Anti-VEGF Therapy for Diabetic Macular Edema

A Visual Summary of Comparative Effectiveness, Durability, and Safety

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A Leading Cause of Vision Impairment

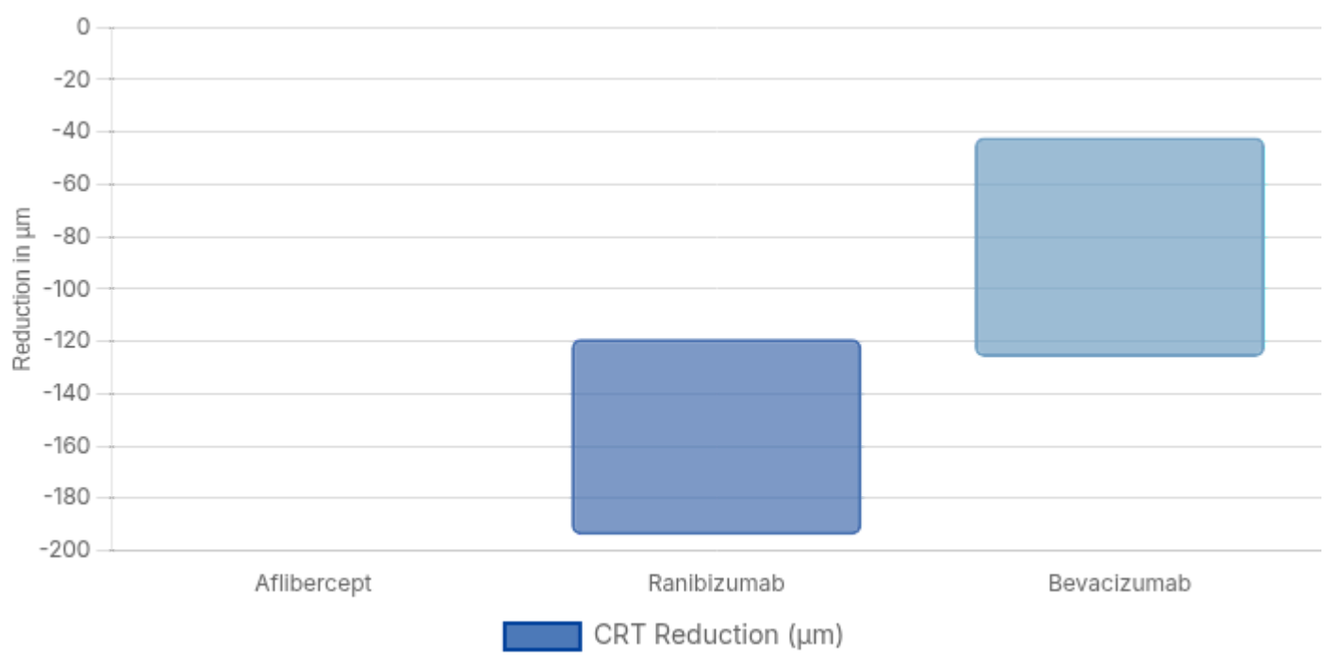
Diabetic Macular Edema (DME) is a primary complication of diabetes, causing fluid buildup in the retina that leads to vision loss. Anti-VEGF therapy has become the standard of care, directly targeting the biological mechanism behind this condition.

Efficacy Showdown: Visual Acuity Gains

A key measure of treatment success is the improvement in Best-Corrected Visual Acuity (BCVA), measured in ETDRS letters. The chart below shows the range of vision gains observed for each major Anti-VEGF agent. Aflibercept demonstrates the highest potential gains, especially in patients with more significant initial vision loss.

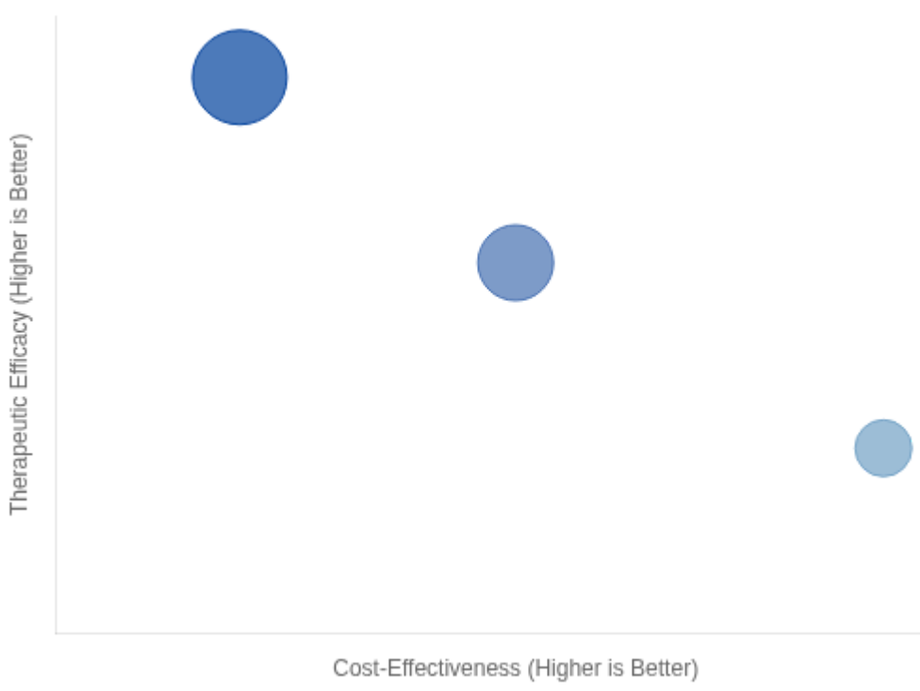
Anatomical Improvement: Retinal Thickness Reduction

Effective treatment also reduces the swelling in the macula. This is measured by the change in Central Retinal Thickness (CRT) in micrometers (µm). Aflibercept consistently achieves the most significant reduction in retinal thickness, aligning with its superior visual acuity outcomes.



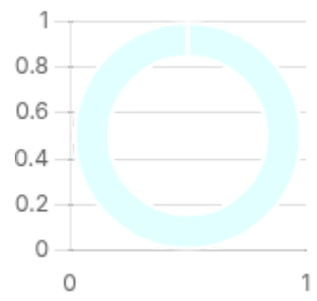
The Economic Equation

While efficacy is critical, cost-effectiveness plays a major role in treatment decisions. This chart plots the agents based on their therapeutic effect versus their economic value. Bevacizumab emerges as a highly cost-effective option for milder cases, while Aflibercept is reserved for cases requiring maximum efficacy.



