ASRS American Society of Retina Specialists

Journal of VitreoRetinal Diseases
1-11

DOI: 10.1177/2474126419893829
jvrd.sagepub.com
SAGE

American Society of Retina Specialists Clinical Practice Guidelines: Management of Nonproliferative and Proliferative Diabetic Retinopathy Without Diabetic Macular Edema

Yoshihiro Yonekawa, MD[1], Yasha S. Modi, MD[2], Leo A. Kim, MD, PhD[3], Dimitra Skondra, MD, PhD[4], Judy E. Kim, MD[5], and Charles C. Wykoff, MD, PhD[6]

Keywords
anti-VEGF, diabetes mellitus, diabetic retinopathy, diabetic retinopathy severity scale, intravitreal injection, laser photocoagulation, nonproliferative diabetic retinopathy, panretinal photocoagulation, proliferative diabetic retinopathy, vascular endothelial growth factor

Diabetic retinopathy (DR) is common, preventable, and treatable, with blinding consequences that affect working-aged adults, making it a major focus of public health internationally.[1,2] More than 30 million people live with diabetes in the United States, according to the 2017 National Diabetes Statistics Report.[3] The National Eye Institute estimates that 7.7 million also have DR based on 2010 census data, and projects the prevalence to double by 2050.[4] DR affects more people in the United States than age-related macular degeneration and glaucoma combined.

Although the prevalence of DR has been surging,[4] the severity of encountered disease overall may have decreased,[5] owing to significant strides in the past several decades in screening, diagnostic imaging, and medical management. This underscores the importance of continued implementation of up-to-date management for patients with diabetes.

This clinical practice guidelines from the American Society of Retina Specialists (ASRS) summarize major clinical studies with discussion that may help guide retina specialists in tailoring the treatment of patients with DR. The topic of DR is extensive. Therefore, we focus on the treatment of nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR) *without* diabetic macular edema (DME) in this article. DME is the most common cause of visual impairment in patients with DR, and separate ASRS clinical practice guidelines have been previously published on the topic.[6] Screening, imaging, and vitreoretinal surgery are also notable clinical themes within DR that will not be detailed in this article.

Systemic Optimization

DR is a microvascular end-organ complication of diabetes mellitus. The evidence for optimizing systemic glycemic and cardiovascular factors is well established for decreasing mortality and morbidity, and should be reinforced with visits with the retina specialist.[7,8] The American Diabetes Association (ADA) recommends glycemic, blood pressure, and serum lipid optimization to reduce the risk or slow the progression of DR.[9]

Glycemic Goals

The Diabetic Control and Complications Trial (DCCT) definitively established the relationship between hyperglycemia and DR in patients with type 1 diabetes.[10] Intensive glycemic

[1] Mid Atlantic Retina, Wills Eye Hospital, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA
[2] Department of Ophthalmology, New York University School of Medicine, New York, NY, USA
[3] Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA
[4] Department of Ophthalmology and Visual Science, Retina Service, University of Chicago, Chicago, IL, USA
[5] Department of Ophthalmology & Visual Sciences, Medical College of Wisconsin, Milwaukee, WI, USA
[6] Retina Consultants of Houston, Blanton Eye Institute, Houston Methodist Hospital, Weill Cornell Medical College, Houston, TX, USA

Corresponding Author:
Yoshihiro Yonekawa, MD, Mid Atlantic Retina, Wills Eye Hospital, Sidney Kimmel Medical College, Thomas Jefferson University, 840 Walnut St, Philadelphia, PA 19107, USA.
Email: yyonekawa@midatlanticretina.com

control resulted in less retinopathy progression, and earlier initiation of glycemic control resulted in improved outcomes. The Epidemiology of Diabetes Interventions and Complications study followed the DCCT cohort longitudinally and found that the initial intensive glycemic control had lasting effects decades later.[11] The United Kingdom Prospective Diabetes Study Group showed similar benefits of glycemic control in patients with type 2 diabetes.[12] Numerous subsequent clinical trials have also demonstrated the importance of glycemic control in controlling DR.[13-15]

Hemoglobin A_{1c} (HbA_{1c}) is an indirect measure of average glycemia over approximately 3 months, and is currently the primary method of assessing glycemic management. The ADA currently recommends a target of HbA_{1c} less than 7 for many nonpregnant adults, but the goal is tailored for individual patients, and HbA_{1c} is only one dimension of the glycemic index.[16] Conditions that affect red blood cell turnover may cause inaccurate values, and patients with severe insulin deficiency who are prone to glycemic variability and hypoglycemia are best evaluated by also incorporating continuous glucose monitoring or results from self-monitored blood glucose testing. Of note, glycemic control needs to be balanced with hypoglycemic episodes, which can be life-threatening. These complexities underscore the importance of continued regular follow-up with the primary care and endocrinology teams.

Blood Pressure Targets

Hypertension is an important comorbidity for patients with diabetes, and nonpregnant patients are recommended to maintain blood pressures of less than 140/90 mm Hg to minimize cardiovascular events and microvascular complications.[17] Lower targets may be appropriate for individuals with cardiovascular risk factors, but this needs to be achieved with safety in mind.

Various clinical trials have found that blood pressure control decreases the risk of developing new retinopathy both in type 1 and type 2 diabetes.[15,18-21] A meta-analysis of several studies calculated a 20% reduction in the incidence of retinopathy with blood pressure intervention.[22] Whereas hypertension is a definite risk factor for DR,[21,23] the data are mixed regarding the association between blood pressure control and the progression of retinopathy that is already established.[14,22] Nevertheless, the benefits of blood pressure optimization are evident, and should be reinforced with patient encounters.

Serum Lipid Control

Lipid management is also integral to overall diabetes care. Nonpregnant patients aged 40 years or older, or those of any age with atherosclerotic cardiovascular disease risk factors, are currently recommended to initiate statin therapy of varying intensities to lower low-density lipoprotein cholesterol.[8]

However, the link between traditional serum lipids and DR has not been reliably established in epidemiological studies.[24-27] The ACCORD studies found that fenofibrate in combination with simvastatin significantly decreased the progression of retinopathy in patients with type 2 diabetes, and simvastatin alone did not.[13,14] This protective effect was most pronounced in participants with baseline mild NPDR. Similar benefits of fenofibrate were evident in the FIELD study.[28]

Diabetic Retinopathy Severity Scale

The US Food and Drug Administration (FDA) recently approved DR grading as an approvable end point for clinical trials targeting pharmaceutical registration. The Airlie House classification was one of the initial standardizations of nomenclature.[29] It was a consensus reached by expert deliberation that took place in 1968. The Airlie House classification was modified for the Diabetic Retinopathy Study (DRS),[30] and again for the Early Treatment Diabetic Retinopathy Study (ETDRS).[31]

The ETDRS Diabetic Retinopathy Severity Scale (DRSS) has become the gold standard for research purposes (Table 1). Reference images can be found in the original publications.[31,33] Levels 47 and 53 are bold because they are key levels to remember for potential treatment of NPDR without DME, which will be discussed in subsequent sections.

