

# Integrative Management of High-Risk Proliferative Diabetic Retinopathy: Precision Diagnostics via Ultra-Widefield Imaging and Therapeutic Strategies

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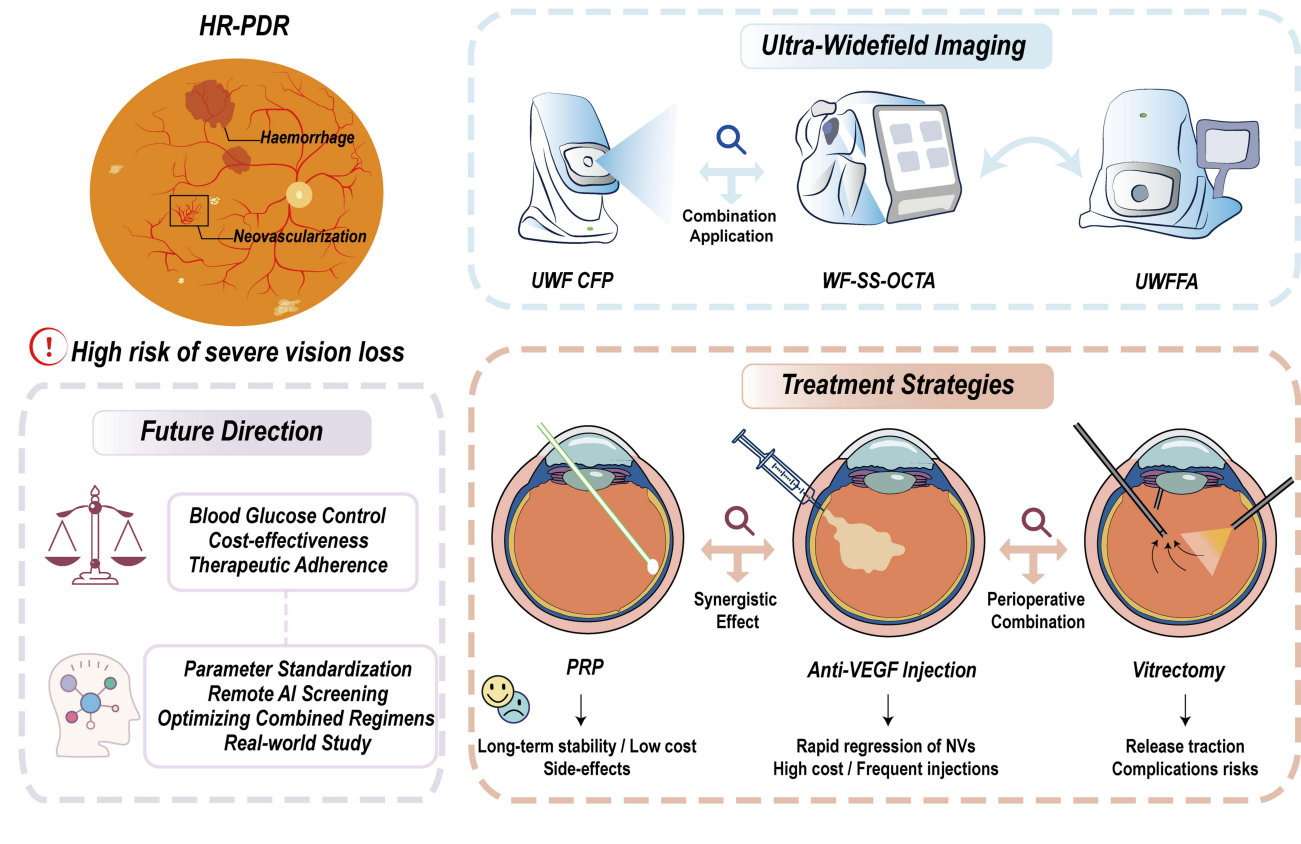
**Abstract:** Diabetic retinopathy (DR) is a leading cause of blindness worldwide. High-risk proliferative diabetic retinopathy (HR-PDR) is an advanced stage and carries a nearly 50% risk of severe vision loss within five years without intervention. Recent advances in ultra-widefield (UWF) imaging technologies enable comprehensive detection of peripheral lesions and facilitate more accurate diagnosis of disease severity, yet standardized quantitative biomarkers for predicting disease progression remain lacking. Current treatments, including pan-retinal photocoagulation (PRP), anti-vascular endothelial growth factor (anti-VEGF) agents, and pars plana vitrectomy (PPV), demonstrate varying levels of efficacy. There is currently no consensus on the optimal treatment regimen for HR-PDR. Therefore, this review analyzes the application value of UWF imaging in HR-PDR, compares the efficacy of different treatment regimens, and considers their cost-effectiveness and practical applicability meanwhile. Using UWF color fundus photography (CFP) combined with widefield swept-source optical coherence tomography angiography (WF-SS-OCTA) may enhance diagnostic and monitoring outcomes for HR-PDR. Anti-VEGF injections followed PRP could provide stable and sustained protective effects; early PPV may improve outcomes in select cases. Future research should prioritize addressing current research gaps, including the identification of optimal anti-VEGF/PRP protocols, strategies to overcome long-term adherence challenges, establishment of consistent retreatment criteria, clarification of surgical indications, and development of socioeconomic strategies.

**Keywords:** high-risk proliferative diabetic retinopathy, treatment methods, diagnostic techniques, review

## Introduction

Diabetic retinopathy (DR), the primary microvascular complication of diabetes, is a leading cause of vision loss in middle-aged and elderly individuals. Globally, an estimated 160 million individuals were affected by DR in 2020, with projections indicating a rise to 242 million by 2045.<sup>1,2</sup> As a progressive microvascular disease, DR is broadly classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), based on the presence of abnormal neovascularization. PDR is the most advanced stage, caused by severe retinal ischemia resulting from capillary closure. According to the Early Treatment Diabetic Retinopathy Study (ETDRS), high-risk proliferative diabetic retinopathy (HR-PDR) is defined as neovascularization of the disc (NVD) exceeding 1/4 disc area; vitreous or preretinal hemorrhage associated with any NVD; or neovascularization elsewhere (NVE) exceeding 1/2 disc area with vitreous or preretinal hemorrhage.<sup>3</sup> Without intervention, nearly 25% of eyes with HR-PDR experience severe vision loss within two years, rising to 44% after four years.<sup>4,5</sup> Vision-threatening complications, including vitreous hemorrhage (VH), tractional retinal detachment (TRD), and neovascular glaucoma (NVG), occur more frequently in HR-PDR eyes than in less severe PDR.<sup>6,7</sup>

## Graphical Abstract



Advances in retinal imaging modalities, such as ultra-widefield (UWF) color fundus photography (UWF CFP), UWF fluorescein angiography (UWFFA), and optical coherence tomography angiography (OCTA), have revolutionized HR-PDR diagnosis. UWF imaging captures approximately 110° to 220° of the retina, enabling more comprehensive peripheral lesion detection without pupillary dilation,<sup>8</sup> while OCTA provides three-dimensional reconstructions of the microvasculature across all layers and enables quantitative assessment.<sup>9</sup> Despite these innovations, their efficiency in diagnosing lesions in HR-PDR has not been reviewed or discussed in the past.

