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Factors Associated with Worsening Proliferative Diabetic Retinopathy in Eyes Treated with Panretinal Photocoagulation or Ranibizumab

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Purpose: To compare rates and identify predictive factors for events that represent worsening of proliferative diabetic retinopathy (PDR) in eyes treated with panretinal photocoagulation (PRP) or ranibizumab.

Design: Randomized clinical trial (55 United States sites).

Participants: Three hundred ninety-four study eyes from 305 adults with PDR, visual acuity (VA) 20/320 or better, and no history of PRP.

Intervention: Panretinal photocoagulation or intravitreous ranibizumab injections (0.5 mg/0.05 ml).

Main Outcome Measures: Time from randomization to a composite PDR-worsening outcome defined as the first occurrence of vitreous hemorrhage, retinal detachment, anterior segment neovascularization, or neovascular glaucoma.

Results: Through 2 years, the cumulative probability of worsening PDR was 42% (PRP) versus 34% (ranibizumab; hazard ratio [HR], 1.33; 99% confidence interval [CI], 0.90 to 1.98; $P = 0.063$). Worse baseline levels of diabetic retinopathy severity (Early Treatment Diabetic Retinopathy Study scale) were associated with increased risk of worsening PDR, regardless of treatment group (64% [high-risk PDR or worse] vs. 23% [moderate PDR or better]; HR, 3.97; 99% CI, 2.48 to 6.36; $P < 0.001$). In the PRP group, eyes receiving pattern scan versus conventional single-spot PRP also were at higher risk for worsening PDR (60% vs. 39%; HR, 2.04; 99% CI, 1.02 to 4.08; $P = 0.008$), regardless of the number of spots placed or the number of sittings to complete the initial PRP. Eyes in both groups with vision-impairing (VA 20/32 or worse) center-involved diabetic macular edema (DME) at baseline were required to receive ranibizumab for center-involved DME. Therefore the composite outcome was compared by treatment in the subgroup of eyes that did not have vision-impairing center-involved DME at baseline. For these eyes, the rate of PDR-worsening was greater with PRP than ranibizumab (45% vs. 31%; HR, 1.62; 99% CI, 1.01 to 2.60; $P = 0.008$).

Conclusions: In eyes with PDR, ranibizumab resulted in less PDR worsening compared with PRP, especially in eyes not required to receive ranibizumab for center-involved DME. Although anti-vascular endothelial growth factor therapy requires a more frequent visit schedule than PRP, these findings provide additional evidence supporting the use of ranibizumab as an alternative therapy to PRP for PDR, at least through 2 years. *Ophthalmology 2017;124:431-439 © 2017 by the American Academy of Ophthalmology*

*Supplemental material available at www.aaojournal.org.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) published 2-year primary outcome results from protocol S comparing panretinal photocoagulation (PRP) with intravitreal ranibizumab injections to manage proliferative diabetic retinopathy (PDR).[1] At the 2-year visit, eyes assigned to ranibizumab had an electronic Early Treatment Diabetic Retinopathy (ETDRS) visual acuity (VA) letter score that was no more than 5 letters worse than (noninferior to) eyes managed with PRP. Averaged over the 2-year follow-up, VA (area under the curve) was superior with ranibizumab. Ranibizumab-treated eyes also had less visual field loss (central [30-2] and peripheral [60-4] test patterns) and lower rates of vision-impairing center-involved diabetic macular edema (DME) development. No new safety concerns, systemic or ocular, were identified. Rates of endophthalmitis were low (only 1 eye [0.5%] in the ranibizumab group), and cataract extractions were infrequent, with only 4 (2%) in the ranibizumab group versus 12 (6%) in the PRP group. Although PRP often is considered a so-called one-and-done treatment, 45% of the eyes assigned to PRP required supplemental PRP administration to manage active PDR after completion of initial PRP.

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Events that may represent worsening of PDR include vitreous hemorrhage (VH), retinal detachment (RD), anterior segment neovascularization (neovascularization of the iris [NVI] or neovascularization of the angle [NVA]), neovascular glaucoma (NVG), vitrectomy, and administration of PRP in the ranibizumab group or supplemental PRP in the PRP group. The objective of this study was to compare the development, timing, and severity of these events and interventions in eyes assigned to PRP versus ranibizumab for PDR. Potential predictive factors of these events also were explored.

Methods

Study procedures were reported previously and are summarized briefly.[1] The protocol is available on the DRCR.net web site (www.drcr.net; accessed July 7, 2016) and is registered at clinicaltrials.gov (identification, NCT01489189).