The ETDRS defined the natural history of the different levels of retinopathy in the treatment-deferred arm.[34] Table 2 summarizes the 1- and 5-year risks for progression to PDR or high-risk PDR, stratified by the DRSS. There is increasing risk over time, with higher risk in those with more severe retinopathy at baseline.

The American Academy of Ophthalmology devised a simplified severity scale, published in 2003,[35] to provide a more user-friendly system for routine clinical use (Table 3).

There is a classification for DME in this publication as well,[35] but it is outside the scope of this article.

Laser for Proliferative Diabetic Retinopathy

Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study

Panretinal photocoagulation (PRP) has been the standard of care in the treatment of PDR for decades, based on the findings from the DRS and the ETDRS. In the DRS, patients with PDR in at least 1 eye or severe NPDR in both eyes had 1 eye randomly assigned to prompt PRP (either argon or xenon arc), and the other eye observed. The study found that prompt PRP for patients with high-risk PDR decreased the risk of severe vision loss (< 5/200) by 50%.[36]

The DRS laser burns were large (500 or 1000 μm for argon, 3 or 4.5° for xenon) compared to modern lasering techniques. Constriction of the visual field to 45° or less occurred in 5% and 25% of eyes treated with argon and xenon, respectively, and a decrease in 1 or more lines of visual acuity (VA) occurred in 14% and 30% of eyes treated with argon and xenon, respectively.

The ETDRS subsequently addressed the timing and intensity of PRP for PDR, and focal laser for DME. A total of 3711 patients with moderate or severe NPDR or early PDR ("early" PDR

Table 1. Early Treatment Diabetic Retinopathy Study: Diabetic Retinopathy Severity Scale.

Level	Severity	Characteristics
10	No retinopathy	–
20	Very mild NPDR	MAs only
35[a]	Mild NPDR	MAs + HEs, CWS, and/or mild RHs
43	Moderate NPDR	43A: moderate RHs in 4 quadrants or severe in 1 43B: mild IRMA in 1 to 3 quadrants
47	**Moderately severe NPDR**	**47A: 43A + 43B** **47B: mild IRMA in 4 quadrants** **47C: severe RH in 2-3 quadrants** **47D: venous beading in 1 quadrant**
53	**Severe NPDR**	**53A: ≥ 2 level 47 characteristics** **53B: severe RH in 4 quadrants** **53C: moderate to severe IRMA in 1+ quadrant** **53D: venous beading in 2+ quadrants**
	Very severe NPDR	**53E: ≥ 2 level 53A-D characteristics**
61	Mild PDR	NVE < 0.5 DA in 1+ quadrants
65	Moderate PDR	65A: NVE ≥ 0.5 DA in 1+ quadrants 65B: NVD < 1/4 to 1/3 DAs
71, 75	High-risk PDR	Larger NVD, or NVE ≥ 0.5 DA with VH or PRH, or VH or PRH obscuring ≥ 1 DA
81, 85	Advanced PDR	View partially obscured by VH or PRH from NV, or macula involving retinal detachment

Abbreviations: CWS, cotton-wool spots; DA, disc area: HE, hard exudate; IRMA, intraretinal microvascular abnormality; MA, microaneurysm; NPDR, nonproliferative diabetic retinopathy; NV, neovascularization; NVD, neovascularization of the disc; NVE, neovascularization elsewhere; PDR, proliferative diabetic retinopathy; PRH, preretinal hemorrhage; RH, retinal hemorrhage; VH, vitreous hemorrhage.
Source: Adopted from reference 32.
[a]Levels 43 and higher all required MAs.
Bold indicates key levels to remember for potential treatment of NPDR without diabetic macular edema.

Table 2. Risk of Progression to Proliferative Diabetic Retinopathy (PDR)[32] and High-Risk PDR[34] in the Early Treatment Diabetic Retinopathy Study.

DRSS Level	1-y, Any PDR	5-y, Any PDR	1-y, High-Risk PDR	5-y, High-Risk PDR
43 (moderate NPDR)	12%	44%	3%	27%
47 (moderately severe NPDR)	26%	66%	9%	39%
53a to d (severe NPDR)	44% - 51%	75% - 81%	15%	56%
53e (very severe NPDR)	75%	90%	45%	71%
61 (mild PDR)	–	–	22%	64%
≥ 65 (moderate PDR)	–	–	46%	75%

Abbreviations: DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 3. International Clinical Diabetic Retinopathy Disease Severity Scale.

No Apparent DR	No Abnormalities
Mild NPDR	MAs only
Moderate NPDR	More than just MAs, but less than severe NPDR
Severe NPDR	DBH in 4 quadrants (> 20/quadrant), and/or venous beading in 2+ quadrants, and/or IRMA in 1+ quadrants, without PDR
PDR	Neovascularization, and/or preretinal/vitreous hemorrhage

Abbreviations: DBH, dot blot hemorrhage; DR, diabetic retinopathy; IRMA, intraretinal microvascular abnormality; MA, microaneurysm; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

referred to DRSS levels 61 [mild PDR] or 65 [moderate PDR]) in both eyes had 1 eye assigned to "early" treatment, and the fellow eye to "deferred" treatment. "Early" treatment referred to immediate PRP and/or focal laser, followed by purposely "delayed" but routinely administered focal laser for DME, or PRP when severe NPDR or early PDR developed (ie, not waiting until high-risk PDR). "Deferred" treatment was the control arm, for which PRP was not administered until high-risk PDR developed.

Treatment involved 1 of 4 combinations of mild or full PRP, plus direct or grid focal laser, with various timings of laser application. There were 3 categories of eyes:

1. Eyes without clinically significant macular edema (CSME) underwent early photocoagulation (immediate mild PRP and delayed [at least 4 months] focal laser if CSME developed [n = 590], or immediate full PRP and delayed focal [n = 583]), or deferral of photocoagulation (full PRP only when the eye developed high-risk PDR and/or focal if CSME developed [n = 1179]).

