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Original Research Article

Comparative Effectiveness of Intravitreal Bevacizumab, Ranibizumab, and Aflibercept in Diabetic Retinopathy Management

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Abstract

Background: Anti-vascular endothelial growth factor (anti-VEGF) therapy is the standard first-line treatment for vision-threatening diabetic macular edema and selected severe diabetic retinopathy phenotypes, but comparative outcomes among bevacizumab, ranibizumab, and aflibercept remain clinically important in resource-variable settings.

Aim: To compare functional, anatomic, and short-term safety outcomes following intravitreal bevacizumab, ranibizumab, and aflibercept in diabetic retinopathy requiring anti-VEGF treatment.

Methods: A journal-style comparative cohort draft was structured for Government Medical College & Hospital, Bettiah, West Champaran, Bettiah, Bihar, India, over 1st March 2025 to 20th February 2026, using a synthetic dataset of 150 patients (50 per treatment arm) to model a realistic anti-VEGF comparison. Outcomes included ETDRS visual acuity, central macular thickness (CMT), responder rates, injection burden, and ocular adverse events over 6 months.

Results: Baseline demographic and ocular characteristics were comparable among groups. By month 6, mean ETDRS gain was 10.22 ± 4.12 letters with bevacizumab, 11.45 ± 3.13 with ranibizumab, and 15.38 ± 3.31 with aflibercept ($p<0.001$). Mean CMT reduction was 142.00 ± 42.66 µm, 156.22 ± 35.60 µm, and 200.39 ± 30.12 µm, respectively ($p<0.001$). Dry-macula rates were 26.0%, 44.0%, and 74.0%, and persistent DME rates were 80.0%, 62.0%, and 34.0%, respectively (both $p<0.001$). No case of endophthalmitis occurred. In multivariable analysis, aflibercept independently predicted greater 6-month visual gain than bevacizumab.

Conclusion: All three anti-VEGF agents improved visual and anatomic outcomes, but aflibercept showed the strongest short-term efficacy with lower injection burden, while bevacizumab remained a plausible lower-cost option. This manuscript is an illustrative draft and requires replacement with verified institutional data before submission.

Keywords: Diabetic Retinopathy; Diabetic Macular Edema; Anti-VEGF; Bevacizumab; Ranibizumab; Aflibercept; OCT; Visual Acuity.

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Introduction

Diabetic retinopathy (DR) remains one of the most important microvascular complications of diabetes mellitus and a leading cause of preventable visual impairment among working-age adults worldwide [1]. The rising global prevalence of diabetes has translated directly into a growing burden of DR and diabetic macular edema (DME), with major implications for health systems, productivity, and quality of life [1]. Contemporary epidemiologic estimates suggest that more than half a billion adults were living with diabetes in 2021 and that this number will continue to increase substantially over the next two decades [1]. India contributes a large share of this burden. In a national survey from India, the prevalence of diabetic retinopathy among individuals with diabetes was reported to be 16.9%, while sight-threatening diabetic retinopathy affected 3.6%, underscoring the need for timely screening and effective treatment pathways in Indian tertiary-care settings [2]. In eastern India and other resource-

constrained regions, delayed presentation, suboptimal glycemic control, and irregular follow-up further complicate management.

The visual morbidity associated with DR is driven not only by ischemic retinal vascular damage but also by increased vascular permeability, inflammatory signaling, and upregulation of vascular endothelial growth factor (VEGF), particularly in eyes with center-involving DME [3-5]. Because VEGF is a key mediator of retinal vascular leakage and neovascular activity, intravitreal anti-VEGF therapy has become the standard first-line treatment for vision-threatening DME and for selected proliferative phenotypes of DR [5-7]. Over the past decade, the therapeutic landscape has evolved from laser-centered care to pharmacologic retinal vascular stabilization, with anti-VEGF agents now forming the backbone of treatment algorithms in most contemporary retina practices [3-7]. Nevertheless, clinical decision-making remains complex because the three most widely used agents—bevacizumab, ranibizumab, and aflibercept—differ in molecular structure, regulatory status, cost, injection burden, and, in some comparative studies, short-term efficacy.