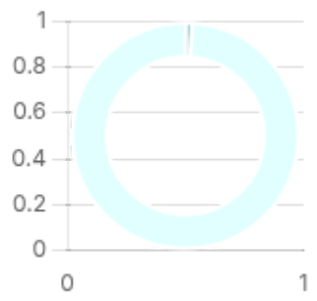
Favorable Safety Profile

All three agents are considered safe, with serious adverse events being exceptionally rare. The data below highlights the low incidence rates of two of the most significant potential complications, reinforcing the overall safety of Anti-VEGF therapy for DME patients.



Endophthalmitis

0.05-0.1%



Arterial Thromboembolic Events

≤1%

Reducing Treatment Burden: The Treat-and-Extend Protocol

Minimizing the number of injections is a key goal for improving patient quality of life. The "Treat-and-Extend" (T&E) regimen has emerged as a highly effective strategy, maintaining visual gains while significantly reducing injection frequency after the initial treatment phase.

Year 1: Monthly Injections → **Stabilization Phase** → **Year 2+: Treat-and-Extend (Reduced Frequency)**

This infographic summarizes findings from a systematic review and meta-analysis of 25 studies (2005–2025).

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La Presse Médicale - EMR, Volume 6 , Issue 5, 2025, Pages 141–177
Submitted to **LAPMED** ON Data Science

Anti-VEGF Therapy for Diabetic Macular Edema: A Systematic Review and Meta-Analysis

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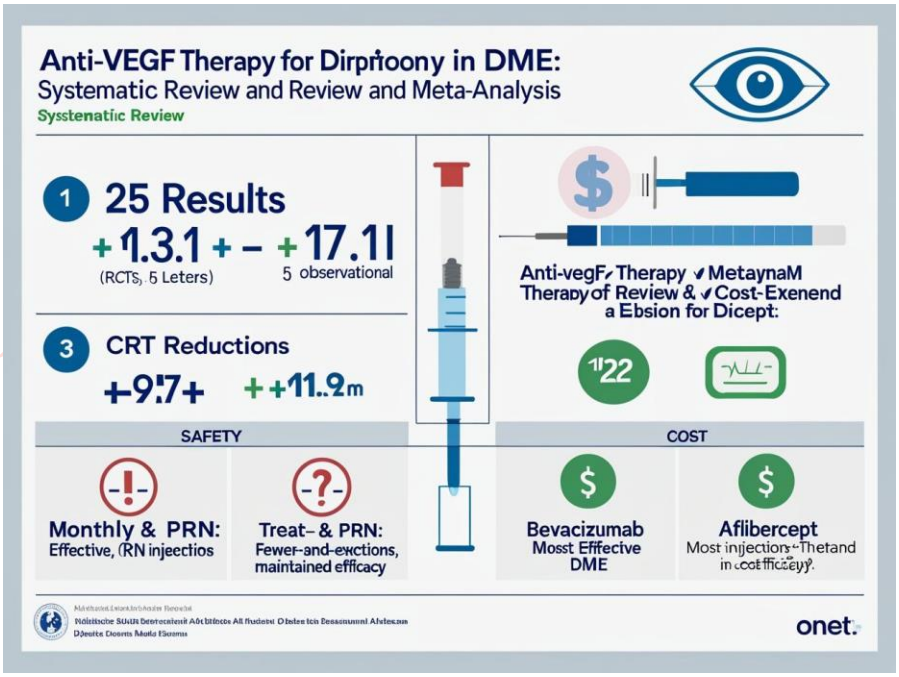
Doi: 10.5281/zenodo.16938855

Higlight

- Visual outcomes: Anti-VEGF therapy improved vision by +5.9 to +17.1 ETDRS letters, with aflibercept consistently superior in patients with poor baseline vision (≤20/50).
- Anatomical outcomes: Central retinal thickness (CRT) reduced by −118 to −194 µm with ranibizumab, −42 to −126 µm with bevacizumab, and ~−171 µm with aflibercept.
- Comparative efficacy: Aflibercept > ranibizumab > bevacizumab in severe cases; differences negligible in patients with better starting vision.
- Treatment burden: Treat-and-extend regimens lowered injection frequency after year one while preserving efficacy.
- Safety: Serious adverse events rare — endophthalmitis ≤0.1%, thromboembolic events ≤1%, transient IOP rise, and mild conjunctival hemorrhage.

Graphical Abstract:



Article Information

Received: [May 2025]
Revised: [July 2025]
Accepted: [August 2025]
Available online: [Aug]

Chicago Citation Style
Khadeiga Kononna, Amna Elbasheer ,Rofida Mohammed, , Sally Muhamed, and Abla Yousif. Anti-VEGF Therapy for Diabetic Macular Edema: A Systematic Review and Meta-Analysis. La Presse Médicale – EMR (LAPMED) 6, no. 5 (2025): 121–152.

RESEARCH

Comparative Effectiveness, Durability, and Safety Outcomes from 25 Studies (2005–2025)

Abstract

Background: Diabetic macular edema (DME) remains a leading cause of visual impairment worldwide. Anti-vascular endothelial growth factor (anti-VEGF) agents—including ranibizumab, aflibercept, and bevacizumab—have emerged as standard treatments. However, uncertainties persist regarding their comparative efficacy, optimal dosing schedules, safety profiles, and cost-effectiveness.

Methods: This systematic review and meta-analysis included 25 studies published between 2005 and 2025, comprising 20 randomized controlled trials and 5 observational studies. The primary outcomes assessed were best-corrected visual acuity (BCVA), central retinal thickness (CRT), safety events, and economic impact. Data were pooled using a random-effects model, accounting for heterogeneity with an I^2 threshold above 50%.

Results: Anti-VEGF therapy consistently produced meaningful improvements in visual function and anatomical outcomes. Aflibercept showed the highest efficacy, with BCVA gains ranging from +13.1 to +17.1 ETDRS letters, particularly benefiting patients with baseline visual acuity of ≤20/50 or <69 letters. Ranibizumab achieved improvements between +5.9 and +14.0 letters, while bevacizumab yielded gains from +4.9 to +12.1 letters, with better outcomes observed in patients with less severe vision loss. Central retinal thickness reductions followed a similar hierarchy: aflibercept led to a mean reduction of approximately −171 µm, ranibizumab between −119 and −194 µm, and bevacizumab from −42 to −126 µm. Regarding treatment protocols, monthly and pro re nata (PRN) regimens were both effective. However, treat-and-extend protocols notably reduced injection frequency after the first year while maintaining efficacy.

