• Review Article •

Impact of different treatment regimens on long-term prognosis in patients with proliferative diabetic retinopathy: a systematic review

Yu-Man Li[1], Feng Zhao[2], Wen-Tao Li[3], Ying Cui[1], Lei Xi[1]

[1]Department of Ophthalmology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510060, Guangdong Province, China
[2]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangzhou 510060, Guangdong Province, China
[3]Department of Ophthalmology, Huizhou Third People's Hospital, Guangzhou Medical University, Huizhou 516000, Guangdong Province, China
Correspondence to: Lei Xi. Department of Ophthalmology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, 106 Zhongshan Er Road, Guangzhou 510080, Guangdong Province, China. xilei@gdph.org.cn
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Abstract

• **AIM:** To evaluate the long-term prognostic outcomes associated with different treatment regimens for PDR, including panretinal photocoagulation (PRP), anti-vascular endothelial growth factor (anti-VEGF) therapy, vitrectomy, and combination approaches.

• **METHODS:** A comprehensive literature search was conducted across PubMed, Embase, Web of Science, and the Cochrane Library from database inception through March 31, 2024, with manual supplementary screening extended to June 30, 2024. Randomized controlled trials (RCTs) and comparative observational studies that directly evaluated at least two treatment regimens with a minimum follow-up of 1y were included in the principal therapeutic synthesis; imaging, screening, epidemiologic, and disease-characterization studies were retained as contextual evidence. Owing to substantial clinical and methodological heterogeneity, findings were synthesized through structured narrative synthesis in accordance with SWiM guidance, with evidence certainty assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.

• **RESULTS:** The evidence base comprised 20 studies encompassing 8742 participants and 9521 eyes. Major comparative trials, interpreted as moderate-certainty evidence, indicated that anti-VEGF therapy (ranibizumab) and PRP achieved broadly comparable long-term visual acuity outcomes in selected trial populations receiving structured follow-up. Anti-VEGF therapy was associated with better visual field preservation and a lower cumulative incidence of vision-impairing diabetic macular edema (DME) compared with PRP [22% *vs* 38%; hazard ratio (HR) 0.4, 95%CI: 0.3-0.7]. Combination therapy (PRP plus ranibizumab) demonstrated favorable neovascular regression in selected small comparative studies, and perioperative anti-VEGF adjuncts improved intraoperative conditions and reduced early postoperative hemorrhage in vitrectomy-treated eyes.

• **CONCLUSION:** Anti-VEGF therapy and PRP may provide broadly comparable long-term visual acuity outcomes in selected PDR patients, though important differences exist in treatment burden, visual field preservation, and complication profiles. Treatment selection should be individualized according to DME status, vitreous hemorrhage, tractional or fibrovascular components, prior PRP, anticipated adherence, and healthcare accessibility, with long-term surveillance remaining essential given the chronic and progressive nature of PDR.

• **KEYWORDS:** proliferative diabetic retinopathy; treatment regimens; long-term prognosis; systematic review
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INTRODUCTION

Proliferative diabetic retinopathy (PDR) is a severe complication of diabetes mellitus, characterized by neovascularization, vitreous hemorrhage, and tractional retinal detachment. It is the leading cause of vision loss and blindness

among working-age adults worldwide[1]. Diabetes patients with a longer disease duration and poor glycemic control have a higher prevalence of PDR[2]. As diabetes incidence rises, the burden of PDR is expected to increase, posing significant challenge to healthcare systems and patients' quality of life[3].

The pathogenesis of PDR involves a complex interplay of metabolic, inflammatory, and angiogenic factors. Chronic hyperglycemia induces oxidative stress, advanced glycation end-product formation, mitochondrial dysfunction, inflammatory activation, and retinal microvascular injury, ultimately contributing to capillary nonperfusion and ischemia[4-5]. Angiogenic factors, particularly vascular endothelial growth factor (VEGF), are upregulated by hypoxia in the retina, which stimulates the growth of retinal neovascularization (RNV)[6]. These mechanisms also underscore that ocular treatment should be interpreted within the broader context of systemic metabolic control and vascular risk modification rather than as an isolated local intervention. Vision-threatening complications such as vitreous hemorrhage and tractional retinal detachment are caused by leakage and hemorrhaging of these fragile neovascular structures[7].

The management of PDR has evolved significantly, with panretinal photocoagulation (PRP) as a mainstay since the 1970s[8-12]. PRP reduces neovascularization and vision loss risk by applying laser burns to the peripheral retina. However, it may cause peripheral vision loss, decreased night vision, and exacerbation of macular edema[13-14]. Recently, anti-VEGF therapy, including bevacizumab, ranibizumab, and aflibercept, has emerged as an alternative or adjunct to PRP, reducing neovascularization and improving visual outcomes[11]. Vitrectomy, a surgical procedure to remove the vitreous gel and relieve retinal traction, is used in advanced cases with non-clearing vitreous hemorrhage or tractional retinal detachment[15].

In the broader diabetic retinopathy treatment landscape, PDR management represents one component of a hierarchical approach that also includes systemic risk-factor control, screening, treatment of diabetic macular edema (DME), and timely intervention for vision-threatening disease. Recent reviews of diabetic retinopathy treatment strategies have emphasized that PRP, anti-VEGF therapy, corticosteroid-based approaches for macular edema, and vitreoretinal surgery should be positioned according to disease severity, ocular phenotype, treatment burden, and healthcare-resource availability[16-17]. In parallel, systemic lipid-modifying therapies, nutritional status, and metabolic risk modification may influence diabetic retinopathy progression and long-term prognosis, complementing but not replacing ocular interventions[18-19].

While there are several treatment options available for PDR, the long-term prognosis remains unclear. Previous systematic reviews have focused on short-term efficacy and safety, with limited evidence of long-term prognosis[20-21]. This systematic review aimed to address these knowledge gaps by evaluating the long-term prognosis of PDR patients with different treatment regimens. We compared the long-term efficacy of treatments [including PRP, anti-VEGF, pars plana vitrectomy (PPV), and combination therapy] by assessing vision, incidence of complications, and the need for additional interventions or retreatment. Additionally, we identified factors that may affect long-term prognosis, such as baseline characteristics, disease severity, and treatment compliance.

MATERIALS AND METHODS

Ethical Approval This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews 2020 statement and Meta-analyses (PRISMA) guidelines[22].

Eligibility Criteria

Types of studies Inclusion: For the principal therapeutic synthesis, we included randomized controlled trials (RCTs), secondary analyses of RCTs, and comparative observational studies that directly evaluated at least two treatment regimens for PDR and reported prognostic outcomes with a minimum follow-up duration of 1y. Eligible treatment regimens included PRP, anti-VEGF therapy, PPV, and combination approaches such as PRP plus anti-VEGF therapy or PPV plus perioperative anti-VEGF therapy. The PICO framework for the core evidence was defined as follows: adult patients with PDR; interventions consisting of active PDR treatment regimens; comparators consisting of alternative PDR treatment regimens, sham/control injection, or different procedural/dosing strategies; and outcomes including long-term visual acuity (VA), neovascular regression or progression, visual field changes, treatment-related complications, or need for additional interventions.