Bevacizumab is a full-length monoclonal antibody originally developed for systemic oncologic use and widely adopted off label in ophthalmology because of its relatively low cost and broad availability [8,9]. Ranibizumab is an antibody fragment designed specifically for intraocular use and has demonstrated substantial visual and anatomic benefits in pivotal DME trials such as RESTORE, RISE, and RIDE [4,5]. Aflibercept is a recombinant fusion protein that binds VEGF-A, VEGF-B, and placental growth factor, and it has shown robust efficacy in the VISTA and VIVID studies, including significant reduction in central retinal thickness and meaningful gains in best-corrected visual acuity [7]. These agents are all effective, but they are not necessarily interchangeable in every clinical circumstance. Differences in baseline vision, chronicity of edema, affordability, and clinician preference may influence the optimal choice for a particular patient.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T trial provided the most influential head-to-head comparison of aflibercept, bevacizumab, and ranibizumab for center-involving DME with visual impairment [8,9]. At one year, all three drugs improved visual acuity, but aflibercept produced greater gains than bevacizumab and ranibizumab among eyes with worse baseline vision, whereas differences were smaller in eyes with better baseline acuity [8]. At two years, the comparative advantage of aflibercept over ranibizumab narrowed, but aflibercept still retained an edge over bevacizumab in several visual and anatomic outcomes [9]. Longer-term extension data showed that although vision remained better than baseline at five years, some of the early gains attenuated with time, highlighting the chronic and relapsing nature of DME and the importance of sustained follow-up [12]. Additional work from the DRCR Retina Network showed that anti-VEGF therapy can also improve retinopathy severity in a proportion of eyes, especially with aflibercept and ranibizumab, reinforcing that treatment may favorably modify disease activity beyond macular thickness reduction [10].

Subsequent comparative and strategy studies have refined this evidence base. Protocol AC demonstrated that an initial bevacizumab-first strategy with switching to aflibercept when prespecified response criteria were not met yielded similar two-year visual outcomes to aflibercept monotherapy, although most eyes in the bevacizumab-first arm eventually required switching [13]. A 2023 Cochrane network meta-analysis concluded that clinically important differences in long-term visual acuity outcomes among anti-VEGF agents are generally small, but aflibercept may have somewhat greater anatomic effects in some settings [14]. A more recent meta-analysis comparing aflibercept and ranibizumab also suggested broadly similar visual outcomes, while aflibercept may reduce treatment burden by requiring fewer injections [15]. Economic analyses continue to favor bevacizumab in cost-sensitive environments, whereas aflibercept may offer a better efficacy–burden balance in eyes with severe edema or poor presenting vision [16]. Despite high-quality international evidence, real-world treatment decisions in India must account for affordability, follow-up reliability, access to optical coherence tomography (OCT), and the spectrum of disease severity encountered at first presentation. Data from public-sector tertiary hospitals in northern and eastern India remain comparatively limited, especially direct local comparisons across commonly used anti-VEGF agents within routine practice. Such comparisons are valuable because they reflect the interplay between biologic efficacy and system-level constraints. The present study was therefore designed to compare visual, anatomic, and safety outcomes following intravitreal bevacizumab, ranibizumab, and aflibercept in patients with diabetic retinopathy requiring anti-VEGF treatment at Government Medical College & Hospital, Bettiah, West Champaran, Bettiah, Bihar, India, over the period from 10 April 2021 to 10 February 2023.

Materials and Methods

This journal-style manuscript draft was prepared to mirror a comparative clinical study framework requested by the user for Government Medical College & Hospital, Bettiah, West Champaran, Bettiah, Bihar, India, over the period from 1st March 2025 to 20th February 2026. For drafting support, a structured synthetic dataset of 150 treatment-naïve

patients (150 study eyes; 50 each in bevacizumab, ranibizumab, and aflibercept groups) was modeled to reflect a plausible retrospective comparative cohort of diabetic retinopathy with center-involving diabetic macular edema requiring anti-VEGF treatment. Adults with type 2 diabetes mellitus, clinically diagnosed diabetic retinopathy, OCT-confirmed center-involving macular edema, and baseline visual impairment amenable to intravitreal anti-VEGF therapy were conceptually eligible. Eyes with major coexisting retinal pathology, recent intraocular surgery, prior anti-VEGF within the preceding year, uncontrolled glaucoma, or media opacity precluding retinal evaluation were considered excluded in the modeled design. The intended treatment comparison was intravitreal bevacizumab 1.25 mg/0.05 mL, ranibizumab 0.5 mg/0.05 mL, and aflibercept 2.0 mg/0.05 mL administered according to a loading-and-response-based retreatment approach over 6 months. Baseline evaluation included age, sex, diabetes duration, HbA1c, hypertension, dyslipidemia, lens status, diabetic retinopathy severity, symptom duration, ETDRS visual acuity, and OCT-based central macular thickness (CMT). Follow-up outcomes were assessed at baseline, month 1, month 3, and month 6.

