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ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY AND RISK OF TRACTION RETINAL DETACHMENT IN EYES WITH PROLIFERATIVE DIABETIC RETINOPATHY

Pooled Analysis of Five DRCR Retina Network Randomized Clinical Trials

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Purpose: To investigate whether anti–vascular endothelial growth factor (anti-VEGF) for diabetic macular edema or proliferative diabetic retinopathy (PDR) increases the risk of traction retinal detachment (TRD) among eyes with PDR.

Methods: Pooled analysis of PDR eyes from Protocols I, J, N, S, or T with Early Treatment Diabetic Retinopathy Study level ≥61 (prompt vitrectomy was not planned) randomly assigned to the control group (laser photocoagulation, sham, or intravitreal saline; 396 eyes) or anti-VEGF (487 eyes). The primary outcome was investigator-identified TRD within 1 year of randomization.

Results: The 1-year cumulative probability of TRD was 6.8% (95% confidence interval: 4.6%–9.9%, 25 events) in control-group eyes and 4.8% (95% confidence interval: 3.2%–7.3%, 22 events) in anti-VEGF group eyes (hazard ratio = 0.95 [95% confidence interval: 0.54–1.66, $P = 0.86$]). The cumulative probability of vitrectomy for TRD was 4.4% (16 events) in control-group eyes and 2.2% (9 events) in anti-VEGF group eyes ($P = 0.19$). Percentage with TRD and vitrectomy for TRD were similar within strata of diabetic retinopathy severity.

Conclusion: These findings do not support the hypothesis that anti-VEGF therapy for diabetic macular edema or PDR increases the risk of TRD among eyes with PDR similar to those enrolled in five DRCR Retina Network protocols for which prompt vitrectomy was not planned.

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Clinical confirmation that intravitreous anti–vascular endothelial growth factor (anti-VEGF) causes regression of retinal neovascularization from proliferative diabetic retinopathy (PDR) was first reported in post hoc analyses of studies using pegaptanib for diabetic macular edema (DME) and bevacizumab for PDR.[1,2] Subsequently, two Phase III trials designed to evaluate anti-VEGF therapy to manage PDR demonstrated both safety and efficacy of anti-VEGF therapy relative to panretinal photocoagulation (PRP) for PDR using ranibizumab (Protocol S) and aflibercept (CLARITY).[3,4] The goal of the PDR trials was to prevent severe vision loss from PDR due to nonclearing vitreous hemorrhage or traction retinal detachment (TRD). Each of these events would likely need vitrectomy; however, severe vision loss could still occur despite vitrectomy.

A 2008 report by Arevalo et al[5] from several clinical centers first raised potential safety concerns regarding TRD when intravitreous anti-VEGF agents were used in eyes with PDR. Among 211 eyes with PDR that underwent vitrectomy and received 1.25-mg bevacizumab as a preoperative adjuvant therapy, clinical chart review identified 11 eyes (5.2%) that later showed development or progression of TRD. At a mean time of 13 days (range 3–31) after injection, 7 eyes had worsening of pre-existing TRD, and 4 eyes had newly developed TRD.

These potential safety concerns gained further attention when Chan[6] offered the term "ROP crunch" to describe a potential relationship between intravitreous bevacizumab and TRD when used in eyes with retinopathy of prematurity. In 2011, a subsequent multicenter clinical chart review by Arevalo et al raised additional concerns about a potential adverse relationship between anti-VEGF therapy and TRD in eyes with PDR. Twenty-five of 698 eyes (3.5%) experienced progression of pre-existing TRD or development of new TRD following intravitreous bevacizumab that was administered before vitrectomy for PDR. The authors suggested that extreme care was needed when dosing bevacizumab at 2.5 mg in eyes with PDR, as the incidence was higher with the 2.5-mg dose (6 of 72, 8.3%) than the 1.25-mg dose (19 of 626, 3%).[7] Without a control group, the study design could not rule out the possibility that the TRDs were a result of the natural history of the disease, nor could it control for potential confounding from the possible association between the dose of bevacizumab and disease severity.

