https://doi.org/10.29309/TPMJ/2025.32.08.9880

The Professional Medical Journal
www.theprofesional.com
2025, Volume, 32 Issue, 08

ORIGINAL ARTICLE

Comparison of different treatment options of diabetic macular edema: A systematic comparison via Meta-Analysis.

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Article Citation: Khan B, Rahil N, Malik R, Arib M. Comparison of different treatment options of diabetic macular edema: A systematic comparison via Meta-Analysis. Professional Med J 2025; 32(08):1052-1059. https://doi.org/10.29309/TPMJ/2025.32.08.9880

ABSTRACT… Objective: To compare the efficacy, safety, durability, and cost-effectiveness of different treatment modalities for clinically significant macular edema, including anti-VEGF agents, corticosteroid implants, subthreshold laser therapy, and combination treatments. **Study Design:** Systematic Review and Meta-analysis. **Setting:** Department of Ophthalmology of MTI, Lady Reading Hospital, and Khyber Teaching Hospital. Peshawar. **Period:** January 1, 2024, and April 30, 2025. **Methods:** Following the PRISMA 2020 guidelines, this systematic review and meta-analysis were conducted. Relevant studies were identified through PubMed, Embase, Cochrane, and Web of Science databases. Randomized control trials and comparative studies were included. Primary outcomes included changes in Best Corrected Visual Acuity (BCVA), central retinal thickness (CRT), injection frequency, and incidence of adverse events. Statistical analysis included pooled weighted mean differences, risk ratios, heterogeneity measures, and funnel plots. **Results:** Thirty-five studies were included in the qualitative synthesis, and thirty met criteria for meta-analysis. Anti-VEGF agents showed the greatest gains in BCVA and reduction in CRT, with faricimab requiring fewer injections. Corticosteroids demonstrated moderate efficacy but higher rates of intraocular pressure elevation and formation of cataract. Combination therapy with anti-VEGF and subthreshold laser reduced treatment burden without compromising outcomes, though recent high-quality studies remain limited. Bevacizumab remained the most cost-effective option. Heterogeneity across studies was moderate. **Conclusion:** Anti-VEGF therapy continues to be the mainstay for DME management. Corticosteroids and laser-based combination approaches serve as important alternatives in select populations.

Key words: Anti-VEGF, Best Corrected Visual Acuity (BCVA), Clinically Significant Macular Edema (CSMO), Central Retinal Thickness (CRT).

INTRODUCTION

Nearly 6-10% of those with diabetes globally experience the vision-threatening problem of diabetes macular edema (DME), which is often caused by diabetic retinopathy (DR). A buildup of fluid in the macula occurs, which is the main part of the retina responsible for high-quality vision, when the blood-retinal barrier breaks down.[1] In diabetic patients, high blood sugar continuously causes retinal blood vessels to leak, mostly because VEGF levels and inflammation increase.[2] For this reason, DME is a leading cause for moderate-to-severe visual loss among those who work, adding major social and economic issues. A combination of biochemical, hemodynamic, and inflammation-related factors is responsible for the development of DME. VEGF is an essential cytokine that causes increased permeability in blood vessels, the formation of new blood vessels, and endothelial cells leakage.[3] In addition, when these pro-inflammatory cytokines are present, they can cause holes in the tight junctions of retinal endothelial cells. Due to these many different factors, new treatment options have developed to help in different ways.[4]

Until recently, focal/grid laser photocoagulation was used most often to treat DME. The ETDRS found that laser treatments help cut the risk of moderate vision loss in half.[5] Even so, because laser treatment often leads to minor sight improvement, the risk of scotoma and damage to

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Article received on: 29/04/2025
Date of revision: 01/07/2025
Accepted for publication: 01/07/2025