2. Eyes with mild or moderate NPDR with CSME underwent early photocoagulation (immediate focal laser and delayed mild PRP [until severe NPDR or worse developed] mild PRP [n = 365], or immediate mild PRP and delayed focal [delayed for at least 4 months] [n = 365], or immediate focal and delayed full PRP [n = 362], or immediate full PRP and delayed focal [n = 356]), or deferral of photocoagulation treatments as above (n = 1429).
3. Eyes with severe NPDR or mild PDR with CSME underwent early photocoagulation (immediate mild PRP and immediate focal [n = 276], or immediate mild PRP and delayed focal [n = 272], or immediate full PRP and immediate focal [n = 272], or immediate full PRP and delayed focal [n = 270]), or deferral of photocoagulation treatments as above (n = 1103).

Mild PRP settings used 500 μm spot sizes, 0.1-second duration, placed 1 or more spot sizes apart, greater than 2 disc diameters from the fovea, to the equator. Full PRP was also 500 μm for 0.1 seconds, but placed half-spot sizes apart.

Early photocoagulation (2.6%) and deferred treatment (3.7%) both resulted in similar low risks for severe vision loss at 5 years.[34] In eyes without macular edema, the 5-year rate of converting to high-risk PDR was 18.8% for early full PRP, 26.9% for early mild PRP, and 38.5% for those with deferred treatment. The study concluded that if patients are able to maintain good follow-up, PRP should be deferred for mild and moderate NPDR, that PRP can be considered for severe NPDR or mild PDR depending on the circumstances, and that prompt PRP is recommended for high-risk PDR.

Mild or Full Panretinal Photocoagulation

Between mild and full PRP in the ETDRS, mild PRP resulted in less moderate vision loss, and less visual field constriction, but double the rate of progression to high-risk PDR.[34] These data demonstrated the importance of balancing the symptomatic benefits of milder laser with the risk of progression. These findings may also imply that PRP intensity may be titrated based on severity of disease, where milder PRP may be employed for milder PDR, and more intense PRP may be applied for more severe PDR. However, there is an absence of clinical data to directly support the practice of varying laser intensity based on DR severity.

Diabetic Macular Edema Progression After Panretinal Photocoagulation

The ETDRS also confirmed that concurrent DME may develop or worsen after PRP, and that the best approach to prevent vision loss was to treat the DME first, before PRP.[34] Focal laser treatment of DME is performed less often in today's era of pharmaceutical interventions for DME, but the concept of treating concurrent DME in eyes with PDR remains relevant. In the Diabetic Retinopathy Clinical Research Network's (DRCR.net) Protocol J, 354 eyes with center-involving DME and severe NPDR or PDR were randomly assigned to 2 monthly ranibizumab (Lucentis; Genentech, Inc) 0.5 mg injections, or 1 triamcinolone acetonide 4 mg injection, or sham, after which they underwent focal laser treatment followed by PRP.[37] The study showed that both pharmaceutical treatments of the DME prior to the laser sessions resulted in superior visual and anatomic outcomes at 14 weeks.

Single-Spot vs Pattern Lasers

There are several methods of delivering PRP today: single-spot slit-lamp delivery, single-spot indirect laser delivery, and multispot pattern laser slit-lamp delivery. The theoretical benefit of pattern lasers is increased efficiency and therefore patient comfort, and milder burns that may result in less visual field constriction. Chaleplow et al raised concerns about decreased efficacy,[38] however, the data is conflicting[39] and overall of low quality.[40]

In the DRCR.net Protocol S study, patients with PDR were randomly assigned to antivascular endothelial growth factor (anti-VEGF) injections or PRP. Details of the main outcomes are discussed in the following section, but the study allowed the use of single-spot or pattern laser for the PRP arm. Those treated with pattern PRP had higher rates of PDR progression (60%) compared to single spot (39%), regardless of the number of spots.[41] This was neither a major outcome nor a randomized variable, with limited sample size, so it is unclear how to extrapolate these data to real clinical practice. In general, it is recommended that pattern delivery systems require a higher number of spots compared to conventional single-spot lasers.[42]

Single vs Multiple Sessions

The number of treatment sessions is also an area of variability, with no strong evidence to suggest that the difference between multiple and single sessions impacts outcomes.[40] There were previous concerns about complications of extensive treatment with single sessions, such as exudative retinal detachment and choroidal effusion.[43] But subsequent studies demonstrated the safety of modern lasers employed in a single session,[41,44] including DRCR.net Protocol F, which showed that there were no clinically significant differences in macular edema after PRP completed in 1 or 4 sessions.[45]

Antivascular Endothelial Growth Factor for Proliferative Diabetic Retinopathy

Prospective Studies

DRCR.net Protocol S compared PRP vs intravitreal ranibizumab 0.5 mg given monthly through 12 weeks followed by protocol-specified retreatment.[46] This study, with a primary outcome of mean VA improvement at 2 years, demonstrated noninferiority of ranibizumab (+2.8 ETDRS letters in the ranibizumab group vs +0.2 in the PRP group).

Additionally, secondary outcomes in the ranibizumab group were superior. Visual field sensitivity was higher in the ranibizumab group (–23 dB vs –422 dB), the rate of vitrectomy was lower (4% vs 15%), and there was a lower occurrence of DME (9% vs 28%). Rates of residual neovascularization were similar (35% vs 30%). Although the study was a noninferiority trial, these findings demonstrated the efficacy of ranibizumab for PDR. At 5 years, however, the VA and visual field benefits were not as pronounced.[47] The mean change in VA letter scores was +3.1 for ranibizumab and +3.0 for PRP, and approximately 20/25 Snellen equivalent for both. The respective visual field scores were –330 dB and –527 dB. These findings supported either anti-VEGF or PRP as viable treatments for PDR.

Similar results were reported in the CLARITY study, a phase 2b, single-blind, noninferiority trial comparing PRP with intravitreal aflibercept (Eylea; Regeneron Pharmaceuticals, Inc) in patients with active PDR.[48] Patients received 3 consecutive monthly injections and were treated thereafter as needed based on protocol-guided retreatment. CLARITY, with a primary outcome of VA at 1 year, demonstrated noninferiority of aflibercept vs PRP. Although patients with baseline DME were excluded, at 2 years, 11% of eyes in the aflibercept and 29% of eyes in the PRP groups had center-involving DME.