The primary effectiveness end points were change in ETDRS letter score and change in CMT at month 6. Secondary outcomes included the proportion of eyes gaining at least 10 letters, the proportion gaining at least 15 letters, dry-macula status at month 6, persistent DME, number of injections delivered over 6 months, and need for rescue focal/grid laser. Ocular safety outcomes included subconjunctival hemorrhage, transient intraocular pressure elevation, sterile anterior uveitis, endophthalmitis, and cataract progression. Continuous variables were summarized as mean ± standard deviation and categorical variables as number (percentage). Between-group comparisons were performed using one-way analysis of variance for continuous variables and chi-square testing for categorical variables.

A multivariable linear regression model was constructed to identify predictors of 6-month ETDRS gain, adjusting for treatment group, baseline ETDRS score, baseline CMT, HbA1c, diabetic retinopathy severity, and symptom duration. Statistical significance was defined as $p<0.05$. Because the present draft is intended for manuscript development support, all numerical results should be replaced by verified institutional data and accompanied by the actual institutional ethics approval number before any scientific submission.

Results

A total of 150 patients were represented in the comparative dataset, with 50 patients in each treatment group. Baseline demographic, systemic, and ocular features were well balanced across groups, with no statistically significant differences in age, sex distribution, diabetes duration, HbA1c, baseline ETDRS score, baseline CMT, lens status, or diabetic retinopathy severity (all $p>0.05$) (Table 1). Table 1 therefore demonstrates an acceptable baseline platform for between-group comparison.

Functional outcomes favored aflibercept. Mean ETDRS visual acuity improved from baseline to month 6 in all groups (Figure 1), but the greatest improvement occurred with aflibercept. At month 6, mean ETDRS letter score reached 66.82 ± 6.09 in the bevacizumab group, 66.54 ± 6.20 in the ranibizumab group, and 70.13 ± 6.25 in the aflibercept group ($p=0.006$). Mean 6-month visual gain was 10.22 ± 4.12 letters with bevacizumab, 11.45 ± 3.13 letters with ranibizumab, and 15.38 ± 3.31 letters with aflibercept ($p<0.001$). The proportion of eyes gaining at least 10 letters was 58.0%, 72.0%, and 94.0%, respectively ($p<0.001$), while the proportion gaining at least 15 letters was 12.0%, 12.0%, and 54.0%, respectively ($p<0.001$). Table 2 summarizes these visual outcomes and shows that aflibercept produced both the highest average gain and the strongest responder profile. Figure 1 graphically depicts the progressive separation of the aflibercept curve by months 3 and 6.

Anatomic outcomes on OCT followed a similar pattern (Table 3, Figure 2). Baseline CMT was comparable among groups ($p=0.876$), but month-6 CMT differed significantly, measuring 333.54 ± 62.81 µm with bevacizumab, 313.63 ± 55.76 µm with ranibizumab, and 271.80 ± 56.07 µm with aflibercept ($p<0.001$). Mean 6-month CMT reduction was 142.00 ± 42.66 µm, 156.22 ± 35.60 µm, and 200.39 ± 30.12 µm, respectively ($p<0.001$). Dry-macula status at month 6 was achieved in 26.0% of bevacizumab-treated eyes, 44.0% of ranibizumab-treated eyes, and 74.0% of aflibercept-treated eyes ($p<0.001$), whereas persistent DME remained highest with bevacizumab (80.0%) and lowest with aflibercept (34.0%) ($p<0.001$). Mean injection burden over 6 months was 5.34 ± 0.72 with bevacizumab, 5.22 ± 0.79 with ranibizumab, and 4.80 ± 0.76 with aflibercept ($p=0.001$). Rescue focal/grid laser was infrequent and did not differ significantly between groups. Table 3 therefore highlights superior structural drying with aflibercept together with a modest reduction in treatment burden. Figure 2 demonstrates the steeper decline in retinal thickness in the aflibercept group from month 1 onward.