Fifty-five clinical sites enrolled 305 participants (394 study eyes) with a mean age of 52 years; 44% were female, and 52% were white, all study eyes had PDR, no prior PRP, and best-corrected VA letter score of 24 or more (Snellen equivalent, 20/320 or better).[1] Participants with 1 study eye were assigned randomly to prompt PRP (completed in 1−3 sittings) or ranibizumab injections (Lucentis; Genentech, Inc, South San Francisco, CA), whereas participants with 2 study eyes underwent PRP in 1 eye and received ranibizumab treatment in the other. In both treatment groups, all eyes with vision-impairing (VA letter score ≤78 [Snellen equivalent 20/32 or worse]) center-involved DME received ranibizumab at baseline followed by as-needed administration to treat center-involved DME. Randomization to PRP or ranibizumab was stratified by the presence of center-involved DME.

All participants had visits at 16, 32, 52, 68, 84, and 104 weeks. In addition, participants assigned to ranibizumab also had visits every 4 weeks in the first year to determine the need to retreat neovascularization. Visits could be extended up to 16 weeks in the second year if injections were deferred continually. All participants with baseline vision-impairing center-involved DME or those who were administered ranibizumab for center-involved DME (at the investigator's discretion) at any time point may have had additional study visits to assess and treat center-involved DME. The protocol allowed PRP in the ranibizumab group if prespecified failure criteria were met. In the PRP group, supplemental PRP was permitted if the size or amount of neovascularization increased. Best-corrected VA using the Electronic-Early Treatment Diabetic Retinopathy Study test was obtained at all study visits.[2]

Outcomes

The occurrence of VH, RD (traction, rhegmatogenous, or unspecified type), NVI or NVA, and NVG was captured on case report forms completed during study visits by an unmasked investigator. Procedures after randomization including vitrectomy and PRP also were collected. Supplemental PRP was defined as PRP after completion of initial PRP. The indication for vitrectomy was acquired through a query to site personnel after the 2-year follow-up visits were completed. A composite outcome of adverse events representing PDR worsening included the first occurrence of VH, RD, NVI or NVA, or NVG. The number of days from randomization to the date of the event onset or study procedure was used for time-to-event analyses.

Statistical Analyses

Proportional hazards regression was used to test for treatment group differences in rates of PDR-worsening events. For the composite and the supplemental PRP outcomes, 18 baseline and treatment characteristics were evaluated as potential predictive factors (Table S1, available at www.aaojournal.org). Univariate analyses were conducted for each factor while controlling for treatment group. The possibility that baseline characteristic effects differed by treatment group was investigated by including a baseline characteristic by treatment group interaction in a separate model. A multivariate analysis including predictive factors from the univariate analyses with $P < 0.10$ was performed to identify factors associated with PDR-worsening events. Backward stepwise regression was used to construct a final model. A sensitivity analysis of final models considered only participants with nonmissing baseline and treatment characteristic data and produced similar results (data not shown). Severity of VH or RD was explored by calculating the change in VA between the measurement obtained at the visit immediately preceding the event and the visit at which the event was documented.

In these exploratory analyses, there was no formal adjustment for multiple hypothesis testing, and therefore $P < 0.01$ was considered suggestive, rather than definitive, of a true difference and 99% confidence intervals (CIs) are presented. In proportional hazard regressions, a robust sandwich estimate of the covariance matrix was used to control for correlations from participants contributing 2 study eyes. The proportional hazards assumption was verified by testing a time-by-treatment group or time-by-baseline characteristic interaction. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Timing of Events Signifying Worsening of Proliferative Diabetic Retinopathy

The occurrence and frequency of vitrectomy, individual events that represent worsening of PDR (VH, RD, NVI or NVA, and NVG), and the composite outcome by treatment group through 2 years is shown in Table S2 (available at www.aaojournal.org). For the composite outcome, which is the first occurrence of VH, RD, NVI or NVA, or NVG, the cumulative probability was 42% in the PRP group (99% CI, 33% to 52%), compared with 34% (99% CI, 25% to 44%) in the ranibizumab group (hazard ratio [HR], 1.33; 99% CI, 0.90 to 1.98; $P = 0.063$; Fig 1A). The 2-year cumulative probability of VH was 39% (99% CI, 30% to 49%) for the PRP group and 30% (99% CI, 22% to 40%) for the ranibizumab group (HR, 1.38; 99% CI, 0.91 to 2.10; $P = 0.048$; Fig 1B). However, the HR may not have been uniform over the 2 years ($P = 0.032$). Through the first 2 assessment visits at 16 and 32 weeks, the VH rate was greater in the PRP group (HR, 2.15; 99% CI, 1.02 to 4.50; $P = 0.008$), whereas during the remainder of the 2 years of follow-up, this effect was not identified (HR, 1.14; 99% CI, 0.88 to 1.47; $P = 0.20$). The 2-year cumulative probability of RD was low in each treatment group at 11% (99% CI, 6% to 19%) for the PRP group and 5% (99% CI, 2% to 13%) for the ranibizumab group (HR, 2.13; 99% CI, 0.80 to 5.65; $P = 0.046$; Fig 1C). Retinal detachments primarily were tractional: 55% of all RDs in the ranibizumab group and 71% in the PRP group (Table S2, available at www.aaojournal.org). The 2-year