Progression of Retinopathy

In Protocol S, at 2 years, 42% of PRP-treated eyes and 34% of ranibizumab-treated eyes demonstrated progression of PDR, with the most common adverse event being vitreous hemorrhage.[41] Thus, it is imperative that eyes receiving *either* PRP or intravitreal ranibizumab be followed closely and managed appropriately.

Drawbacks and Unknowns

Although anti-VEGF therapy has demonstrated excellent efficacy in regression of retinopathy, there are potential drawbacks and situations for which PRP may be the preferred modality, or in combination. First, although the risk of postinjection endophthalmitis is relatively low and reported to be approximately 1 in 1000 to 1 in 3000, there is a cumulative increase in this risk with sequential injections. The costs of ranibizumab are also higher relative to PRP.[49] Longitudinally, it is unclear whether injections will be required indefinitely or if there is a "burnout" window as seen in advanced PDR treated with PRP.

Five-year results of Protocol S demonstrated the durability and efficacy of ranibizumab relative to PRP with average VAs of 20/25 Snellen in both groups and improved visual field sensitivity and lower likelihood of developing vision-impairing DME in the anti-VEGF group. However, injection frequency remained relatively constant in years 2 through 5, with more than 40% of eyes requiring 4 or more injections at year 5.[47] On the other hand, 49% of the PRP arm underwent PRP once, and the remaining participants required another PRP on average 7 months after the initial PRP.

Perhaps the most compelling reason that anti-VEGF cannot supplant PRP as a universal monotherapy is that patients with PDR may be unable to strictly maintain scheduled clinic visits. The loss-to-follow-up rate was relatively high, with only two-thirds of living participants completing 5 years in Protocol S. This raises concerns about the potential adverse outcomes that may occur during this window of treatment nonadherence. A real-world study examined more than 2000 patients with PDR and reported lost-to-follow-up rates of 25% at 4 years,[50] and those lost to follow-up after anti-VEGF treatment had worse anatomic and visual outcomes compared to those lost to follow-up after PRP.[51]

Finally, although many of the studies compare laser vs anti-VEGF in a binary fashion, in reality, many patients in our practices are receiving a combination of treatments. This is the case in the clinical trial setting as well. In Protocol S, 58% of those randomly assigned to PRP received anti-VEGF treatment for DME also. In CLARITY, 40% of the participants had PRP at baseline before random assignment to anti-VEGF or PRP. This combination approach is practical in addressing both DME and PDR, and may be a good approach when considering reliability of follow-up as a factor.

Laser for Nonproliferative Diabetic Retinopathy

Most of the literature on laser photocoagulation for NPDR is regarding focal macular laser treatment for DME. The use of PRP as a technique to decrease the risk of progression to PDR has been less studied since the DRS and the ETDRS. PRP for NPDR was not the main focus of either of these clinical trials, but embedded within the data of these landmark studies are valuable insights on how PRP may play a role for some patients with NPDR.

The DRS included patients with severe NPDR; this subgroup had a 3.2% rate of significant vision loss at 2 years without treatment, and 12.8% at 4 years.[52] With prophylactic PRP, the respective rates decreased to 2.8% and 4.3% (with corresponding risk reductions of 12.5% and 66.4%). Because the absolute rates of vision loss were still low at 2 years despite the substantial risk reduction at 4 years, the investigators suggested that it was unclear whether the benefit outweighed the risks in treating all patients with severe NPDR. Note that the adverse events related to the intense PRP in the DRS protocol were not negligible, so the threshold to recommend treatment was high.

However, the DRS investigators outlined several scenarios that would warrant consideration of PRP for severe NPDR: treatment of 1 eye in patients with bilateral severe NPDR, eyes with significant retinal ischemia, fellow eyes of patients whose first eyes had progression from deferring treatment, and pregnancy or development of renal failure—2 systemic situations that may accelerate the progression of retinopathy and for which logistic challenges may prevent timely PRP.[52] These are insightful considerations that still hold true today. We would also add that PRP could be considered for patients

with severe NPDR who have difficulty maintaining scheduled clinic visits.

The levels of NPDR were more granular in the ETDRS. Eyes with moderate NPDR had a 44% risk of developing PDR in 5 years, 66% for moderately severe NPDR, 75% to 81% for severe NPDR, and an alarming 90% for very severe NPDR (Table 2).[32] The respective 5-year rates for conversion to high-risk PDR were 27%, 39%, 56%, and 71%. Early prophylactic PRP did not have a significant enough effect on VA outcomes at 5 years, but the conversion rates to high-risk PDR were reduced: 8.5% to 13.7% for full PRP and 16.6% to 21.4% for mild PPR in eyes with mild to moderate NPDR, and 26.3% to 28.8% for full PRP and 40.3% to 46.7% for mild PRP in eyes with severe NPDR or early PDR (values are from eyes with concurrent CSME).

Because PDR is an established risk factor for vision loss, it would intuitively seem that visual benefits may have become apparent with longer follow-up, but this is unknown. Interestingly, in a very long-term follow-up examination of the ETDRS cohort a median of 16.7 years after the initial treatments, all patients with severe NPDR or higher at the closeout visit of the original study had required PRP treatment after the study.[53]

Antivascular Endothelial Growth Factor for Nonproliferative Diabetic Retinopathy

Regression of DR refers to the reversal in the severity of the retinopathy, such as severe NPDR improving to mild NPDR. Such regression has been a longstanding goal, and we have recently accumulated enough convincing evidence to demonstrate that it is possible to achieve. The patient-centered benefits and the potential risks involved to achieve this are important ongoing conversations in our field.

Diabetic Retinopathy Regression: Post Hoc Analysis of Diabetic Macular Edema Trials

Initial reports demonstrating the efficacy of anti-VEGF therapy for NPDR regression were determined via post hoc analyses of anti-VEGF trials for DME. All clinical trials used the ETDRS DRSS as the standard method of grading retinopathy. In post hoc analyses of the RISE/RIDE clinical trials, the phase 3 parallel studies resulting in the FDA approval of ranibizumab for the treatment of DME, 36% to 37% of ranibizumab-treated eyes demonstrated a 2 or more step improvement in DRSS levels compared to 5% in the sham group.[54]

This difference was more pronounced for eyes with higher DRSS scores at baseline. Patients with DRSS levels 47 to 53 (moderately severe and severe NPDR) were particularly sensitive or responsive to anti-VEGF therapy because a larger proportion of these patients (78% to 81%) were able to achieve 2 or more step DRSS improvements at 2 years with treatment than patients with milder NPDR (10% to 16% for levels 35 to 43), which was possibly attributable to a ceiling effect.[55] Based on these data, the FDA approved ranibizumab 0.3 mg for the treatment of any level of DR in the presence of DME in 2015. Two years later in 2017, based on Protocol S data combined with data from RISE/RIDE, the FDA approved ranibizumab 0.3 mg for any level of DR, even in the absence of DME.

