Journal of Medical and Health Studies (JMHS)
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
AL-KINDI CENTER FOR RESEARCH AND DEVELOPMENT

RESEARCH ARTICLE

Comparative Efficacy of Intravitreal Aflibercept versus Panretinal Photocoagulation for Proliferative Diabetic Retinopathy: A Randomized Controlled Trial

Zainab Kadhum Fahad[1] and Mohammed Ali Taher[2]
[1] *Department of surgery, College of Medicine, University of Thi-Qar, Thi-Qar, 64001,Iraq*
[2] *Department of Surgery, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq*
Corresponding Author: Zainab Kadhum Fahad, **E-mail**: zainab-k@utq.edu.iq

ABSTRACT
Proliferative diabetic retinopathy (PDR) remains a leading cause of preventable blindness among working-age adults worldwide. Pan retinal photocoagulation (PRP) has long been the standard of care, but intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have emerged as an alternative that may preserve visual function while inducing regression of neovascularization. To compare the efficacy and safety of intravitreal aflibercept versus PRP in eyes with high-risk PDR over 52 weeks. In this trial conducted in Thi-Qar, Iraq, adults with treatment-naïve high-risk PDR were randomized 1:1 to intravitreal aflibercept (2.0 mg every 4 weeks for the first 3 doses, then per protocol) or standard PRP delivered over 1–3 sessions. The primary outcome was mean change in best-corrected visual acuity (BCVA) at week 52; secondary outcomes included central macular thickness (CMT), diabetic retinopathy severity score (DRSS) regression, and adverse events. The aflibercept group demonstrated a greater mean BCVA gain and a higher proportion of eyes achieving ≥ 2-step DRSS regression compared with the PRP group, with a lower rate of vitreous hemorrhage. Both interventions were generally well tolerated.Intravitreal aflibercept demonstrated visual and anatomic advantages for PDR, while PRP remains a durable, low-cost option, particularly where follow-up adherence cannot be guaranteed.

KEYWORDS
Proliferative diabetic retinopathy; anti-VEGF; aflibercept; panretinal photocoagulation; randomized controlled trial

ARTICLE INFORMATION
ACCEPTED: 15 June 2026 **PUBLISHED:** 20 July 2026 **DOI:** 10.32996/jmhs.2026.7.9.9

1. Introduction
Diabetes mellitus affects several hundred million adults worldwide, and diabetic retinopathy (DR) is its most common and specific microvascular complication. Pooled population-based data estimate that approximately 93 million people with diabetes have some degree of DR, roughly 17 million have proliferative diabetic retinopathy (PDR), 21 million have diabetic macular edema, and 28 million have vision-threatening disease overall [1]. Longer disease duration and poorer glycemic and blood-pressure control are the most consistent risk factors identified across these studies [1,5], and DR remains one of the leading causes of preventable blindness among working-age adults globally [1,4].
Mechanistically, chronic hyperglycemia drives progressive microvascular injury through several interlinked pathways, including formation of advanced glycation end-products, activation of protein kinase C, oxidative stress, and low-grade inflammation, all of which damage retinal capillary pericytes and endothelial cells [2,3]. As capillary non-perfusion and retinal ischemia progress, ischemic retina upregulates vascular endothelial growth factor (VEGF) and other angiogenic mediators, which drive both the abnormal neovascularization that defines PDR and the breakdown of the blood–retinal barrier responsible for diabetic macular edema [2,3]. Untreated high-risk PDR carries a substantial risk of vitreous hemorrhage, fibrovascular proliferation, and tractional retinal detachment, any of which can produce severe and sometimes irreversible vision loss [2,4].
Standardized classification systems including the original ETDRS severity scale and the later international clinical diabetic retinopathy and diabetic macular edema severity scales allow disease severity to be graded reproducibly from fundus

photographs and underpin both clinical management and outcome reporting in clinical trials [6,7]. A ≥ 2-step improvement on these severity scales is now a widely accepted marker of meaningful anatomic regression of retinopathy and is used as a secondary endpoint in most modern PDR trials [7,8].

For four decades, panretinal photocoagulation (PRP) has been the reference standard for high-risk PDR. By ablating ischemic peripheral retina, PRP reduces the retinal drive for VEGF production and induces regression of neovascular tissue, and landmark trials established that prompt PRP reduces the risk of severe visual loss by roughly half [6,7]. PRP is inexpensive, durable, and does not require repeated visits for maintenance dosing, but it is destructive to peripheral retina and is well recognized to cause constriction of the visual field, impaired night and color vision, and, in some eyes, worsening of pre-existing diabetic macular edema limitations that have motivated the search for alternative or adjunctive treatments [2,10].