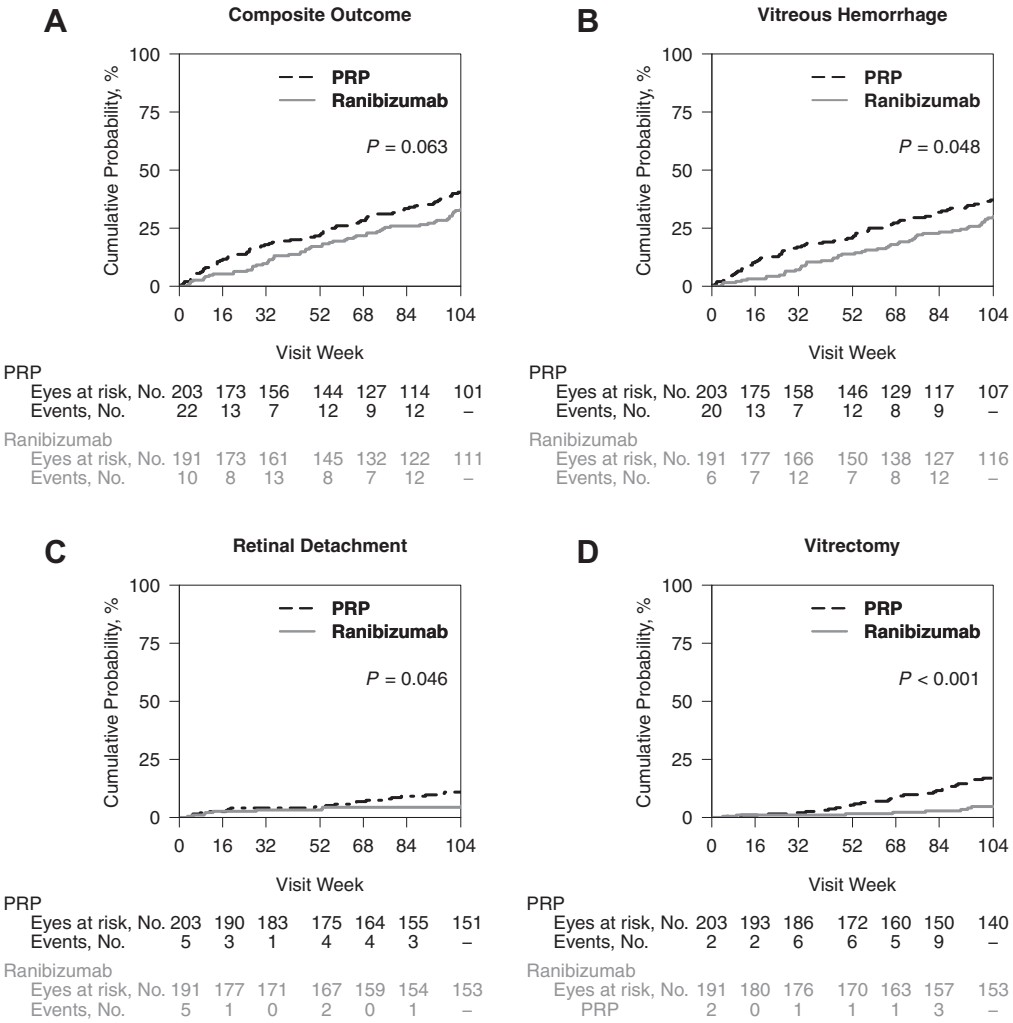

Figure 1. Kaplan-Meier curves showing the cumulative probability of (**A**) the composite outcome of proliferative diabetic retinopathy (PDR)-worsening events (first occurrence of vitreous hemorrhage, retinal detachment, neovascularization of the iris or angle, or neovascular glaucoma), (**B**) vitreous hemorrhage, (**C**) retinal detachment, or (**D**) vitrectomy for eyes assigned to panretinal photocoagulation (PRP; *dashed black*) or to ranibizumab (*solid gray*) to manage PDR.

cumulative probability of vitrectomy was greater among PRP eyes (17%; 99% CI, 11% to 26%) compared with ranibizumab eyes (5%; 99% CI, 2% to 11%; HR, 3.81; 99% CI, 1.46 to 9.91; $P < 0.001$; Fig 1D).