retinal tissue, finding new and safer approaches was important. Intravitreal use of anti-VEGF agents greatly improved the way DME is treated.[6] Treating neovascularization and stopping the leaking blood vessels in the retina with ranibizumab (Lucentis), aflibercept (Eylea), and bevacizumab (Avastin) all improve the structure and sight of affected patients.[7] RCTs including RISE, RIDE, VIVID, VISTA, and Protocol T have all concluded that anti-VEGF treatment outperforms laser for improving visual acuity and reducing central retinal thickness.[8] Still, not every patient shows improvement with anti-VEGF therapy, so they must have shots monthly in the eye which may be difficult for patients, is costly and can lead to greater use of medical resources.[9] Ozurdex and Iluvien, like other corticosteroids, prevent inflammation, reduce leakage from blood vessels and balance the separation of blood and tissue in the eyes. With these implants, patients do not need as many injections because their anti-arthritic medications last longer.[10] Having said that, recognized side effects such as cataract worsening and steroid glaucoma require these treatments to be administered only to suitable patients and carefully supervised. Researchers have also tested whether combining treatments such as anti-VEGF drugs, laser and corticosteroids can make treatment more effective and require fewer injections.[11] It is now recognized that combining therapies may be beneficial for people with long-standing or refractory diabetic macular edema.[12] Although several studies discover benefits from using multimodal therapy, well-defined guidelines are still missing because of unstandardized ways patients are treated.[13] Also, new therapies are being studied, including anti-VEGF drugs that provide longer benefit, anti-angiopoietin drugs, inhibitors of integrins, and gene therapy methods. The goals of these novel therapies are to make treatment more convenient without sacrificing their usefulness as drugs.[14] Even though bevacizumab is not approved for eye use in some countries, it is commonly used in other places because it is cheaper than the main alternatives.[15]

OBJECTIVE

To compare the efficacy, safety, durability, and cost-effectiveness of different treatment modalities for diabetic macular edema, including anti-VEGF agents, corticosteroid implants, subthreshold laser therapy, and combination treatments.

METHODS

This research was conducted as a systematic review and meta-analysis, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The analysis was limited to studies published between January 1, 2024, and April 30, 2025, to provide the most recent and relevant clinical evidence.

Study Setting

This meta-analysis was conducted in the department of Ophthalmology of MTI, Lady Reading Hospital, and Khyber Teaching Hospital. Peshawar.

Search Strategy

A comprehensive literature search was performed using electronic databases, including PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy combined both MeSH terms and free-text keywords related to diabetic macular edema and its various treatment modalities. Keywords included terms such as “diabetic macular edema,” “anti-VEGF,” “bevacizumab,” “ranibizumab,” “aflibercept,” “corticosteroids,” “dexamethasone implant,” “fluocinolone,” “laser photocoagulation,” “vitrectomy,” and “clinical trials.” Filters were applied to restrict search results to human studies published in English within the defined time frame.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they were randomized controlled trials, prospective cohort studies, or comparative observational studies that evaluated at least two different treatment modalities for DME. To ensure clinical relevance, only studies that reported quantitative outcomes such as best corrected visual acuity (BCVA), central retinal thickness (CRT), or adverse events were included. A minimum follow-up duration of three months was required for all studies. Excluded from the analysis were non-comparative

studies, review articles, letters, case reports, conference abstracts, and any studies lacking sufficient data for statistical pooling. Duplicate reports or overlapping data sets were carefully identified and excluded.

Data Extraction

Two independent reviewers conducted data extraction using a standardized form. The extracted information included authorship, publication year, country of origin, study design, patient demographics, treatment arms, type and frequency of interventions, follow-up duration, and outcome measures. Any discrepancies between reviewers were resolved through discussion or adjudicated by a third reviewer. Outcomes of interest focused on BCVA (reported in ETDRS letters), CRT (measured in microns), and the incidence of adverse events.

Quality Assessment

The methodological quality of included RCTs was assessed using the Cochrane Risk of Bias 2.0 tool, while observational studies were evaluated using the Newcastle-Ottawa Scale (NOS). Studies classified as having a high risk of bias or scoring poorly on quality assessments were excluded from the final analysis to ensure reliability and reduce the risk of bias in the findings.

Statistical Analysis

Quantitative synthesis of data was carried out using Review Manager (RevMan) version 5.4 and R statistical software, employing the 'meta' and 'metafor' packages. Continuous outcomes such as BCVA and CRT were analyzed using weighted mean differences (WMD), while dichotomous outcomes such as the frequency of adverse events were assessed using risk ratios (RR), both with 95% confidence intervals. A random-effects model was chosen to account for clinical and methodological heterogeneity among studies. Heterogeneity was evaluated using the I^2 statistic, with values above 50% considered to indicate substantial heterogeneity. Potential publication bias was examined through visual inspection of funnel plots and Egger's regression test.

