International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	SWITCHING BETWEEN ANTI-VEGF AGENTS IN DIABETIC MACULAR EDEMA: A NARRATIVE REVIEW OF EVIDENCE AND CLINICAL PRACTICE
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5576
RECEIVED	15 April 2026
ACCEPTED	27 June 2026
PUBLISHED	30 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

SWITCHING BETWEEN ANTI-VEGF AGENTS IN DIABETIC MACULAR EDEMA: A NARRATIVE REVIEW OF EVIDENCE AND CLINICAL PRACTICE

Rami Mallah *(Corresponding Author, Email: rami.mallah@outlook.com)*
Hospital of Saint Vincent a Paulo, Gdynia, Poland
ORCID ID: 0009-0001-1184-5557

Alia Echtay Yarbou
Lazarski University, Warsaw, Mazovia, Poland
ORCID ID: 0009-0005-9146-4680

Dominika Julia Kozdroń
University Clinical Centre in Gdańsk, Poland
ORCID ID: 0009-0007-3089-3582

Michalina Weronika Nieścioruk
7th Navy Hospital, Polanki 117, 80-305 Gdańsk, Poland
ORCID ID: 0009-0000-4769-0350

Paulina Szczepańska
Masovian Dental Center, Nowy Zjazd 1, 00-301 Warsaw, Poland
ORCID ID: 0009-0006-5494-0550

Jacek Kowalski
University Clinical Centre in Gdańsk, Poland
ORCID ID: 0009-0000-9524-3061

Dominika Dutkiewicz
Independent Public Health Care Centre of the Ministry of the Interior and Administration in Gdańsk, Poland
ORCID ID: 0009-0006-2035-8079

Adrian Mikołajuk
Nowy Chełm Medical Clinic, Poland
ORCID ID: 0009-0001-6494-2932

ABSTRACT

Background: Diabetic macular edema (DME) is a leading cause of vision impairment among patients with diabetic retinopathy. Intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy has become the first-line treatment; however, a significant proportion of patients demonstrate suboptimal response or require frequent injections, highlighting the need for alternative therapeutic strategies.
Objective: To review the rationale, clinical evidence, and outcomes associated with switching between anti-VEGF agents in the management of DME, with a focus on real-world data and emerging therapies.
Methods: A narrative review of the literature was conducted, including randomized controlled trials, observational studies, and meta-analyses evaluating anti-VEGF therapy and switching strategies in DME. Particular attention was given to studies assessing treatment response, predictors of outcomes, and newer agents such as faricimab.
Results: Evidence suggests that a substantial proportion of patients exhibit incomplete anatomical or functional response to initial anti-VEGF therapy. Switching between agents, particularly from ranibizumab or bevacizumab to aflibercept, has been associated with improvements in retinal thickness and stabilization or modest gains in visual acuity. The introduction of faricimab, a dual inhibitor of VEGF-A and angiopoietin-2, has demonstrated comparable efficacy to aflibercept with extended dosing intervals in phase 3 trials and promising real-world outcomes. Meta-analyses confirm overall effectiveness of anti-VEGF therapy while highlighting variability in individual response.
Conclusion: Switching between anti-VEGF agents represents a practical and evidence-based strategy in patients with DME who demonstrate suboptimal response to initial therapy. Emerging treatments such as faricimab further expand therapeutic options and may reduce treatment burden. Individualized treatment approaches and timely therapy modification are essential for optimizing long-term outcomes.

KEYWORDS

Diabetic Macular Edema, Anti-VEGF Therapy, Switching Therapy, Aflibercept, Ranibizumab, Faricimab, Intravitreal Injections

CITATION

Rami Mallah, Alia Echtay Yarbou, Dominika Julia Kozdroń, Michalina Weronika Nieścioruk, Paulina Szczepańska, Jacek Kowalski, Dominika Dutkiewicz, Adrian Mikołajuk. (2026) Switching Between Anti-VEGF Agents in Diabetic Macular Edema: a Narrative Review of Evidence and Clinical Practice. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5576

1. Introduction

Diabetic retinopathy (DR) remains one of the leading causes of visual impairment worldwide, particularly among working-age adults. Among its complications, diabetic macular edema (DME) represents a major cause of central vision loss and reduced quality of life. The increasing global prevalence of diabetes has led to a corresponding rise in the burden of DME, making its effective management a critical component of modern ophthalmic care [10,11,13]. Over the past two decades, significant advances in pharmacologic therapy have transformed the treatment landscape, with intravitreal anti–vascular endothelial growth factor (anti-VEGF) agents becoming the standard of care.