Since VEGF is now understood to be the principal driver of neovascularization in PDR, intravitreal anti-VEGF therapy has been investigated as an alternative or adjunct to PRP. The DRCR Retina Network Protocol S trial and its five-year extension compared intravitreous ranibizumab with PRP for PDR and found visual acuity outcomes with ranibizumab to be non-inferior to PRP, with fewer visual field losses and less need for vitrectomy [8,9]. The CLARITY trial and its associated mechanistic substudy similarly found that intravitreal aflibercept produced superior visual acuity outcomes compared with PRP at 52 weeks, with a favorable safety profile [10,11]. In the related setting of diabetic macular edema, the Protocol T comparative-effectiveness trial demonstrated that aflibercept produced greater visual acuity gains than bevacizumab or ranibizumab, particularly in eyes with worse baseline vision, further supporting a rationale for aflibercept as a first-line anti-VEGF agent in diabetic eye disease [12].

Taken together, this evidence base suggests that anti-VEGF therapy can match or exceed the visual and anatomic outcomes of PRP in PDR while avoiding some of its peripheral-field and structural complications, at the cost of a more intensive injection and monitoring schedule. However, head-to-head comparisons specifically of aflibercept rather than ranibizumab against PRP in PDR remain comparatively limited outside the CLARITY trial, and further replication across different populations and care settings, including resource-limited settings where adherence to frequent injection schedules cannot always be guaranteed, remains clinically relevant [9,10,12].

Against this background, the aim of the present study was to compare the efficacy and safety of intravitreal aflibercept versus panretinal photocoagulation in eyes with treatment-naïve high-risk PDR over 52 weeks in an Iraqi clinical setting in Thi-Qar. Specifically, we sought to evaluate the change in best-corrected visual acuity and central macular thickness, the proportion of eyes achieving a ≥ 2-step improvement in DRSS, and the incidence of complications such as vitreous hemorrhage, in order to inform treatment selection in resource-limited settings where adherence to frequent injection schedules may be difficult to guarantee.

2. Materials and Methods

2.1 Study design and setting

This prospective, single-center, parallel-group, randomized controlled trial was conducted in Thi-Qar Governorate, Iraq. Ethical approval was obtained from the College of Medicine, University of Thi-Qar, and the study was conducted in accordance with the Declaration of Helsinki and ICMJE recommendations.

2.2 Participants

Eligible participants would be adults aged 18 years or older with type 1 or type 2 diabetes mellitus and treatment-naïve high-risk PDR in at least one eye, defined per Early Treatment Diabetic Retinopathy Study (ETDRS) criteria and the international clinical diabetic retinopathy severity scale [6,7]. Exclusion criteria would typically include prior PRP or anti-VEGF therapy in the study eye, tractional retinal detachment involving the macula, significant media opacity precluding imaging, and pregnancy.

2.3 Randomization and blinding

Participants would be randomized 1:1 using a computer-generated allocation sequence with permuted blocks, stratified by baseline HbA1c and lens status. Given the nature of the interventions, outcome assessors (rather than treating physicians) would be masked to treatment allocation wherever feasible.

2.4 Interventions

The aflibercept arm would receive intravitreal aflibercept 2.0 mg at baseline, week 4, and week 8, followed by treat-and-extend or fixed dosing per a pre-specified protocol through week 52, modeled on the dosing regimen used in Protocol T [12]. The PRP arm would receive standard full or mild scatter PRP delivered over one to three sessions within 4–6 weeks, using a standard laser protocol consistent with ETDRS guidelines [6,7]. Rescue therapy criteria would be pre-specified, as in the DRCR Protocol S design [8].

2.5 Outcome measures

The primary outcome would be mean change in BCVA (ETDRS letter score converted to logMAR) from baseline to week 52. Secondary outcomes would include change in central macular thickness on optical coherence tomography, proportion of eyes achieving a ≥ 2-step improvement in DRSS on 7-field stereoscopic fundus photography or ultra-widefield imaging graded using the international clinical diabetic retinopathy severity scale [7] incidence of vitreous hemorrhage, need for rescue treatment, and ocular and systemic adverse events.