Each of these outcomes was re-evaluated by whether baseline vision-impairing center-involved DME was present, for which ranibizumab was required in both groups (Table S3, available at www.aaojournal.org). When baseline vision-impairing center-involved DME was not present (n = 302 eyes [77%]), the composite outcome event rate was higher in the PRP group (45%; 99% CI, 35% to 56%) compared with the ranibizumab group (31%, 99% CI, 22% to 42%; HR, 1.62; 99% CI, 1.01 to 2.60; $P = 0.008$; Fig S1, available at www.aaojournal.org). Similar findings for individual rates of VH, RD, and vitrectomy are shown in Table S3 (available at www.aaojournal.org).

The 2-year cumulative probability for supplemental PRP administration in the PRP group was 50% (99% CI, 41% to 60%). Most of these procedures (67/92 [73%]) were performed through the 1-year visit, with 35% (32/92) occurring through the 16-week visit (Fig 2). Supplemental PRP may have been administered less frequently in eyes with baseline vision-impairing center-involved DME, which were required to receive ranibizumab (37% vs. 54%; HR, 0.59; 99% CI, 0.29 to 1.23; $P = 0.063$).

Predictive Factors Analysis

Univariate analyses identified several baseline characteristics indicating greater risk of the composite outcome ($P < 0.01$), including the following baseline variables: presence of epiretinal membrane, NVD with NVE on clinical examination, more severe retinopathy on the ETDRS severity scale,[3] and presence of VH (Table 1). The impact of these factors on the composite outcome did not seem to be affected by the treatment group ($P > 0.01$ for all treatment groups by baseline characteristic interactions; Table S4, available at www.aaojournal.org). A total of 11 factors with $P < 0.10$ were entered into the backward stepwise selection process, resulting in a final model with only 1 factor associated with greater risk of the composite outcome among all

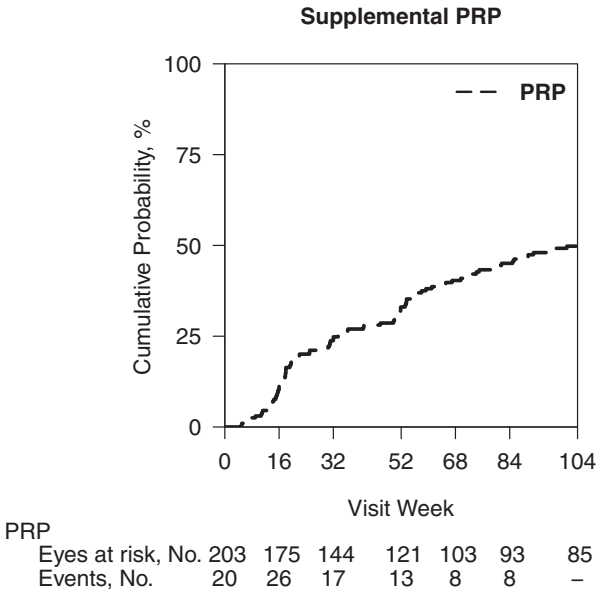

Figure 2. Kaplan-Meier curve showing the cumulative probability of supplemental panretinal photocoagulation (PRP) after completion of the initial PRP for eyes assigned to PRP.

participants: ETDRS diabetic retinopathy severity level (64% [ETDRS level ≥71, high-risk PDR or worse] vs. 23% [ETDRS level ≤65, moderate PDR or better]; HR, 3.97; 99% CI, 2.48 to 6.36; $P < 0.001$). After adjusting for ETDRS retinopathy level, the HR for treatment group (PRP vs. ranibizumab) increased from 1.33 to 1.45 (99% CI, 0.95 to 2.21; $P = 0.024$); similarly among the subgroup of eyes without vision-impairing center-involved DME at baseline, the HR for treatment group also increased, from 1.62 to 1.72 (99% CI, 1.05 to 2.81; $P = 0.004$).

Panretinal Photocoagulation Group Only. With reference to the PRP group, 1 additional factor was associated with greater risk of the composite outcome: PRP laser type (60% [pattern scan] vs. 39% [single spot]; HR, 2.04; 99% CI, 1.02 to 4.08; $P = 0.008$). Allocation to pattern scan or single-spot laser was not randomized and was left to laser availability and investigator discretion. However, baseline participant and ocular factors seemed balanced between eyes receiving pattern scan or single-spot PRP (Table S5, available at www.aaojournal.org), except perhaps epiretinal membrane, which was more common in the single-spot group (51% vs. 34%). Furthermore, of the 19 investigators who used pattern scan laser, 13 (68%) used this method exclusively.

The univariate analysis exploring baseline factors associated with delivery of supplemental PRP (Table 2) identified 3 baseline factors with $P < 0.01$, including younger age, NVD with NVE, and higher ETDRS retinopathy level. Six factors with $P < 0.10$ were entered into the stepwise selection process, resulting in a final model with 2 predictive factors: ETDRS retinopathy level (67% [ETDRS level, ≥71] vs. 41% [ETDRS level, ≤65]; HR, 2.16; 99% CI, 1.26 to 3.72; $P < 0.001$) and age (61% [<50 years] vs. 43% [≥50 years]; HR, 1.85; 99% CI, 1.07 to 3.20; $P = 0.008$).