VEGF plays a central role in the pathophysiology of DME by promoting increased vascular permeability, breakdown of the blood–retinal barrier, and accumulation of intraretinal fluid. Targeting this pathway has been shown to significantly improve both anatomical and functional outcomes in patients with DME [10,13]. Large randomized clinical trials, such as the Diabetic Retinopathy Clinical Research Network Protocol T study, demonstrated that anti-VEGF agents—including aflibercept, bevacizumab, and ranibizumab—can lead to meaningful improvements in visual acuity and retinal thickness [1]. These findings established anti-VEGF therapy as the first-line treatment for center-involving DME and have been widely adopted in clinical practice.

Despite these advances, a substantial proportion of patients do not achieve optimal outcomes with initial anti-VEGF therapy. Persistent macular edema and incomplete visual recovery remain common challenges, even with regular treatment. Secondary analyses of clinical trials have shown that a significant number of

patients continue to exhibit residual retinal thickening despite ongoing therapy [2]. Furthermore, real-world studies suggest that treatment outcomes in routine clinical practice may be less favorable than those observed in controlled trial settings, often due to factors such as undertreatment, poor adherence, and variability in clinical decision-making [4,6].

The variability in treatment response has led to increasing interest in identifying predictors of therapeutic success and failure. Clinical and imaging-based factors, including baseline visual acuity, retinal thickness, and specific optical coherence tomography (OCT) features, have been associated with differential responses to anti-VEGF therapy [8]. Understanding these predictors is essential for optimizing treatment strategies and improving patient outcomes. However, even with careful patient selection, a subset of individuals continues to demonstrate suboptimal or inadequate responses.

In this context, switching between anti-VEGF agents has emerged as a potential strategy to address treatment resistance or insufficient response. Differences in molecular structure, binding affinity, and pharmacokinetics among available agents may contribute to variability in clinical efficacy. For example, aflibercept has been shown to have a higher binding affinity for VEGF compared to other agents, which may translate into improved outcomes in certain patient populations [9]. Additionally, the development of newer therapies, such as faricimab—which targets both VEGF and angiopoietin-2 pathways—has introduced new possibilities for patients who do not respond adequately to conventional anti-VEGF monotherapy [15–17].

Recent clinical trials and real-world studies have provided growing evidence supporting the role of switching strategies in the management of DME. Multicenter studies have demonstrated that switching from one anti-VEGF agent to another can result in anatomical and, in some cases, functional improvement in patients with persistent disease [5]. Moreover, advances in treatment approaches, including treat-and-extend regimens and individualized therapy based on disease activity, have further emphasized the importance of flexible and patient-specific management strategies [16,17].

Given the expanding range of therapeutic options and the complexity of treatment decision-making, there is a need for a comprehensive evaluation of the evidence supporting switching between anti-VEGF agents. This is particularly relevant in the era of emerging therapies and increasing emphasis on personalized medicine.

The aim of this narrative review is to summarize current evidence on the rationale, effectiveness, and clinical implications of switching between anti-VEGF agents in the management of diabetic retinopathy and diabetic macular edema. Particular attention is given to real-world outcomes, emerging therapies, and factors that may guide individualized treatment strategies.

2. Anti-VEGF Therapy Overview

The introduction of intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the management of diabetic macular edema (DME). By directly targeting one of the key mediators of vascular permeability and angiogenesis, these agents have significantly improved both visual and anatomical outcomes compared to previous treatment modalities such as laser photocoagulation [10,13]. Anti-VEGF therapy is now widely regarded as the first-line treatment for center-involving DME and is used extensively in both clinical trials and routine practice.