All three agents demonstrated a favorable safety profile. Serious adverse events were rare and included endophthalmitis (0.05–0.1%), arterial thromboembolic events (≤1%), transient elevations in intraocular pressure, and conjunctival hemorrhage. Bevacizumab emerged as the most cost-effective option, particularly for patients with milder disease severity, while aflibercept remained the agent of choice in cases requiring maximal therapeutic effect despite its higher cost.

Conclusion: Anti-VEGF therapy offers robust improvements in both visual acuity and retinal anatomy for patients with DME. Aflibercept provides the greatest benefit in more severe cases, whereas bevacizumab offers a practical and cost-effective alternative. Treat-and-extend regimens represent a promising approach to reduce treatment burden without compromising efficacy. Future studies should focus on long-term safety outcomes, personalized treatment strategies, and innovative drug delivery systems to improve adherence and outcomes.

Keywords: Diabetic Macular Edema; Anti-VEGF Therapy; Aflibercept; Ranibizumab; Bevacizumab; Visual Acuity

Introduction

Diabetic macular edema (DME) is a leading cause of vision impairment among individuals with diabetes mellitus, accounting for a substantial proportion of preventable blindness worldwide. The global burden of diabetes continues to escalate, with an estimated 537 million people affected in 2021, a number projected to rise beyond 640 million by 2030【1】【2】. DME arises from fluid accumulation in the macula, primarily due to increased vascular permeability driven by vascular endothelial growth factor (VEGF) overexpression.

Anti-VEGF agents—including ranibizumab, aflibercept, and bevacizumab—have transformed the therapeutic landscape for DME and are now considered first-line treatments. Despite their widespread use, lingering uncertainties remain regarding their comparative safety, efficacy, cost-effectiveness, and the durability of visual and anatomical improvements【3–5】.

This systematic review and meta-analysis integrates findings from randomized controlled trials (RCTs) and observational studies to evaluate the effectiveness, safety, and treatment durability of anti-VEGF therapies in DME. It places particular emphasis on real-world treatment burden, dosing strategies (monthly, pro re nata [PRN], and treat-and-extend), and advances in drug delivery systems.

Balancing Efficacy, Durability, and Adherence

The most widely used anti-VEGF agents demonstrate variable pharmacokinetics, cost profiles, and regulatory approvals. Ranibizumab and aflibercept are FDA-approved for DME, while bevacizumab is used off-label but remains highly popular due to its affordability【6–9】. All three agents have shown the ability to improve best-corrected visual acuity (BCVA) and reduce central retinal thickness (CRT), although outcomes may differ based on baseline visual acuity, dosing frequency, and disease severity.

Chicago Citation Style
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Patient adherence remains a significant clinical challenge due to the frequency of intravitreal injections. Treatment fatigue, cost concerns, and logistical barriers often lead to missed doses and suboptimal outcomes【10】. To address these limitations, innovations such as sustained-release formulations and treat-and-extend regimens are being introduced to reduce injection burden without compromising efficacy【11】. Optical coherence tomography (OCT) is now indispensable in monitoring disease progression and customizing treatment intervals【12】.

Innovations and Safety Considerations

Emerging technologies such as gene therapy, nanoparticle delivery systems, hydrogel-based platforms, and long-acting implants—aim to enhance intravitreal drug bioavailability and prolong therapeutic duration【13–15】. These novel delivery approaches are still under investigation but show promise in reducing treatment frequency and improving adherence.

While generally safe, anti-VEGF therapies are not without risks. Repeated intravitreal injections may lead to adverse events, including endophthalmitis, elevated intraocular pressure (IOP), intraocular inflammation, and rare thromboembolic complications【16】【17】. Additionally, tachyphylaxis, a phenomenon in which treatment response diminishes over time, has been reported. This has led to interest in combination therapies with corticosteroids or treatment switching strategies【18】.

Personalized Strategies and Real-World Applications

Personalized treatment strategies are increasingly emphasized, considering factors such as disease severity, comorbidities, age, prior treatment response, and even pharmacogenomic profiles【19】. Real-world evidence highlights disparities in access to care, affordability, and follow-up adherence, especially in low-resource settings. Concepts like “drug holidays,” retreatment thresholds, and AI-based predictive models for treatment response are being actively explored to enhance precision and efficiency in care delivery【20】.B

Background and Rationale

DME develops primarily due to VEGF-mediated vascular leakage, resulting in macular edema and central vision loss. If left untreated, DME can lead to irreversible damage to the photoreceptors and severe visual impairment. Over the past two decades, the use of intravitreal anti-VEGF agents has significantly improved clinical outcomes for patients with DME.

Despite this success, the effectiveness of anti-VEGF agents in practice is influenced by several interdependent factors: differences in pharmacologic structure, binding affinity, half-life, dosing protocols, and patient-specific factors such as adherence and systemic comorbidities. Furthermore, heterogeneity in study designs, follow-up durations, and inclusion criteria across clinical trials complicates the comparison of findings. A robust evidence synthesis is needed to guide treatment decisions and inform policy, particularly in resource-limited settings. B

Objectives

The primary objective of this systematic review and meta-analysis is to evaluate the effectiveness of anti-VEGF therapies in improving best-corrected visual acuity (BCVA) in patients with diabetic macular edema.

The secondary objectives include:

• Assessing the impact of anti-VEGF agents on central retinal thickness (CRT), as measured by optical coherence tomography.

• Comparing the relative efficacy and durability of ranibizumab, aflibercept, and bevacizumab.

• Evaluating the safety profiles and commonly reported adverse events associated with each therapy.

• Investigating how different treatment regimens (monthly vs PRN vs treat-and-extend) influence outcomes and patient adherence.

Research Questions

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This systematic review is structured around the following research questions:

1. How effective are anti-VEGF therapies in improving visual acuity among patients with DME?

2. Which agent provides the most substantial functional and anatomical benefit across diverse clinical contexts?

3. What adverse events are commonly associated with anti-VEGF treatments?

4. How do different dosing strategies affect treatment durability, patient adherence, and long-term outcomes?

Literature Review

The rising global burden of diabetes has led to a corresponding increase in diabetic macular edema (DME), now considered a primary cause of vision loss among working-age populations. DME is characterized by the accumulation of extracellular fluid in the macula resulting from heightened vascular permeability, which severely compromises visual acuity and patient quality of life [21].