To learn more about the putative relationship between anti-VEGF and TRD among eyes with PDR, we conducted a post hoc analysis with data pooled from five DRCR Retina Network trials. The objective was to determine whether rates of TRD and vitrectomy for TRD, among eyes with PDR, were higher when these eyes were treated primarily with anti-VEGF therapy (for DME, PDR, or both) versus modalities other than anti-VEGF agents, such as laser photocoagulation or sham injections. Analyses included eyes meeting the eligibility criteria for these protocols and without pre-existing TRD for which prompt vitrectomy was planned.

Methods

Methods for each DRCR Retina Network protocol in this analysis have been published elsewhere with the complete protocols available online (www.drcr.net). All studies adhered to the tenets of the Declaration of Helsinki. Study participants provided written informed consent. The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by the institutional review board associated with each participating center.

All eyes included in the present set of analyses were enrolled into one of the following DRCR Retina Network randomized clinical trials: Protocol I, Protocol J, Protocol N, Protocol S, or Protocol T (Table 1).[3,8–11] Macula-threatening and macula-involving TRD were exclusion criteria for these trials. Analyses were limited to eyes with PDR defined as Early Treatment Diabetic Retinopathy Study (ETDRS) Level 61 (mild PDR) or greater upon reading-center review of color fundus photographs or investigator-determined nonclearing vitreous hemorrhage at baseline presumed to be from PDR (i.e., eyes enrolled into Protocol N).[12] The presence of pre-existing extramacular TRD was not an exclusion criterion. However, eyes were excluded if the investigator believed vitrectomy for TRD was warranted. Therefore, no patient began with a TRD deemed to require prompt surgery.

For inclusion in the present analysis, eyes must have been randomly assigned to anti-VEGF treatment or a control treatment that did not include anti-VEGF or intraocular corticosteroid injection as the primary treatment. This control group included eyes randomly assigned to sham injection, laser photocoagulation, or intravitreous saline injection to manage PDR or DME. Eyes assigned to intraocular corticosteroid injection were excluded in case corticosteroids affected the rate of TRD.

All eyes in Protocol S with vision-impairing (20/32 or worse) center-involved DME at baseline (N = 88),

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None of the authors has any conflicting interests to disclose.

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Table 1. Original Randomized Treatment Groups of Eyes Analyzed

Protocol Treatment Group*, No. of Eyes (%)	Control Group (N = 396)	Anti-VEGF Group (N = 487)
Protocol I: intravitreal ranibizumab or triamcinolone acetonide in combination with laser photocoagulation for DME		
Control: sham + focal/grid laser	40 (10.1)	0
Anti-VEGF: ranibizumab (0.5 mg) + prompt focal/grid laser	0	28 (5.7)
Anti-VEGF: ranibizumab (0.5 mg) + deferred focal/grid laser	0	23 (4.7)
Protocol J: intravitreal ranibizumab or triamcinolone acetonide as adjunctive treatment to PRP for PDR		
Control: sham + focal/grid/PRP laser	89 (22.5)	0
Anti-VEGF: ranibizumab (0.5 mg) + focal/grid/PRP laser	0	81 (16.6)
Protocol N: an evaluation of intravitreal ranibizumab for vitreous hemorrhage due to PDR		
Control: intravitreous saline	136 (34.3)	0
Anti-VEGF: ranibizumab (0.5 mg)	0	125 (25.7)
Protocol S: prompt PRP versus intravitreal ranibizumab with deferred PRP for PDR		
Control: PRP	131 (33.1)	0
Anti-VEGF: ranibizumab (0.5 mg)	0	130 (26.7)
Protocol T: a comparative effectiveness study of intravitreal aflibercept, bevacizumab, and ranibizumab for DME		
Anti-VEGF: aflibercept (2.0 mg)	0	30 (6.2)
Anti-VEGF: bevacizumab (1.25 mg)	0	38 (7.8)
Anti-VEGF: ranibizumab (0.3 mg)	0	32 (6.6)