VEGF is a critical factor in the development of DME. Chronic hyperglycemia leads to microvascular damage, resulting in increased expression of VEGF within the retina. This, in turn, promotes disruption of the blood–retinal barrier, increased vascular permeability, and accumulation of extracellular fluid in the macula [10]. By inhibiting VEGF activity, anti-VEGF agents reduce retinal edema and help restore normal retinal architecture, which is associated with improved visual acuity outcomes.

Several anti-VEGF agents are currently used in clinical practice, including ranibizumab, aflibercept, and bevacizumab. Although these drugs share a common mechanism of action, they differ in molecular structure, binding affinity, and pharmacokinetic properties, which may influence their clinical effectiveness. Ranibizumab is a monoclonal antibody fragment specifically designed for intraocular use, while bevacizumab is a full-length antibody originally developed for systemic oncology indications and commonly used off-label in ophthalmology. Aflibercept is a fusion protein that acts as a decoy receptor for VEGF, with high binding affinity and a longer duration of action compared to other agents [10,11].

Comparative studies have demonstrated differences in efficacy among these agents, particularly in specific patient subgroups. The Protocol T trial showed that aflibercept may provide greater visual acuity gains in patients with worse baseline vision compared to ranibizumab and bevacizumab, although outcomes were more similar in patients with milder vision loss [1]. These findings highlight the importance of individualized treatment selection based on baseline characteristics and disease severity.

Despite the proven efficacy of anti-VEGF therapy in controlled clinical trials, real-world outcomes often differ. Studies have shown that patients in routine clinical practice tend to receive fewer injections and less frequent monitoring compared to those enrolled in clinical trials, which may lead to suboptimal outcomes [4,6]. Treatment burden, including the need for repeated intravitreal injections and frequent follow-up visits, represents a significant challenge for both patients and healthcare systems. This has led to the development of alternative dosing strategies, such as treat-and-extend regimens, which aim to maintain efficacy while reducing the frequency of injections.

In addition to the established anti-VEGF agents, newer therapies have been developed to address limitations of existing treatments. Faricimab is a bispecific antibody that targets both VEGF-A and angiopoietin-2 (Ang-2), offering a dual mechanism of action that may provide enhanced vascular stability and longer durability of effect [15,16]. Phase 3 clinical trials, including the YOSEMITE and RHINE studies, demonstrated that faricimab can achieve visual and anatomical outcomes comparable to aflibercept, with the potential for extended dosing intervals of up to 16 weeks in a significant proportion of patients [16,17]. This represents an important advancement in reducing treatment burden while maintaining therapeutic effectiveness.

Overall, anti-VEGF therapy remains the cornerstone of DME management. However, differences between agents, variability in patient response, and the challenges associated with long-term treatment highlight the need for individualized therapeutic approaches. Understanding the characteristics and limitations of each anti-VEGF agent is essential for optimizing treatment strategies and provides the foundation for considering alternative approaches, including switching between therapies when clinical response is inadequate.

3. Limitations of Anti-VEGF Therapy

Despite the significant advances achieved with anti-VEGF therapy, several limitations remain in the management of diabetic macular edema (DME). While many patients experience meaningful improvements in visual acuity and retinal morphology, a substantial proportion demonstrate incomplete or suboptimal responses. These limitations represent a major challenge in clinical practice and are a primary reason for considering alternative strategies, including switching between therapeutic agents.

One of the most important limitations is the presence of non-responders or partial responders. Clinical studies have shown that not all patients achieve the expected anatomical or functional improvement following anti-VEGF treatment. In particular, persistent macular edema remains a common finding even after multiple injections. Secondary analyses of randomized trials have demonstrated that a considerable number of patients continue to exhibit retinal thickening despite ongoing therapy, highlighting the variability in treatment response [2]. This incomplete response may be due to multiple factors, including chronic structural changes in the retina, alternative pathogenic pathways, or differences in individual pharmacologic sensitivity.