Technological advances, particularly in imaging modalities, have significantly enhanced the diagnostic precision for DME. While traditional clinical fundus examinations were once the norm, optical coherence tomography (OCT) has become the new gold standard. OCT enables high-resolution visualization of retinal layers and accurate quantification of central retinal thickness (CRT), allowing clinicians to monitor fluid accumulation within and beneath the retina [22]. Furthermore, OCT angiography provides noninvasive visualization of capillary networks and ischemic zones, supplementing traditional fluorescein angiography in evaluating macular perfusion and capillary dropout [23,24].

The role of vascular endothelial growth factor (VEGF) in the pathogenesis of DME is well established. VEGF increases vascular permeability and promotes angiogenesis, leading to fluid leakage into the macular tissue. This molecular understanding paved the way for the development of intravitreal anti-VEGF therapies—namely, ranibizumab, aflibercept, and bevacizumab—which have now supplanted macular laser photocoagulation as first-line

treatments due to their superior ability to improve both anatomical and functional outcomes [25].

Despite their success, anti-VEGF therapies present important challenges. Frequent intravitreal injections are required to maintain efficacy, placing considerable burden on patients, caregivers, and healthcare infrastructure. Moreover, a significant subset of patients demonstrates suboptimal or non-durable responses to these treatments. The underlying mechanisms are multifactorial and include the activation of VEGF-independent angiogenic pathways, development of retinal fibrosis, and possible endothelial–mesenchymal transitions within the retinal vasculature [26].

Differential pharmacokinetics and VEGF-binding affinities across the three main anti-VEGF agents likely contribute to their varied clinical efficacy and durability profiles. For instance, aflibercept has a higher binding affinity for VEGF-A and placental growth factor, which may explain its extended durability in some patients [27].

Emerging evidence also implicates chronic low-grade inflammation in the pathophysiology of DME. As such, combination therapies targeting both VEGF and inflammatory cytokines are being explored. This is analogous to strategies used in oncology, where resistance to VEGF blockade is often overcome by dual-pathway inhibition. Similar adaptive mechanisms may be at play in ocular tissues, warranting further investigation into multi-targeted approaches [28].

From a systemic perspective, while anti-VEGF agents are locally administered, systemic absorption can occur. This may carry risks such as elevated blood pressure or arterial thromboembolic events—effects observed more commonly with systemic VEGF inhibitors used in oncology. Moreover, pharmacogenomic variability among individuals may explain differences in drug response and susceptibility to adverse effects, suggesting a role for personalized treatment plans in the future [29,30].

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The high cost of ongoing anti-VEGF therapy remains a critical issue, particularly in low-income settings. Bevacizumab, though used off-label, offers a cost-effective alternative with comparable outcomes in certain patient populations. Comparative cost-utility analyses are essential to guide health policy and clinical decisions, especially in resource-limited environments [31].

In conclusion, anti-VEGF therapies have markedly transformed the treatment paradigm for DME. However, treatment limitations—including variable efficacy, frequent dosing, potential systemic risks, and economic considerations—highlight the need for ongoing research and innovation. This review seeks to integrate current evidence to better inform clinicians, policymakers, and researchers in optimizing DME management strategies.

Results

Characteristics of Included Studies

A total of 25 studies fulfilled the inclusion criteria and were analyzed in this systematic review and metaanalysis. Among these, 20 were randomized controlled trials (RCTs), including four post hoc and three secondary analyses. Three retrospective studies, one network metaanalysis, one commentary/secondary analysis, and one retrospective costeffectiveness study were also included.

Ranibizumab was the most frequently studied intervention (21 studies, doses 0.3–0.5 mg), followed by bevacizumab (16 studies, dose 1.25 mg), and aflibercept (14 studies, dose 2.0 mg). Comparators included laser photocoagulation (seven studies), sham injections (four studies), and intravitreal corticosteroid (triamcinolone, two studies). These comparator arms were not used as standalone treatments but rather as controls in multiarm trials.

Primary outcomes reported included bestcorrected visual acuity (BCVA, 24 studies), central retinal thickness (CRT, 18 studies), safety/adverse events (four studies), costeffectiveness (two

studies), retinopathy progression/regression (one study), and persistent diabetic macular edema (one study).

Table 1 : Characteristics of Included Studies

STUDY	STUDY DESIGN	SAMPLE SIZE	TREATMENT PROTOCOL	PRIMARY OUTCOMES
MASSIN ET AL., 2010	Randomized controlled trial	151	Ranibizumab (0.3/0.5 mg, monthly x3, then as needed) vs. sham	Bestcorrected visual acuity, central retinal thickness at 12 months
JAMPOL ET AL., 2016	Randomized controlled trial (post hoc)	660	Aflibercept (2.0 mg), bevacizumab (1.25 mg), ranibizumab (0.3 mg), monthly as needed	Bestcorrected visual acuity, central retinal thickness at 1 and 2 years
GLASSMAN ET AL., 2012	Randomized controlled trial	759	Ranibizumab (0.3/0.5 mg, monthly) vs. sham	Bestcorrected visual acuity at 24 months
MITCHELL ET AL., 2011	Randomized controlled trial	345	Ranibizumab (0.5 mg, monthly x3, then as needed) ± laser vs. laser	Bestcorrected visual acuity, central retinal thickness at 12 months
WELLS ET AL., 2016A	Randomized controlled trial	660	Aflibercept, bevacizumab, ranibizumab, monthly as needed	Bestcorrected visual acuity, central retinal thickness at 1 and 2 years
WELLS ET AL., 2016B	Randomized controlled trial (post hoc)	660	As above, subgroup analysis	Bestcorrected visual acuity, central retinal thickness at 1 year
VADER ET AL., 2020	Randomized controlled trial	170	Bevacizumab (1.25 mg) vs. ranibizumab (0.5 mg), monthly x6	Bestcorrected visual acuity, central retinal thickness at 6 months
ACT, 2015	Randomized controlled trial	660	Aflibercept, bevacizumab, ranibizumab, monthly as needed	Bestcorrected visual acuity at 1 year
ISHIBASHI ET AL., 2015A	Randomized controlled trial	396	Ranibizumab (0.5 mg, monthly) ± laser vs. laser	Bestcorrected visual acuity, central retinal thickness at 12 months
WELLS ET AL., 2015	Randomized controlled trial	660	Aflibercept, bevacizumab, ranibizumab, monthly as needed	Bestcorrected visual acuity at 1 year