*Total number of eyes randomized by the protocol: 854 (I), 364 (J), 261 (N), 394 (S), and 660 (T). DME, diabetic macular edema; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.

regardless of the randomization group, were excluded because they were required to receive anti-VEGF at baseline to treat the DME. As an aside, among these 88 eyes, 3 of 46 assigned to the PRP group and 1 of 42 assigned to the anti-VEGF group had a TRD within 1 year of randomization. In addition, all eyes in Protocol S were eligible to receive ranibizumab for DME at any follow-up time per investigator discretion. In the present analysis, 45 of 131 eyes (34.4%) in the control group from Protocol S (prompt PRP) received anti-VEGF for DME in the first year of follow-up.

The primary outcome was TRD (i.e., new TRD or worsening of pre-existing TRD, including TRD combined and those not combined with a rhegmatogenous retinal detachment) within 1 year of randomization (within the predefined 1-year analysis window for each trial) identified by a study investigator (retina specialist) during prospective data collection. Events beyond 1 year were not included because the previously reported cases of development or worsening of TRD after anti-VEGF were noted soon after initial exposure to anti-VEGF. In Protocols N and S, there was a specific question on follow-up case report forms regarding the presence of TRD. In Protocols I, J, and T, investigators were asked to report any adverse events noted, and it was presumed for this analysis that new TRD would have been captured. In all trials, if the visual acuity letter score was zero (approximate Snellen equivalent worse than 20/800) or if visual acuity decreased by 10 or more letters from baseline, then investigators were required to enter a corresponding adverse event; one of the suggested prespecified options on the electronic case report form was TRD. Follow-up schedules varied across protocols and between treatment groups within protocols; however, all eyes randomized to anti-VEGF had their first follow-up visit within 4 weeks of the initial exposure.

Vitrectomy to treat TRD performed at discretion of the physician was a secondary outcome and collected prospectively. Vitrectomies to treat TRD occurring within the 1-year analysis window were analyzed regardless of when the vitrectomy was performed.

The cumulative probability of experiencing an event (e.g., TRD) was computed using the Kaplan–Meier method. Multiple episodes of the same event, e.g., TRD occurring more than once over the follow-up period, were not considered. Time-to-event analyses were conducted using stratified Cox proportional hazards regression with adjustment for differences between protocols (as a stratification variable) in all analyses and baseline retinopathy severity (as a fixed effect), a known risk factor for TRD, in a sensitivity analysis limited to eyes with gradable color photographs at baseline[13,14]; correlations arising from participants contributing two eyes to the analysis were modeled using a robust sandwich estimate of the covariance matrix.[15] Data from eyes not experiencing an event were censored at the time of the last completed visit. All P values are

two-sided. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

The analysis cohort included 883 eyes with PDR randomized across 5 protocols (34.9% of the 2,533 eyes in these 5 protocols; Table 1 includes a listing of the original treatment groups by the protocol). Baseline characteristics of patients and eyes included in this analysis appeared balanced for most features (Table 2). In the control and anti-VEGF groups, respectively, study participants were 42.9% (170 of 396) and 45.2% (220 of 487) women, 52.5% (208) and 56.5% (275) non-hispanic whites, and had a median age of 54 and 56 years. Among eyes, the median visual acuity letter score (Snellen equivalent) was 66 (20/50) and 68 (20/50). Among eyes in the anti-VEGF group, 6.2% (30), 7.8% (38), and 86.0% (419) were randomized to aflibercept, bevacizumab, and ranibizumab, respectively.