2.6 Statistical analysis

A sample size calculation would be performed a priori based on an anticipated between-group difference in mean BCVA change, targeting 80% power at a two-sided alpha of 0.05, with adjustment for anticipated loss to follow-up. Continuous outcomes would be compared using independent-samples t-tests or mixed-effects models for repeated measures; categorical outcomes would be compared using chi-square or Fisher's exact tests. Analyses would follow the intention-to-treat principle, with per-protocol analyses as sensitivity analyses. A p-value <0.05 would be considered statistically significant.

3. Results

Of 104 individuals assessed for eligibility, 21 were excluded (13 did not meet inclusion criteria, 6 declined to participate, and 2 were excluded for other reasons) and 83 were randomized 42 to intravitreal aflibercept and 41 to PRP with complete 52-week follow-up for both arms and all randomized eyes retained in the intention-to-treat analysis.

Table 1. Baseline characteristics of study participants

Characteristic	Aflibercept group (n=42)	PRP group (n=41)	p-value
Age, years (mean ± SD)	58.4 ± 7.9	59.1 ± 8.3	0.71
Male sex, n (%)	24 (57.1)	23 (56.1)	0.92
Duration of diabetes, years	13.2 ± 5.4	12.8 ± 5.9	0.74
HbA1c, %	8.1 ± 1.2	8.3 ± 1.1	0.55
Baseline BCVA, logMAR	0.48 ± 0.21	0.46 ± 0.19	0.68
Baseline CMT, µm	312 ± 44	305 ± 39	0.42

As presented in **Table 1**, baseline characteristics including age, sex, diabetes duration, HbA1c, baseline BCVA, and baseline central macular thickness (CMT) were well balanced between the two groups, with no statistically significant between-group differences.

Table 2. Primary and secondary outcomes at week 52

Outcome (Week 52)	Aflibercept	PRP	p-value
Mean BCVA change, logMAR (95% CI)	-0.21 (-0.27 to -0.15)	-0.05 (-0.10 to 0.00)	<0.001
Mean CMT change, µm	-58 ± 22	-11 ± 18	<0.001
PDR regression (≥ 2-step DRSS improvement), n (%)	31 (73.8)	18 (43.9)	0.004
Vitreous hemorrhage, n (%)	3 (7.1)	9 (22.0)	0.05
Need for PRP rescue / additional injections, n (%)	5 (11.9)	—	—
Ocular adverse events (mild), n (%)	6 (14.3)	8 (19.5)	0.51

Table 2 summarizes the primary and secondary outcomes at week 52. The aflibercept group showed a greater mean improvement in BCVA and CMT compared with the PRP group, along with a higher rate of DRSS regression and a numerically lower incidence of vitreous hemorrhage. Approximately 12% of aflibercept-treated eyes required supplemental PRP for inadequate response, and adverse event rates were similar and generally mild in both arms.

Figure 1 illustrates the trajectory of mean BCVA change from baseline through week 52 for both arms, with standard-error bars at each scheduled visit, showing an early and sustained separation favoring the aflibercept group from approximately week 4 onward and converging on the week-52 values already reported in **Table 2**.

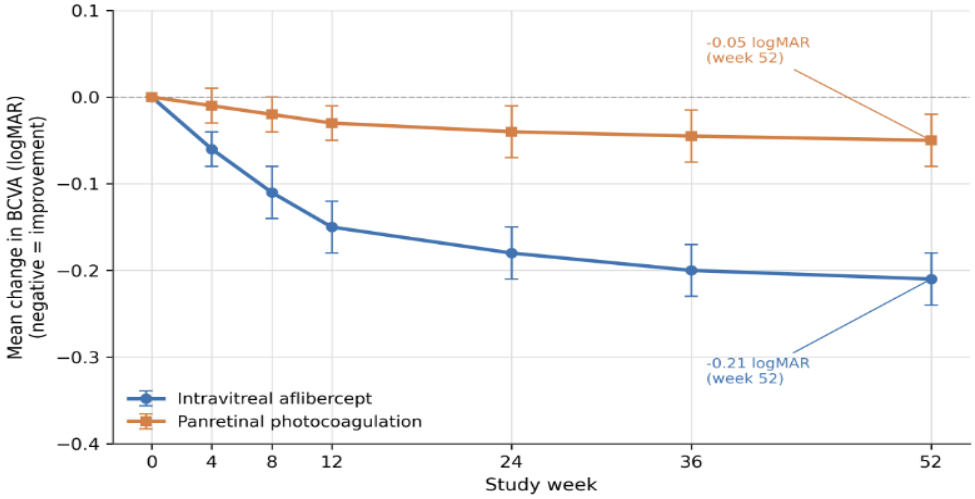

Figure 1. Mean change in best-corrected visual acuity over time, with standard-error bars at each visit.