Indications for Vitrectomy and Use of Panretinal Photocoagulation during Vitrectomy. Vitreous hemorrhage was the primary indication for most vitrectomies, including 24 of 30 (80%) and 6 of 8 (75%) vitrectomy procedures in the PRP and ranibizumab groups, respectively (Table S6, available at www.aaojournal.org). Panretinal photocoagulation, presumably through endolaser or indirect ophthalmoscopic laser delivery systems, was a component of the vitrectomy for 24 of the 30 (80%) procedures in the PRP group and all procedures in the ranibizumab group. Only 1 eye in the ranibizumab group received PRP independent of vitrectomy.

Change in Vision with Vitreous Hemorrhage or Retinal Detachment. The change (mean ± standard deviation) in VA between the 2 visits straddling a VH event was −19.2±24.9 letters for the 69 PRP group eyes and −14.8±28.3 letters for the 52 ranibizumab group eyes (Table S7, available at www.aaojournal.org). The adjusted mean treatment group difference in change in VA straddling a VH event (ranibizumab minus PRP), adjusted for VA before VH, was 5.0 letters worse in the PRP group than the ranibizumab group (99% CI, -7.2 to 17.2; P = 0.29). A 10-letter or more decrease in VA occurred in association with VH in 58% and 42% of cases in the PRP and ranibizumab groups, respectively (ranibizumab minus PRP difference, −16%; 99% CI, −34% to 2%; $P = 0.076$). Only 3 eyes (all in the PRP group) underwent vitrectomy between the onset of VH and the first subsequent VA measurement. Loss of VA associated with RD was, on average, 6.1 letters worse in the PRP group (99% CI, −19.6 to 31.7; $P = 0.48$). Only 2 eyes (both in PRP group) underwent vitrectomy between the onset of RD and the first subsequent VA measurement.

Discussion

Eyes assigned to ranibizumab experienced fewer events that represent worsening of PDR than eyes assigned to PRP (34% vs. 42%; Fig 1A), although this difference did not reach statistical significance ($P = 0.063$). In both treatment groups, eyes with more advanced PDR at study entry were at greater risk for the composite outcome. A treatment group difference was more apparent when the analysis was adjusted for baseline retinopathy severity ($P = 0.024$) and in the subgroup of eyes without vision-impairing center-involved DME at baseline ($P = 0.004$, adjusting for baseline retinopathy severity). This subgroup partially removes the potential confounding effect of ranibizumab use in the PRP group for the treatment of center-involved DME because eyes with baseline vision-impairing center-involved DME were required to receive ranibizumab for center-involved DME treatment.

In the PRP group, eyes that received pattern scan PRP were more likely to have PDR-worsening events compared with eyes treated with single-spot PRP (Table 1). Although approximately two-thirds of the investigators using pattern scan PRP used this method exclusively, eyes were not assigned randomly to pattern scan or single-spot PRP, subjecting these results to potential bias and confounding. Possible explanations for a difference in efficacy include the type and number of burns or total area of retinal ablation created by the laser. While controlling for laser type, the number of laser burns initiated according to the instrument counter was not associated with worsening of PDR. This exploratory analysis of laser type used prospective data from participants who seemed to have mostly similar baseline characteristics (Table S5, available at www.aaojournal.org).

Table 1. Univariate Analyses of Baseline Characteristics as Potential Predictive Factors for Proliferative Diabetic Retinopathy Worsening (Vitreous Hemorrhage, Retinal Detachment, Anterior Segment Neovascularization, or Neovascular Glaucoma)