Central subfield thickness (time-domain [Zeiss Stratus] equivalent)[17] was thinner in the control group compared with the anti-VEGF group: median (interquartile range) 253 (214–356) μm versus 286 (224–404) μm.[16] This was, in part, because all Protocol T eyes had DME and only contributed to the anti-VEGF group. Retinopathy severity was somewhat worse in the control group, as 73.5% of eyes (191 of 260) with gradable color fundus photographs had moderate or worse PDR, compared with 63.8% (231 of 362) in the anti-VEGF group. High-risk PDR (Levels 71 and 75) was noted in 36.9% (96) and 31.2% (113) of eyes in the control and anti-VEGF groups; note that this grade alone does not indicate whether there was extramacular TRD.

Traction Retinal Detachments

Within the first year of treatment, the Kaplan–Meier cumulative probability of having a TRD was 6.8% (95% confidence interval [CI]: 4.6%–9.9%, 25 events) in the control group and 4.8% (3.2%–7.3%, 22 events) in the anti-VEGF group. Within the first 60 days of follow-up, the cumulative probability of TRD was 2.6% (10 events) among control eyes and 1.5% (6 events) among anti-VEGF eyes. Over 1 year, the hazard ratio for TRD in the anti-VEGF group versus the control group was 0.95 (95% CI: 0.54–1.66, $P = 0.86$, Figure 1).

In a sensitivity analysis, all types of retinal detachments were considered (traction, rhegmatogenous, and unspecified). The Kaplan–Meier cumulative probability of having any retinal detachment was 7.9% (95% CI: 5.5%–11.2%, 29 events) in the control group and 5.5% (3.8%–8.1%, 25 events) in the anti-VEGF group. The 1-year hazard ratio for any retinal detachment in the anti-VEGF group versus the control group was 0.92 (95% CI: 0.55–1.55, $P = 0.76$, see **eFigure 1**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B67).

When an assessment could be made by the investigator, data as to whether a TRD involved the macula when the TRD was first noted were collected in Protocols N and S. In Protocol N, the macula was involved in two of six cases in the control group and four of seven cases in the anti-VEGF group. In Protocol S, the macula was involved in one of eight cases in the control group and zero of five cases in the anti-VEGF group.

The presence of TRD at baseline was not collected systematically; however, for this pooled analysis, the fundus photograph reading center retrospectively graded available baseline photographs of eyes noted to have TRD at follow-up for the presence of baseline TRD. Among 13 evaluable eyes in the control group, baseline TRD was absent in 7 (54%), questionable in 3 (23%), and definite in 3 (23%). Among 11 evaluable eyes in the anti-VEGF group, baseline TRD was absent in 4 (36%), questionable in 2 (18%), and definite in 5 (45%).

The Kaplan–Meier cumulative probability of undergoing vitrectomy to treat TRD was 4.4% (95% CI: 2.7%–7.1%, 16 events) in the control group and 2.2% (1.1%–4.2%, 9 events) in the anti-VEGF group. The 1-year hazard ratio of vitrectomy for TRD in the anti-VEGF group versus the control group was 0.60 (95% CI: 0.27–1.30, $P = 0.19$, Figure 2). Among eyes that developed TRD, the percentage that underwent vitrectomy at the discretion of the investigator was 64% (16 of 25) in the control group and 41% (9 of 22) in the anti-VEGF group. The distribution of visual acuity before and after vitrectomy is shown in **Supplemental Digital Content 1** (see **eTable 1**, http://links.lww.com/IAE/B67).

In a sensitivity analysis, vitrectomy for all types of retinal detachments was considered (traction, rhegmatogenous, and unspecified). The Kaplan–Meier cumulative probability of undergoing vitrectomy for any retinal detachment was 4.9% (95% CI: 3.1%–7.7%, 18 events) in the control group and 3.0% (95% CI: 1.7%–5.3%, 12 events) in the anti-VEGF group. Over 1 year, the hazard ratio of vitrectomy for any retinal detachment in the anti-VEGF group versus the control group was 0.70 (95% CI: 0.35–1.41, $P = 0.31$, see **eFigure 2**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B67).