Studies that did not directly compare treatment regimens or did not meet the minimum follow-up requirement were not included in the principal therapeutic synthesis. However, imaging-focused studies, screening studies, epidemiologic studies, prevalence studies, and disease-characterization or progression analyses were retained as contextual supporting evidence when they provided clinically relevant information for PDR assessment, disease monitoring, treatment planning, or interpretation of long-term prognosis. These studies were summarized separately and were not used to infer comparative treatment effectiveness.

Exclusion: Studies with the follow-up of less than 1y, those with only one treatment regimen and no comparison group and case reports, case series, reviews, commentary, and conference abstracts were excluded. Patients with non-PDR or other retinal diseases were also excluded, unless separate data for PDR patients were available.

Types of participants We included studies involving adult patients (aged 18y or older) with a diagnosis of PDR, as defined by the presence of neovascularization on the optic disc, retina, or iris, with or without vitreous hemorrhage or tractional retinal detachment. Studies that included patients with non-PDR or other retinal diseases were excluded, unless separate data for PDR patients were available. When reported, baseline glycated hemoglobin (HbA1c), diabetes type and duration, and prior ocular interventions were extracted. Most studies did not stratify outcomes by these factors, which were considered narratively where data permitted.

Types of interventions We included studies that compared at least two of the following treatment regimens for PDR: PRP, anti-VEGF therapy (bevacizumab, ranibizumab, or aflibercept), vitrectomy, combination therapies (*e.g.*, PRP+anti-VEGF, vitrectomy+anti-VEGF). Studies that evaluated only one treatment regimen without a comparison group were excluded.

Types of outcome measures The primary outcome was VA at the end of follow-up. To facilitate cross-study comparison, VA was reported using logMAR whenever available or convertible. Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores were retained as reported for major randomized trials and, when necessary for cross-study comparison, converted using the formula logMAR=(85-ETDRS letters)×0.02. Snellen fractions were converted to logMAR using standard conversion tables. When conversion was not feasible or could introduce misleading precision, the original metric was retained with the scale explicitly stated. Secondary outcomes were the incidence of vitreous hemorrhage, incidence of retinal detachment, need for additional interventions or retreatments, adverse events related to the treatment.

For each outcome, the unit of analysis was extracted and reported as eyes or patients. Because several ophthalmic studies enrolled or analyzed eyes rather than individual patients, we did not combine outcomes quantitatively across studies unless inter-eye correlation was appropriately handled or only one eye per participant was included. In the narrative synthesis, results based on eyes were interpreted cautiously because treating two eyes from the same patient as independent observations may overestimate precision.

Information Sources and Search Strategy PubMed, Embase, Web of Science, and the Cochrane Library were searched from database inception to March 31, 2024, with an updated manual search through June 30, 2024. The June 2024 update consisted of manual supplementary screening rather than a full structured rerun of all electronic databases. The search strategy was developed in consultation with a medical librarian. It includes a combination of Medical Subject Headings (MeSH) terms and keywords related to PDR, treatment regimens, and long-term prognosis. Database-specific search adaptations were applied according to indexing requirements. We also manually searched the reference lists of included studies and relevant systematic reviews for additional eligible studies. No language restrictions were initially imposed during database searching. However, only studies with sufficient English-language data for assessment were ultimately included. Grey literature, conference abstracts, editorials, case reports, and unpublished studies were excluded because of insufficient outcome reporting and methodological detail. All retrieved citations were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA), and duplicate records were removed using both automated software detection and manual verification.

Study Selection Two reviewers (Xi L and Zhao F) independently screened titles and abstracts of retrieved records for eligibility. Full texts of potentially relevant studies were then assessed against predefined criteria. Discrepancies were resolved through discussion or consultation with a third reviewer (Li WT). The reasons for excluding studies at the full-text stage were recorded. The study selection process was documented using a PRISMA flow diagram.

Data Extraction The reviewers will independently extract the following information from the included studies: study characteristics (authors, year of publication, country/region, study design, sample size, follow-up duration); participant characteristics (age, sex, diabetes duration, baseline PDR severity); intervention details (type of treatment regimen, dose, frequency, duration); outcome measures (VA, incidence of vitreous hemorrhage and retinal detachment, need for additional interventions, adverse events).

Any disagreement between the reviewers was resolved through discussion or consultation with a third reviewer. If necessary, we contacted the study authors for clarification or additional data.

Risk of Bias Assessment The risk of bias in the included studies was assessed using the Cochrane Risk of Bias tool for RCTs[20] and the Newcastle-Ottawa Scale (NOS) for observational studies[21]. Two reviewers independently assessed the risk of bias, and any disagreements were resolved through discussion or consultation with a third reviewer.

For RCTs, the following domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain was judged as having a low, high, or unclear risk of bias.

For observational studies, the NOS was used to assess the quality of the studies based on three domains: selection of study groups, comparability of groups, and assessment of

exposure and outcomes. Studies were awarded stars for each quality item, with a maximum of nine stars indicating the highest quality.

Data Synthesis and Analysis Because of substantial clinical and methodological heterogeneity across study designs, treatment indications, follow-up durations, outcome definitions, and units of analysis, formal Meta-analysis was not performed. Findings were synthesized narratively in accordance with the Synthesis Without Meta-analysis (SWiM) reporting guidance[23]. The synthesis was structured by clinically meaningful treatment comparisons, including anti-VEGF therapy versus PRP, aflibercept versus vitrectomy with PRP for vitreous hemorrhage, perioperative anti-VEGF use around vitrectomy, PRP plus anti-VEGF combination therapy, and vitrectomy for advanced PDR complications.

Effect estimates, confidence intervals, and *P* values were reported as presented in the original studies. No pooled effect estimates, I^2 statistics, Cochran's *Q* tests, funnel plots, Egger tests, or Meta-regression analyses were generated. Publication bias was considered qualitatively within the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, particularly for outcomes supported by few small studies or by selective outcome reporting. Because many ophthalmic studies reported outcomes at the eye level and inter-eye correlation was inconsistently addressed, we did not statistically combine eye-level data across studies.

Grading the Quality of Evidence The certainty of evidence was assessed using the GRADE framework on an outcome-specific basis rather than by assigning a single certainty rating to each study. For each clinically relevant outcome, certainty was judged according to risk of bias, inconsistency, indirectness, imprecision, and publication bias. RCT-derived evidence initially started as high certainty, whereas observational evidence initially started as low certainty. Certainty was downgraded when there were concerns regarding attrition, lack of masking, heterogeneity in outcome definitions, indirectness of the study population or intervention, small sample size, wide confidence intervals (CIs), or limited numbers of contributing studies.

Because formal Meta-analysis was not performed for most outcomes, GRADE judgments were based on structured narrative synthesis, the number and design of contributing studies, study-specific risk-of-bias assessments, consistency of direction of effect within clinically comparable comparisons, precision of reported estimates, and applicability to the target PDR population. Consistency across heterogeneous designs was not interpreted as automatically strengthening causal inference.