Treatment modalities for HR-PDR include pan-retinal photocoagulation (PRP), anti-vascular endothelial growth factor (anti-VEGF) agents, and pars plana vitrectomy (PPV). PRP is considered the gold-standard for reducing severe visual loss in patients with severe NPDR and PDR.<sup>10,11</sup> Anti-VEGF therapy is the first-line option for cases with central-involved diabetic macular edema (CI-DME), while recent studies have confirmed its effects in inhibiting PDR progression and established it as a potential alternative.<sup>12</sup> For eyes with significant complications like VH or TRD, PPV is essential but often associated with suboptimal visual outcomes.<sup>5,13</sup> Approximately one-third of HR-PDR patients require additional surgery after initial therapy due to recurrent VH or fibrotic traction.<sup>14,15</sup>

This review is therefore the first to provide a comprehensive overview of the diagnosis and treatment of HR-PDR. The primary aim is to evaluate the diagnostic value of UWF imaging technology in identifying the pathological features of HR-PDR, and to compare the efficacy of current treatment methods based on anatomical and functional outcomes, taking into account treatment safety, cost-effectiveness, and clinical application. The review discusses current research gaps across multiple fields and provides guidance for future translational medicine and clinical research.

## Wide-Field Imaging Modalities

### UWF CFP

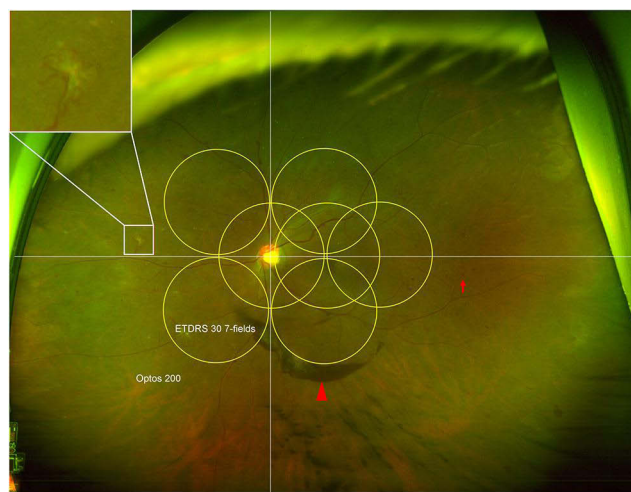
UWF CFP captures up to 200° of fundus in a single image, representing approximately 80% of the total retinal area (Figure 1).<sup>16</sup> Previous studies have confirmed moderate to substantial consistency between ETDRS 7-field photographs and UWF CFP in DR severity grading.<sup>17,18</sup> Notably, UWF CFP identifies additional peripheral lesions outside the ETDRS 7-field area in approximately one-third of patients, resulting in DR severity upgrades for 10–15% of eyes.<sup>19,20</sup> The clinical significance of these peripheral lesions remains controversial in longitudinal studies. Predominantly peripheral lesions (PPLs) on UWF CFP may independently correlate with DR progression,<sup>21–23</sup> however, larger prospective cohort studies are needed to validate this association.

UWF CFP is the preferred imaging modality for rapid screening and diagnosis of HR-PDR. However, UWF CFP exhibits limitations including pseudocolor representation, peripheral distortion, and susceptibility to artifacts from eyelids and lashes that may compromise both image quality and field of view (FOV).<sup>16</sup> In addition, it is challenging to differentiate intraretinal microvascular abnormalities (IRMAs) from retinal neovascularization (NVs), and almost impossible to identify retinal non-perfused areas (NPAs).<sup>24</sup>

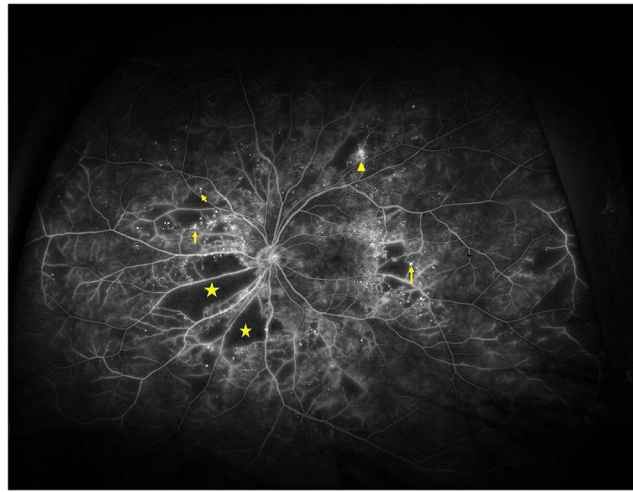
### UWFFA

Currently, fundus fluorescein angiography (FFA) is still considered the gold standard for detecting and monitoring NVs in retinal vascular diseases. Unlike conventional 30° to 55° FFA, UWFFA imaging system captures up to 200° retinal images in a single acquisition without requiring patient refixation.<sup>25</sup> As an effective modality for visualizing subtle vascular pathology, UWFFA enhances dynamic assessment of microaneurysms (MAs), NPAs and leaking NVs (Figure 2). In a comparative analysis by Ying Cui et al, UWFFA demonstrated superior detection rates to UWF CFP for DR lesions, including MAs (97.9% vs 88.2%), IRMA (87.5% vs 44.1%) and NVs (NVE: 56.3% vs 28.9%; NVE +NVD: 75.0% vs 30.0%), although statistical values were not reported.<sup>24</sup> The Diabetic Retinopathy Clinical Research (DRCR) Network Protocol AA study further supports UWFFA's predictive utility for PDR progression through its enhanced identification of PPLs.<sup>21,26</sup> Additionally, UWFFA helps to guide targeted laser therapy and personalized retreatment protocols in HR-PDR eyes.<sup>25,27</sup>

Unfortunately, the invasive nature, prolonged duration, and risk of serious dye-related adverse events limit UWFFA's adoption in clinical practice. In terms of distinguishing NVs from IRMAs, UWFFA offers no advantage due to its inability to provide depth-resolved retinal segmentation, particularly when compared to OCTA.<sup>28</sup> Future studies should



**Figure 1** Representative 200°UWF CFP overlaid with simulated ETDRS 7-standard 30-degree field images (yellow circles shown). Microaneurysms (red arrow), NVs (red rectangle), and preretinal hemorrhage (red triangle) can be observed in the peripheral retina outside the 7-standard field of view.



**Figure 2** Representative UWFFA showing MAs (yellow arrows), leaking NVs (yellow triangle) and NPAs (pentagrams).

establish the correlation between UWFFA-derived quantitative metrics (eg, pan-retinal leakage index and ischemic index) and the risk of DR progression or visual prognosis.<sup>29</sup>

## Wide-Field Swept-Source OCTA (WF-SS-OCTA)

As a noninvasive, safe, and repeatable retinal blood flow imaging system, WF-SS-OCTA has been extensively applied in the diagnosis, screening, and monitoring of HR-PDR. Unlike early OCTA systems limited to macular imaging, WF-SS-OCTA significantly increases the FOV to 50° to 80° or more. This allows visualization of retinal capillary perfusion at the posterior pole and mid-periphery in all retinal layers.<sup>30</sup> WF-SS-OCTA has been shown to be superior to UWF CFP and non-inferior to UWFFA in detecting IRMAs, NVs and NPAs in PDR,<sup>30–33</sup> even perform better in analyzing quantitative parameters,<sup>34</sup> despite a relatively narrower FOV. Regarding MAs, while WF-SS-OCTA can locate their depth, it is less sensitive than FFA due to its relative insensitivity to the slow blood flow.<sup>35</sup> In addition, WF-SS-OCTA can be used to evaluate the therapeutic response of PDR eyes to PRP and intravitreal injections of anti-VEGF agents.<sup>36</sup>

OCT B-scans with overlaid flow signals exhibit high sensitivity in detecting NVs, which can be observed as hyperreflective blood flow structures breaking through the internal limiting membrane (ILM) and projecting into the vitreous (Figure 3).<sup>37</sup> The combined vitreoretinal interface (VRI) slab analysis enhances NVs detection rates to 99.1%.<sup>38</sup> Meanwhile, the adhesion relationship between the posterior vitreous cortex (PVC) and the retina, known as the type of posterior vitreous detachment (PVD), can also be observed in the structural OCT B-scan (Figure 4).