Relationship Between Diabetic Retinopathy Severity and Traction Retinal Detachment

The likelihood of TRD appeared to increase with the baseline retinopathy severity level in both groups

Table 2. Baseline Participant and Ocular Characteristics by the Treatment Group

	Control Group (N = 396)	Anti-VEGF Group (N = 487)
Female sex, no. (%)	170 (42.9)	220 (45.2)
Race/ethnicity, no. (%)		
Non-Hispanic white	208 (52.5)	275 (56.5)
Non-Hispanic black/African American	101 (25.5)	108 (22.2)
Black/African American	65 (16.4)	87 (17.9)
Asian	9 (2.3)	5 (1.0)
American Indian or Alaskan Native	3 (0.8)	1 (0.2)
Native Hawaiian or Pacific Islander	1 (0.3)	3 (0.6)
More than one race	3 (0.8)	3 (0.6)
Unknown or not reported	6 (1.5)	5 (1.0)
Age (y), median (IQR)	54 (45–61)	56 (47–64)
Diabetes type, no. (%)		
Type 1	84 (21.2)	89 (18.3)
Type 2	301 (76.0)	383 (78.6)
Uncertain	11 (2.8)	15 (3.1)
HbA1c (%), median (IQR)*	8.2 (7.1–9.9)	8.1 (7.0–9.3)
Two study eyes in the present analysis, no. (%)†	58 (14.6)	58 (11.9)
Phakic lens status, no. (%)	334 (84.3)	398 (81.7)
Visual acuity, median (IQR)		
Letter score	66 (78–43)	68 (76–51)
Approximate Snellen equivalent	20/50 (20/32–20/160)	20/50 (20/32–20/100)
OCT central subfield thickness (μm, time-domain equivalent),[16] median (IQR)‡	253 (214–356)	286 (224–404)
ETDRS retinopathy severity level, no. (%)§		
Mild PDR (Level 61)	69 (26.5)	131 (36.2)
Moderate PDR (Level 65)	94 (36.2)	116 (32.0)
High-risk PDR (Levels 71 and 75)	96 (36.9)	113 (31.2)
Advanced PDR (Levels 81 and 85)	1 (0.4)	2 (0.6)
Protocol, no. (%)		
Protocol I	40 (10.1)	51 (10.5)
Protocol J	89 (22.5)	81 (16.6)
Protocol N	136 (34.3)	125 (25.7)
Protocol S	131 (33.1)	130 (26.7)
Protocol T	0	100 (20.5)
Anti-VEGF agent assigned at randomization, no. (%)		
Aflibercept	0	30 (6.2)
Bevacizumab	0	38 (7.8)
Ranibizumab	0	419 (86.0)

IQR, interquartile range; OCT, optical coherence tomography.

*HbA1c was unavailable for 17 eyes in the control group and 24 eyes in the anti-VEGF group.

†Participants could contribute two study eyes in Protocol I, Protocol J, and Protocol S.

‡Central subfield thickness was unavailable for 136 eyes in the control group and 128 eyes in the anti-VEGF group. Optical coherence tomography scans were not gradable at baseline in Protocol N due to vitreous hemorrhage (261 of 264 unavailable values).

§Diabetic retinopathy severity was unavailable for 136 eyes in the control group and 125 eyes in the anti-VEGF group. Fundus photographs were not gradable at baseline in Protocol N due to vitreous hemorrhage (261 of 261 unavailable values). ETDRS, Early Treatment Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy.