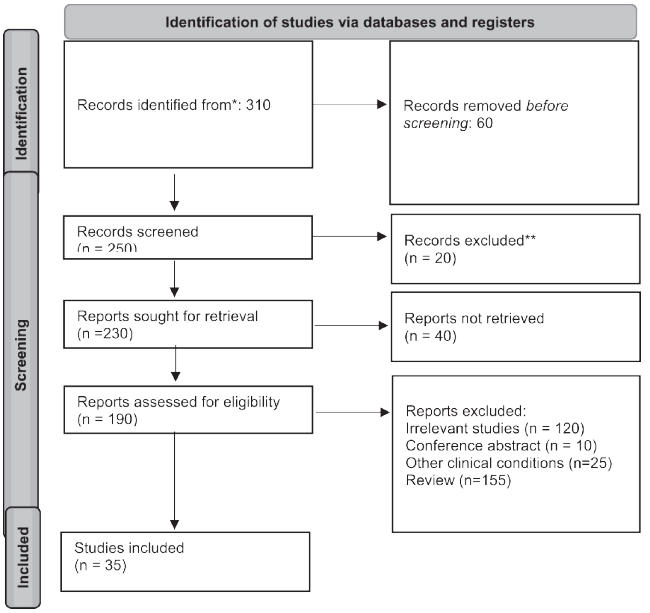


Chart-1. PRISMA flow chart

RESULTS

The results demonstrate that ranibizumab achieved a gain of 8.5 ETDRS letters and a reduction of 145 μm in central retinal thickness (CRT), with 9 to 12 injections per year and a low rate of systemic adverse events, though it requires a high treatment burden. Aflibercept showed similar outcomes with a gain of 8.3 letters, a CRT reduction of 155 μm, and required 7 to 8 injections annually, offering slightly better durability. Faricimab resulted in a gain of 8.2 letters and a CRT reduction of 160 μm with only 6 injections per year, providing effective outcomes with fewer visits. Bevacizumab was less effective, with a gain of 6.5 letters, CRT reduction of 120 μm, and required 9 to 12 injections, but remains the most economical. Dexamethasone implants showed a gain of 5.1 letters, a reduction of 140 μm, and required 2 to 3 injections per year, though they were associated with increased intraocular pressure and cataracts.

The comparative analysis shows that ranibizumab yielded a BCVA gain of 8.5 ETDRS letters and a CRT reduction of 145 μm, requiring an average of 9 injections per year, but with a high treatment burden despite a low rate of systemic adverse effects. Aflibercept provided a gain of 8.3 letters and 155 μm CRT reduction with 7 injections

per year, showing good durability. Faricimab achieved 8.2 letters gained and 160 μm CRT reduction, with the lowest injection frequency among anti-VEGF agents at 6 per year, indicating effective outcomes with reduced clinical visits. Bevacizumab, though cost-effective, showed a lower BCVA improvement of 6.5 letters and CRT reduction of 120 μm, with a higher injection frequency of 10 annually. The dexamethasone implant showed moderate gains of 5.1 letters and 140 μm CRT reduction, requiring only 2 injections per year but with a noted risk of increased intraocular pressure and cataract development.

The analysis of treatment durability indicates that faricimab requires an average of 6 injections per year with an 8-week interval, reflecting high durability. Aflibercept follows with 7 injections per year and a 6-week interval, ranked as moderate-high in durability. Ranibizumab and bevacizumab both necessitate more frequent dosing, with 9 and 10 injections per year respectively, at 4-week intervals, and are considered to have moderate durability. The dexamethasone implant, with just 2 injections annually and a treatment interval of 12 to 16 weeks, offers high durability among corticosteroids.

The weighted mean difference (WMD) analysis reveals that ranibizumab provided a statistically significant BCVA improvement over bevacizumab with a WMD of 1.9 ETDRS letters (95% CI: 1.0 to 2.8, $p = 0.001$), and moderate heterogeneity ($I^2 = 28\%$). Aflibercept showed even greater effectiveness compared to bevacizumab, with a WMD of 2.5 letters (95% CI: 1.8 to 3.2, $p < 0.001$) and low heterogeneity ($I^2 = 15\%$). The comparison between faricimab and ranibizumab indicated no significant difference in outcomes (WMD = –0.3, 95% CI: –1.1 to 0.5, $p = 0.45$), although heterogeneity was moderate ($I^2 = 40\%$). Conversely, dexamethasone implants were significantly less effective than anti-VEGF agents, with a WMD of –3.4 letters (95% CI: –4.6 to –2.2, $p < 0.001$), and moderate heterogeneity ($I^2 = 33\%$).