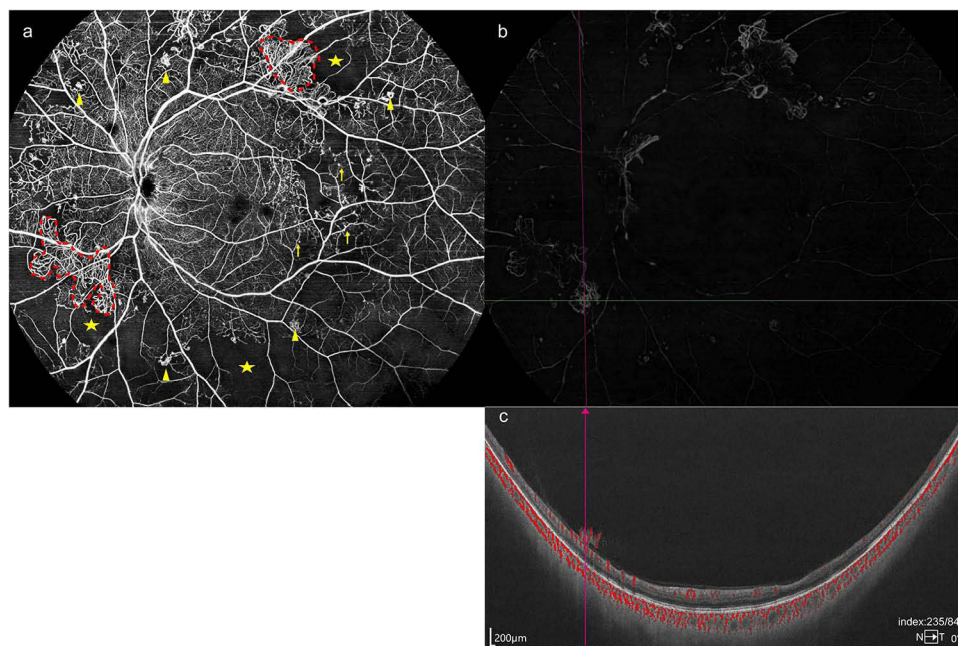
The currently available research suggests that WF-SS-OCTA could be an alternative to UWFFA (Table 1). Some studies propose that combining WF-SS-OCTA with UWF CFP offers a practical approach for DR diagnosis, monitoring and screening, as UWF CFP could somewhat compensate for the lack of a small FOV and increase the detection of DR lesions.<sup>24,39</sup> However, it should be noted that SS-OCTA does not detect leakage, so it may miss some MAs and fibrotic retinal NVs.<sup>40</sup> At the same time, a wider FOV means more susceptibility to imaging artifacts and segmentation errors. Quantitative OCTA metrics can vary significantly between different devices or image processing software, and these differences limit meaningful comparisons between studies (Table 2).

## Treatment Strategies

### Pan-Retinal Photocoagulation

#### Clinical Applications and Effects

Since its introduction in the 1960s, PRP has been considered the mainstay treatment for PDR, effectively preventing severe visual loss in patients with severe NPDR and PDR.<sup>10</sup> The precise mechanism through which laser therapy improves retinal vascular disease remains incompletely understood. One possible therapeutic mechanism is that retinal



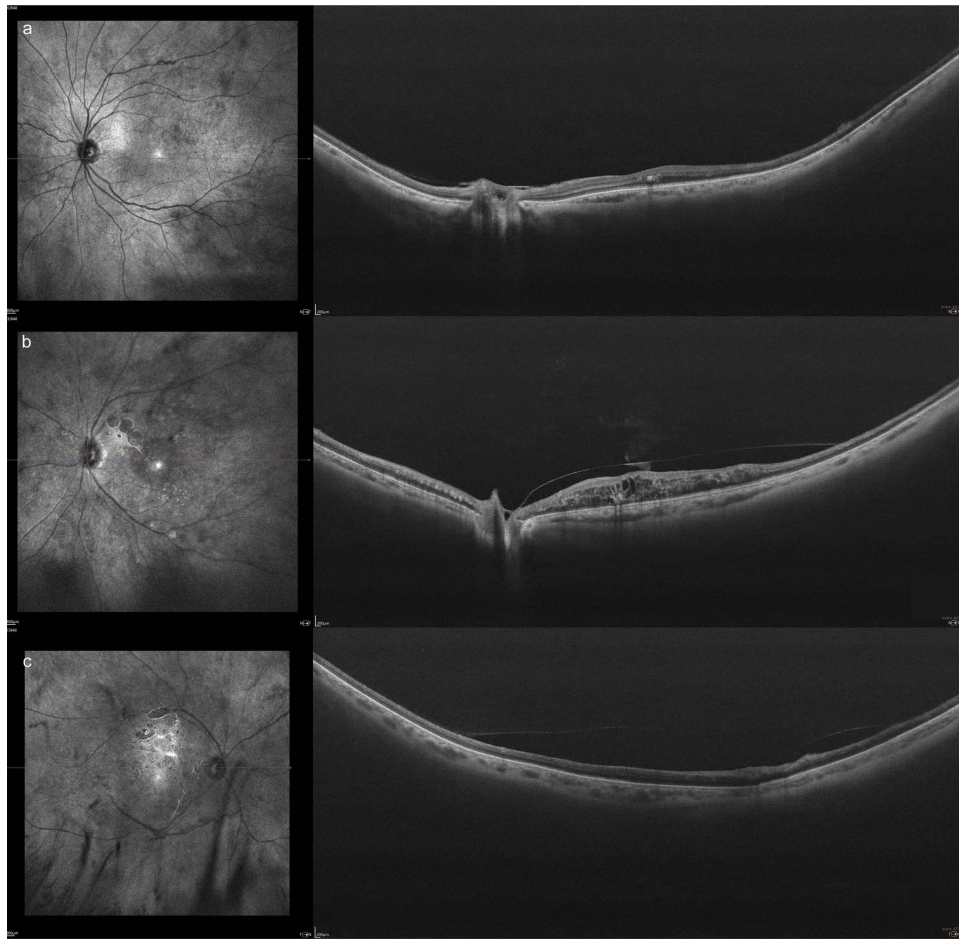
**Figure 3** Representative 24×20 mm UWF SS-OCTA image. (a) Retinal slab shows lesions including MAs (yellow arrows), intraretinal microvascular abnormalities (yellow triangles), NVs (red dashed lines), and NPAs (pentagrams). (b) VRI slab shows abnormal blood vessels growing into the vitreous and appearing above the retina (pink and green lines intersect at a cluster of neovascularization). (c) Corresponding B-scan of the horizontal retinal section shown by green line. NVs with blood flow signals (red) can be observed penetrating through the ILM and extending into the vitreous (pink lines in (b) and (c) corresponded to the same position).

laser permanently destroys retinal pigment epithelial cells and overlying tissue in the peripheral retina. This reduces overall retinal metabolic demand, thereby alleviating the level of retinal hypoxia and downregulating angiogenic factors like VEGF, ultimately mediating NVs regression.<sup>47</sup>

The Diabetic Retinopathy Study (DRS) demonstrated that without treatment, the risk of severe vision loss in HR-PDR patients within two years is about 25–30%, while prompt PRP treatment can reduce the risk by about 50–60%.<sup>48</sup> The ETDRS further demonstrated that early PRP significantly reduces vitrectomy requirements compared to deferred treatment, using either full or mild scatter photocoagulation.<sup>49</sup> Approximately 60% of treatment-naïve patients exhibit rapid response of abnormal NVs regression, beginning as early as one week after the first PRP treatment and continuing for at least 3 months.<sup>50,51</sup> PRP-induced NVs regression is usually stable and persistent, particularly in eyes with initial favorable responses.<sup>51</sup> Long-term retrospective studies have confirmed that PRP can provide durable anatomical and visual outcomes for 10 years or even longer in HR-PDR patients.<sup>52</sup> Early treatment is superior to delayed treatment. Ohlhausen et al reported that delaying PRP treatment for more than 31 days leads to poorer long-term visual acuity and extended treatment courses than earlier intervention.<sup>53</sup> Their findings suggested that the optimal PRP treatment onset time is the day of diagnosis for HR-PDR patients, since these patients achieved superior vision outcomes compared to others at 2-year post-treatment follow-up. Given its definitive and enduring efficacy, PRP remains the cornerstone intervention for PDR.