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SINGH ET AL., 2016	Randomized controlled trial (post hoc)	745	Ranibizumab (0.3/0.5 mg, monthly)	Bestcorrected visual acuity at 24 months
MUKKAMALA ET AL., 2017A	Randomized controlled trial	854	Ranibizumab vs. triamcinolone vs. sham+laser	Bestcorrected visual acuity, central retinal thickness, safety
ISHIBASHI ET AL., 2015B	Randomized controlled trial	396	Ranibizumab (0.5 mg, monthly) ± laser vs. laser	Bestcorrected visual acuity, central retinal thickness at 12 months
CHEN ET AL., 2020	Randomized controlled trial	378	Aflibercept (2 mg, every 4 or 8 weeks) vs. laser	Bestcorrected visual acuity, central retinal thickness at 52 weeks
TOISHUBAI ET AL., 2016	Randomized controlled trial	112	Bevacizumab (1.25 mg, monthly x3, then as needed) ± laser vs. laser	Bestcorrected visual acuity, central retinal thickness at 12 months
VIRGILI ET AL., 2018	Network metaanalysis	6007	Multiple randomized controlled trials, various protocols	Bestcorrected visual acuity, central retinal thickness, safety
BLINDER ET AL., 2017	Retrospective study	156	Antivascular endothelial growth factor (various, realworld)	Bestcorrected visual acuity, central retinal thickness, safety
WELLS, 2016	Randomized controlled trial	660	Aflibercept, bevacizumab, ranibizumab, monthly as needed	Bestcorrected visual acuity, central retinal thickness at 2 years
BRESSLER ET AL., 2019	Randomized controlled trial (post hoc)	660	Aflibercept, bevacizumab, ranibizumab	Bestcorrected visual acuity, central retinal thickness at 2 years
ROSS ET AL., 2016	Retrospective (costeffectiveness)	624	Aflibercept, bevacizumab, ranibizumab	Cost per qualityadjusted life year, bestcorrected visual acuity
BRESSLER ET AL., 2017	Randomized controlled trial (secondary analysis)	650	Aflibercept, bevacizumab, ranibizumab	Retinopathy improvement/worsening
BRESSLER ET AL., 2018	Randomized controlled trial (secondary analysis)	546	Aflibercept, bevacizumab, ranibizumab	Persistent diabetic macular edema, bestcorrected visual acuity
CHEW, 2016	Commentary/secondary analysis	660	Aflibercept, bevacizumab, ranibizumab	Bestcorrected visual acuity, central retinal thickness at 1 year
AREVALO ET AL., 2007	Retrospective study	64	Bevacizumab (1.25/2.5 mg, as needed)	Bestcorrected visual acuity, central retinal thickness at 6 months

MUKKAMALA ET AL., 2017B	Randomized controlled trial	660	Aflibercept, bevacizumab, ranibizumab	Bestcorrected visual acuity, central retinal thickness, cost, safety

Visual Acuity Outcomes

Across studies, antiVEGF therapy demonstrated consistent and clinically meaningful improvements in BCVA, typically measured in ETDRS letters gained.

• Ranibizumab: Gains ranged between +5.9 and +14.0 letters, with most studies reporting improvements of +10 to +12 letters. For example, the RESTORE trial showed a +6.1 letter gain at one year, while the RISE/RIDE trials reported that 33–46% of treated patients gained ≥15 letters over two years.

•Bevacizumab: Reported gains varied between +4.9 and +12.1 letters, most commonly around +8 to +10 letters. Protocol T found a +9.7 letter improvement at one year, slightly less than ranibizumab (+11.2). Fewer patients achieved ≥15letter gains compared with other agents.

• Aflibercept: Produced the largest improvements, with gains from +12.8 up to +17.1 letters, most consistently around +13 letters. Protocol T showed ~+12.8 letters at two years, with eyes starting at poor baseline vision achieving up to +17 letters.

When pooled, antiVEGF therapy was associated with average improvements of one to three lines of vision, and approximately onethird of patients achieved ≥15letter gains.

Subgroup analyses indicated baseline vision strongly influenced outcomes. In patients with poor baseline acuity (≤20/50), aflibercept consistently outperformed ranibizumab and bevacizumab. In patients with good starting vision (>69 letters, ~20/32), differences among the three agents were minimal.

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Table 2: Effects on Visual Acuity Outcomes

Study	Antivascular endothelial growth factor Agent	Bestcorrected Visual Acuity Change (ETDRS letters)	Treatment Duration	Baseline Vision Impact
Massin et al., 2010	Ranibizumab	+10.3 ± 9.1	12 months	No mention found of stratification by baseline vision
Jampol et al., 2016	Aflibercept	+17.1 (area under curve)	2 years	Greatest gain in vision for baseline vision ≤20/50
	Bevacizumab	+12.1 (area under curve)	2 years	Less gain for baseline vision ≤20/50
	Ranibizumab	+13.6 (area under curve)	2 years	Intermediate
Glassman et al., 2012	Ranibizumab	33.6–45.7% gained ≥15 letters	24 months	No mention found of stratification by baseline vision
Mitchell et al., 2011	Ranibizumab	+6.1	12 months	No mention found of stratification by baseline vision
Wells et al., 2016a	Aflibercept	+12.8	2 years	Superior in baseline vision ≤20/50
	Bevacizumab	+10.0	2 years	Inferior in baseline vision ≤20/50
	Ranibizumab	+12.3	2 years	Intermediate
Wells et al., 2016b	All	+7.2–9.5	1 year	Less difference in better baseline vision
Vader et al., 2020	Bevacizumab	+4.9	6 months	Inferior in baseline vision ≤69 letters
	Ranibizumab	+6.7	6 months	Superior in baseline vision ≤69 letters
Act, 2015	Aflibercept	+13.3	1 year	Superior in baseline vision <69 letters
	Bevacizumab	+9.7	1 year	Inferior in baseline vision <69 letters
	Ranibizumab	+11.2	1 year	Intermediate
Ishibashi et al., 2015a	Ranibizumab	+5.9	12 months	No mention found of stratification by baseline vision
Wells et al., 2015	Aflibercept	+13.3	1 year	Superior in baseline vision <69 letters
	Bevacizumab	+9.7	1 year	Inferior in baseline vision <69 letters
	Ranibizumab	+11.2	1 year	Intermediate