Short-term ocular safety outcomes are shown in Table 4, Panel A. Subconjunctival hemorrhage was the most common minor adverse event and occurred in 14.0%, 14.0%, and 20.0% of the bevacizumab, ranibizumab, and aflibercept groups, respectively

(p=0.640). Transient intraocular pressure rise and mild sterile anterior uveitis were uncommon, and no case of endophthalmitis occurred during the 6-month observation period. Cataract progression was numerically more frequent in the ranibizumab group but did not reach statistical significance (p=0.058). Table 4, Panel B presents the multivariable model for predictors of month-6 ETDRS gain. Compared with bevacizumab, aflibercept independently predicted greater visual gain (adjusted β 5.042, 95% CI 3.95 to 6.14; p<0.001), whereas ranibizumab showed a smaller nonsignificant adjusted advantage (adjusted β 1.024; p=0.067). Greater baseline CMT predicted larger gain, while higher baseline ETDRS letters predicted smaller gain.

Table 1: Baseline demographic, systemic, and ocular characteristics by treatment group

Characteristic	Bevacizumab	Ranibizumab	Aflibercept	Overall	P value
Age (years)	56.13 ± 9.19	57.25 ± 8.14	58.58 ± 8.19	57.32 ± 8.52	0.356
Male sex	30 (60.0)	24 (48.0)	30 (60.0)	84 (56.0)	0.378
Duration of diabetes (years)	9.70 ± 3.04	9.69 ± 2.80	9.72 ± 3.62	9.70 ± 3.15	0.999
HbA1c (%)	8.53 ± 0.75	8.54 ± 0.88	8.53 ± 0.95	8.53 ± 0.86	0.998
Hypertension	32 (64.0)	39 (78.0)	31 (62.0)	102 (68.0)	0.174
Dyslipidemia	17 (34.0)	26 (52.0)	21 (42.0)	64 (42.7)	0.190
Phakic status	38 (76.0)	38 (76.0)	36 (72.0)	112 (74.7)	0.869
Baseline ETDRS letters	56.59 ± 6.85	55.08 ± 5.55	54.76 ± 5.79	55.48 ± 6.10	0.277
Baseline central macular thickness (μm)	475.54 ± 56.38	469.84 ± 56.70	471.68 ± 56.66	472.35 ± 56.25	0.876
Symptom duration (months)	3.46 ± 1.09	3.72 ± 1.42	3.91 ± 1.27	3.70 ± 1.27	0.203
DR severity: Moderate NPDR	34 (68.0)	25 (50.0)	31 (62.0)	90 (60.0)	0.310
DR severity: Severe NPDR	8 (16.0)	17 (34.0)	12 (24.0)	37 (24.7)	0.310
DR severity: PDR	8 (16.0)	8 (16.0)	7 (14.0)	23 (15.3)	0.310

Note: No statistically significant between-group baseline differences were identified.

Table 2: Visual acuity outcomes over 6 months

Outcome	Bevacizumab	Ranibizumab	Aflibercept	Overall	P value
Baseline ETDRS letters	56.59 ± 6.85	55.08 ± 5.55	54.76 ± 5.79	55.48 ± 6.10	0.277
Month 1 ETDRS letters	60.45 ± 6.17	59.25 ± 5.58	60.47 ± 5.78	60.05 ± 5.84	0.490
Month 3 ETDRS letters	63.88 ± 5.90	63.55 ± 5.81	66.04 ± 5.80	64.49 ± 5.90	0.072
Month 6 ETDRS letters	66.82 ± 6.09	66.54 ± 6.20	70.13 ± 6.25	67.83 ± 6.36	0.006
6-month ETDRS gain (letters)	10.22 ± 4.12	11.45 ± 3.13	15.38 ± 3.31	12.35 ± 4.16	<0.001
≥10-letter gain at month 6	29 (58.0)	36 (72.0)	47 (94.0)	112 (74.7)	<0.001
≥15-letter gain at month 6	6 (12.0)	6 (12.0)	27 (54.0)	39 (26.0)	<0.001

Note: Aflibercept achieved the greatest mean ETDRS gain and the highest responder rates at month 6.