However, lasers cannot stop the progression of DR completely. Even with adequate PRP treatment, patients remain at risk of vision deterioration, particularly in cases of HR-PDR. At two-year follow-up, approximately 34–37% of treated eyes still developed VH, 10% developed TRD, and 15% underwent PPV.<sup>51,54</sup> Nearly one-third of PDR patients necessitate vitrectomy within 10 years post-PRP.<sup>55</sup> OCTA follow-up also revealed a tendency of NVs recurrence after 6 months of PRP treatment.<sup>50</sup> Trials show that a relatively large portion of PRP-treated eyes (approximately 50%) eventually require supplemental treatment.<sup>54,56</sup>

Factors associated with PDR worsening are investigated, and the severity of DR at baseline was found to be an independent risk factor.<sup>6,57</sup> Ravi Parikh reported that 34.4% of PDR eyes with VH received PPV within two years of initial PRP treatment, which was 2.78 times higher than for PDR alone.<sup>58</sup> In addition, eyes treated with pattern or mixed laser



**Figure 4** Structural OCT B-scan shows the adhesion relationship between the PVC and the retina, known as the type of PVD. Considering the status of the macular and optic disc regions, (a–c) show no PVD, partial PVD, and complete PVD, respectively.

modalities exhibit higher progression risk than those receiving single-spot laser, potentially due to the longer stabilization time required.<sup>6,57</sup> Consequently, HR-PDR patients require more intensive monitoring and consideration of supplemental laser therapy. No consensus exists, however, regarding optimal treatment initiation timing and interval protocols.

### Side Effects and Limitations

Conventional retinal photocoagulation has several potential side effects and limitations. Of note, PRP generally preserves rather than improves vision, and may lead to permanent peripheral visual field loss or exacerbate DME.<sup>59</sup> Another possible risk is that initiating PRP therapy may cause a transient angio-fibrotic switch, thereby increasing the likelihood of TRD progression, particularly in eyes with posterior hyaloid shrinkage and preretinal fibrosis.<sup>60</sup> To mitigate adverse effects and patient discomfort, complete PRP should be divided into three or four sessions. However, the prolonged completion period increases the risk of hemorrhage during the treatment. If bleeding occurs, blood clots in the vitreous cavity can obstruct the retinal visual field, making adequate PRP more challenging and reducing the effectiveness of laser by absorbing its energy before it reaches the retina. In such cases, one option is to wait for the hemorrhage to resolve or, alternatively, to perform a vitrectomy.

## Anti-Vascular Endothelial Growth Factor Injection

### Clinical Applications and Effects

Intravitreal injections of anti-VEGF agents are emerging as an alternative therapy for PDR. Anti-VEGF therapy has traditionally been indicated for CI-DME, while recent studies have demonstrated its ability to slow the progression of DR

**Table 1** Comparison of Wide-Field Optical Coherence Tomography Angiography (WF-OCTA) with Reference Standards for Detecting Diabetic Retinopathy Lesions: Sensitivity and Specificity Summary

Study (Year)	Disease Group	Technology	Result				Key Finding
			Target Lesion	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	Reference Standard	
Hirano et al (2020) <sup>41</sup>	PDR	WF-SS-OCTA VRI	NVs	73 <sup>a</sup> 84 <sup>b</sup>	–	UWFFA	Comparable efficacy to FFA in detecting NVs.
Lu et al (2022) <sup>38</sup>	Mixed DR	WF-SS-OCTA VRI Angio	NVs	91.9	–	OCTA B-scan	SS-OCTA VRI slab and SS-OCT VRI Structure imaging detected NV with high sensitivity.
Arya et al (2020) <sup>28</sup>	Severe NPDR or PDR	WF-SS-OCTA	Differentiating IRMAs and NVs	92 [74.9–99.1]	99 [92.3–100]	UWFFA	High agreement in identifying IRMAs and NVs (ICC=0.92).
Papayannis et al (2021) <sup>42</sup>	Diabetic	SS-OCTA	NVD	100 [85.7–100]	100 [96.9–100]	FFA/UWFFA	Effective for monitoring NV activity.
Sawada et al (2018) <sup>43</sup>	DR	WF-SS-OCTA	NVE	96.5 [82.7–99.9]	100 [96.9–100]	UWFFA	Clinically useful for detection of NPAs or NVs, but with lower specificity for NPAs.
			NPAs	98	82		
Hirano et al (2018) <sup>44</sup>	DR	WF-SS-OCTA with EFI	NVs	100	97	FFA (55°)	Satisfactory performance of EFI SS-OCTA in quantitative assessing.
			NPAs	96	100		
Salz et al (2016) <sup>35</sup>	Diabetic and normal	SS-OCTA	MAs	85 [53–97]	75 [21–98]	FFA (55°)	Located MAs exact intraretinal depth.
Cui et al (2021) <sup>24</sup>	Mixed DR	WF-SS-OCTA	NVs	96.55 [82.24–99.91]	94.74 [73.92–99.87]	UWFFA	WF-SS-OCTA plus UWF CFP may be a less invasive alternative to FFA.
Pichi et al (2020) <sup>31</sup>	PDR	WF-SS-OCTA	NVD, NVE	100, 100	100, 95	OCTA B-scan	Non-inferior detection rate to UWFFA for NVs.
		UWFFA		94.6, 96.8	100, 90		
		UWF CFP		35.1, 62.9	97.8, 70		

**Notes:** <sup>a</sup>Auto-segmentation; <sup>b</sup>Manual segmentation. Mixed DR: including PDR, NPDR and no DR. Scan details: WF-OCTA scans: 12×12 mm<sup>1, 3, 4, 5, 6</sup>, 15×15 mm<sup>2, 8</sup>, multiple 12×12 mm<sup>4, 5</sup>, 3×3 mm or 6×6 mm<sup>7</sup>, 6×6 mm or 9×9 mm<sup>9</sup>. Reference standards: UWFFA (Optos 200Tx<sup>®1, 5, 8, 9</sup>, Heidelberg Spectralis<sup>2, 4, 6, 7, 9</sup>), FFA ~55°<sup>6, 7</sup> (1-9 indicates the order of references in the table).

**Abbreviations:** WF, wide-field; SS-OCTA, swept-source optical coherence tomography angiography; UWF, ultra-widefield; UWFFA, UWF fluorescein angiography; FFA, fundus fluorescein angiography; CFP, color fundus photography; VRI, vitreoretinal interface; EFI, extended field imaging; CI, confidence interval; NV, neovascularization; NVD, neovascularization of the disc; NVE, neovascularization elsewhere; MA, microaneurysm; IRMA, intraretinal microvascular abnormality; NPA, nonperfusion area; DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR.