RESULTS

Study Selection Due to substantial heterogeneity across study designs, treatment protocols, and outcome reporting, formal pooled Meta-analysis was not appropriate for most endpoints. Our systematic literature search across PubMed, Embase, Web of Science, and Cochrane Library databases yielded 1247 potentially relevant records. After removing 261 duplicates, 986 records were screened by title and abstract. Following this initial screening, 875 articles were excluded as they did not meet our inclusion criteria. The remaining 111 full-text articles were assessed for eligibility, with 91 articles subsequently excluded due to: insufficient follow-up duration (*n*=42), non-comparative studies (*n*=29), irrelevant outcomes (*n*=15), and conference abstracts/letters (*n*=5). Ultimately, 20 studies were retained for review. Among these, 8 studies met the PICO-based criteria for the principal comparative treatment synthesis, including randomized trials, secondary analyses of randomized trials, or comparative follow-up studies directly evaluating PDR treatment regimens[24-31]. The remaining 12 studies were classified as contextual supporting evidence because they primarily addressed surgical case characteristics, imaging assessment, screening strategies, epidemiology, prevalence, or disease progression rather than direct long-term comparative treatment effects[32-43]. These contextual studies were used to inform clinical interpretation and individualized management considerations but were not treated as core evidence for comparative treatment efficacy. The PRISMA flow diagram of study selection process is presented in Figure 1. The final search included records identified through database searches up to March 31, 2024, supplemented by manual screening updates through June 30, 2024.

Characteristics of Included Studies The evidence base was reorganized into two categories: core comparative treatment studies and contextual supporting evidence. The core comparative treatment studies directly evaluated treatment regimens for PDR, including PRP, anti-VEGF therapy, vitrectomy with PRP, and combination approaches, and were used for the principal therapeutic synthesis[24-31]. Contextual supporting studies addressed related issues such as surgical outcomes in selected PDR cohorts, imaging-based detection and monitoring, individualized screening, epidemiology, prevalence, and risk of progression[32-43]. These studies were retained because they provided clinically relevant information for interpreting PDR prognosis and individualized treatment planning, but they were not considered primary evidence for comparative long-term treatment efficacy. Key characteristics of both evidence categories are summarized in Table 1[24-43]. Of the 20 retained studies, most ophthalmic treatment studies reported outcomes at the eye level, whereas several registry, screening, or epidemiologic studies reported outcomes at the patient level. The unit of analysis for each study is presented in Table 1. For the principal therapeutic synthesis, outcomes from

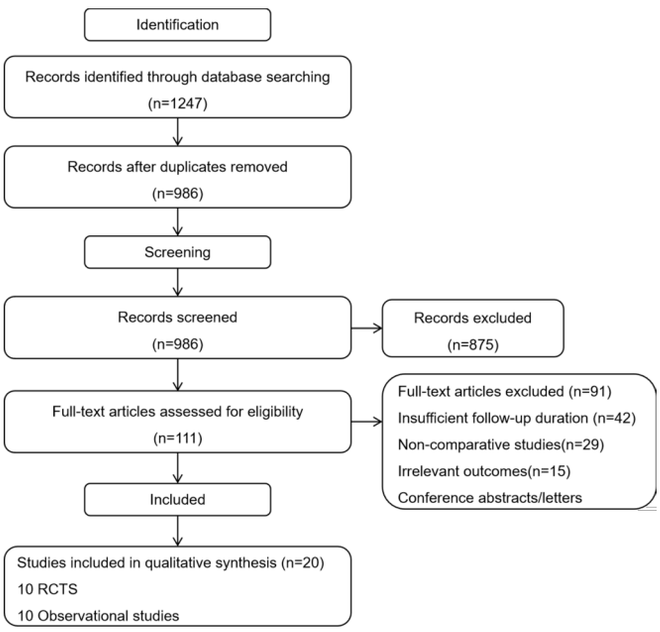


Figure 1 The PRISMA flow diagram of the study selection process
PRISMA: Preferred Reporting Items for Systematic Reviews 2020 statement and Meta-analyses; RCTs: Randomized controlled trials.

eye-level studies were interpreted according to the original study design and were not statistically pooled across studies because inter-eye correlation was inconsistently addressed. Therefore, reported CIs and *P* values from individual studies should be interpreted as study-specific estimates rather than as pooled precision estimates across the review. The total dataset encompassed 8742 participants and 9521 eyes with PDR.

Risk of Bias Assessment Risk of bias assessment was performed primarily for studies contributing to the principal comparative treatment synthesis. RCTs and secondary analyses of RCTs were assessed using the Cochrane Risk of Bias tool, whereas comparative observational studies were assessed using the NOS. Contextual supporting studies, including imaging, screening, epidemiologic, and disease-characterization studies, were not used to determine comparative treatment effects; therefore, their methodological features were summarized descriptively rather than incorporated into the GRADE assessment of therapeutic outcomes. The results of this assessment are summarized in Table 2[24-26,28-30,32-33] for RCTs and Table 3[31,34-43] for observational studies.

Risk of Bias in Randomized Controlled Trials The risk-of-bias assessment for randomized trials and comparative treatment studies contributing to the principal therapeutic synthesis is summarized in Table 2. Most interventional ophthalmology studies had inherent performance-bias concerns because masking of participants and treating clinicians was difficult or impossible for laser, injection, and surgical interventions. Outcome assessment was masked in several major trials, but incomplete outcome data and attrition were important concerns, particularly in longer-term follow-up. In brief, three studies[24-25,33] demonstrated low risk of bias across most domains. Blinding of participants and personnel was uniformly challenging due to the nature of the interventions, though most trials employed masked outcome assessment.

Attrition was interpreted as a clinically important source of bias rather than a minor methodological issue. In long-term PDR management, missed visits and discontinuation of repeated anti-VEGF therapy may be associated with recurrent neovascularization, vitreous hemorrhage, or tractional complications. Therefore, attrition in long-term anti-VEGF studies affects both internal validity and real-world applicability, especially when trial follow-up intensity exceeds routine clinical care.

Risk of Bias in Observational Studies The methodological quality of the 11 included observational studies, assessed using the NOS, is detailed in Table 3. Quality ratings ranged from 5 to 9 stars. Studies employing standardized imaging protocols and rigorous confounder adjustment—such as those by Heloterä *et al*[41] and Aiello *et al*[39]—achieved the highest quality scores.

Overall Assessment of Evidence Quality The certainty of evidence varied by outcome and clinical comparison. For long-term VA outcomes comparing ranibizumab with PRP, the evidence was rated as moderate certainty, primarily because the estimate was driven by one major 5-year randomized trial with attrition concerns[24]. Evidence for visual field preservation and vision-impairing DME was also rated as moderate certainty but remained dependent on limited trial evidence[24]. Evidence for aflibercept versus vitrectomy with PRP in vitreous hemorrhage was rated as low to moderate depending on the outcome, reflecting a single major trial, crossover, and imprecision[25,27]. Evidence for combination therapy and perioperative anti-VEGF adjuncts was rated as low because of small sample sizes, shorter follow-up, heterogeneity in treatment protocols, and limited long-term outcome data[26,28,30,33].

We did not interpret apparent consistency across heterogeneous RCTs, observational surgical studies, imaging studies, and registry data as automatically strengthening causal inference. Contextual evidence was used to support interpretation of disease assessment, monitoring, or prognosis, but it was not used to upgrade certainty for comparative treatment effects.