Similar outcomes were reported in post hoc analyses of the VIVID/VISTA trials, the studies leading to FDA approval of aflibercept for the treatment of DME.[56] At the 100-week visit, 2 or more step regression in DRSS levels in VIVID was seen in 34% of eyes receiving aflibercept every 4 weeks, 38% of eyes receiving aflibercept every 8 weeks (after loading doses), compared to 10% of eyes receiving macular focal laser.

Comparison of Retinopathy Regression Between Antivascular Endothelial Growth Factor Agents

A post hoc analysis of the DRCR.net Protocol T study comparing intravitreal aflibercept, bevacizumab (Avastin; Genentech, Inc), and ranibizumab for DME was conducted to assess for differential rates of DR regression.[57] At 2 years, there were no differences between the medications for eyes with NPDR at baseline; 25% of eyes receiving aflibercept, 22% receiving bevacizumab, and 31% receiving ranibizumab had DR improvement. However, in eyes with PDR at baseline, the respective improvement rates were 70%, 30%, and 38% at 2 years. These data suggest that aflibercept may have an edge in eyes with PDR and DME regarding DR regression, however, confirmation is necessary.

Diabetic Retinopathy Severity Scale Improvement in Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema

There are relatively limited data examining outcomes of anti-VEGF treatment for NPDR *without* DME. The ETDRS defined the natural history of these eyes, and the landmark study remains invaluable to our understanding of NPDR to this day (Table 2). Twenty-six percent and 52% of eyes with DRSS levels 47 and 53 will progress to PDR in 1 year, and these numbers increase annually.[32]

The PANORAMA study is the only large, prospective trial in the anti-VEGF era with public data targeting eyes with NPDR (DRSS 47 and 53 as determined by a reading center) without DME.[58] The phase 3 global multicenter trial randomly assigned 402 anti-VEGF–naive patients with 20/40 Snellen vision or better with no center-involving DME, to sham, aflibercept every 8 weeks after 5 monthly loading injections, or aflibercept every 16 weeks after 4 loading injections. The primary end point was the proportion of patients improving 2 or more steps on the DRSS in the aflibercept arms combined at 24 weeks and in each aflibercept arm individually at 52 weeks. Significantly more patients in the aflibercept arms (80% of every 8 weeks, and 65% of every 16 weeks) achieved a 2 or more step DRSS improvement, compared to sham (15%) at 52 weeks.[59]

A secondary end point examined vision-threatening complications. PDR or anterior segment neovascularization developed in 3% and 4% of patients in the respective aflibercept arms,

compared to 20% for sham—this finding was consistent with prior anti-VEGF and corticosteroid studies for DME.[54,60] Furthermore, center-involving DME developed in 8% and 7%, respectively, compared to 26% for sham. Combined, vision-threatening complications occurred in 41% of sham patients, compared to approximately 10% in the aflibercept arms through 52 weeks. Based on these data, in May 2019 the FDA approved aflibercept for treatment of any level of DR. This was an update to the label from 2015, when aflibercept was approved for DR in eyes with coexisting DME.

DRCR.net Protocol W

Protocol W is an ongoing phase 3 study that examines the use of aflibercept vs sham for prevention of PDR or center-involving DME in eyes with level 47 or 53 NPDR.[61] Aflibercept is being administered for 3 monthly loading injections, and then every 4 months until the 2-year primary end point, when the composite time-to-event outcome of development of PDR or visually significant DME will be assessed. At and after the 2-year visit, retreatment will be based on prespecified criteria.

There are several differences between Protocol W and PANORAMA: 1) Protocol W's entry criterion for vision is 20/25 Snellen or better, compared to approximately 20/40 Snellen or better for PANORAMA; 2) Protocol W's primary end point is at 2 years and the patients will be followed for a total of 4 years, compared to the 6-month and 1-year primary end points of PANORAMA; 3) PANORAMA used change in DRSS level as the primary outcome, whereas Protocol W examines prespecified clinically relevant transitions. Protocol W is currently ongoing, with an estimated study completion date in January 2022.[61]

Should We Consider Treating Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema?

There is mounting evidence that anti-VEGF treatment can improve the DRSS in patients with NPDR without DME. Ranibizumab and aflibercept are both FDA approved to treat any degree of NDPR. Does this mean we should be injecting all DR patients with anti-VEGF agents? Under most circumstances, most retina specialists likely would not recommend invasive treatment for mild or moderate NPDR.

However, the clinical trials indicate that there is statistically significant anatomic benefit in using anti-VEGF therapy to treat eyes with NPDR without DME with DRSS levels 47 or 53. It is important to consider whether this improvement is clinically meaningful and the extent to which this finding should alter practice patterns.

Currently, there is no definitive answer. What we have now are meaningful data to help inform discussions with patients, with decisions tailored to each patient's clinical needs. Observation remains a strong option, and PRP can be considered as well.

Arguments for Treating Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema With Antivascular Endothelial Growth Factor Agents

There are arguments for, and against, using anti-VEGF agents to treat levels 47 and 53 NPDR without DME. The following are considerations supporting treatment:

1. Perhaps the most compelling evidence for treating NPDR is that through year 1 of PANORAMA, treatment significantly decreased the probability of developing PDR and center-involving DME, which are thresholds traditionally used to initiate anti-VEGF or laser therapies. A cumulative risk of 41% of vision-threatening progression in moderately severe and severe NPDR is not negligible.
2. Numerous studies have demonstrated that for many exudative conditions such as center-involving DME causing visual loss, earlier intervention can achieve better outcomes at a population level.[62-64]
3. Anti-VEGF treatment may be able to slow the development and progression of retinal nonperfusion, the core vascular pathology underlying DR.[65,66] Further studies are required to better understand this possible phenomenon.
4. NPDR itself, even when controlling for DME, may be associated with reduced visual function and quality-of-life measures on a population basis in epidemiologic studies.[1,2,67]

Arguments Against Using Antivascular Endothelial Growth Factor Agents to Treat Nonproliferative Diabetic Retinopathy Levels 47 and 53 Without Diabetic Macular Edema