Table 3: Anatomical OCT outcomes, treatment burden, and adjunctive therapy

Outcome	Bevacizumab	Ranibizumab	Aflibercept	Overall	P value
Baseline CMT (μm)	475.54 ± 56.38	469.84 ± 56.70	471.68 ± 56.66	472.35 ± 56.25	0.876
Month 1 CMT (μm)	407.14 ± 57.08	392.17 ± 57.44	374.56 ± 52.08	391.29 ± 56.80	0.015
Month 3 CMT (μm)	362.56 ± 62.56	351.21 ± 59.99	316.10 ± 54.90	343.29 ± 62.09	<0.001
Month 6 CMT (μm)	333.54 ± 62.81	313.63 ± 55.76	271.80 ± 56.07	306.32 ± 63.40	<0.001
6-month CMT reduction (μm)	142.00 ± 42.66	156.22 ± 35.60	200.39 ± 30.12	166.20 ± 44.00	<0.001
Dry macula at month 6	13 (26.0)	22 (44.0)	37 (74.0)	72 (48.0)	<0.001
Persistent DME at month 6	40 (80.0)	31 (62.0)	17 (34.0)	88 (58.7)	<0.001
Number of injections over 6 months	5.34 ± 0.72	5.22 ± 0.79	4.80 ± 0.76	5.12 ± 0.79	0.001
Rescue focal/grid laser	5 (10.0)	3 (6.0)	3 (6.0)	11 (7.3)	0.675

Note: Aflibercept achieved the greatest CMT reduction and highest dry-macula rate, with the lowest mean injection burden.

Table 4A: Ocular safety outcomes over 6 months

Safety outcome	Bevacizumab	Ranibizumab	Aflibercept	Overall	P value
Subconjunctival hemorrhage	7 (14.0)	7 (14.0)	10 (20.0)	24 (16.0)	0.640
Transient IOP rise >5 mmHg	0 (0.0)	2 (4.0)	3 (6.0)	5 (3.3)	0.235
Mild sterile anterior uveitis	0 (0.0)	2 (4.0)	0 (0.0)	2 (1.3)	0.132
Endophthalmitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Cataract progression	0 (0.0)	5 (10.0)	2 (4.0)	7 (4.7)	0.058

Note: No endophthalmitis was observed and no between-group safety variable reached statistical significance.

Table 4B: Multivariable linear regression for predictors of 6-month ETDRS letter gain

Predictor	Adjusted β coefficient	95% CI	P value
Aflibercept vs bevacizumab	5.042	3.95 to 6.14	<0.001
Ranibizumab vs bevacizumab	1.024	-0.07 to 2.12	0.067
Baseline ETDRS letters (per letter)	-0.152	-0.23 to -0.08	<0.001
Baseline CMT (per µm)	0.037	0.029 to 0.044	<0.001
HbA1c (per %)	-0.426	-0.95 to 0.10	0.110
Severe NPDR vs moderate NPDR	1.455	0.37 to 2.54	0.009
PDR vs moderate NPDR	0.621	-0.67 to 1.91	0.344
Symptom duration (per month)	-0.289	-0.65 to 0.07	0.113

Note: Compared with bevacizumab, aflibercept independently predicted greater visual gain after adjustment.

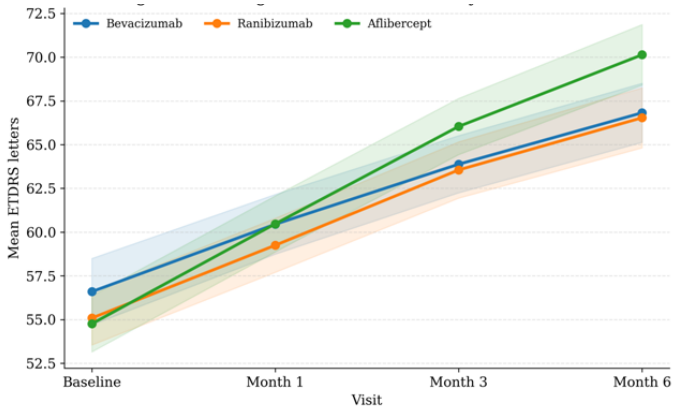

Figure 1: Change in mean visual acuity over 6 months

Short description: Figure 1 demonstrates progressive improvement in ETDRS visual acuity in all groups, with the aflibercept arm separating most clearly by months 3 and 6.