**Table 2** Summary of Advantages and Disadvantages of UWF CFP, UWF FA, and WF-SS-OCTA

	<b>UWF CFP</b>	<b>UWFFA</b>	<b>WF-SS-OCTA</b>
Advantages	<ul style="list-style-type: none"> <li>• Fast imaging</li> <li>• Noninvasive</li> <li>• Periphery retina view</li> </ul>	<ul style="list-style-type: none"> <li>• Dynamically visualize MAs, IRMAs, NPAs and leaking NVs</li> <li>• Differentiate filling delay from ischemia</li> <li>• Periphery retina view</li> <li>• Less artifacts<sup>45</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Noninvasive and repeatable</li> <li>• Quantitative assessment<sup>9</sup></li> <li>• Structural B-scan and <i>en-face</i> images</li> <li>• Visualize deeper vessels including choriocapillaris<sup>46</sup></li> </ul>
Disadvantages	<ul style="list-style-type: none"> <li>• Pseudocolor</li> <li>• Peripheral distortion</li> <li>• Difficult in: IRMAs and NVs differentiation NPAs detection</li> </ul>	<ul style="list-style-type: none"> <li>• Invasive</li> <li>• Time-consuming</li> <li>• Dye-related adverse events</li> <li>• Leakage-related masking effects</li> <li>• Two-dimensional images</li> </ul>	<ul style="list-style-type: none"> <li>• Imaging artifacts and segmentation errors</li> <li>• No leakage signal</li> <li>• IRMAs detection</li> <li>• Poor comparability of parameters</li> </ul>

and even improve retinopathy severity scores.<sup>61,62</sup> Anti-VEGF drugs primarily exert anti-angiogenic and anti-edematous effects by binding to VEGF-A isoforms, which exhibit the strongest pro-angiogenic activity and increase vascular permeability.<sup>63</sup> Rather than removing hemorrhages directly, anti-VEGF therapy targets the underlying pathophysiology, including neovascular regression while facilitating the absorption of accumulated hemorrhages through vascular stabilization, thereby preventing rebleeding.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S evaluated the effect of PRP versus intravitreal ranibizumab for PDR eyes (37% of whom were HR-PDR). Results demonstrated that ranibizumab therapy was noninferior to PRP in terms of change in visual acuity at 2 years, along with lower rates of vision-impairing DME, reduced peripheral visual field loss, and fewer vitrectomies.<sup>54</sup> Further five-year follow-up maintained similar results and was accompanied by a lower incidence of TRD.<sup>64</sup> However, visual field loss progressed in the anti-VEGF treated group, and nearly half of the affected eyes in both groups developed VH within follow-up.<sup>14</sup> The PRIDE study confirmed that ranibizumab monotherapy is more effective than PRP alone at reducing NV leakage and area, and provides better visual acuity within 12 months.<sup>65</sup> Similarly, the CLARITY trial showed that aflibercept achieved noninferior or superior best corrected visual acuity (BCVA) versus PRP alone at 52 weeks in PDR patients (25% of whom were HR-PDR).<sup>56</sup> Moreover, the RECOVERY study reported statistically significant improvement in the progression of DR severity after aflibercept 1-year injection in PDR eyes without DME.<sup>61</sup> The studies above seem to indicate that, at least in the short term, anti-VEGF therapy is noninferior to PRP for HR-PDR management.

### Disadvantages and Limitations

Intravitreal injections require long-term follow-up, high patient compliance, and relatively high treatment costs. Anti-VEGF induced NVs regression can occur as early as 24 hours post-administration and persist for at least 4 weeks, but recurrence may develop subsequently.<sup>66,67</sup> While previous studies indicated that PDR eyes require an average of 4–7 injections in the first year and typically fewer in subsequent years to maintain remission,<sup>54,56</sup> no consensus exists regarding the optimal injection frequency and appropriate time to stop safely (if ever). Retrospective data from Wubben et al further indicates that anti-VEGF alone treated patients, particularly HR-PDR, who are unintentionally lost to follow-up (LTFU), face elevated risk of irreversible vision loss caused by NVG or TRD.<sup>68,69</sup> This is a real concern, as approximately 25% of PDR patients will be LTFU within 4 years, whether received anti-VEGF or PRP treatment.<sup>70</sup> By contrast, PRP generally provides longer-lasting effects with lower treatment burden and may offer an early protection against vision loss in high risk LTFU patients.<sup>69,71</sup>

The cost differential between anti-VEGF injections and PRP is substantial. Cost-effectiveness analysis indicates that when PRP served as the primary treatment, the 2-year cost per quality-adjusted life years (QALY) was \$7988; while when intravitreal ranibizumab was primary treatment, the 2-year cost QALY was \$19,150.<sup>72</sup> Long-term analysis further confirmed markedly less favorable incremental cost-effectiveness ratios (ICERs) for ranibizumab versus PRP in patients without CI-DME at baseline: \$552,268/QALY at 5 years and \$742,202/QALY at 10 years. For patients with baseline CI-DME, ICERs were favorable \$65,576/QALY at 5 years and \$63,930/QALY at 10 years.<sup>73</sup> Consequently, anti-VEGFs demonstrate significant cost-effectiveness potential in the treatment of PDR only under specific conditions.<sup>74,75</sup> Using bevacizumab as an alternative to ranibizumab and aflibercept could reduce associated incremental costs.<sup>74</sup> However, considering drug prices and medical insurance constraints in low- and middle-income countries, PRP retains a cost advantage in resource-limited settings.

Similar to PRP, anti-VEGF therapy cannot fundamentally reverse retinal ischemia or fully address the complex pathophysiology of DR. Anti-VEGF therapy appears to fail to consistently improve retinal perfusion,<sup>62</sup> despite occasional reperfusion observations.<sup>76</sup> Even with monthly injections, disease progression and visual deterioration remain possible.<sup>77,78</sup> Additionally, it is important to be aware that anti-VEGF treatment may accelerate the transition from angiogenic dominance to fibrotic dominance in HR-PDR, contributing to TRD incidence rates ranging from 1.5% to 18.4%.<sup>79</sup>

Despite its demonstrated efficacy, anti-VEGF monotherapy is not currently recommended as an alternative to PRP for the treatment of PDR due to its uncertainty of long-term benefits compared to PRP, as well as the significant cost burden and elevated risks associated with LTFU. Instead, anti-VEGF therapy is recommended as a temporary adjunct therapy to

PRP in PDR management or as a cost-effective intervention for patients with CI-DME requiring vision preservation.<sup>68,80</sup> Further research should focus on long-term visual acuity outcomes under anti-VEGFs and PRP, the respective rates of vision-threatening complications, and the impact of nonadherence on final visual prognosis.

## PRP Combined with Anti-VEGF Agent

### Clinical Applications and Effects

Multiple studies have confirmed that combining PRP and anti-VEGF treatment has a synergistic effect, making it the preferred approach in clinical practice. Anti-VEGF injections reduce the necessary laser energy and volume, thereby alleviating adverse effects such as peripheral vision impairment and DME development. Meanwhile, PRP can have a longer-lasting effect on the regression of NVs, reducing the frequency of required injections and thus lowering long-term costs.