Characteristic	Percentage of Eyes with an Event (No. of Eyes/Total)		P Value	Hazard Ratio (99% Confidence Interval)
	Ranibizumab	*Panretinal Photocoagulation*		
All eyes	30 (58/191)	37 (75/203)		
Gender				
Female	25 (21/83)	32 (29/92)	0.075	—
Male	34 (37/108)	41 (46/111)		1.42 (0.85–2.37)
Age (yrs)				
<50	28 (23/83)	44 (42/95)	0.014	1.16 (0.71–1.89)
≥50	32 (35/108)	31 (33/108)		—
Race/ethnicity*				
White	22 (22/100)	34 (34/101)	0.014	—
Nonwhite	40 (36/89)	40 (40/99)		1.61 (0.98–2.66)
Diabetes type†				
1	28 (12/43)	44 (18/41)	0.82	1.05 (0.59–1.87)
2	31 (44/140)	36 (56/155)		—
Diabetes duration (yrs)				
<20	29 (31/106)	36 (43/119)	0.67	—
≥20	32 (27/85)	38 (32/84)		1.07 (0.65–1.74)
HbA_{1c} (%)‡				
<9	26 (28/106)	32 (32/101)	0.20	—
≥9	37 (29/78)	42 (41/97)		1.55 (0.94–2.56)
Hypertension				
No	32 (20/63)	40 (25/62)	0.64	—
Yes	30 (38/128)	35 (50/141)		0.91 (0.53–1.55)
Visual acuity				
20/25 or better (letter score ≥79)	23 (20/87)	42 (39/93)	0.063	—
20/32 or worse (letter score <79)	37 (38/104)	33 (36/110)		1.17 (0.72–1.89)
Central subfield thickness, (Stratus equivalent)§				
<250	27 (34/125)	41 (55/134)	0.88	1.00 (0.61–1.67)
≥250	36 (23/64)	30 (20/67)		—
Vision-impairing center-involved DME§				
No	28 (41/147)	40 (62/155)	0.85	—
Yes	38 (16/42)	28 (13/46)		0.96 (0.54–1.70)
Epiretinal membrane (on OCT)‖				
No	23 (19/84)	28 (28/101)	<0.001	—
Yes	35 (34/97)	48 (45/93)		1.94 (1.17–3.19)
Vitreomacular traction (on OCT)¶				
No	28 (33/118)	37 (53/145)	0.63	—
Yes	32 (19/59)	41 (21/51)		1.10 (0.67–1.80)
Neovascularization on clinical examination#				
NVD or NVE only	25 (29/114)	28 (35/125)	<0.001	—
NVD and NVE	38 (27/71)	53 (39/74)		2.13 (1.34–3.39)
Diabetic retinopathy severity (ETDRS)**				
Moderate PDR (level 65) or better	15 (17/117)	25 (31/125)	<0.001	—
High-risk PDR (level 71) or worse	57 (41/72)	58 (43/74)		3.97 (2.47–6.39)
Lens status				
Phakic	29 (50/170)	37 (70/187)	0.34	—
PC IOL	38 (8/21)	31 (5/16)		1.36 (0.59–3.12)
Vitreous hemorrhage at baseline				
No	25 (33/131)	29 (38/133)	<0.001	—
Yes	42 (25/60)	53 (37/70)		2.28 (1.43–3.63)
PRP laser type††				
Conventional single spot		34 (56/164)		—
Pattern scan		49 (19/39)	0.018	1.87 (0.95–3.68)
No. of PRP spots††,‡‡				
Conventional single spot <1400 or pattern scan <2200		44 (46/105)	0.19	—
Conventional single spot ≥1400 or pattern scan ≥2200		30 (29/98)		1.49 (0.81–2.77)

(*Continued*)

Table 1. (Continued.)

Characteristic	Percentage of Eyes with an Event (No. of Eyes/Total)		P Value	Hazard Ratio (99% Confidence Interval)
	Ranibizumab	*Panretinal Photocoagulation*		
No. of PRP sittings[††]				
1		39 (42/109)	0.59	—
2 to 3		35 (33/94)		0.88 (0.49–1.60)

DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA_{1c} = glycosylated hemoglobin; NVD = neovascularization of the disc; NVE = neovascularization elsewhere; OCT = optical coherence tomography; PC IOL = posterior chamber intraocular lens; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; — = reference category.
*Data missing for 2 eyes in the ranibizumab group and 3 eyes in the PRP group.
[†]Data missing for 8 eyes in the ranibizumab group and 7 eyes in the PRP group.
[‡]Data missing for 7 eyes in the ranibizumab group and 5 eyes in the PRP group.
[§]Data missing for 2 eyes in each group.
[||]Data missing for 10 eyes in the ranibizumab group and 9 eyes in the PRP group.
[¶]Data missing for 14 eyes in the ranibizumab group and 7 eyes in the PRP group.
[#]Data missing for 6 eyes in the ranibizumab group and 4 eyes in the PRP group.
**Data missing for 2 eyes in the ranibizumab group and 4 eyes in the PRP group.
[††]Panretinal photocoagulation group only.
[‡‡]These are median values rounded to the nearest hundred. *P* value is from analysis with number of spots as a continuous variable and controlling for PRP laser type.

Furthermore, this observation of worse outcomes with pattern scan laser is consistent with a retrospective comparative case series that found pattern scan PRP less effective for regression of retinal neovascularization.[4] Nonetheless, the clinical relevance of this finding is difficult to determine from this study.

Nearly half of the PRP eyes required supplemental PRP, regardless of the number of spots and regardless of whether the initial PRP was completed in 1 or multiple sessions. Higher baseline levels of ETDRS retinopathy also were associated with higher rates of supplemental PRP in the PRP group, as was younger age at enrollment (Table 2). This finding provides further evidence to support regular monitoring of eyes with PDR after completion of initial PRP, particularly those with higher levels of retinopathy and those who are not receiving anti-VEGF therapy for DME, because they remain at continued risk of vision loss.