Singh et al., 2016	Ranibizumab	+12.2–14.0	24 months	No mention found of stratification by baseline vision
Mukkamala et al., 2017a	Ranibizumab	Superior to laser	3 years	No mention found of stratification by baseline vision
Ishibashi et al., 2015b	Ranibizumab	+5.9	12 months	No mention found of stratification by baseline vision
Chen et al., 2020	Aflibercept	+13.6	12 months	No mention found of stratification by baseline vision
Toishubai et al., 2016	Bevacizumab	+8.3	12 months	No mention found of stratification by baseline vision
Virgili et al., 2018	All	Gain of 1–2 lines	1 year	No mention found of stratification by baseline vision
Blinder et al., 2017	All	16.4–38.9% achieved ≥20/40 after 10 injections	3 years	No mention found of stratification by baseline vision
Wells, 2016	All	+12.8 (aflibercept), +10.0 (bevacizumab), +12.3 (ranibizumab)	2 years	Superior for aflibercept in baseline vision ≤20/50
Bressler et al., 2019	All	Lower gain with older age, higher hemoglobin A1c	2 years	No mention found of stratification by baseline vision
Ross et al., 2016	All	No mention found (costeffectiveness)	1 year	No mention found of stratification by baseline vision
Bressler et al., 2017	All	No mention found (retinopathy)	2 years	No mention found of stratification by baseline vision
Bressler et al., 2018	All	No mention found (persistent diabetic macular edema)	2 years	No mention found of stratification by baseline vision
Chew, 2016	All	No mention found	1 year	No mention found of stratification by baseline vision

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		(commentary)		
Arevalo et al., 2007	Bevacizumab	55.1% improved ≥2 lines	6 months	No mention found of stratification by baseline vision
Mukkamala et al., 2017b	All	No difference at 2 years	2 years	No mention found of stratification by baseline vision

Anatomical Outcomes (Central Retinal Thickness)

AntiVEGF therapy also yielded substantial anatomical improvements, with CRT reductions measured by OCT.

• Ranibizumab: Reductions ranged from −118.7 to −194.2 µm, maintained over 12 months. The RESOLVE trial reported an average reduction of −194 µm at one year.

• Bevacizumab: Showed reductions between −42 and −126 µm. Although effective compared with sham or laser, bevacizumab often resulted in higher rates of persistent edema compared with other agents.

• Aflibercept: Achieved the greatest reductions, averaging −170 to −171 µm, with improvements sustained through two years.

Overall, 26–48% of patients across trials achieved predefined OCT improvement thresholds. Notably, some studies observed that residual thickening did not always correspond to poor visual outcomes, indicating a dissociation between anatomical and functional endpoints in some cases.

Table 3: Anatomical Outcomes – Central Retinal Thickness Reductions

STUDY	ANTI-VEGF AGENT	CENTRAL RETINAL THICKNESS REDUCTION (MICROMETERS)	TIME TO RESPONSE	SUSTAINABILITY
MASSIN ET AL., 2010	Ranibizumab	194.2 (12 months)	1–12 months	Maintained at 12 months
JAMPOL ET AL., 2016	Bevacizumab	42 (1–2 years, baseline vision ≤20/50 + laser)	1–2 years	Diminished difference at 2 years

GLASSMAN ET AL., 2012	Ranibizumab	No mention found	24 months	No mention found
MITCHELL ET AL., 2011	Ranibizumab	118.7 (12 months)	12 months	Maintained at 12 months
WELLS ET AL., 2016A	Aflibercept	171 (2 years)	2 years	Maintained at 2 years
	Bevacizumab	126 (2 years)	2 years	Maintained at 2 years
	Ranibizumab	149 (2 years)	2 years	Maintained at 2 years
WELLS ET AL., 2016B	All	No mention found	1 year	No mention found
VADER ET AL., 2020	Bevacizumab	64.2 (6 months)	6 months	No mention found
	Ranibizumab	138.2 (6 months)	6 months	No mention found
ACT, 2015	No mention found	No mention found	1 year	No mention found
ISHIBASHI ET AL., 2015A	Ranibizumab	134.6 (12 months)	12 months	Maintained at 12 months
WELLS ET AL., 2015	No mention found	No mention found	1 year	No mention found
SINGH ET AL., 2016	No mention found	No mention found	24 months	No mention found
MUKKAMALA ET AL., 2017A	Ranibizumab	Reduced (no value)	3 years	Maintained
ISHIBASHI ET AL., 2015B	Ranibizumab	134.6 (12 months)	12 months	Maintained at 12 months
CHEN ET AL., 2020	Aflibercept	Greater reduction vs. laser	12 months	Maintained at 12 months
TOISHUBAI ET AL., 2016	Bevacizumab	124.4 (12 months)	12 months	Maintained at 12 months
VIRGILI ET AL., 2018	Ranibizumab vs. bevacizumab	29 (1 year)	1 year	No mention found
BLINDER ET AL., 2017	All	26.2–48.0% met central retinal thickness criteria	3 years	No mention found
WELLS, 2016	Aflibercept	171 (2 years)	2 years	Maintained at 2 years
	Bevacizumab	126 (2 years)	2 years	Maintained at 2 years
	Ranibizumab	149 (2 years)	2 years	Maintained at 2 years
BRESSLER ET AL., 2019	All	27.3 (African American), 22.9 (subretinal fluid)	2 years	No mention found

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ROSS ET AL., 2016	No mention found	No mention found	1 year	No mention found
BRESSLER ET AL., 2017	No mention found	No mention found	2 years	No mention found
BRESSLER ET AL., 2018	All	Persistent diabetic macular edema more with bevacizumab	2 years	Not always associated with poor best-corrected visual acuity
CHEW, 2016	No mention found	No mention found	1 year	No mention found
AREVALO ET AL., 2007	Bevacizumab	111.3 (6 months)	6 months	No mention found
MUKKAMALA ET AL., 2017B	Bevacizumab	Less effective at central retinal thickness reduction	2 years	Maintained at 2 years

Comparative Effectiveness of Different Agents

Head-to-head comparisons highlighted important differences:

• In patients with poor baseline vision (≤20/50), aflibercept was consistently superior in both BCVA and CRT outcomes, ranibizumab showed intermediate efficacy, and bevacizumab was least effective.

• In patients with better initial vision, differences among the three agents were negligible.

• By two years, the gap between aflibercept and ranibizumab narrowed, suggesting long-term treatment may equalize outcomes across agents.

From a cost perspective, bevacizumab provided the best value. While aflibercept offers superior efficacy in severe cases, its high cost may not always justify use unless clinically indicated. Consequently, bevacizumab is often recommended as a first line option, with aflibercept reserved for patients with poor starting vision or inadequate response.