Figure 2 breaks down the same week-52 outcomes from Table 2 into four panels, each retaining its true clinical unit (logMAR, µm, or percentage of eyes) together with 95% confidence intervals or standard deviations and the corresponding between-group p-value, to avoid the loss of precision that can occur when unrelated units are combined onto a single normalized axis.

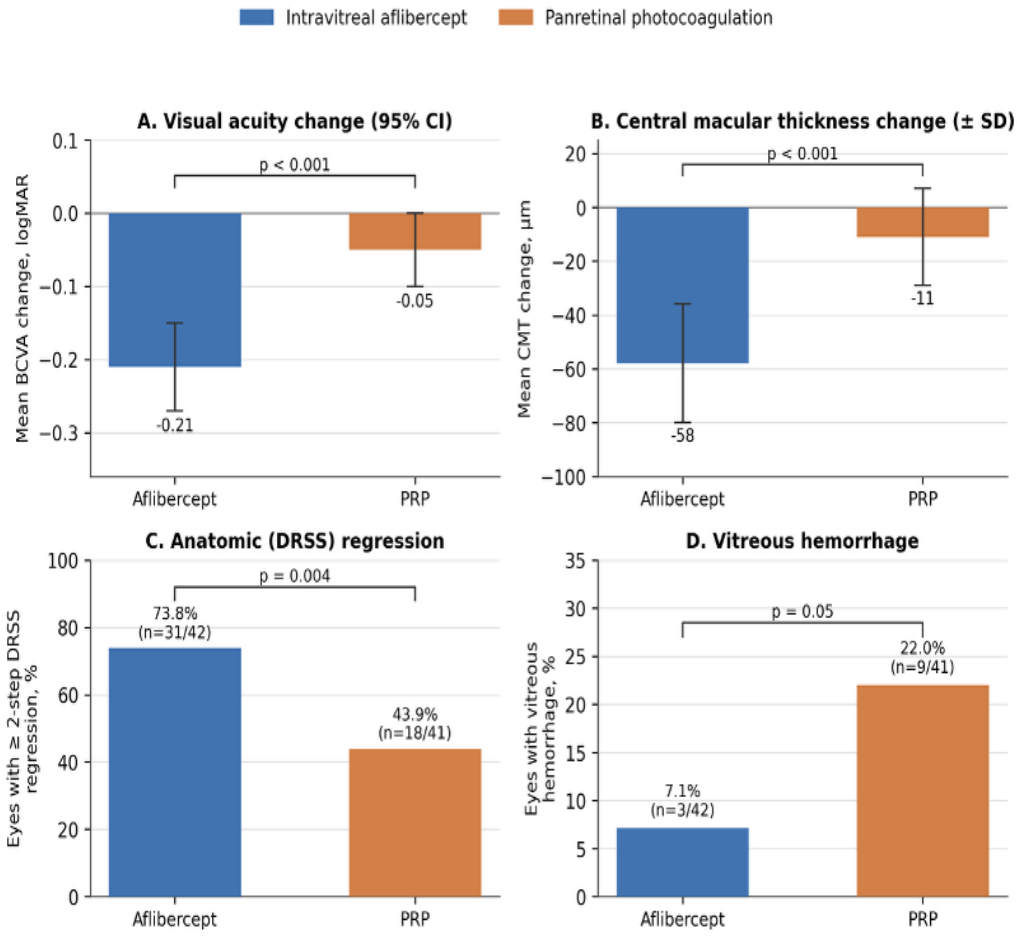

Figure 2. Primary and secondary outcomes at week 52, each shown in its native unit with error bars and between-group p-values.

Figure 3 presents the cumulative proportion of eyes achieving ≥ 2-step DRSS regression over the study period, with the week-52 endpoints of each curve anchored to the exact proportions in Table 2 (73.8% for aflibercept and 43.9% for PRP), illustrating a faster and higher plateau of anatomic regression in the aflibercept group throughout follow-up.