Certainty of Evidence The certainty of evidence for each principal outcome is summarized in Table 4[24-31,33,35]. GRADE ratings were assigned by outcome and clinical comparison rather than by study. Long-term VA for ranibizumab versus PRP was rated as moderate certainty, downgraded for attrition and imprecision because the conclusion relied mainly on one major 5-year randomized trial[24]. Visual field preservation and vision-impairing DME outcomes were also rated as moderate

Table 1 Characteristics of core comparative treatment studies and contextual supporting evidence

Author (year)	Country/region	Study design	Sample size	Mean age (y)	Intervention	Comparator	Follow-up	Primary outcome	Evidence category
Gross *et al* (2018)[24]	United States	RCT	394 eyes	52	Ranibizumab	PRP	5y	Visual acuity change	Core comparative treatment study
Antoszyk *et al* (2020)[25]	United States	RCT	205 eyes	57	Aflibercept	Vitrectomy+PRP	2y	Visual acuity change	Core comparative treatment study
Li *et al* (2022)[26]	China	RCT	48 eyes	53.2	Pre-vitrectomy ranibizumab	Sham injection	6mo	Surgical outcomes	Core comparative/supportive surgical treatment evidence
Beaulieu *et al* (2023)[27]	United States	Secondary analysis of RCT	204 eyes	57	Aflibercept	Vitrectomy+PRP	2y	Activity impairment	Core comparative treatment study
Liu *et al* (2023)[32]	China	RCT	52 eyes	56.5	27G vitrectomy	25G vitrectomy	6mo	Surgical efficiency	Contextual supporting evidence
Toscano *et al* (2021)[28]	Brazil	RCT	28 eyes	54.2	PRP+ranibizumab	Targeted photocoagulation+ranibizumab	1y	Fluorescein leakage area	Core comparative treatment study
Lang *et al* (2022)[29]	Germany	Observational follow-up	73 eyes	55.3	Ranibizumab	PRP	2y	Neovascularization area	Core comparative treatment study
Figueira *et al* (2016)[30]	Portugal	RCT	35 eyes	53.4	Ranibizumab *vs* PRP+ranibizumab	PRP	1y	NV regression	Core comparative treatment study
Su *et al* (2024)[33]	China	RCT	87 eyes	50.8	1.0 mg ranibizumab+vitrectomy	0.5 mg ranibizumab+vitrectomy	6mo	Postoperative outcomes	Contextual supporting evidence
Schwartz *et al* (2020)[34]	United Kingdom	Observational	47 eyes	56.2	OCT/OCTA evaluation	Standard clinical evaluation	12mo	NV detection rate	Contextual supporting evidence
Alshaikhsalama *et al* (2024)[35]	United States	Retrospective	933 eyes	52	PPV for PDR complications	NA	≥6mo	Visual outcomes	Contextual supporting evidence
Bek *et al* (2024)[36]	Denmark	Observational	2446 participants	NA	Individualized screening	Standard screening	25y	PDR/DME detection	Contextual supporting evidence
Nidhi *et al* (2023)[37]	India	Prospective observational	253 eyes	56	UWFFA	7-field imaging	NA	NV distribution	Contextual supporting evidence
Gonzalez *et al* (2021)[31]	United States	Post hoc analysis	759 eyes	61.8	Ranibizumab	Sham	2y	PRP retreatment rates	Core comparative treatment study
Yuan *et al* (2025)[38]	United States	Cross-sectional	249 eyes	58	NA	NA	NA	Foveal NV prevalence	Contextual supporting evidence
Aiello *et al* (2024)[39]	United States	Cross-sectional	785 eyes	61	UWF imaging	7-field imaging	NA	DR grading correlation	Contextual supporting evidence
Lange *et al* (2018)[40]	Australia	Cross-sectional	43 eyes	NA	NA	NA	NA	Regional ischemia patterns	Contextual supporting evidence
Heloterä *et al* (2024)[41]	Finland	Population registry	>20000 participants	NA	Intravitreal treatment patterns	NA	10y	PDR/DME incidence	Contextual supporting evidence
Poráčová *et al* (2023)[42]	Slovakia	Cross-sectional	3951 participants	NA	NA	NA	NA	PDR prevalence	Contextual supporting evidence
Rahimy *et al* (2025)[43]	United States	Retrospective cohort	23862 participants	NA	NPDR with OSA *vs* without OSA	NA	5y	PDR progression	Contextual supporting evidence

Data extracted from each study included: study design, sample size, baseline characteristics, intervention/comparator, follow-up duration, and prespecified outcomes (visual acuity, neovascularization regression/progression, complications, and additional interventions). RCT: Randomized controlled trial; PRP: Panretinal photocoagulation; PPV: Pars plana vitrectomy; NV: Neovascularization; UWFFA: Ultra-widefield fluorescein angiography; OCT: Optical coherence tomography; OCTA: OCT angiography; UWF: Ultra-widefield; NA: Not applicable; OSA: Obstructive sleep apnea; DR: Diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NPDR: Nonproliferative diabetic retinopathy; DME: Diabetic macular edema.

Table 2 Risk of bias assessment for randomized controlled trials

Study	Random sequence generation	Allocation concealment	Blinding of participants/personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk
Gross *et al* (2018)[24]	Low	Low	High	Low	Moderate	Low	Low-moderate
Antoszyk *et al* (2020)[25]	Low	Low	High	Low	Low	Low	Low-moderate
Li *et al* (2022)[26]	Low	Unclear	High	Low	Low	Low	Moderate
Toscano *et al* (2021)[28]	Low	Unclear	High	Low	Moderate	Unclear	Moderate
Lang *et al* (2022)[29]	N/A[b]	N/A[b]	High	Low	High	Low	Moderate-high
Figueira *et al* (2016)[30]	Low	Unclear	High	Low	Moderate	Unclear	Moderate
Su *et al* (2024)[33]	Low	Low	High	Low	Low	Low	Low-moderate
Liu *et al* (2023)[32]	Low	Low	High	Low	Low	Low	Low-moderate

[b]Lang *et al*[29] was an observational follow-up to a randomized controlled trial, so initial randomization procedures were not applicable to this phase.

Table 3 Newcastle-Ottawa Scale assessment for observational studies

Study	Selection (0–4★)	Comparability (0–2★)	Outcome (0–3★)	Total score
Schwartz *et al* (2020)[34]	★★★★	★★	★★★	9★
Alshaikhsalama *et al* (2024)[35]	★★★★	★★	★★	8★
Bek *et al* (2024)[36]	★★★	★	★	5★
Nidhi *et al* (2023)[37]	★★★	★★	★★	7★
Gonzalez *et al* (2021)[31]	★★★	★★	★★	7★
Yuan *et al* (2025)[38]	★★★	★	★★	6★
Aiello *et al* (2024)[39]	★★★★	★★	★★	8★
Lange *et al* (2018)[40]	★★★	★	★★	6★
Heloterä *et al* (2024)[41]	★★★★	★★	★★★	9★
Poráčová *et al* (2023)[42]	★★	★	★★	5★
Rahimy *et al* (2025)[43]	★★★	★★	★★	7★

certainty but remained dependent on limited trial evidence from the same clinical comparison[24]. Outcomes involving aflibercept versus vitrectomy with PRP, treatment crossover, activity impairment, neovascular regression, and perioperative anti-VEGF adjuncts were rated as low or low-to-moderate certainty because of small numbers of contributing studies, heterogeneous treatment protocols, crossover, indirectness, limited follow-up, or imprecision[25-28,30,33].