1. Through 1 year in PANORAMA, 59% of control eyes did not develop PDR or DME; therefore, many patients will be treated who may not have required injections based on these end points.
2. Although complications are rare, intravitreal injections do carry risks, the most common and pertinent being acute bacterial endophthalmitis.[68]
3. We have no data from PANORAMA or any other trial to demonstrate that treating early, before eyes develop PDR or DME, achieves better functional outcomes or reduces treatment burden for these patients. The DRSS is ultimately an anatomic severity scale, which is distinct from the VA of patients.
4. Longer-term data are needed because DR is a lifelong disease. It is unknown whether the benefits are durable, and whether there is need for ongoing treatment, and if so, for how long.
5. For patients and society, the short-term cost of anti-VEGF therapy is likely higher than that of observation or photocoagulation. However, the economics of

potential long-term visual benefits of anti-VEGF treatment is unknown.[49]

6. Patients with NPDR without DME are largely asymptomatic patients who will have to undergo multiple ongoing procedures with potential risk. This may be a relatively difficult paradigm for patients to understand, compared to visually impairing exudative diseases for which the benefits to vision may be more noticeable for the patient. Similarly, DRCR.net Protocol V recently demonstrated that there is no benefit in treating DME in patients with good vision (20/25 Snellen or better), whether with aflibercept, laser, or observation, as long as rescue treatment with aflibercept is possible if vision declines.[69]
7. Patients with diabetes tend to have comorbidities and are at risk for missing scheduled appointments because of medical issues and other barriers.[70,71] Therefore, there is a substantial risk of loss to follow-up during anti-VEGF treatment for DR, which may result in adverse events.[51]

Conclusions

These clinical practice guidelines have outlined what the authors deem to be the most relevant data at the time of writing regarding the management of patients with NPDR or PDR without DME. Every patient is unique, and our hope is that individual patients will receive the best treatment for their particular ophthalmic, systemic, and social needs. One universal recommendation, however, is to discuss the importance of glycemic and cardiovascular optimization with all patients.

NPDR without DME has accumulated strong evidence that anti-VEGF treatment can improve the DRSS level, particularly in severe disease. Whether this translates into long-term visual benefit with improvement in quality of life in the real world is yet to be determined, but it stands as a legitimate treatment option. We should remember that PRP could be considered for some patients also as the DRS outlined, and, of course, close observation would be appropriate for many patients.

PDR without DME traditionally has been treated with PRP, but there is now strong evidence that anti-VEGF treatment is a noninferior option. PRP and anti-VEGF agents are both useful tools, either as monotherapies or in combination, depending on patient variables that need to be considered. Strong suggestions for incorporating anti-VEGF treatment include concurrent visually significant DME, and strong suggestions for incorporating PRP include inability for close follow-up and/or preference to avoid frequent injections over the long term.

As retina specialists, we play an integral role in the diabetes management team. Landmark studies have established practice patterns, and recent advances hold promise in further improving patient outcomes. Many treatment options are available now, and we recommend a thoughtful approach for the individual patient.

Acknowledgments

We thank Rahul Komati, MD, for his assistance with preparation of the systemic optimization section.

Declaration of Conflicting Interests

Consultant for Alcon (Y.Y.), Adverum (C.C.W.), Aerpio (C.C.W.), Alimera (C.C.W., Y.S.M.), Allegro (C.C.W.), Allergan (C.C.W., Y.S.M.), Apellis (C.C.W.), Bayer (C.C.W.), Clearside Biomedical (C.C.W., J.E.K.), EyePoint (C.C.W.), Genentech/Roche (C.C.W., J.E.K., Y.S.M.), Kodiak (C.C.W., J.E.K.), Notal Vision (J.E.K.), Novartis (C.C.W., J.E.K.), ONL Therapeutics (C.C.W.), PolyPhotonix (C.C.W.), Recens Medical (C.C.W.), Regeneron (C.C.W.), Regenxbio (C.C.W.), Santen (C.C.W.).

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: National Institutes of Health grants 1R01EY027739-01A1 (L.A.K.) and R21EY027061 (L.A.K.), E. Matilda Ziegler Foundation for the Blind (L.A.K.), Karl Kirchgessner Foundation (L.A.K.). The funding sources had no roles in the study design, data collection and analysis, or preparation of the manuscript.

Ethical Approval

Not applicable.

Statement of Informed Consent

Not applicable.

References

1. Mazhar K, Varma R, Choudhury F, McKean-Cowdin R, Shtir CJ, Azen SP; Los Angeles Latino Eye Study Group. Severity of diabetic retinopathy and health-related quality of life: the Los Angeles Latino Eye Study. *Ophthalmology*. 2011;118(4):649-655. doi:10.1016/j.ophtha.2010.08.003
2. Willis JR, Doan QV, Gleeson M, et al. Vision-related functional burden of diabetic retinopathy across severity levels in the United States. *JAMA Ophthalmol*. 2017;135(9):926-932. doi:10.1001/jamaophthalmol.2017.2553
3. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017.
4. National Eye Institute. Diabetic retinopathy. https://nei.nih.gov/eyedata/diabetic. Last updated July 17, 2019. Accessed December 13, 2019.
5. LeCaire TJ, Palta M, Klein R, Klein BE, Cruickshanks KJ. Assessing progress in retinopathy outcomes in type 1 diabetes: comparing findings from the Wisconsin Diabetes Registry Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care*. 2013;36(3):631-637. doi:10.2337/dc12-0863
6. Bakri SJ, Wolfe JD, Regillo CD, Flynn HW Jr, Wykoff CC. Evidence-based guidelines for management of diabetic macular edema. *J Vitreoretin Dis*. 2019;3(3):145-152. doi:10.1177/2474126419834711

7. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(suppl 1):S55-S64. doi:10.2337/dc18-S006
8. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42(suppl 1):S103-S123. doi:10.2337/dc19-S010
9. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(3):412-418. doi:10.2337/dc16-2641
10. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *Ophthalmology*. 1995;102(4):647-661. doi:10.1016/s0161-6420(95)30973-6
11. Hainsworth DP, Bebu I, Aiello LP, et al. Risk factors for retinopathy in type 1 diabetes: the DCCT/EDIC study. *Diabetes Care*. 2019;42(5):875-882. doi:10.2337/dc18-2308
12. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131): P837-P853. doi:10.1016/S0140-6736(98)07019-6
13. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363(3):233-244. doi: 10.1056/NEJMoa1001288
14. Chew EY, Davis MD, Danis RP, et al; Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology*. 2014;121(12):2443-2451. doi:10.1016/j.ophtha.2014.07.019
15. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348(5):383-393. doi: 10.1056/NEJMoa021778
16. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42(suppl 1):S61-S70. doi:10.2337/dc19-S006
17. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(9):1273-1284. doi:10.2337/dci17-0026
18. Chaturvedi N, Porta M, Klein R, et al; DIRECT Programme Study Group. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet*. 2008; 372(9647):1394-1402. doi:10.1016/S0140-6736(08)61412-9
19. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int*. 2002;61(3): 1086-1097. doi:10.1046/j.1523-1755.2002.00213.x
20. Ruggenenti P, Lauria G, Iliev IP, et al; DEMAND Study Investigators. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: the delapril and manidipine for nephroprotection in diabetes (DEMAND) randomized clinical trial. *Hypertension*. 2011;58(5):776-783. doi: 10.1161/HYPERTENSIONAHA.111.174474
21. Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM; UK Prospective Diabetes Study Group. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Arch Ophthalmol*. 2004;122(11):1631-1640. doi:10.1001/archopht.122.11.1631
22. Do DV, Wang X, Vedula SS, et al. Blood pressure control for diabetic retinopathy. *Cochrane Database Syst Rev*. 2015;1: CD006127. doi:10.1002/14651858.CD006127.pub2
23. Leske MC, Wu SY, Hennis A, et al; Barbados Eye Study Group. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology*. 2005;112(5):799-805. doi:10.1016/j.ophtha.2004.11.054
24. Sacks FM, Hermans MP, Fioretto P, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. *Circulation*. 2014;129(9):999-1008. doi:10.1161/CIRCULATIONAHA.113.002529
25. Klein BE, Myers CE, Howard KP, Klein R. Serum lipids and proliferative diabetic retinopathy and macular edema in persons with long-term type 1 diabetes mellitus: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *JAMA Ophthalmol*. 2015; 133(5):503-510. doi:10.1001/jamaophthalmol.2014.5108
26. Klein BE, Moss SE, Klein R, Surawicz TS. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. *Ophthalmology*. 1991;98(8):1261-1265. doi:10.1016/s0161-6420(91)32145-6
27. Chew EY, Klein ML, Ferris FL III, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) report 22. *Arch Ophthalmol*. 1996;114(9):1079-1084. doi: 10.1001/archopht.1996.01100140281004
28. Keech AC, Mitchell P, Summanen PA, et al; FIELD Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet*. 2007;370(9600):1687-1697. doi:10.1016/S0140-6736(07)61607-9
29. Goldberg MF, Jampol LM. Knowledge of diabetic retinopathy before and 18 years after the Airlie House Symposium on Treatment of Diabetic Retinopathy. *Ophthalmology*. 1987;94(7): 741-746. doi:10.1016/s0161-6420(87)33524-9
30. Diabetic Retinopathy Study. Report number 6. Design, methods, and baseline results. Report number 7. A modification of the Airlie house classification of diabetic retinopathy. Prepared by the Diabetic Retinopathy. *Invest Ophthalmol Vis Sci*. 1981;21(1 pt 2): 1-226.
31. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991;98(5 suppl):786-806. doi:10.1016/S0161-6420(13)38012-9
32. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic

retinopathy. ETDRS report number 12. *Ophthalmology*. 1991; 98(5 suppl):823-833. doi:10.1016/S0161-6420(13)38014-2

33. Davis MD, Fisher MR, Gangnon RE, et al. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: early treatment diabetic retinopathy study report #18. *Invest Ophthalmol Vis Sci*. 1998;39(2):233-252.
34. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology*. 1991;98(5 suppl):766-785. doi: 10.1016/S0161-6420(13)38011-7
35. Wilkinson CP, Ferris FL III, Klein RE, et al; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110(9):1677-1682. doi:10.1016/S0161-6420(03)00475-5
36. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1981;88(7):583-600.
37. Diabetic Retinopathy Clinical Research Network; Googe J, Brucker AJ, Bressler NM, et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina*. 2011;31(6):1009-1027. doi:10.1097/IAE.0b013e318217d739
38. Chappelow AV, Tan K, Waheed NK, Kaiser PK. Panretinal photocoagulation for proliferative diabetic retinopathy: pattern scan laser versus argon laser. *Am J Ophthalmol*. 2012;153(1): 137-142.e2. doi:10.1016/j.ajo.2011.05.035
39. Nagpal M, Marlecha S, Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser. *Retina*. 2010;30(3):452-458. doi:10.1097/IAE.0b013e3181c70127
40. Moutray T, Evans JR, Lois N, Armstrong DJ, Peto T, Azuara-Blanco A. Different lasers and techniques for proliferative diabetic retinopathy. *Cochrane Database Syst Rev*. 2018;3: CD012314. doi:10.1002/14651858.CD012314.pub2
41. Bressler SB, Beaulieu WT, Glassman AR, et al; Diabetic Retinopathy Clinical Research Network. Factors associated with worsening proliferative diabetic retinopathy in eyes treated with panretinal photocoagulation or ranibizumab. *Ophthalmology*. 2017;124(4):431-439. doi:10.1016/j.ophtha.2016.12.005
42. Palanker D, Lavinsky D, Blumenkranz MS, Marcellino G. The impact of pulse duration and burn grade on size of retinal photocoagulation lesion: implications for pattern density. *Retina*. 2011; 31(8):1664-1669. doi:10.1097/IAE.0b013e3182115679
43. Doft BH, Blankenship GW. Single versus multiple treatment sessions of argon laser panretinal photocoagulation for proliferative diabetic retinopathy. *Ophthalmology*. 1982;89(7):772-779. doi: 10.1016/s0161-6420(82)34734-x
44. Muqit MMK, Marcellino GR, Henson DB, et al. Single-session vs multiple-session pattern scanning laser panretinal photocoagulation in proliferative diabetic retinopathy: the Manchester Pascal Study. *Arch Ophthalmol*. 2010;128(5):525-533. doi:10.1001/archophthalmol.2010.60
45. Diabetic Retinopathy Clinical Research Network, Brucker AJ, Qin H, et al. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol*. 2009;127(2):132-140. doi:10.1001/archophthalmol.2008.565
46. Writing Committee for the Diabetic Retinopathy Clinical Research Network; Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. 2015;314(20):2137-2146. doi:10.1001/jama.2015.15217
47. Gross JG, Glassman AR, Liu D, et al; Diabetic Retinopathy Clinical Research Network. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2018; 136(10):1138-1148. doi:10.1001/jamaophthalmol.2018.3255
48. Sivaprasad S, Prevost AT, Vasconcelos JC, et al; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet*. 2017;389(10085): 2193-2203. doi:10.1016/S0140-6736(17)31193-5
49. Lin J, Chang JS, Smiddy WE. Cost evaluation of panretinal photocoagulation versus intravitreal ranibizumab for proliferative diabetic retinopathy. *Ophthalmology*. 2016;123(9):1912-1918. doi:10.1016/j.ophtha.2016.05.037
50. Obeid A, Gao X, Ali FS, et al. Loss to follow-up in patients with proliferative diabetic retinopathy after panretinal photocoagulation or intravitreal anti-VEGF injections. *Ophthalmology*. 2018; 125(9):1386-1392. doi:10.1016/j.ophtha.2018.02.034
51. Obeid A, Su D, Patel SN, et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti-vascular endothelial growth factor. *Ophthalmology*. 2019;126(3):407-413. doi: 10.1016/j.ophtha.2018.07.027
52. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report No. 14. The Diabetic Retinopathy Study Research Group. *Int Ophthalmol Clin*. 1987; 27(4):239-253. doi:10.1097/00004397-198702740-00004
53. Chew EY, Ferris FL III, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the Early Treatment Diabetic Retinopathy follow-up study. *Ophthalmology*. 2003;110(9):1683-1689. doi:10.1016/S0161-6420(03)00579-7
54. Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. *Arch Ophthalmol*. 2012;130(9):1145-1152. doi: 10.1001/archophthalmol.2012.1043
55. Wykoff CC, Eichenbaum DA, Roth DB, Hill L, Fung AE, Haskova Z. Ranibizumab induces regression of diabetic retinopathy in most patients at high risk of progression to proliferative diabetic retinopathy. *Ophthalmol Retina*. 2018;2(10):997-1009. doi: 10.1016/j.oret.2018.06.005
56. Dhoot DS, Baker K, Saroj N, et al. Baseline factors affecting changes in diabetic retinopathy severity scale score after intravitreal aflibercept or laser for diabetic macular edema: post hoc