In the PROTEUS study, a 1-year randomized trial focusing exclusively on HR-PDR, Figueira et al demonstrated that PRP combined with ranibizumab three-needle basal therapy was more effective than PRP monotherapy in regressing the total NVs area, but no significant differences in BCVA were observed between two groups at any visits.<sup>81</sup> Another 1-year retrospective study reported that three-needle basal conbercept plus PRP therapy achieved a higher rate of NVs resolution, greater BCVA improvement, and lower average central macular thickness (CMT). It also reduced the need for vitrectomy in HR-PDR patients compared to PRP alone.<sup>82</sup> Similar results have also been confirmed in PRP combined with other anti-VEGF drugs, such as aflibercept and bevacizumab, in the short-term follow-up of 6 months to 1 year.<sup>83,84</sup> Pretreatment with a single anti-VEGF injection before PRP enhances treatment completion rates and patient satisfaction by reducing the incidence of VH, especially in baseline HR-PDR patients.<sup>85</sup> Notably, combination therapy achieved the greatest reduction in disease severity grade among HR-PDR patients compared with either anti-VEGF or PRP monotherapy.<sup>65</sup> While current evidence consistently supports combination therapy for accelerating NVs regression and improving short-term anatomical structures, its impact on sustained visual acuity gains remains inconsistent.<sup>81,86–89</sup> Long-term benefits of combination therapy for HR-PDR beyond one to two years require validation through extended trials.

### Recommend Combination Therapy Strategies

The recommended combination regimen prioritizes intravitreal anti-VEGF administration before PRP. The sequence leverages differential therapeutic timelines. As mentioned above, PRP initiates NVs regression as early as 1 week but requires more than 3 weeks for maximal effect, whereas anti-VEGF therapy acts rapidly.<sup>67,89</sup> Patients receiving anti-VEGF followed by PRP exhibit lower 5-year rates of PDR complications and PPV requirements compared to those treated with PRP-first sequencing.<sup>90</sup> For HR-PDR patients, preemptive anti-VEGF is critical to mitigate VH risk during PRP. Evidence-based protocols recommend administering anti-VEGF injections 1 week prior to PRP and completing in 3–4 sessions over 2 months (2-week intervals each time).<sup>84,85</sup> Increasing the loading doses may function in improving retinal structure, but no further visual function enhancement was achieved.<sup>84</sup> For patients with DME at baseline, three monthly anti-VEGF loading doses during PRP are strongly recommended.<sup>81,91</sup> Economically, single-dose is much more acceptable than triple-dose in clinical practice. Significant knowledge gaps remain regarding the optimal anti-VEGF dosage during PRP treatment and personalized maintenance strategies for HR-PDR patients with different clinical phenotypes.

## Pars Plana Vitrectomy

### Clinical Applications and Effects

The traditional indications for PPV in eyes with PDR include non-resolving or recurrent visually impairing VH and/or tractional retinal complications threatening or involving the macula.<sup>92</sup> By mechanically removing vitreous opacities, fibrovascular membranes, and PVCs, vitrectomy achieves earlier visual benefits and effectively releases macula-threatening traction factors by reducing both tangential and antero-posterior traction forces.<sup>93</sup> Successful vitrectomy also induces a long-term reduction in VEGF levels, shifting the intraocular environment towards an anti-angiogenic state and partially alleviating the progression of retinopathy.<sup>94,95</sup>

Recent advances in surgical instrumentation and vitrectomy techniques have expanded the indications for PPV, prompting retinal specialists to intervene earlier in the disease course. In eyes with advanced PDR, postoperative anatomical success rates reached 87% to 98%; however, visual acuity improvement remained limited (ranging from approximately 0.68logMAR to 1.4logMAR), with an elevated risk of adverse events including visual instability and recurrent retinal detachment.<sup>96–99</sup> Several studies suggest that early surgical intervention for HR-PDR patients, with or without VH, is a potential option to improve long-term visual outcomes and minimize treatment burden. The landmark Diabetic Retinopathy Vitrectomy Study (DRVS) first demonstrated this benefit in PDR eyes with useful vision ( $BCVA \geq 10/200$ ) and active, extensive NVs or fibrovascular proliferations. Within 4 years, the early vitrectomy group achieved superior visual outcomes compared to conventional management, with no increased risk of complications.<sup>13</sup> Similarly, a recent study found that pre-emptive vitrectomy was safe and effective in eyes with extensive, persistent, non-fibrotic retinal neovascularization and good baseline vision ( $BCVA \geq 20/50$ ). These eyes maintained stable visual outcomes at approximately 0.15logMAR through the 12-month follow-up period.<sup>100</sup> This result significantly outperforms visual outcomes typically achieved with PPV for advanced PDR, where postoperative vision is frequently compromised by fibrotic complications and macular edema. However, the benefits of early vitrectomy appear to increase with greater baseline neovascular severity and poorer baseline visual acuity.<sup>101</sup> An eight-year real-world study demonstrated the advantages of PPV over conventional treatment in terms of long-term visual improvement and reduced reoperation rates, particularly in patients under the age of 50, although the study included eyes with complications.<sup>102</sup> In addition, Elhamid<sup>103</sup> and Antoszyk<sup>104</sup> confirmed that early vitrectomy accelerates visual recovery and reduces the likelihood of recurrent VH and TRD compared to anti-VEGF monotherapy or anti-VEGF/PRP combination therapy. This therapeutic advantage may stem from the fact that PPV can directly remove tractional forces on residual neovascular complexes.

The economic benefits of early PPV are also noteworthy. Cost-utility analyses from Protocol S demonstrated that early PPV was as cost-effective as PRP for treating PDR eyes without DME, both within the initial 2 years and over a lifetime. In contrast, the cost-effectiveness gap between anti-VEGF therapy and early PPV widened significantly over time, from 2.4 to 3 times in the first 2 years, to 5.3 to 10.8 times cost/QALY in lifetime.<sup>105</sup> Cost-analysis from Protocol AB revealed that PPV plus PRP-first strategy saves approximately half therapeutic cost compared to aflibercept-first strategy for managing non-clearing VH in PDR patients over 104 weeks.<sup>106</sup>

### Effects of Posterior Vitreous Detachment and Age

Evidence indicates that the progression of DR is influenced by the status of the PVD. Vitreoretinal adhesion constitutes a crucial factor mediating the development of retinal NVs.<sup>107</sup> Current consensus states that partial PVD is a characteristic vitreous alteration in PDR and a predisposing factor for disease progression, whereas complete PVD represents a strong negative risk factor.<sup>107–109</sup> A retrospective study of 403 eyes with DR found that eyes with partial PVD or no PVD exhibited significantly higher progression rates over 3 years compared to those with complete PVD. Notably, eyes exhibiting partial PVD with thickened PVC approached a progression rate of nearly 100%.<sup>107</sup> Additionally, studies have reported that younger PDR patients present with more severe disease manifestations, including a heightened risk of visual loss and TRD, compared to older patients, irrespective of prior PRP therapy.<sup>102,110</sup> This disparity may be attributed to the prevalence of firm peripheral vitreoretinal adhesion and active, extensive fibrovascular proliferation at the vitreoretinal interface in younger PDR cohorts.

