in DRSS score occurring in a greater proportion of patients treated with intravitreal aflibercept compared with laser, regardless of baseline DRSS score. At both time points, ≥2 step DRSS improvement was greater in the subgroup of patients with baseline DRSS score ≥53 compared with the other baseline DRSS score subgroups.

Strengths of the present study include the use of masked graders from two reading centres to evaluate fundus photographs and determine baseline DRSS scores, as well as the fixed dosing and strict protocols. However, although VIVID-DME and VISTA-DME were well-designed randomised clinical trials, this article reports findings from an exploratory post hoc analysis, and further prospective research is needed to confirm the current findings.

In conclusion, these post hoc analyses through week 100 demonstrate the benefits of intravitreal aflibercept over laser in patients with DME regardless of baseline DR severity, suggesting that even patients with severe DR can experience visual and anatomical improvements after treatment with intravitreal aflibercept.

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Competing interests GS is a consultant to Novartis, Bayer, Allergan, Genentech, Roche, Heidelberg Engineering, and Alcon. He has also received support for travel to meetings from Bayer HealthCare, Centervue, Heidelberg Engineering, and Novartis. He has received payment for lectures from Zeiss, and is a patent holder in conjunction with Ocular Instruments, Inc. He has received payment for development of educational presentations for Roche. NF is a consultant to Alimera, and has received funding from Novartis, Allergan, Alimera, Bayer, and Heidelberg Engineering. JJA is a member of advisory boards for Novartis, Bayer, and Allergan. She has received personal fees and others from Novartis and others from Bayer. TA Katz is an employee of Bayer. CM is an employee of Bayer. CL is an employee of Bayer. FGH is a consultant to Acucela, Genentech/Roche, Novartis, Bayer, Alcon, OPTOS, Heidelberg Engineering, Carl Zeiss Meditec, Allergan, and Pfizer, and has received financial support from OPTOS, Heidelberg Engineering, Carl Zeiss Meditec, Alcon, Genentech/Roche, Bayer, and Novartis.

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