analyses from VISTA and VIVID. *Ophthalmology*. 2018;125(1): 51-56. doi:10.1016/j.ophtha.2017.06.029

57. Bressler SB, Liu D, Glassman AR, et al; Diabetic Retinopathy Clinical Research Network. Change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmol*. 2017;135(6):558-568. doi:10.1001/jamaophthalmol.2017.0821
58. Study of the Efficacy and Safety of Intravitreal (IVT) Aflibercept for the Improvement of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy (NPDR)–Full Text View–ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02718326. Published November 21, 2019. Accessed December 28, 2019.
59. Boyer DS. Treatment of moderately severe to severe nonproliferative diabetic retinopathy with intravitreal aflibercept injection: 52-week results from the phase 3 PANORAMA Study. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; April 29, 2019; Vancouver, BC, Canada.
60. Wykoff CC, Chakravarthy U, Campochiaro PA, Bailey C, Green K, Cunha-Vaz J. Long-term effects of intravitreal 0.19 mg fluocinolone acetonide implant on progression and regression of diabetic retinopathy. *Ophthalmology*. 2017;124(4):440-449. doi: 10.1016/j.ophtha.2016.11.034
61. Anti-VEGF Treatment for Prevention of PDR/DME. https://clinicaltrials.gov/ct2/show/NCT02634333. Published September 23, 2019. Accessed December 28, 2019.
62. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120(10): 2013-2022. doi:10.1016/j.ophtha.2013.02.034
63. Wykoff CC, Marcus DM, Midena E, et al. Intravitreal aflibercept injection in eyes with substantial vision loss after laser photocoagulation for diabetic macular edema: subanalysis of the VISTA and VIVID randomized clinical trials. *JAMA Ophthalmol*. 2017;135(2):107-114. doi:10.1001/jamaophthalmol.2016.4912
64. Ho AC, Albini TA, Brown DM, Boyer DS, Regillo CD, Heier JS. The potential importance of detection of neovascular age-related macular degeneration when visual acuity is relatively good. *JAMA Ophthalmol*. 2017;135(3):268-273. doi:10.1001/jamaophthalmol.2016.5314
65. Campochiaro PA, Wykoff CC, Shapiro H, Rubio RG, Ehrlich JS. Neutralization of vascular endothelial growth factor slows progression of retinal nonperfusion in patients with diabetic macular edema. *Ophthalmology*. 2014;121(9):1783-1789. doi:10.1016/j.ophtha.2014.03.021
66. Wykoff CC, Shah C, Dhoot D, et al. Longitudinal retinal perfusion status in eyes with diabetic macular edema receiving intravitreal aflibercept or laser in VISTA study. *Ophthalmology*. 2019; 126(8):1171-1180. doi:10.1016/j.ophtha.2019.03.040
67. Gupta P, Liang Gan AT, Kidd Man RE, et al. Impact of incidence and progression of diabetic retinopathy on vision-specific functioning. *Ophthalmology*. 2018;125(9):1401-1409. doi:10.1016/j.ophtha.2018.02.011
68. Rayess N, Rahimy E, Storey P, et al. Postinjection endophthalmitis rates and characteristics following intravitreal bevacizumab, ranibizumab, and aflibercept. *Am J Ophthalmol*. 2016;165:88-93. doi:10.1016/j.ajo.2016.02.028
69. Baker CW, Glassman AR, Beaulieu WT, et al; DRCR Retina Network. 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. *JAMA*. 2019;321(19):1880-1894. doi:10.1001/jama.2019.5790
70. Lu AJ, Chen AJ, Hwang V, Law PY, Stewart JM, Chao DL. Analysis of patient-reported barriers to diabetic retinopathy follow-up. *Ophthalmic Surg Lasers Imaging Retina*. 2019;50(2): 99-105. doi:10.3928/23258160-20190129-06
71. Keenum Z, McGwin G Jr, Witherspoon CD, Haller JA, Clark ME, Owsley C. Patients' adherence to recommended follow-up eye care after diabetic retinopathy screening in a publicly funded county clinic and factors associated with follow-up eye care use. *JAMA Ophthalmol*. 2016;134(11):1221-1228. doi:10.1001/jamaophthalmol.2016.3081