(Figure 3). In the control group, the Kaplan–Meier cumulative probability of TRD was 1.5% (1 event), 2.5% (2 events), and 12.2% (11 events) for eyes with mild (Level 61), moderate (Level 65), and high-risk PDR (Levels 71 and 75), respectively. Similarly, in the anti-VEGF group, the Kaplan–Meier cumulative probability of TRD was 0.8% (1 event), 0% (0 events), and 8.6% (9 events) for eyes with mild, moderate, and high-risk PDR. Adjusting for the baseline retinopathy severity level (excluding eyes without gradable photographs; hazard ratio for 1-step increase in the ETDRS retinopathy severity level = 2.63, 95% CI: 1.75–3.94,

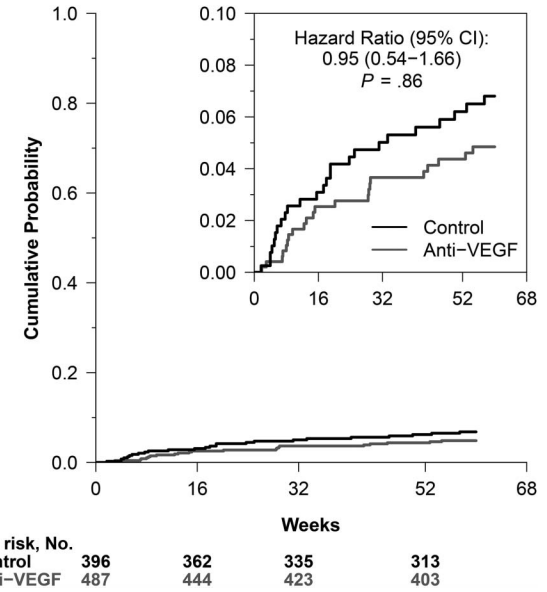

Fig. 1. Traction retinal detachment must have occurred within the first year after randomization. Inset shows y-axis magnified tenfold. Hazard ratio for the anti-VEGF group versus the control group and *P* value are from Cox proportional hazards regression. The Kaplan–Meier cumulative probability of TRD was 6.8% (95% CI: 4.6%–9.9%) in the control group and 4.8% (95% CI: 3.2%–7.3%) in the anti-VEGF group.

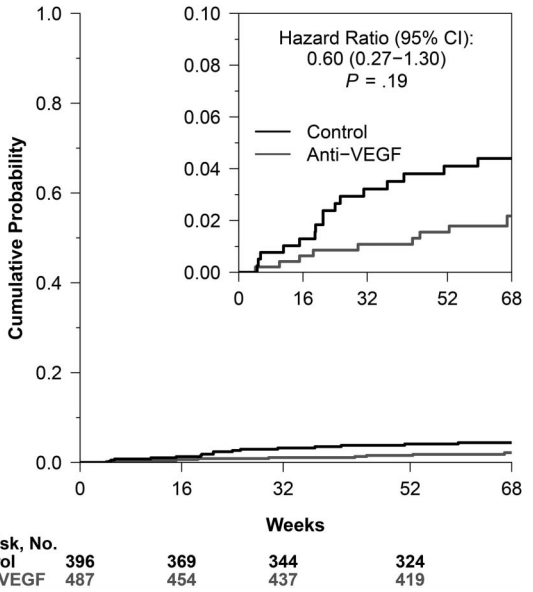

Fig. 2. The traction retinal detachment for which vitrectomy was performed must have occurred within the first year after randomization. Inset shows y-axis magnified tenfold. Hazard ratio for the anti-VEGF group versus the control group and *P* value are from Cox proportional hazards regression. The Kaplan–Meier cumulative probability of vitrectomy for traction retinal detachment was 4.4% (95% CI: 2.7%–7.1%) in the control group and 2.2% (95% CI: 1.1%–4.2%) in the anti-VEGF group.

$P < 0.001$), the hazard ratio for time to TRD in the anti-VEGF group versus the control group was 0.87 (95% CI: 0.40–1.89, $P = 0.72$), which is similar to the unadjusted analysis. The frequency of events by the protocol is shown in **Supplemental Digital Content 1** (see **eTable 2**, http://links.lww.com/IAE/B67).