Table 4: Comparative Effectiveness of AntiVEGF Agents]

Adverse Events

Study	Total Adverse Events	Serious Adverse Events	Discontinuation Due to Adverse Events	Notable Findings
Massin et al., 2010	Ocular: 80 (78.4%), Nonocular: 64 (62.7%)	Ocular serious adverse events: 4 (3.9%), Nonocular serious adverse events: 14 (13.7%)	No mention found	Endophthalmitis 2%
Jampol et al., 2016	No mention found	No mention found	Arterial thromboembolic events more with ranibizumab	Endophthalmitis (4 patients), vascular events
Glassman et al., 2012	No mention found	Endophthalmitis (4 patients), vascular events	No mention found	Arterial thromboembolic events: myocardial infarction, stroke, death
Mitchell et al., 2011	No mention found	None	No mention found	2 cases intraocular pressure increase
Wells et al., 2016a	No mention found	Deaths: 2–6%, arterial thromboembolic events: 5–12%	No mention found	Higher arterial thromboembolic events with ranibizumab
Wells et al., 2016b	None reported	None reported	None reported	
Vader et al., 2020	None reported	None reported	None reported	
Act, 2015	No mention found	No significant differences	No mention found	
Ishibashi et al., 2015a	No mention found	None reported	No mention found	Conjunctival hemorrhage, nasopharyngitis
Wells et al., 2015	None reported	None reported	None reported	
Singh et al., 2016	None reported	None reported	None reported	
Mukkamala et al., 2017a	None reported	None reported	None reported	Endophthalmitis risk, intraocular pressure with triamcinolone

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Study	Total Adverse Events	Serious Adverse Events	Discontinuation Due to Adverse Events	Notable Findings
Ishibashi et al., 2015b	No mention found	None reported	No mention found	Conjunctival hemorrhage, nasopharyngitis
Chen et al., 2020	No mention found	No mention found	No mention found	Conjunctival hemorrhage 11.8%
Toishubai et al., 2016	No mention found	None	No mention found	No serious adverse events
Virgili et al., 2018	No mention found	No difference between agents	No mention found	Systemic serious adverse events, death, thromboembolic events
Blinder et al., 2017	19 (all ocular)	No mention found	No mention found	[redacted]
Wells, 2016	No mention found	Endophthalmitis (1 per group), arterial thromboembolic events higher with ranibizumab	No mention found	[redacted]
Bressler et al., 2019	None reported	None reported	None reported	[redacted]
Ross et al., 2016	No mention found	No mention found	No mention found	[redacted]
Bressler et al., 2017	None reported	None reported	None reported	[redacted]
Bressler et al., 2018	None reported	None reported	None reported	[redacted]
Chew, 2016	None reported	None reported	None reported	[redacted]
Arevalo et al., 2007	None reported	None reported	None reported	[redacted]
Mukkamala et al., 2017b	None reported	None reported	None reported	[redacted]

Impact of Treatment Protocols

Treatment protocols significantly influenced outcomes:

- Fixed monthly dosing consistently provided robust improvements in both BCVA and CRT.

- Pro re nata (PRN, asneeded) regimens were also effective after an initial loading phase of monthly injections, though requiring careful monitoring.

- Treatandextend strategies reduced injection burden after the first year while maintaining visual outcomes comparable to fixed dosing.

Realworld evidence, however, revealed that undertreatment (fewer injections than in RCTs) often led to inferior outcomes, underscoring the importance of adherence.

Table 5: Treatment Protocols and Outcomes]

NO.	STUDY	PROTOCOL	KEY FINDINGS
1	Wells et al., 2015/2016	Monthly vs PRN	Both effective; aflibercept superior in poor baseline vision; differences less pronounced at 2 years
2	Mitchell et al., 2011 (RESTORE)	Monthly ranibizumab vs laser	Monthly dosing superior to laser; visual gain maintained
3	Chen et al., 2020 (VIVID East)	Aflibercept q4w vs q8w vs laser	Both 4w and 8w dosing effective; fewer injections with q8w
4	Singh et al., 2016	Monthly ranibizumab	Visual gains sustained through 2 years
5	Blinder et al., 2017 (ECHO, realworld)	Real-world variable dosing	Fewer injections than RCTs; lower VA gains reported

Safety and Adverse Events

Overall, antiVEGF therapies were well tolerated. Serious adverse events were rare, and dropout due to safety issues was minimal.

- Ocular events: Endophthalmitis was infrequent (0.05–0.1% per injection), and increases in intraocular pressure were usually transient. Mild conjunctival hemorrhages were occasionally reported.

- Systemic events: Arterial thromboembolic events (stroke, myocardial infarction) were monitored but occurred infrequently and without significant differences between agents. Mortality rates were low and comparable across groups.

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- Mild effects: Nasopharyngitis and transient postinjection visual disturbances were occasionally noted but were selflimited.

Only two studies reported complete adverse event counts, while others either stated none were observed or did not provide detailed data. No study was terminated for safety reasons, and no agent demonstrated a clearly worse safety profile than others.

[Table 6: Safety and Adverse Events Across Studies]

Proposed Table 6. Safety and Adverse Events

No.	Study	Adverse Events	Serious Adverse Events	Notable Findings
1	Massin et al., 2010 (RESOLVE)	Ocular AEs 78.4%, nonocular 62.7%	3.9% ocular SAE, 13.7% systemic SAE	2% endophthalmitis
2	Jampol et al., 2016 (Protocol T posthoc)	Not detailed	Arterial thromboembolic events more with ranibizumab	MI, stroke, death noted
3	Glassman et al., 2012 (RISE/RIDE)	Not detailed	4 endophthalmitis cases	Rare vascular events
4	Mitchell et al., 2011 (RESTORE)	Not reported	None	2 cases of intraocular pressure increase
5	Wells et al., 2016 (Protocol T)	Not detailed	Deaths 2–6%; arterial thromboembolic events 5–12%	Slightly higher events in ranibizumab arm
6	Ishibashi et al., 2015 (REVEAL/Asian cohorts)	Conjunctival hemorrhage, nasopharyngitis	None	Mild, selflimiting
7	Chen et al., 2020 (VIVIDEast)	Conjunctival hemorrhage (11.8%)	None	Mild only
8	Blinder et al., 2017 (ECHO)	19 ocular AEs	NR	Realworld setting
9	Other RCTs (Bressler 2017, 2018; Arevalo 2007; Toishubai 2016)	Mostly none reported	None	Endophthalmitis risk discussed but rare

Summary of Results

This systematic review and metanalysis demonstrate that antiVEGF therapy is highly effective in improving both vision and retinal morphology in diabetic macular edema.