Because no formal meta-analysis was performed, the GRADE assessment did not use pooled effect estimates. Publication bias could not be formally assessed with funnel plots or Egger tests and was therefore judged qualitatively, particularly for outcomes supported by small studies or single-study evidence.

In the following therapeutic synthesis, conclusions regarding comparative treatment effectiveness were drawn from core comparative treatment studies only[24-31]. Studies classified as contextual supporting evidence were cited only where they informed surgical feasibility, imaging-based assessment, disease monitoring, or interpretation of prognostic heterogeneity[32-43].

Treatment Outcomes To improve clinical interpretability, therapeutic findings were organized according to prespecified clinical questions rather than by outcome domain alone. Conclusions regarding comparative treatment effects were based on core comparative treatment studies[24-31], whereas contextual studies were cited separately when relevant to surgical feasibility, imaging assessment, or prognostic interpretation[32-43]. VA outcomes are reported primarily in logMAR or ETDRS letters, with Snellen equivalents provided only for clinical interpretation. The unit of analysis was specified as eyes or patients according to the original study.

Anti-VEGF therapy versus PRP in PDR without mandatory immediate surgery The principal long-term comparison between anti-VEGF therapy and PRP was supported mainly by the 5-year randomized trial reported by Gross *et al*[24], which analyzed 394 eyes. At 5y, mean VA was approximately 20/25 in both groups, and the adjusted treatment-group difference was 0.6 ETDRS letters (95%CI, -2.3 to 3.5; P=0.68). Expressed on the logMAR scale, the mean change in VA was similar in both groups (ranibizumab: -0.06±0.29 logMAR; PRP: -0.06±0.21 logMAR). Ranibizumab was associated with less visual field loss and a lower cumulative incidence of vision-impairing DME compared with PRP, with DME occurring in 22% versus 38% of eyes, respectively (hazard ratio 0.4; 95%CI, 0.3–0.7)[24]. The long-term visual acuity outcomes are illustrated in Figure 2.

Table 4 Outcome-specific summary of findings and GRADE assessment for major comparative outcomes in PDR

Outcome and comparison	Illustrative comparative results	Contributing evidence	Certainty	GRADE justification
Long-term VA: ranibizumab *vs* PRP	At 5y, mean VA was approximately 20/25 in both groups; adjusted difference 0.6 ETDRS letters, 95%CI -2.3 to 3.5[24]	394 eyes from 1 major RCT[24], with supportive contextual/post-hoc evidence[29,31]	Moderate ★★★☆	Downgraded for risk of bias due to attrition in long-term follow-up and for imprecision because the conclusion was driven mainly by one trial. No downgrading for indirectness within trial-like PDR populations, but applicability is limited for poor adherence, recurrent VH, TRD, or limited access to injections. Publication bias not formally assessable
Visual field preservation: ranibizumab *vs* PRP	Less cumulative visual field loss with ranibizumab than PRP at 5y[24]	394 eyes from 1 RCT[24]	Moderate ★★★☆	Downgraded for imprecision/single-study evidence. Risk of bias concerns included attrition and unmasked treatment. Indirectness was limited for the trial population but relevant for real-world settings with poor follow-up. Publication bias not formally assessable
Vision-impairing DME: ranibizumab *vs* PRP	Lower cumulative incidence with ranibizumab: 22% *vs* 38%; HR 0.4, 95%CI 0.3–0.7[24]	394 eyes from 1 RCT[24]	Moderate ★★★☆	Downgraded for imprecision/single major study and attrition concerns. Effect estimate was clinically relevant, but applicability may differ in patients with variable injection adherence or limited follow-up access. Publication bias not formally assessable
VA and treatment course: aflibercept *vs* vitrectomy+PRP for VH	By 2y, mean VA was similar between groups; crossover was common[25]	205 eyes from 1 RCT[25]	Low to moderate ★★☆–★★★☆	Downgraded for imprecision and indirectness due to crossover and treatment pathway complexity. Risk of bias was not high overall, but masking was not feasible. Single-study evidence limited certainty
Activity impairment: vitrectomy+PRP *vs* aflibercept for VH	Less activity impairment with surgery at 24wk; differences no longer evident by 104wk[27]	204 eyes from secondary analysis of RCT[27]	Low ★★☆☆	Downgraded for indirectness because this was a secondary outcome analysis, and for imprecision due to single-study evidence. Publication bias not formally assessable
Neovascular regression: PRP+ranibizumab *vs* monotherapy	Combination therapy showed numerically higher regression rates in selected small studies[28,30]	63 eyes from 2 small RCTs[28,30]	Low ★★☆☆	Downgraded for imprecision, small sample size, heterogeneous laser strategies, and limited follow-up. Inconsistency could not be robustly assessed because of few studies
Surgical outcomes: perioperative anti-VEGF adjuncts around vitrectomy	Improved intraoperative conditions or reduced early postoperative hemorrhage in selected studies[26,33]	135 eyes from 2 RCTs with follow-up <1y[26,33]	Low ★★☆☆	Downgraded for indirectness because follow-up was shorter than the review's long-term prognosis criterion, and for imprecision due to small sample size. These studies were interpreted as supportive perioperative evidence rather than long-term comparative prognosis evidence
Vitrectomy outcomes for advanced PDR complications	Outcomes varied by indication; worse postoperative VA in TRD than VH or vitreomacular interface abnormalities[35]	933 eyes from retrospective surgical cohort[35]	Low ★★☆☆	Observational evidence started as low certainty. Downgraded/limited by confounding by indication, baseline severity, and heterogeneous surgical indications. Useful for contextual prognosis but not for causal comparison with anti-VEGF or PRP

GRADE ratings were assigned by outcome and clinical comparison, not by study. No pooled effect estimates were calculated because formal Meta-analysis was not performed. Publication bias was not assessed using funnel plots or Egger tests because the number of clinically comparable studies per outcome was insufficient. Most therapeutic studies reported outcomes at the eye level; inter-eye correlation was inconsistently reported and therefore eye-level estimates were interpreted cautiously. VA: Visual acuity; PRP: Panretinal photocoagulation; anti-VEGF: Anti-vascular endothelial growth factor; VH: Vitreous hemorrhage; TRD: Tractional retinal detachment; DME: Diabetic macular edema; RCT: Randomized controlled trial; ETDRS: Early Treatment Diabetic Retinopathy Study; HR: Hazard ratio; CI: Confidence interval; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation.

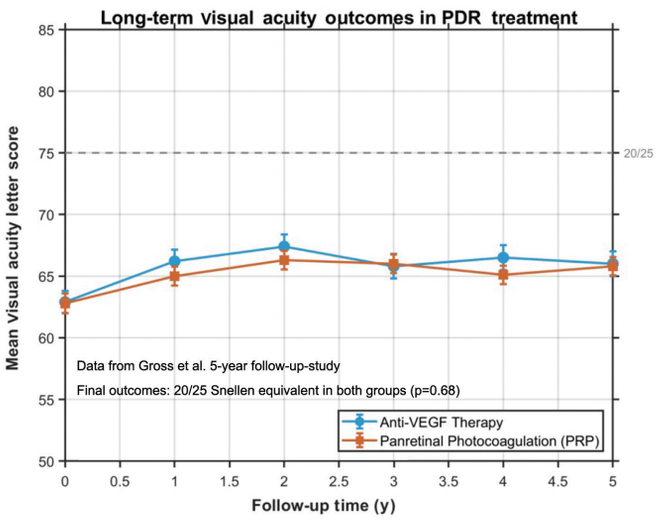


Figure 2 Long-term visual acuity outcomes comparing ranibizumab versus PRP in selected PDR eyes from the 5-year randomized trial by Gross *et al*[24] Data shown are adapted from Gross *et al*[24] for illustrative purposes and do not represent pooled Meta-analysis. Visual acuity is presented as ETDRS letters and/or logMAR where available. PRP: Panretinal photocoagulation; anti-VEGF: Anti-vascular endothelial growth factor; PDR: Proliferative diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study.