### Complications

The primary concern regarding early vitrectomy is the high incidence of postoperative complications. Previous studies have established postoperative vitreous cavity hemorrhage (POVCH) as a well-recognized complication, with reported incidence rates ranging from 12% to 40%.<sup>100,103,111,112</sup> Elevated VEGF levels at the time of initial vitrectomy constitute an independent risk factor for POVCH development.<sup>111,112</sup> Early POVCH (<4 weeks) is primarily associated with lysis of residual blood clots in the peripheral vitreous skirt, persistent hemorrhage from fragile vessels transected during surgery, and incomplete removal of fibrovascular tissue.<sup>113</sup> Conversely, late POVCH (>4 weeks) is predominantly caused by neovascularization growth at the entry sites and recurrence on the retinal surface, driven by sustained intraocular VEGF overproduction following surgery.<sup>112</sup> Therefore, meticulous surgical technique is

important, emphasizing the complete removal of vitreous surrounding the entry sites, fibrovascular membranes and vitreous cortex. Furthermore, patients need to be counseled preoperatively regarding the risk of transient visual impairment in the early postoperative period and the potential necessity for secondary surgery before long-term visual stability is achieved.<sup>100</sup>

Cataract formation is another highly prevalent complication following vitrectomy. A large retrospective study reported that nearly 50% of phakic eyes undergoing PPV alone developed cataracts within 6 months postoperatively.<sup>114</sup> Similarly, Ben et al demonstrated that all phakic eyes developed cataracts requiring surgery at 4-year follow-up after comparing PPV alone and PPV combined with phacoemulsification for the treatment of PDR eyes.<sup>115</sup> While combined surgery significantly enhances intraoperative visualization of anterior vitreous structures, facilitating more thorough PRP and vitreous removal, it also prolongs the operative duration and increases the risk of anterior chamber instability, corneal edema, and postoperative NVG. Therefore, although combined surgery may be a suitable approach for PDR patients with significant pre-existing cataracts, the substantial risk of NVG development necessitates careful consideration.

NVG following vitrectomy in PDR patients is the most severe complication, portending a poor visual prognosis, with reported incidence rates ranging from approximately 2% to 15%.<sup>110,116</sup> Main risk factors identified include younger age, elevated preoperative intraocular pressure, uncontrolled diabetes mellitus, absence of prior PRP, postoperative VH, and undergoing combined cataract extraction with vitrectomy.<sup>116–118</sup> Postoperative anti-VEGF injections appear to protect against NVG occurrence.<sup>119</sup>

### Summary and Limitations

Overall, vitrectomy is considered to be a cost-effective and durable therapeutic approach for PDR. When considering early PPV for eyes with HR-PDR, critical issues to focus on include whether to combine cataract surgery and how to reduce perioperative complications. The status of the PVD and patients' age are essential considerations in the decision-making process. Eyes exhibiting partial or absent PVD, particularly in younger individuals with advanced disease, may derive significant benefit from early vitrectomy with complete hyaloid removal, coupled with extensive intraoperative anti-proliferative photocoagulation.<sup>102</sup>

However, a standardized definition of "early" intervention and the optimal time to perform vitrectomy remain undefined. Current available studies predominantly use BCVA, fundus lesion characteristics, or duration of VH as indicators for early surgical intervention. Some authors propose performing vitrectomy if persistent VH shows inadequate absorption after 4–6 weeks; nevertheless, there is no standardized consensus. Current recommendations for early vitrectomy are largely based on retrospective studies with low levels of evidence. Further prospective, high-quality research is imperative to establish definitive surgical timing criteria and evaluate long-term prognosis.

## PPV Combined with Anti-VEGF Agents and/or PRP

### PPV Combined with PRP

Preoperative or intraoperative PRP reduces the incidence of POVCH in eyes with PDR, potentially mediated by decreased vitreous VEGF concentration and accelerated regression of NVs.<sup>15,120,121</sup> Intraoperative PRP can be delivered more anteriorly than that performed with a slit lamp. The DRCR.net Protocol AB study demonstrated that PPV combined with intraoperative PRP achieved superior early visual acuity gains compared to anti-VEGF monotherapy, although long-term benefits at 24 weeks were not significant.<sup>104</sup> For HR-PDR patients presenting with VH, combined vitrectomy and concurrent intraoperative laser may obviate the need for preoperative PRP, potentially reducing surgical waiting times, follow-up burden, and low-vision related costs.<sup>122</sup> Notably, the DRVS group did not advocate vitrectomy as an alternative to photocoagulation, but rather as an adjunctive intervention for severe complications following PRP or when preoperative PRP is unfeasible.<sup>13</sup>

### PPV Combined with Anti-VEGF Agents

Perioperative injection of anti-VEGF is widely considered as a necessary adjunctive therapy to minimize intraoperative and postoperative complications and maximize surgical outcomes. By effectively reducing intravitreal VEGF levels,

preoperative anti-VEGF injections induce NVs regression and facilitate surgical procedures such as the dissection of fibrovascular membranes.<sup>123</sup> Meta-analyses confirm that preoperative anti-VEGF treatment reduces intraoperative bleeding, shortens surgery duration, and decreases complication rates, including intraoperative iatrogenic retinal breaks and POVCH.<sup>124–126</sup> Reinjection at PPV conclusion replenishes the drug eliminated during vitrectomy, mitigates pharmacokinetic-related efficacy loss, and further reduces the likelihood of POVCH associated with postoperative VEGF surge.<sup>112,127,128</sup> Further, perioperative anti-VEGF injection is associated with a slight improvement in postoperative BCVA.<sup>125–127,129</sup> Given the transient intravitreal VEGF suppression achieved (approximately 4 weeks) with current anti-VEGF agents,<sup>130</sup> adequate preoperative or intraoperative PRP remains crucial to prevent NVs recurrence and ensure long-term stability.

However, the optimal interval between preoperative intravitreal anti-VEGF injection and vitrectomy remains contentious. Theoretically, vitrectomy should be performed after significant NVs regression but before fibrovascular complex constriction exacerbates the progression of TRD.<sup>113</sup> Russo et al reported that longer injection-to-surgery intervals significantly increased the risk of macular traction, and it is relatively safe to perform surgery within 10 days after injection.<sup>131</sup> El-Sabagh et al found that the pan-endothelial marker CD34, expressed in neovascular vessels, showed no significant decrease until day 5 post-injection, indicating that too early surgical intervention may be insufficient for NVs regression.<sup>132</sup> Their findings also revealed marked reduction in the proliferative vascular component without significant contractile component accumulation around day 10, potentially defining an optimal window. Additional evidence suggests that a preoperative interval of 6 to 14 days may maximize efficacy in improving postoperative BCVA, reducing surgery time, and minimizing recurrent VH incidence.<sup>126</sup> While higher anti-VEGF doses may reduce the severity and incidence of early POVCH without increasing the risk of other complications, supporting evidence is limited.<sup>133</sup> Further randomized prospective trials are needed to explore the optimal timing and dosing regimens for specific anti-VEGF agents.

## Barriers to Clinical Application in Real-World

Early detection of microvascular abnormalities and prompt intervention can prevent severe visual impairment in DR. However, patients often present with poor vision and already meet the diagnostic criteria for HR-PDR at their initial visit. Large-scale systematic DR screening programs for all diabetes patients enable earlier detection and intervention, but significant infrastructure investment and time requirements limit implementation, particularly in middle- and low-income regions.<sup>134,135</sup> Vacancies and uneven distribution of experts hinder the application of techniques. While UWF imaging technology offers potential advantages in DR screening and management, it may be costly and unsuitable for remote areas. Advances in artificial intelligence (AI), deep learning algorithms, and telemedicine are expected to enable personalized, automated real-time medicine, potentially bridging the current gap.<sup>135–137</sup>

The relatively low cost and long-term efficacy of PRP contribute to its accessibility. Conversely, the extensive application of anti-VEGF therapy in PDR patients without CI-DME is constrained by frequent administration, intensive follow-up, suboptimal cost-effectiveness, uncertain long-term effectiveness, and potential ocular or systemic adverse events.<sup>138,139</sup> Although evidence suggests comparable effectiveness among different anti-VEGF agents, real-world variations in individual patient sensitivity exist. Additionally, extended and uncertain treatment regimens can lead to patient fatigue. When combined with treatment non-compliance due to regulatory hurdles (eg, reimbursement limitations), the risk of vision-threatening complications increases, often leading to unsatisfactory long-term outcomes. In addition, early surgical intervention is often poorly accepted for specific high-risk patients despite good baseline vision. Supporting evidence is currently insufficient, and further exploratory studies focusing on long-term visual acuity and complication risks are required.