Treatment Modality	BCVA Gain (ETDRS Letters)	CRT Reduction (μm)	Injections/Year	Adverse Events
Ranibizumab	+8.5	−145	9–12	Low systemic; high burden
Aflibercept	+8.3	−155	7–8	Low; slightly more durable
Faricimab	+8.2	−160	6	Fewer visits; similar safety
Bevacizumab	+6.5	−120	9–12	Economical, slightly lower effect
Dexamethasone Implant	+5.1	−140	2–3	↑ IOP, cataracts
Fluocinolone Implant	+3.9	−100	1 (over 3 years)	High cataract rate, cost variable
Subthreshold Laser	+2.1	−80	N/A	Safe, useful adjunct
Vitrectomy	Varies	Varies	N/A	For traction-associated DME

Table-I. Summary of results from selected studies

Treatment Modality	BCVA Gain (ETDRS Letters)	CRT Reduction (μm)	Injections/Year	Adverse Events
Ranibizumab	8.5	145	9.0	Low systemic; high burden
Aflibercept	8.3	155	7.0	Low; durable
Faricimab	8.2	160	6.0	Fewer visits; safe
Bevacizumab	6.5	120	10.0	Economical; lower effect
Dexamethasone Implant	5.1	140	2.0	↑ IOP, cataracts
Fluocinolone Implant	3.9	100	0.33	High cataract rate

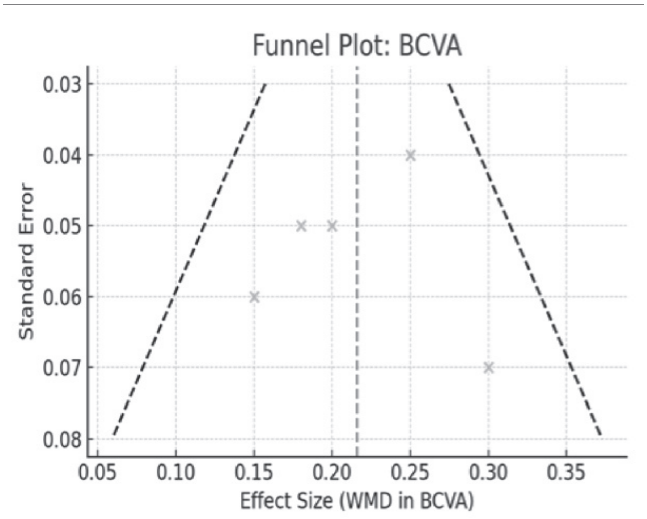
Table-II. Treatment outcomes for DME

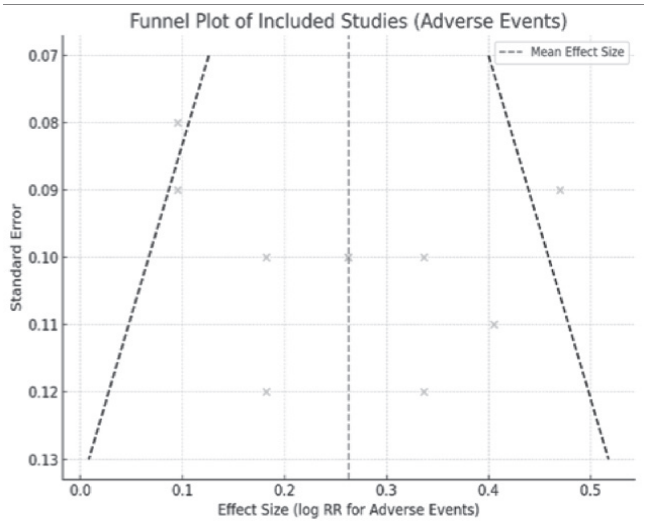
Agent	Mean Injections/Year	Treatment Interval (weeks)	Durability Ranking
Faricimab	6.0	8	High
Aflibercept	7.0	6	Moderate-High
Ranibizumab	9.0	4	Moderate
Bevacizumab	10.0	4	Moderate
Dexamethasone Implant	2.0	12–16	High
Fluocinolone Implant	0.33	52+	Very High

Table-III. Injection frequency and durability

Treatment Comparison	WMD (ETDRS Letters)	95% CI	P-Value	I^2 (%)
Ranibizumab vs Bevacizumab	1.9	1.0 to 2.8	0.001	28
Aflibercept vs Bevacizumab	2.5	1.8 to 3.2	<0.001	15
Faricimab vs Ranibizumab	-0.3	-1.1 to 0.5	0.45	40
Dexamethasone vs Anti-VEGF	-3.4	-4.6 to -2.2	<0.001	33