These findings suggest broadly comparable long-term VA outcomes between ranibizumab and PRP in selected trial populations receiving structured follow-up. However, this conclusion should not be generalized to all PDR phenotypes. The evidence is most applicable to patients similar to those enrolled in major comparative trials and may not apply to eyes with poor adherence to repeated injections, limited access to close monitoring, tractional retinal detachment, recurrent or non-clearing vitreous hemorrhage, or other advanced PDR complications requiring surgery.

Gonzalez *et al*[31], in a post-hoc analysis of the RIDE and RISE trials, provided supportive evidence that ranibizumab reduced the need for additional PRP, although the study was not designed as a direct long-term PDR treatment-comparison trial. PRP retreatment occurred in both patients with prior PRP and those without prior PRP, supporting the concept that PDR often requires ongoing monitoring and retreatment rather than a single definitive intervention[31].

Aflibercept versus vitrectomy with PRP for vitreous hemorrhage from PDR For eyes presenting with vitreous hemorrhage from PDR, Antoszyk *et al*[25] compared intravitreous aflibercept with vitrectomy plus PRP in 205 eyes. At 24wk, mean VA was 0.51 logMAR in the aflibercept group and 0.44 logMAR in the vitrectomy plus PRP group, corresponding to an adjusted difference of -5.0 ETDRS letters (95%CI, -10.2 to 0.3; *P*=0.06). By 2y, visual outcomes were similar between groups, with mean VA of 0.23 versus 0.28 logMAR and an adjusted difference of 2.7 ETDRS letters (95%CI, -3.1 to 8.4; *P*=0.36)[25].

Treatment crossover was common: 33% of eyes initially treated with aflibercept underwent vitrectomy within 2y, whereas 32% of eyes initially assigned to vitrectomy received subsequent aflibercept[25]. These findings indicate that anti-VEGF therapy and vitrectomy plus PRP may serve complementary roles in vitreous hemorrhage from PDR rather than representing mutually exclusive strategies.

Beaulieu *et al*[27], a secondary analysis of the same clinical context, reported that initial vitrectomy plus PRP was associated with less activity impairment at 24wk compared with aflibercept, but functional differences were no longer evident by 104wk. This suggests that surgery may provide earlier functional recovery in selected patients with vitreous hemorrhage, while longer-term functional outcomes may converge[27].

Perioperative anti-VEGF therapy before or around vitrectomy Two studies addressed perioperative anti-VEGF use in vitrectomy-treated PDR eyes[26,33]. Li *et al*[26] evaluated preoperative intravitreal ranibizumab before vitrectomy in 48 eyes with PDR-related vitreous hemorrhage and reported improved intraoperative conditions without an increased risk of tractional retinal detachment. Su *et al*[33] compared 1.0 mg versus 0.5 mg ranibizumab with PPV in 87 eyes and found that the higher dose reduced early postoperative vitreous hemorrhage compared with the standard dose (35.0% *vs* 63.4%, *P*=0.0195).

Because these studies had follow-up durations shorter than 1y, they were interpreted as supportive perioperative surgical evidence rather than core evidence for long-term prognosis. Their findings support the potential role of anti-VEGF adjuncts in improving early surgical and postoperative outcomes, but they do not establish long-term comparative effectiveness.

PRP plus anti-VEGF combination therapy Combination treatment was evaluated in small comparative studies[28,30]. Toscano *et al*[28] compared PRP plus ranibizumab with targeted photocoagulation plus ranibizumab and reported differences in fluorescein leakage area over 1y. Figueira *et al*[30] compared ranibizumab, PRP plus ranibizumab, and PRP in high-risk PDR. Complete regression of neovessels elsewhere occurred in 100% of eyes receiving combined PRP and ranibizumab, compared with 75% receiving ranibizumab alone and 69.2% receiving PRP alone. For disc neovascularization, regression rates were 44.4%, 37.5%, and 30.8%, respectively[30].

These studies suggest that PRP plus anti-VEGF therapy may enhance neovascular regression in selected eyes, consistent with complementary mechanisms of rapid VEGF suppression and more durable ischemic drive reduction. However, the evidence remains limited by small sample sizes, heterogeneous

laser strategies, and relatively short follow-up. Therefore, combination therapy should be interpreted as a potentially useful individualized strategy rather than as a universally superior regimen (Figure 3).

Vitrectomy for advanced PDR complications Evidence regarding vitrectomy for advanced PDR complications was derived from both randomized and contextual surgical studies. Antoszyk *et al*[25] provided randomized evidence in eyes with vitreous hemorrhage, showing that vitrectomy plus PRP and aflibercept achieved similar VA by 2y, although early recovery patterns and subsequent treatment needs differed. Alshaikhsalama *et al*[35] provided contextual surgical evidence from 933 eyes undergoing PPV for PDR complications. Postoperative VA at 6mo differed according to surgical indication, with worse outcomes in eyes with tractional retinal detachment than in those with vitreous hemorrhage or vitreomacular interface abnormalities (0.79 *vs* 0.77 *vs* 1.20 logMAR; $P<0.0001$). Preoperative PRP was associated with better postoperative VA compared with no PRP (0.95 *vs* 1.25 logMAR; $P<0.001$)[35].

These findings support vitrectomy as an essential treatment for advanced PDR complications, particularly non-clearing vitreous hemorrhage and tractional retinal detachment. However, outcomes vary substantially according to baseline pathology, surgical indication, prior PRP, and disease severity. Therefore, surgical evidence should not be pooled indiscriminately with trials of anti-VEGF versus PRP in less surgically advanced PDR.