The likelihood of vitrectomy for TRD also appeared to increase with the diabetic retinopathy severity level in both groups (Figure 3). Kaplan-Meier cumulative probabilities were greatest among eyes with high-risk PDR: 8.9% (8 events) versus 3.5% (3 events) for the control and anti-VEGF groups, respectively. Adjusting for the baseline retinopathy severity level (excluding eyes without gradable photographs; hazard ratio for 1-step increase in the ETDRS retinopathy severity level = 2.49, 95% CI: 1.56–3.99, $P < 0.001$), the hazard ratio for time to vitrectomy for TRD in the anti-VEGF group versus the control group was 0.41 (95% CI: 0.14–1.19, $P = 0.10$), which is similar to the unadjusted analysis.

Discussion

This post hoc analysis pooling five randomized clinical trials suggests that anti-VEGF therapy was not associated with an increased risk of TRD or associated vitrectomy compared with control therapy (laser photocoagulation, sham, or intravitreal saline) over the first year of treatment for PDR or DME among eyes enrolled in these trials. This was true for eyes with all levels of PDR, including high-risk PDR. Because previous studies suggested that TRD formation/progression was within a few weeks, if not a few months of anti-VEGF exposure, this investigation evaluated not only the 1-year results but also the results within the first 60 days of follow-up, wherein the cumulative probability of TRD still was not noted to be greater in the anti-VEGF eyes; specifically, the event rate 2 months after the initiation of anti-VEGF therapy was 2.6% (10 events) among control eyes and 1.5% (6 events) among anti-VEGF eyes.

There is no uniformly accepted definition of "crunch" to describe development or progression of TRD after anti-VEGF treatment. However, the literature[5–7] suggests this description refers to prompt contraction of vascularity of retinal neovascularization with white, sclerotic vessels associated with new or progressive extensive traction detachment. The description has been associated both in the setting of retinopathy of prematurity and in eyes with proliferative retinopathy for which vitrectomy is being planned; neither was evaluated in this investigation. Although some ophthalmologists might extrapolate eyes with PDR in the DRCR Retina Network protocols receiving anti-VEGF for which vitrectomy is not planned to eyes in the literature with proliferative retinopathy for which a "crunch" developed, the results of this investigation suggest that such extrapolation is not warranted.

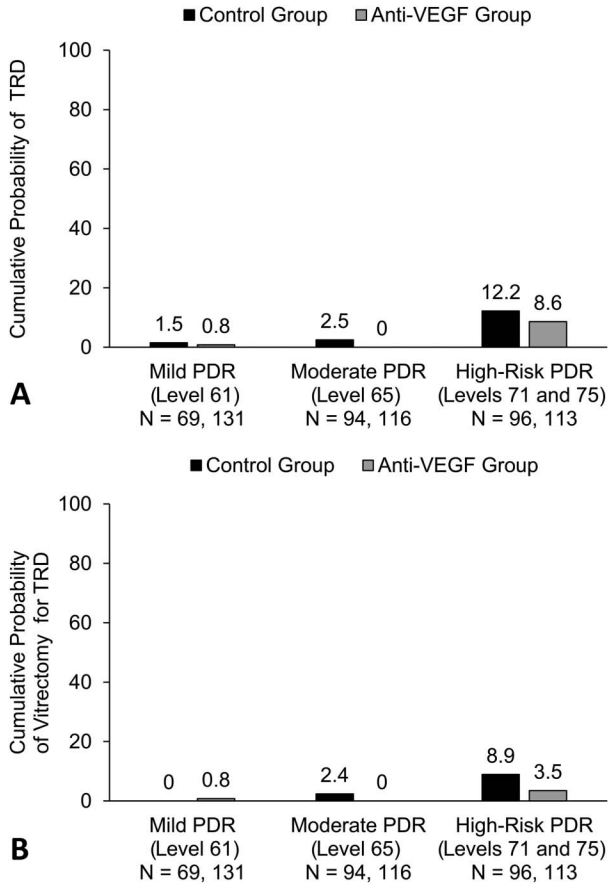

Fig. 3. Cumulative probability of traction retinal detachment (**A**) and vitrectomy to treat traction retinal detachment (**B**) by the Early Treatment Diabetic Retinopathy Study (ETDRS) severity level and treatment group.