While emerging novel imaging and treatment modalities hold significant potential to improve DR clinical outcomes, equitable global implementation of these advances across both high- and low-resource settings is imperative.

## Current Limitations and Future Perspectives

### Application of UWF Imaging Technology

UWF imaging can detect a great number of PPLs in patients with DR. However, its impact on predicting visual impairment and disease progression remains insufficiently characterized. While the assessment of quantitative metrics derived from multimodal UWF imaging, particularly OCTA parameters, has been extensively investigated, data comparability across different devices is limited by the absence of standardized acquisition and analysis protocols established by international consensus.<sup>45</sup> Furthermore, reliable evidence linking these imaging biomarkers to DR progression and long-term visual outcomes is currently lacking. Future research should prioritize establishing the sensitivity and specificity of quantitative UWF and OCTA metrics for predicting visual decline and disease progression. Additionally, the significant biases introduced by imaging artifacts highlight the critical need for research dedicated to optimizing image acquisition techniques and developing advanced artifact correction algorithms.<sup>140</sup>

### Research Limitations and Gaps

The current body of evidence is constrained by several limitations, including short study durations, small sample sizes, significant LTFU, and inconsistent inclusion criteria. Most existing studies are retrospective, with follow-up periods typically limited to 6–12 months, and often fail to report crucial details regarding DM duration and systemic control, which are factors known to profoundly influence treatment efficacy and disease prognosis. To address these limitations, prospective, large-scale, randomized controlled trials (RCTs) with extended follow-up periods (>5 years) and rigorous documentation of baseline DM characteristics are essential for generating reliable comparative prognostic data.

Diabetic patients frequently experience high LTFU rates due to barriers in accessing ophthalmic care. Reported LTFU rates in RCTs range from 15% over 2 years to 45% over 5 years, with real-world data suggesting even higher rates in clinical practice.<sup>141</sup> Potential adverse consequences of inadequate follow-up, especially for patients with HR-PDR, remain poorly understood. Moreover, cost-effectiveness analyses of different treatments often fail to incorporate the significant impact of poor patient adherence. Future high-quality studies should focus on identifying patients at high risk for LTFU using predictive models and developing targeted interventions (eg, telemedicine monitoring, patient education programs, integrated care pathways) to improve retention and reduce vision loss. Although challenging to obtain, incorporating real-world adherence data and LTFU outcomes is essential for improving the practical applicability of research findings.

### Treatment Strategies and Options

A definitive consensus on the optimal management strategy for HR-PDR patients is currently lacking. Prompt PRP remains the standard initial intervention for HR-PDR patients with a clear fundus view,<sup>10,11</sup> however, the timing and efficacy of supplemental laser is inconclusive. When anti-VEGF agents serve as the primary therapy, a regimen of three initial loading doses followed by a pro re nata (PRN) approach is commonly employed. Nevertheless, evidence supporting individualized dosing strategies, criteria for treatment cessation, and long-term outcomes with anti-VEGF monotherapy requires further clarification. Similarly, when anti-VEGF agents are used alongside vitrectomy to reduce perioperative complications, standardized protocols regarding agent selection, dosage, optimal timing, and postoperative regimen are yet to be firmly established.

Clinical guidelines recommend early PPV for PDR patients with dense, non-clearing VH.<sup>11,142,143</sup> However, the definitions of “early” versus “late” intervention remain ambiguous. Performing vitrectomy too early carries a risk of overtreatment in patients with potential for spontaneous hemorrhage resolution, while delaying surgery risks irreversible complications like TRD. Key unresolved questions include: 1) Which patient subgroups benefit most from early PPV? 2) How should postoperative complications, such as POVCH, be managed – with observation, injection of anti-VEGF, or prompt secondary surgery? Future research must address these critical knowledge gaps through well-designed comparative studies and the development of evidence-based algorithms.

### Summary and Conclusion

In summary, this review summarizes the diagnostic utility of UWF imaging in HR-PDR and analyzes comparative treatment outcomes, emphasizing the influence of patient adherence and cost-effectiveness on therapeutic selection. Unlike existing

literature focused on isolated treatment modalities or imaging techniques, this review distinctively bridges the gap between technological innovation, clinical decision-making, and healthcare system implementation in managing HR-PDR. Key limitations include its limited focus on DME management, exclusion of anti-inflammatory treatment modalities, and potential selection bias caused by variable inclusion criteria across referenced studies (eg, incorporation of NPDR cases or concomitant TRD).

UWF imaging has great potential to reshape HR-PDR screening and management. The noninvasive, rapid, and reproducible nature of combined UWF CFP and WF-SS-OCTA supports their utility in HR-PDR diagnosis and monitoring (GRADE 2C: low-quality evidence, weak recommendation).<sup>30,39,144</sup> While conventional and ultra-widefield FFA remain indispensable for detecting vascular leakage, their invasive nature and potential adverse effects necessitate judicious clinical application.

Timely intervention is imperative for HR-PDR due to the high risk of vision-threatening complications associated with delayed treatment. Although anti-VEGF monotherapy can effectively induce neovascular regression and improve visual and anatomical outcomes, the necessity of PRP should be emphasized, particularly for patients with high LTFU risk or limited financial resources.<sup>145</sup> Anti-VEGF therapy and PRP can be performed concurrently in HR-PDR, but long-term visual benefits require further validation in RCTs.<sup>11</sup> For individuals with persistent VH, early vitrectomy with intraoperative PRP is recommended (GRADE 1B: moderate-quality evidence, strong recommendation),<sup>13,100,103,142–144</sup> and perioperative injection of anti-VEGF can reduce the incidence of intraoperative bleeding and early postoperative VH (GRADE 1B: moderate-quality evidence, strong recommendation).<sup>125,129,144</sup> Blood glucose control is the cornerstone of managing all patients with HR-PDR, and is crucial for the success of any ocular intervention and the prevention of further progression or recurrence. Strict adherence to diabetes management guidelines, including medication, diet, and lifestyle modifications, is essential to stabilize retinal vascular structure and reduce systemic factors that drive neovascularization. Real-world treatment selection should balance issues of efficacy, safety, cost, adherence, ocular and systemic factors, with the understanding that poor metabolic control can undermine the effectiveness of local therapies.

## Abbreviations

DR, diabetic retinopathy; HR-PDR, high-risk proliferative diabetic retinopathy; PRP, pan-retinal photocoagulation; VEGF, vascular endothelial growth factor; PPV, pars plana vitrectomy; NVD, neovascularization of the disc; NVE, neovascularization elsewhere; UWF CFP, ultra-widefield color fundus photography; UWFFA, ultra-widefield fluorescein angiography; FFA, fundus fluorescein angiography; WF-SS-OCTA, wide-field swept-source optical coherence tomography angiography; CI-DME, central-involved diabetic macular edema; VH, vitreous hemorrhage; TRD, tractional retinal detachment; IRMA, intraretinal microvascular abnormalities; NPAs, non-perfused areas; VRI, vitreoretinal interface; ILM, internal limiting membrane; PVC, posterior vitreous cortex; PVD, posterior vitreous detachment; BCVA, best corrected visual acuity; POVCH, post-operative vitreous cavity hemorrhage; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

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