DISCUSSION

Summary of Main Findings This systematic review provides a comprehensive analysis of various treatment strategies for PDR and their effects on long-term prognosis, offering important clinical implications for PDR management. The most robust long-term evidence for anti-VEGF therapy versus PRP comes from the 5-year randomized trial by Gross *et al*[24], which showed broadly comparable VA outcomes between ranibizumab and PRP in selected PDR eyes managed under structured follow-up. Importantly, this finding should not be interpreted as evidence that anti-VEGF and PRP are interchangeable for all PDR phenotypes. The applicability of anti-VEGF monotherapy may be limited in patients with poor adherence, limited access to repeated injections or monitoring, recurrent vitreous hemorrhage, tractional retinal detachment, or other advanced complications requiring surgery. PRP remains an important durable treatment option, particularly when treatment access or adherence is uncertain. Thus, the practical distinction between anti-VEGF therapy and PRP is not limited to anatomical or visual outcomes. Anti-VEGF therapy may provide advantages in visual field preservation and reduction of vision-impairing DME[24], but these benefits

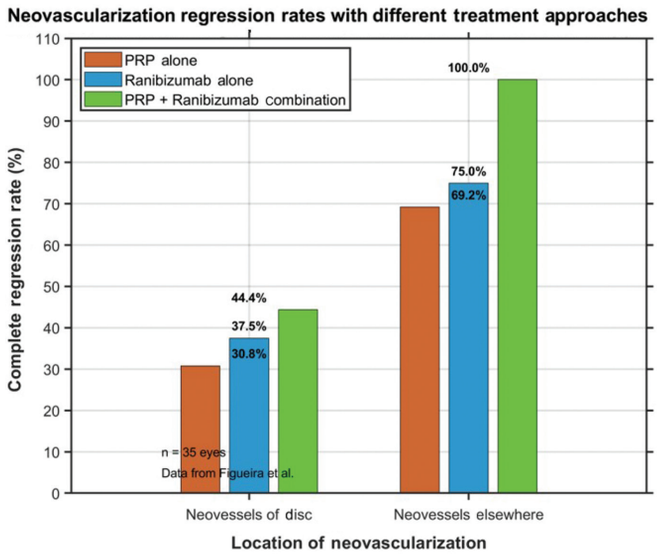


Figure 3 Neovascularization regression rates with different treatment approaches Data shown are adapted from Figueira *et al*[30] (2016) for illustrative purposes and do not represent pooled meta-analysis. PRP: Panretinal photocoagulation.

depend on reliable repeated injections, close monitoring, and sufficient healthcare-system capacity. By contrast, PRP may be less favorable for peripheral visual field or macular edema outcomes, but it offers a more durable treatment effect after completion and may be clinically preferable when follow-up reliability, treatment access, or socioeconomic circumstances are uncertain. Additionally, the analysis demonstrated that PDR treatment requirements are dynamic, as shown by the RIDE and RISE trials[31], which indicated significant PRP retreatment needs despite prior PRP, emphasizing the disease's chronic nature and the need for ongoing monitoring.

Different treatment modalities exhibit complementary roles, with Antoszyk *et al*[25] reporting frequent crossover between anti-VEGF and vitrectomy approaches, while Figueira *et al*[30] demonstrated superior neovascular regression rates with combined PRP and ranibizumab therapy. Treatment complications also vary significantly, with anti-VEGF showing advantages in reducing vision-threatening DME and better preserving visual fields compared to PRP[24]—a crucial consideration given peripheral vision's impact on quality-of-life factors like driving. Contextual imaging evidence, including studies of ultra-widefield imaging and optical coherence tomography angiography (OCTA)[34,37,39], supports more precise disease assessment and may facilitate targeted, personalized treatment approaches. However, these studies were not interpreted as direct evidence of comparative treatment efficacy. A comparison of ultra-widefield imaging and standard 7-field imaging for diabetic retinopathy assessment is presented in Figure 4.

Comparison with Previous Literature Our findings extend prior systematic reviews limited by 1–2y follow-ups[44-45] by

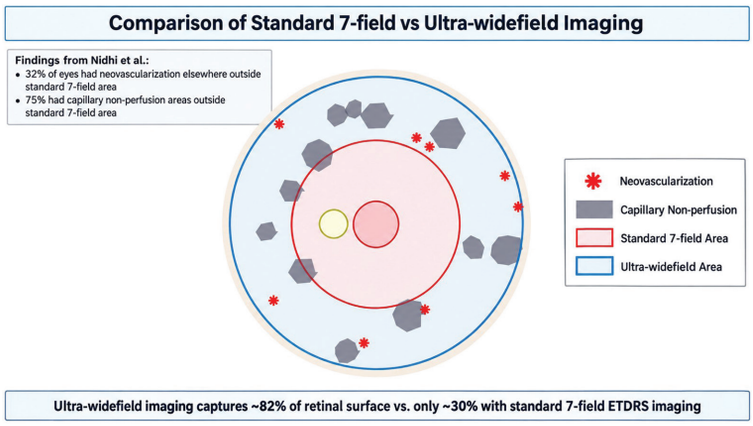


Figure 4 Comparison of ultra-widefield imaging versus standard 7-field imaging for diabetic retinopathy assessment Data shown are adapted from Aiello *et al*[39] (2024) and Nidhi *et al*[37] (2023) for illustrative purposes and do not represent pooled Meta-analysis. ETDRS: Early Treatment Diabetic Retinopathy Study.

incorporating 5-year data, providing moderate-certainty long-term evidence that ranibizumab and PRP can achieve broadly comparable VA outcomes in selected PDR populations under structured follow-up conditions[24]. Recent broader reviews of diabetic retinopathy treatment have compared multiple therapeutic modalities across the DR spectrum and help position the present PDR-focused synthesis within a wider treatment hierarchy that includes screening, systemic risk modification, DME management, PRP, anti-VEGF therapy, and surgery[16-17]. In this context, our review adds a more focused long-term interpretation for PDR-specific therapeutic decisions, particularly the trade-off between anti-VEGF treatment burden and PRP durability. While earlier meta-analyses favored anti-VEGF's short-term visual outcomes over PRP[46], our long-term analysis reveals converging benefits, reflecting PDR's chronic progression and underscoring the importance of extended follow-up in clinical trials. The complementary treatment roles we observed support recent consensus favoring personalized, multimodal approaches based on disease characteristics, patient factors, and treatment response[47]. Furthermore, unlike previous reviews focusing solely on clinical outcomes, we integrate advanced imaging studies[16]—particularly ultra-widefield and OCTA—demonstrating their increasing significance in guiding PDR management and therapeutic decision-making.

Pathophysiological Considerations This systematic review should be interpreted against the mechanistic background of diabetic retinal neurovascular injury. Hyperglycemia-related oxidative stress, advanced glycation end-product accumulation, inflammatory signaling, mitochondrial dysfunction, and microvascular ischemia contribute to VEGF upregulation and progressive retinal damage[5,48]. Anti-VEGF therapy directly targets hypoxia-driven VEGF activity, promoting neovascular regression while preserving retinal function, whereas PRP indirectly reduces VEGF levels by ablating peripheral ischemic retina and lowering oxygen demand. While anti-VEGF requires ongoing treatment due to persistent ischemia[29], PRP provides more sustained effects through permanent oxygen consumption reduction, albeit with functional trade-offs. In eyes with substantial fibrovascular proliferation or pre-existing tractional components, rapid pharmacologic suppression of VEGF may alter the balance between vascular leakage and fibrotic contraction; therefore, anti-VEGF use should be coordinated with surgical planning when traction threatens the macula. This consideration is particularly relevant for eyes with dense vitreous hemorrhage or limited retinal visualization, where the extent of fibrovascular traction may be underestimated before surgery[25-26,35]. The observed synergy in combination therapies reflects their complementary mechanisms: anti-VEGF achieves rapid vascular stabilization while PRP durably modifies retinal oxygenation, supporting their combined use in selected cases. These findings underscore the importance of matching treatment strategies to underlying disease mechanisms.