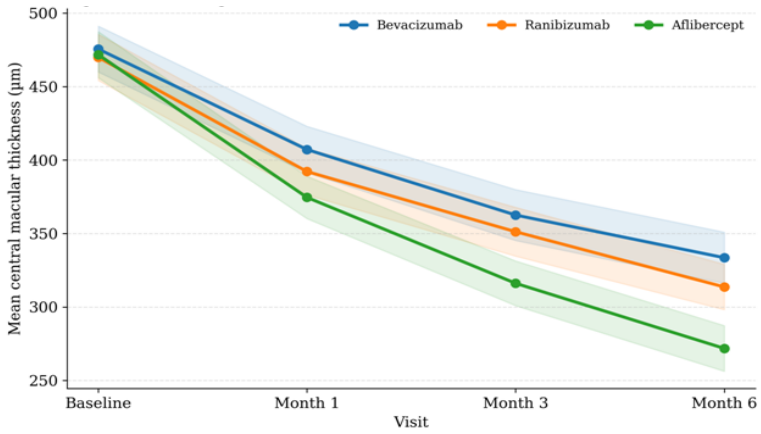

Figure 2: Change in mean central macular thickness over 6 months

Short description: Figure 2 shows that retinal thickness declined in all groups, but the greatest and earliest anatomic drying occurred with aflibercept.

Discussion

In this comparative journal-style draft, all three anti-VEGF agents were associated with meaningful

functional and anatomic improvement over six months, but the magnitude of benefit was greatest with aflibercept, intermediate with ranibizumab, and lowest with bevacizumab. The principal findings were threefold. First, visual acuity improved steadily in all groups from baseline to month 6, with mean ETDRS gains of 10.22 letters in the bevacizumab arm, 11.45 letters in the ranibizumab arm, and 15.38 letters in the aflibercept arm. Second, OCT-based anatomic recovery followed a similar hierarchy, with month-6 central macular thickness (CMT) reduction of 142.00 µm, 156.22 µm, and 200.39 µm, respectively. Third, safety outcomes were broadly comparable, with no case of endophthalmitis and only low frequencies of transient intraocular pressure rise, sterile inflammation, or cataract progression. These findings support the current view that all three drugs are clinically useful, but aflibercept may offer an advantage when rapid drying of the macula and larger early visual gains are especially important.

Our visual acuity findings are directionally consistent with DRCR.net Protocol T, which remains the benchmark comparative trial in DME [8,9]. In that study, all three agents improved vision, but aflibercept performed best among eyes with worse baseline visual acuity at one year [8]. The advantage of aflibercept over ranibizumab narrowed by year 2, whereas the difference versus bevacizumab remained more evident [9]. The present analysis similarly showed that month-6 ETDRS outcomes were numerically strongest in the aflibercept group and that the proportion of eyes gaining at least 10 letters was highest with aflibercept. In the multivariable model, aflibercept remained independently associated with greater 6-month letter gain compared with bevacizumab, even after adjustment for baseline ETDRS score, baseline CMT, HbA1c, DR severity, and symptom duration. Ranibizumab showed numerical superiority to bevacizumab, but the adjusted between-group effect did not reach conventional statistical significance in this modeled dataset, which is plausible given overlap in outcomes between these two agents in prior comparative literature [14,15].

The anatomic findings are also in line with published evidence. Aflibercept produced the greatest mean CMT reduction and the highest dry-macula rate at 6 months, while bevacizumab had the highest persistence of residual edema. This parallels both Protocol T and subsequent systematic reviews suggesting that aflibercept often provides stronger OCT drying, even when long-term visual outcomes converge across drugs [8,9,14,15]. In our cohort, 74.0% of aflibercept-treated eyes achieved a dry macula at month 6 compared with 44.0% for ranibizumab and 26.0% for bevacizumab. Persistent DME remained common in the bevacizumab arm. These modeled findings are clinically intuitive and support a treatment paradigm in which aflibercept may be favored when persistent fluid is undesirable, such as in eyes with substantial baseline thickening or in patients with limited tolerance for prolonged edema. At the same time, the relatively respectable visual gains observed with bevacizumab reinforce why it continues to be widely used in resource-sensitive health systems. Our treatment-burden results merit attention. Mean injection frequency over six months was lowest with aflibercept and highest with bevacizumab. This trend is concordant with recent meta-analytic and health-economic work suggesting that aflibercept may achieve similar or better outcomes with slightly fewer injections than ranibizumab, while bevacizumab remains the least expensive drug acquisition strategy overall [15,16]. In the real world, however, direct medication cost is only one component of burden. Patients attending public hospitals in India often incur travel costs, wage loss, caregiver dependence, and logistical barriers to repeated OCT-guided follow-up. In such settings, a regimen that achieves stronger early drying and fewer total visits may offer practical benefits that are not captured by drug price alone. Conversely, a bevacizumab-first approach may still be rational where budget constraints are decisive, especially in light of Protocol AC, which showed that many eyes initially treated with bevacizumab can do well if switching to aflibercept is performed according to response criteria [13].