Note that eyes with TRD involving or threatening the macula or TRD for which prompt vitrectomy was needed were not enrolled in these studies. Thus, these findings do not necessarily contradict previous reports of new or worsening TRD among eyes receiving bevacizumab for which prompt vitrectomy was planned.[3,5] Although some may extrapolate the observations of previous reports to cases of PDR for which vitrectomy is not planned, the present data do not support such extrapolations.

These findings emphasize the need for comparator groups to determine whether anti-VEGF therapy increases the risk of TRD among eyes with retinal neovascularization for which prompt vitrectomy is not planned. Although anti-VEGF therapy does not eliminate the risk of TRD, comparison with appropriate control groups demonstrates that the risk of TRD in these eyes is unlikely to be increased with anti-VEGF therapy. Future randomized studies of eyes with PDR for which vitrectomy is planned would be helpful to determine the effect of anti-VEGF on TRD risk relative to a control group. The DRCR Retina Network's Protocol AB comparing intravitreous anti-VEGF versus prompt vitrectomy for vitreous hemorrhage from PDR (https://clinicaltrials.gov/; NCT02857491) may provide further insight on this subject.

There are limitations to this post hoc analysis. Outcomes from several trials with varying entry criteria, treatments, and treatment regimens were pooled. The presence of TRD was determined by investigators who were not masked to treatment assignment, and no standardization was provided for the investigators to identify TRD. Traction retinal detachments were not confirmed by reading-center review of fundus photographs. As noted previously, these results may be applicable only to eyes similar to those meeting the eligibility criteria for these DRCR Retina Network studies, notably the exclusion of eyes for which prompt vitrectomy was warranted. Vitrectomy during follow-up within the protocol was performed at investigator discretion, which could introduce bias as to whether an eye went on to vitrectomy because investigators were unmasked to treatment assignment. In most protocols, data on baseline TRD and whether a follow-up TRD involved the macula were not collected. Because the comparison groups were not randomly assigned within a single cohort, characteristics besides anti-VEGF therapy could have contributed to differences in the rates of TRD and vitrectomy. The control group was not completely free of anti-VEGF, as 11.4% (45 of 396 eyes) received ranibizumab per protocol to treat DME in Protocol S within the first year (the analysis window of this study); among the 8 eyes in the control (PRP) group in Protocol S that had a TRD, only 2 received anti-VEGF before the TRD. Strengths of this study include that data were collected prospectively on 883 eyes through a multicenter clinical research network in the context of randomized clinical trials, and each trial had high 1-year retention (95% in Protocol I, 88% in Protocol J, 83% in Protocol N, 90% in Protocol S, and 96% in Protocol T).[3,8–11]

Conclusion

Although eyes with PDR are at risk of developing TRD, this pooled analysis from five DRCR Retina Network protocols does not support the hypothesis that anti-VEGF therapy for DME or PDR increases the risk of TRD or associated vitrectomy compared with a control group. Eyes with all levels of PDR were included in this analysis, including high-risk PDR. However, this conclusion only applies to eyes meeting the eligibility criteria for these protocols and without macula-involving or macula-threatening TRD for

which prompt vitrectomy is planned. Further studies are warranted for eyes with PDR for which prompt vitrectomy is planned. There is little evidence from these five randomized multicenter trials to support a concern that anti-VEGF therapy in eyes with PDR for which prompt vitrectomy is not planned increases the risk of developing TRD (see **Supplemental Digital Content 1**, http://links.lww.com/IAE/B67).

Key words: proliferative diabetic retinopathy, anti–vascular endothelial growth factor, traction retinal detachment.

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