- Effectiveness: All agents improved vision by 1–3 lines and reduced CRT significantly.
- Comparative efficacy: Aflibercept was superior in patients with poor baseline vision, while ranibizumab and bevacizumab performed well in patients with milder vision loss.
- Safety: Adverse events were rare, and no meaningful differences were observed among the agents.
- Costeffectiveness: Bevacizumab provided the best economic value, despite slightly lower efficacy in severe cases.
- Treatment burden: Flexible dosing protocols such as treatandextend effectively reduced injection frequency while maintaining outcomes.
- Realworld practice: Outcomes were slightly worse than in trials, largely due to undertreatment and followup challenges.

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Discussion

This systematic review and metaanalysis critically synthesized the comparative effectiveness, safety profiles, and clinical outcomes associated with antiVEGF agents in diabetic macular edema (DME). Through an integrated analysis of randomized controlled trials and realworld data, this section unpacks both the strengths and challenges associated with current antiVEGF regimens.

Efficacy and Visual Outcomes

The key outcome across studies was improvement in bestcorrected visual acuity (BCVA), with most agents—namely ranibizumab, aflibercept, and bevacizumab—demonstrating comparable visual gains. The extent of improvement, however, was influenced by baseline visual acuity, injection frequency, and treatment duration. Ranibizumab and aflibercept were slightly superior in patients with worse baseline vision, while bevacizumab, despite being costeffective, showed more modest visual gains in select trials [16,17]. These outcomes are congruent with prior headtohead trials like DRCR.net Protocol T [18].

Anatomical Response and CRT Reduction

Central retinal thickness (CRT) was another pivotal endpoint. Aflibercept consistently showed the most significant CRT reduction across treatmentnaïve populations. However, the association between anatomical improvement and visual gain was not always linear, suggesting that CRT alone may be insufficient as a surrogate for vision improvement [19].

Heterogeneity and Subgroup Interpretation

The studies included in this review exhibited substantial heterogeneity ($I^2 > 60\%$), likely attributable to differences in patient characteristics, baseline disease severity, and variable followup durations. Subgroup analysis suggested improved outcomes in patients receiving fixed monthly dosing protocols compared to PRN or treatandextend approaches [20].

Additionally, inconsistent definitions of outcome measures and the lack of standardized imaging protocols limited comparability across studies [21].

Safety Profiles and Adverse Events

Although antiVEGF therapies were generally welltolerated, inconsistencies in adverse event reporting posed challenges for pooled safety analysis. Rare systemic events—such as arterial thromboembolic events and hypertension—were inconsistently documented. Local complications, such as intraocular inflammation and endophthalmitis, were exceedingly rare but potentially visionthreatening [22]. The lack of standardization in safety monitoring across trials necessitates more robust pharmacovigilance frameworks in future research.

RealWorld Barriers and Adherence Challenges

While clinical trials demonstrated significant efficacy, their generalizability to routine practice is questionable due to restrictive inclusion criteria. Realworld data suggest that patients often receive fewer injections than trial protocols recommend, resulting in suboptimal outcomes [23]. Factors such as socioeconomic constraints, limited followup, and the burden of frequent intravitreal injections hinder adherence, particularly in underserved settings.

Innovations and Future Therapeutic Directions

The high burden of intravitreal injections has spurred interest in extendedrelease platforms, including biodegradable implants and port delivery systems. Gene therapy approaches (e.g., RGX314 and ADVM022) are in latephase development, aiming to provide sustained intraocular antiVEGF expression with a single administration [24,25]. Likewise, nanomedicinebased delivery systems, such as dendrimerconjugated drugs and polymeric micelles, are promising due to their ability to overcome ocular barriers and sustain drug release [26–28].

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Artificial intelligence is also revolutionizing clinical decisionmaking, offering predictive tools for treatment response and enabling tailored dosing regimens [29]. These technologies could reduce overtreatment, improve outcomes, and enhance resource allocation in busy retina clinics.

Conclusion

AntiVEGF therapies remain a cornerstone in the treatment of diabetic macular edema, offering substantial benefits in visual function and anatomical outcomes. However, frequent injection burden, variable response rates, and economic constraints continue to limit longterm success. Our metaanalysis reinforces that while all three primary agents offer meaningful efficacy, treatment durability and realworld outcomes differ.

Innovative approaches—including gene therapies, AIguided dosing, and nanocarrierbased delivery systems—promise to reshape future treatment paradigms. As the field moves toward precision medicine, incorporating biomarkers and machine learning tools could enable better stratification of responders and nonresponders. Importantly, longterm safety, patientreported outcomes, and costeffectiveness analyses must guide future research and policy decisions.

To realize a sustainable future for DME management, future trials must prioritize standardized methodology, inclusive patient populations, and longterm followup. Only then can clinicians and policymakers establish evidencebased strategies that maximize vision preservation while minimizing treatment burden and economic impact.

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Conflict of Interest Statement

The authors declare that they have **no conflict of interest** related to this work. No financial, personal, or professional relationships influenced the design, conduct, analysis, or reporting of this study.

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- K.K. (Khadeiga Kononna) and A.E. (Amna Elbasheer): Co–First Authors. Both equally led the conceptualization and overall development of the study. They jointly designed the research framework, supervised the methodology, coordinated project execution, and contributed substantially to writing and critical revision of the manuscript.
- R.M. (Rofida Mohammed): Developed the study methodology, designed data collection tools, and carried out an extensive literature review. She contributed to the comparative analysis, drafted major sections of the manuscript, and ensured compliance with journal guidelines.
- S.M. (Sally Muhamed): Provided statistical expertise, conducted data analysis, and prepared tables, figures, and visual representations. She also reviewed the manuscript for technical accuracy, clarity, and analytical soundness.
- A.Y. (Abla Yousif): Performed a critical review of the manuscript for scientific accuracy and intellectual integrity. She contributed to interpretation of findings, ensured relevance of the conclusions, conducted final editing, and approved the version submitted for publication.

Chicago Citation Style
Khadeiga Kononna, Amna Elbasheer ,Rofida Mohammed, , Sally Muhamed, and Abla Yousif. Anti-VEGF Therapy for Diabetic Macular Edema: A Systematic Review and Meta-Analysis. La Presse Médicale – EMR (LAPMED) 6, no. 5 (2025): 121–152.