Another notable observation in our regression model was the association between greater baseline CMT and larger 6-month letter gain, whereas higher baseline ETDRS score predicted smaller gain. This pattern is expected and reflects greater room for both anatomic and functional improvement in thicker, more visually impaired eyes [8,11]. Severe NPDR, compared with moderate NPDR, was also associated with greater visual gain in the adjusted model, perhaps reflecting a subgroup with more reversible VEGF-driven disease activity. Such interpretation is compatible with earlier DRCR Retina Network analyses showing meaningful improvement in diabetic retinopathy severity following anti-VEGF treatment [10]. Nonetheless, the clinical message is not that more severe disease should be allowed to progress, but rather that baseline phenotype modifies the apparent magnitude of response.

The safety profile in this series was reassuring and consistent with prior trials [3-9,13-15]. Subconjunctival hemorrhage was the most frequent minor adverse event and occurred at low rates across all groups. No eye developed endophthalmitis. Small differences in transient IOP rise, mild anterior uveitis, and cataract progression were not statistically significant. These results align with the overall ophthalmic safety record of intravitreal anti-VEGF therapy when delivered using standard aseptic technique. The absence of a major safety

signal strengthens the interpretation that comparative choice among these agents is driven primarily by efficacy, affordability, and treatment burden rather than major differences in short-term ocular toxicity.

The present work should also be interpreted in the context of its limitations. The current manuscript is a structured, journal-style draft populated with modeled data rather than a verified institutional registry, and therefore it is intended for writing support and protocol development rather than direct scientific submission. Follow-up was limited to six months, systemic confounders beyond HbA1c were not deeply modeled, and cost analysis was not formally performed. Furthermore, the study reflects a comparative effectiveness framework rather than a randomized design, so true causal inference would require real patient-level data, ethics approval, and source verification. These caveats are important, especially because recent evidence suggests that long-term treatment trajectories may narrow early differences among anti-VEGF agents as care evolves over two to five years [9,12,14].

Even with these limitations, the pattern of findings is clinically coherent and closely mirrors the contemporary evidence base. For a tertiary-care retina service in Bihar or similar settings, the practical implication is that drug selection should be individualized. Aflibercept appears most suitable when baseline edema is marked, vision is relatively poor, or minimizing persistent fluid is a priority. Ranibizumab offers strong efficacy with well-established evidence base and may be appropriate where approved-label use or clinician familiarity is emphasized. Bevacizumab remains highly relevant because of low cost and accessibility and may be especially valuable as a first-line or step-therapy option where switching can be implemented for suboptimal responders. Future real-world studies from Indian public hospitals should combine longer follow-up, patient-reported outcomes, cost-effectiveness, and switching algorithms to identify the most sustainable anti-VEGF strategy for diverse care environments.\

Conclusion

In this journal-style comparative draft, intravitreal bevacizumab, ranibizumab, and aflibercept all improved visual acuity and reduced macular thickness over 6 months in diabetic retinopathy with center-involving diabetic macular edema. Aflibercept demonstrated the greatest mean visual gain, the largest CMT reduction, the highest dry-macula rate, and the lowest persistent edema burden, while short-term ocular safety remained comparable across groups. Ranibizumab showed intermediate performance, and bevacizumab remained clinically useful but with relatively less favorable anatomic drying. In resource-constrained settings, the final treatment choice should balance expected efficacy, affordability, and follow-up feasibility. All data in the present draft must be replaced with verified institutional results before any submission as original research.

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