Vitreous hemorrhage was the most common adverse event considered in this analysis. An exploratory analysis indicated a treatment group difference in rates of VH during the early months of follow-up, with the PRP group experiencing VH at a faster rate than the ranibizumab group through 32 weeks. Event rates were similar for the remaining follow-up through 2 years. The ranibizumab group received 4 mandatory monthly injections (with most receiving 6 consecutive doses), but injection frequency requirements were relaxed beyond the 6-month visit based on disease regression. It is unknown how a more intense treatment regimen would have affected outcomes. Nevertheless, recurrent VH (after first VH and within 2 years of randomization) occurred at a low rate in each treatment group, with rebleeding in 18 (9%) and 16 (8%) of PRP and ranibizumab eyes, respectively (Table S2, available at www.aaojournal.org).

Both groups had vision loss associated with VH, which may have been more severe in the PRP eyes (Table S7, available at www.aaojournal.org). The protocol required investigators to wait at least 8 weeks for a nonclearing VH before proceeding to vitrectomy (in the absence of known RD, NVI, or NVA). Investigators, who were not masked to study assignment, may have been more comfortable continuing to observe an eye with VH before proceeding to vitrectomy in the ranibizumab group. Therefore, because VH was the primary indication for surgery in both groups (Table S6, available at www.aaojournal.org), the reduced incidence of VH in the ranibizumab group and the potential difference in VH severity may account for the finding that eyes in the PRP group were more likely to undergo vitrectomy (Fig 1D; HR, 3.81; 99% CI, 1.46 to 9.91; $P < 0.001$). Of note, only 13% (7/52) of VH eyes in the ranibizumab group compared with 42% (29/69) of VH eyes in the PRP group underwent vitrectomy by the end of 2 years, further suggesting that VH may have been associated with more protracted vision impairment in the PRP group, that investigators were more comfortable deferring vitrectomy for eyes receiving anti-vascular endothelial growth factor treatment, or both.

Inclusion criteria of this study had some overlap with inclusion criteria of the Diabetic Retinopathy Study (DRS) and the ETDRS, but were not identical to either. Participants in protocol S were required to have PDR in at least 1 eye, whereas DRS participants had at least 1 eye with PDR or 2 eyes with nonproliferative diabetic retinopathy, and ETDRS participants' eyes had a range of disease that varied from mild NPDR to non–high-risk PDR. The DRS explored predictors of severe vision loss, whereas the ETDRS and this study evaluated factors associated with worsening of retinopathy. In the DRS, the most important predictor of severe vision loss was high-risk PDR.[5] In the ETDRS, a retinopathy severity

Table 2. Univariate Analyses of Baseline Characteristics as Potential Predictive Factors for Supplemental Panretinal Photocoagulation (Panretinal Photocoagulation Group Only)

Characteristic	Percentage of Eyes with an Event (No. of Eyes/Total)	*P* Value	Hazard Ratio (99% Confidence Interval)
All eyes	45 (92/203)		
Gender			
Female	37 (34/92)	0.033	—
Male	52 (58/111)		1.59 (0.91–2.77)
Age (yrs)			
<50	57 (54/95)	0.002	1.89 (1.09–3.27)
≥50	35 (38/108)		—
Race/ethnicity*			
White	45 (45/101)	0.92	—
Nonwhite	45 (45/99)		1.02 (0.59–1.76)
Diabetes type†			
1	51 (21/41)	0.33	1.28 (0.67–2.43)
2	44 (68/155)		—
Diabetes duration (yrs)			
<20	47 (56/119)	0.41	—
≥20	43 (36/84)		0.87 (0.50–1.51)
HbA_{1c} (%)‡			
<9	42 (42/101)	0.18	—
≥9	49 (48/97)		1.34 (0.78–2.32)
Hypertension			
No	50 (31/62)	0.48	—
Yes	43 (61/141)		0.86 (0.49–1.51)
Visual acuity			
20/25 or better (letter score ≥79)	49 (46/93)	0.51	—
20/32 or worse (letter score <79)	42 (46/110)		0.88 (0.51–1.50)
Central subfield thickness, time-domain equivalent (μm)§			
<250	50 (67/134)	0.33	—
≥250	37 (25/67)		0.70 (0.38–1.29)
Vision-impairing center-involved DME§			
No	50 (77/155)	0.063	—
Yes	33 (15/46)		0.59 (0.29–1.23)
Epiretinal membrane (on OCT)‖			
No	45 (45/101)	0.67	—
Yes	47 (44/93)		1.09 (0.63–1.89)
Vitreomacular traction (on OCT)¶			
No	43 (63/145)	0.25	—
Yes	53 (27/51)		1.30 (0.72–2.36)
Diabetic retinopathy severity (clinical examination)#			
NVD or NVE only	37 (46/125)	0.001	—
NVD and NVE	58 (43/74)		1.97 (1.14–3.41)
Diabetic retinopathy severity (ETDRS)**			
Level 65 or less	38 (47/125)	<0.001	—
High-risk PDR (level 71 or more)	61 (45/74)		2.08 (1.21–3.57)
Lens status			
Phakic	45 (85/187)		—
PC IOL	44 (7/16)	0.43	1.36 (0.50–3.76)
Vitreous hemorrhage at baseline			
No	44 (58/133)	0.40	—
Yes	49 (34/70)		1.20 (0.69–2.09)
PRP laser type			
Conventional single spot	44 (72/164)	0.061	—
Pattern scan	51 (20/39)		1.61 (0.84–3.09)
No. of PRP spots††			
Conventional single spot <1400 or pattern scan <2200	53 (56/105)	0.24	—
Conventional single-spot ≥1400 or pattern scan ≥2200	37 (36/98)		1.47 (0.84–2.56)