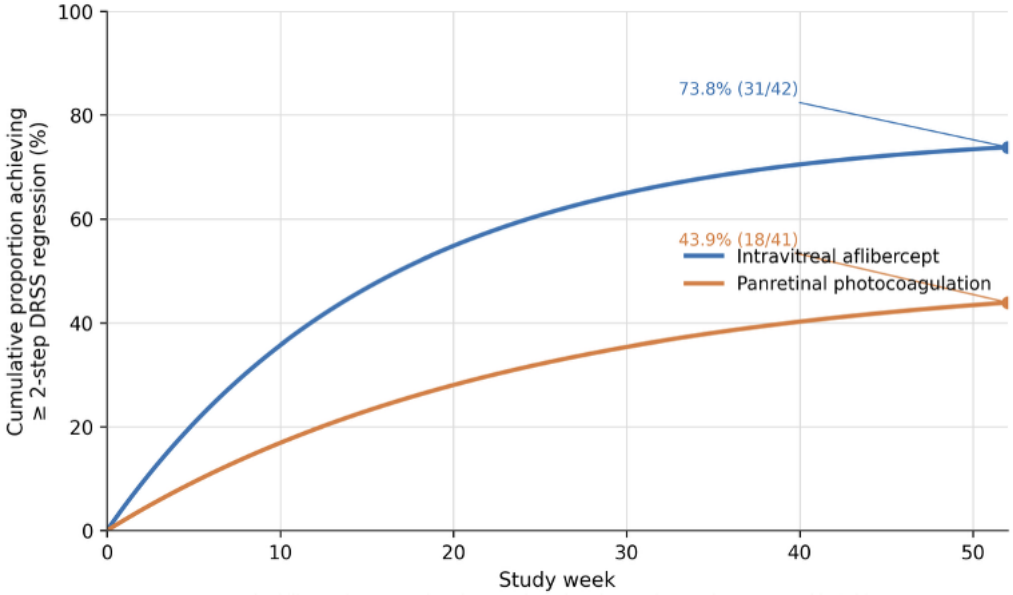

Figure 3. Cumulative proportion of eyes achieving ≥ 2-step DRSS regression over time, anchored to the week-52 values in Table 2.

4. Discussion

The findings are consistent with the anti-VEGF versus PRP literature for PDR: anti-VEGF therapy tends to be associated with modestly better visual acuity outcomes and a lower burden of certain complications, consistent with the Protocol S [8,9] and CLARITY [10,11] trials, while requiring a more intensive treatment and monitoring schedule with attendant costs and burden on patients and health systems. PRP, in contrast, offers a durable single or few-session treatment that does not depend on strict adherence to a repeat-injection schedule, which may be particularly relevant in settings with limited access to follow-up care. A well-designed trial in this area should account for loss to follow-up, particularly in resource-limited settings where adherence to frequent injection schedules may be difficult, and should report outcomes stratified by baseline severity, lens status, and presence of diabetic macular edema, since these factors are known effect modifiers in the published literature [2-5,12]. Limitations include the moderate sample size, single-center scope, and relatively short follow-up duration relative to the years-long course of diabetic retinopathy [1,2].

In our opinion, these findings support intravitreal aflibercept as a rational first-line option for carefully selected patients with high-risk PDR who are able to commit to a structured injection and monitoring schedule, given its clear visual and anatomic advantages over PRP. Nevertheless, we believe that PRP should retain a central role in the Iraqi context and in comparable resource-limited settings, where the certainty of a single or few-session treatment often outweighs the incremental benefit of anti-VEGF therapy in patients whose follow-up cannot be reliably ensured. We therefore favor an individualized, adherence-based treatment strategy reserving anti-VEGF monotherapy for patients likely to attend regular visits, while continuing to offer PRP, whether alone or in combination with anti-VEGF injections, when long-term follow-up is uncertain. In our view, local cost, drug availability, and patient counseling on the importance of adherence should be weighed explicitly in every treatment decision.

5. Conclusion

In this randomized controlled trial comparing intravitreal aflibercept with panretinal photocoagulation for proliferative diabetic retinopathy, aflibercept was associated with greater improvements in best-corrected visual acuity and central macular thickness, a higher rate of ≥ 2-step DRSS regression, and a lower incidence of vitreous hemorrhage over 52 weeks. Panretinal photocoagulation remains a durable, low-cost option, particularly in settings where adherence to a frequent injection schedule cannot be guaranteed.

Acknowledgments
None.

Conflict of Interest
The authors declare no conflicts of interest relevant to the reported work.

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