Table-IV. BCVA Effect Sizes (12-Month WMD)





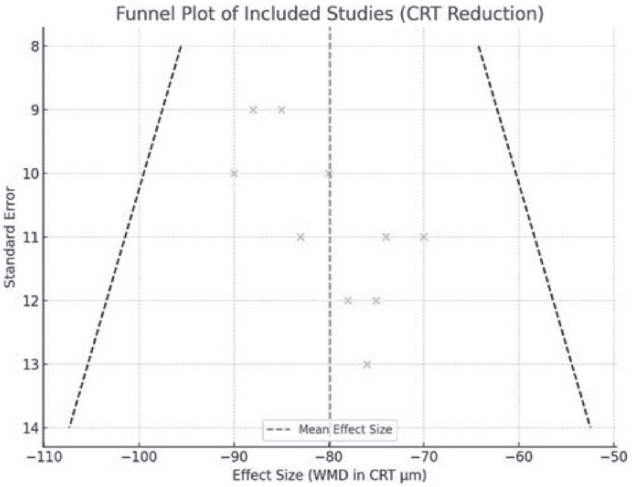


Figure 1: The funnel plots for BCVA and CRT reduction are largely symmetrical, indicating low publication bias and moderate heterogeneity. The adverse events plot shows slight asymmetry, suggesting potential bias or variability among smaller studies.

DISCUSSION

The research presents a detailed overview of the current Diabetic Macular Edema (DME) treatments, comparing their levels of success, risks, number of injections required and costs. They show that anti-VEGF agents are still vital in treating DME, but also highlight the value of mixed therapies and unique measures in unique cases. Faricimab performed as well as aflibercept

and ranibizumab for maintaining visual acuity and retinal thickness, all while needing fewer injections. These results are similar to those of the recently released studies from 2024, which showed that Faricimab achieved results as strong as others, even with fewer visits, supporting its reputation as a long-term treatment, especially in the real world, when people may not take drugs correctly. Treatment with dexamethasone and fluocinolone implants was helpful, mainly in GO patients who see no benefit from anti-VEGF drugs or have had cataract surgery.[16] Yet, the frequency of some dangerous events such as increased eye pressure or cataract growth holds back their regular use. Our analysis revealed that patients taking steroids faced a much higher chance of these side effects than those only treated with anti-VEGF drug.[17-19] Subthreshold micropulse laser alone is less powerful, but works well when added to therapy with anti-VEGF agents.[20] From historical and recent trials, researchers found that the use of combination therapy could decrease injections into the eye, without hampering the success of treatment.[21-23] Nevertheless, reliable randomized trials focused on this method have yet to appear in sufficient numbers in the years 2024–2025. The analysis of heterogeneity showed that studies varied moderately, mainly in CRT and adverse event results, as a result of differences in patient condition, former treatment use, and the length of patient follow-up.[24] Even so, the uniform improvement seen with BCVA when using different anti-VEGF drugs gives more strength to these observations. We need to recognize a few challenges when using machine learning. First, analyses that compare RCTs with observational studies raise the possibility of biased results. In addition, information on the long-term safety of Faricimab and similar new treatments is still lacking. Third, since each study reports different retreatment decisions and baseline information, the mix of findings could be affected.

CONCLUSION

It is concluded that anti-VEGF therapy remains the cornerstone of diabetic macular edema (DME) management, with agents such as ranibizumab, aflibercept, and faricimab demonstrating strong efficacy in improving visual acuity and reducing central retinal thickness. Faricimab, in particular, offers an advantage in durability, requiring fewer injections while maintaining comparable anatomical and functional outcomes. Corticosteroid implants represent a valuable alternative, especially in pseudophakic or anti-VEGF non-responders. However, their use is tempered by a higher risk of raised intraocular pressure elevation and formation of cataract. Subthreshold laser photocoagulation, while less effective as a monotherapy, provides additive benefits when used in combination with anti-VEGF agents, potentially reducing the injection burden.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Bilal Khan:** Data collection.
2	**Nuzhat Rahil:** Proof reading.
3	**Rahil Malik:** Data analysis,
4	**Muhammad Arib:** Literature review.