(*Continued*)

Table 2. (Continued.)

Characteristic	Percentage of Eyes with an Event (No. of Eyes/Total)	P Value	Hazard Ratio (99% Confidence Interval)
No. of PRP sittings			
1	50 (54/109)	0.15	—
≥2	40 (38/94)		0.74 (0.43–1.27)

DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA_{1c} = glycosylated hemoglobin; NVD = neovascularization of the disc; NVE = neovascularization elsewhere; OCT = optical coherence tomography; PC IOL = posterior chamber intraocular lens; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; — = reference category.
*Data missing for 3 eyes.
†Data missing for 7 eyes.
‡Data missing for 5 eyes.
§Data missing for 2 eyes.
||Data missing for 9 eyes.
¶Data missing for 7 eyes.
#Data missing for 4 eyes.
**Data missing for 4 eyes.
††These are median values rounded to the nearest hundred. *P* value is from analysis with number of spots as a continuous variable and controlling for PRP laser type.

scale based on fundus photographic features predicted increased rates of progression to PDR and high-risk PDR.[6] In the present study, the multivariate analysis identified ETDRS retinopathy level as the most important factor for worsening of PDR, regardless of management method.

The exploratory analyses conducted for this report have limitations. Completion of the 2-year visit occurred in 87% of surviving participants, which may have affected observed rates of PDR-worsening events. This level of retention is close to the level seen at 2 years in recent DRCR.net studies of DME (91% in protocol T and 90% in protocol I) and is better than the 84% and 86% seen in VISTA/VIVID and RISE/RIDE at 2 years, respectively.[7–10] The protocol required eyes assigned to the PRP group with vision-impairing center-involved DME at baseline to receive ranibizumab (23% of PRP eyes) and allowed for initiation of ranibizumab for center-involved DME at investigator discretion at baseline (additional 12% of PRP eyes) and follow-up (additional 18% of PRP eyes). The fact that more than half of the PRP eyes were exposed to ranibizumab potentially lowered the rate of PDR-related complications in this treatment group (Table S3, available at www.aaojournal.org). Finally, as previously noted, the nature of the treatments precluded masking participants and clinicians. Although this likely had no bearing on the development or recognition of VH, RD, NVI or NVA, or NVG, it may have influenced decisions to proceed with vitrectomy or supplemental PRP.

In summary, there were generally better outcomes (fewer PDR-worsening events) in eyes treated with ranibizumab versus PRP for PDR. Although anti-vascular endothelial growth factor therapy requires compliance to a more frequent visit schedule than PRP (median of 16 visits with PRP vs. 22 visits with ranibizumab through 2 years), these findings provide additional evidence to support the use of ranibizumab as an alternative therapy to PRP for PDR, at least through 2 years of follow-up. Diligent follow-up is required because more than one-third of eyes treated with either approach may experience a PDR-worsening event in this period. Follow-up through 5 years is ongoing.

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Footnotes and Financial Disclosures

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A complete list of the Diabetic Retinopathy Clinical Research Network investigators who participated in this trial is available in *JAMA*. 2015;314(20):2137−2146.

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Abbreviations and Acronyms:
CI = confidence interval; **DME** = diabetic macular edema; **DRCR.net** = Diabetic Retinopathy Clinical Research Network; **DRS** = Diabetic Retinopathy Study; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **HR** = hazard ratio; **NVA** = neovascularization of the angle; **NVG** = neovascular glaucoma; **NVI** = neovascularization of the iris; **PDR** = proliferative diabetic retinopathy; **PRP** = panretinal photocoagulation; **RIDE** = A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus; **RISE** = A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus; **RD** = retinal detachment; **VA** = visual acuity; **VISTA** = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema; **VIVID** = Intravitreal Aflibercept Injection in Vision Impairment Due to DME; **VH** = vitreous hemorrhage.

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