Clinical Implications This review supports a pragmatic, phenotype-based approach to PDR treatment rather than a single preferred regimen for all patients. Treatment selection should integrate ocular disease features, systemic risk, and feasibility of long-term follow-up. Key ocular factors include baseline DME, prior PRP, extent of fibrovascular proliferation, density and persistence of vitreous hemorrhage, tractional components threatening or involving the macula, lens status, and the feasibility of retinal visualization for PRP. Systemic and contextual factors include renal disease, glycemic control, pregnancy or pregnancy planning, ability to attend repeated visits, insurance or out-of-pocket cost, transportation barriers, and local availability of retina specialists, laser, intravitreal therapy, and vitreoretinal surgery. Systemic risk modification remains an important complement to ocular therapy. Although the present review focused on ocular treatment regimens for PDR, recent evidence suggests that lipid-modifying therapy,

nutritional status, and broader metabolic interventions may influence diabetic retinopathy progression and vascular outcomes[18-19]. These systemic strategies should not be viewed as substitutes for PRP, anti-VEGF therapy, or vitrectomy in established PDR, but they are relevant to long-term disease control, recurrence risk, and individualized prognosis.

A practical decision framework can be summarized as follows. First, in stable PDR without center-involving DME, dense vitreous hemorrhage, or traction threatening the macula, PRP remains a durable standard option, particularly when follow-up reliability is uncertain or repeated injections are difficult. Anti-VEGF therapy may be considered in selected adherent patients who can maintain frequent monitoring and when preservation of peripheral visual field is a priority[24]. Second, in PDR with concurrent DME, anti-VEGF therapy may be favored because it can address both neovascular activity and macular edema, whereas PRP may worsen or unmask macular edema in some eyes[24,31]. In such cases, PRP can still be added when durable neovascular control is needed or when injection adherence is uncertain. Third, in eyes with non-clearing or dense vitreous hemorrhage that prevents adequate PRP or monitoring, vitrectomy with endolaser PRP should be considered, with intravitreal anti-VEGF used as an adjunct in selected perioperative settings to reduce bleeding or early postoperative hemorrhage[25-26,33,35]. Fourth, in eyes with tractional retinal detachment or substantial fibrovascular proliferation, especially when the macula is threatened or involved, vitrectomy is generally required; anti-VEGF should be used cautiously because rapid neovascular contraction may theoretically worsen traction in susceptible eyes, and surgical timing should be planned accordingly[25-26,35]. Fifth, in patients at high risk of poor follow-up because of socioeconomic barriers, limited transportation, poor health-system access, severe systemic illness, or unstable glycemic or renal status, PRP or combined PRP-based strategies may be preferable to anti-VEGF monotherapy because of greater durability after treatment completion.

The clinical consequences of missed follow-up are particularly important when anti-VEGF therapy is used as a primary or long-term strategy. Unlike PRP, which provides a more durable reduction in ischemic drive after treatment completion, anti-VEGF therapy requires repeated visits and reinjection to maintain neovascular suppression. Therefore, loss to follow-up is not merely a methodological limitation of long-term trials but a clinically relevant determinant of prognosis, because delayed retreatment may permit recurrent neovascularization, vitreous hemorrhage, or tractional complications. The review emphasizes the importance of long-term monitoring and retreatment readiness[29,31], facilitated by advanced imaging—ultra-widefield imaging for comprehensive peripheral assessment[37,39] and OCTA for neovascular evaluation[34]. For surgical cases, preoperative anti-VEGF may improve intraoperative conditions[26], while higher-dose ranibizumab may decrease early postoperative hemorrhage risk[33], though optimal dosing and timing require further study.

Strengths and Limitations This review has several key strengths. First, it includes studies with long-term follow-up (up to 5y), providing stronger evidence on sustained treatment effects than prior reviews. Second, by combining randomized trials and observational studies, it offers insights from both controlled environments and real-world practice. Third, we assessed a broad range of outcomes—including visual function, disease progression, complications, and quality of life—yielding a more comprehensive evaluation of treatment impact.

Several limitations should be noted. Although follow-up was longer than in previous reviews, data on outcomes beyond 5y remain scarce, limiting insights into long-term durability. Study heterogeneity—across designs, populations, and outcome measures—prevented meta-analysis in some cases. Another important limitation is that the review incorporated both core comparative treatment studies and contextual supporting evidence. Although this approach allowed broader discussion of PDR assessment, monitoring, and individualized management, only studies meeting the PICO-based criteria were used to support conclusions regarding comparative treatment effectiveness. Imaging-focused, cross-sectional, screening, epidemiologic, and disease-progression studies were retained for contextual interpretation but were not treated as evidence of long-term treatment effect. Additionally, evolving anti-VEGF regimens over time may confound comparisons. Potential publication bias and the predominance of studies from high-income settings may limit generalizability, especially in resource-limited contexts where PRP may be preferred due to feasibility concerns. Most studies enrolled mixed type 1 and type 2 diabetes cohorts without stratifying outcomes by diabetes type, baseline HbA1c, or disease duration. Prior treatments were inconsistently reported. Important clinical modifiers were also inconsistently reported or not stratified across studies, including baseline DME status, prior PRP, fibrovascular proliferation, vitreous hemorrhage density, tractional components, lens status, renal disease, pregnancy status, glycemic control, and socioeconomic barriers to follow-up. As a result, the proposed decision framework is clinically grounded but cannot be validated as a formal predictive algorithm using the currently available evidence. These unmeasured confounders may influence treatment response and limit generalizability. Furthermore, we did not systematically contact study investigators to obtain missing or unpublished data, which may have contributed to incomplete

outcome ascertainment for certain secondary endpoints. Future updates of this review should incorporate author outreach protocols and longer-term follow-up data to address these evidence gaps. In addition, several recent reviews published after the main electronic search window were used only to contextualize the evolving diabetic retinopathy treatment landscape and systemic risk-modification strategies[5,17-19]. They were not incorporated into the core therapeutic evidence synthesis or GRADE assessment.

Future Research Directions Future studies should address the following priorities: a) extended follow-up (beyond 5y) to assess the durability and safety of current treatments; b) personalized treatment strategies, integrating patient-specific factors and biomarkers; c) optimized combination/sequential protocols, defining timing and patient selection; d) new anti-VEGF agents and delivery systems, to reduce injection burden and improve adherence; e) advanced imaging-guided management, using modalities like OCTA and ultra-widefield angiography; f) real-world comparative effectiveness studies across diverse healthcare systems; g) cost-effectiveness analyses, to guide resource allocation and policy development.

In conclusion, this systematic review suggests that anti-VEGF therapy and PRP may achieve broadly comparable long-term VA outcomes in selected patients with PDR, particularly within structured follow-up settings. However, these treatments are not interchangeable across all clinical scenarios. Anti-VEGF therapy may be favored in adherent patients with concurrent DME or when visual field preservation is a priority, whereas PRP remains a durable and often preferable option when follow-up reliability, healthcare access, or socioeconomic conditions limit repeated injections. Vitrectomy remains essential for non-clearing vitreous hemorrhage, tractional retinal detachment, and advanced fibrovascular complications, with perioperative anti-VEGF therapy used selectively. Treatment planning should therefore consider DME status, vitreous hemorrhage, tractional or fibrovascular components, prior PRP, systemic risk, anticipated adherence, and healthcare accessibility. Long-term surveillance and phenotype-based individualized management remain central to PDR care.

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