In addition to biological variability, patient-specific factors play a significant role in determining treatment outcomes. Predictive factors such as baseline visual acuity, duration of disease, and optical coherence tomography (OCT) features have been associated with differential responses to anti-VEGF therapy [8]. For example, the presence of chronic edema, disorganization of retinal inner layers, or certain inflammatory components may reduce the likelihood of a favorable response. These findings emphasize that DME is a heterogeneous condition and that a single therapeutic approach may not be effective for all patients.

Another major limitation of anti-VEGF therapy is the high treatment burden associated with repeated intravitreal injections. Standard treatment regimens often require monthly or frequent injections, particularly during the initial phases of therapy. This can be challenging for patients, especially those with comorbidities or limited access to healthcare. In real-world settings, patients frequently receive fewer injections than recommended in clinical trials, which may lead to suboptimal visual outcomes [4,6]. Factors such as poor adherence, missed appointments, and logistical barriers further contribute to this gap between clinical trial efficacy and real-world effectiveness.

Moreover, long-term treatment raises concerns regarding sustainability and patient compliance. Chronic diseases such as DME require ongoing management, and the need for repeated intravitreal injections can lead to treatment fatigue over time. This may result in decreased adherence and discontinuation of therapy, ultimately affecting visual outcomes. In addition, the cumulative burden on healthcare systems, including clinic capacity and resource allocation, represents an important consideration in the widespread use of anti-VEGF therapy.

Another limitation is that VEGF inhibition alone may not fully address the complex pathophysiology of DME. Although VEGF plays a central role, other pathways—including inflammatory mediators and

angiopoietin signaling—also contribute to disease progression. This may explain why some patients do not respond adequately to VEGF-targeted therapy alone. The recognition of these alternative mechanisms has led to the development of newer therapeutic agents with dual or multi-target approaches, aiming to improve outcomes in patients with refractory disease [15,16].

Finally, safety considerations, although generally favorable, should not be overlooked. Intravitreal injections carry a small risk of complications, including endophthalmitis, intraocular inflammation, and transient increases in intraocular pressure. While these events are relatively rare, they may influence treatment decisions, particularly in patients requiring long-term therapy.

Taken together, these limitations highlight the challenges associated with anti-VEGF therapy in the management of DME. Variability in treatment response, persistent disease activity, high treatment burden, and the complexity of underlying pathophysiology all contribute to suboptimal outcomes in a subset of patients. These factors underscore the need for more individualized treatment approaches and provide a strong rationale for considering alternative strategies, including switching between anti-VEGF agents.

4. Rationale for Switching Anti-VEGF Therapy

Given the limitations of anti-VEGF therapy, particularly in patients with persistent or suboptimal response, switching between anti-VEGF agents has emerged as a clinically relevant strategy in the management of diabetic macular edema (DME). The rationale for switching is based on both biological and pharmacological considerations, as well as practical clinical experience.

A key reason for switching therapy is the presence of an inadequate response to initial treatment. Although anti-VEGF agents share a common target, individual patients may respond differently to specific drugs. In clinical practice, suboptimal response is often defined by persistent intraretinal or subretinal fluid on optical coherence tomography (OCT), limited improvement in visual acuity, or the need for frequent injections without sustained benefit. Studies have demonstrated that a proportion of patients continue to show signs of active disease despite regular treatment, supporting the need for alternative therapeutic approaches [2,8].

The biological basis for switching may be related to differences in the molecular structure and pharmacodynamics of available anti-VEGF agents. For example, aflibercept has a higher binding affinity for VEGF compared to ranibizumab and bevacizumab, which may result in more effective suppression of VEGF activity in certain cases [9]. Additionally, variations in molecular size and intraocular half-life may influence drug penetration, duration of action, and overall therapeutic response. These differences suggest that patients who do not respond adequately to one agent may still benefit from another within the same class.

Another important consideration is the potential role of alternative pathogenic pathways in DME. While VEGF is a central mediator, it is not the only factor involved in disease progression. Inflammation, angiopoietin signaling, and other molecular mechanisms contribute to vascular instability and fluid accumulation. In cases where VEGF inhibition alone is insufficient, switching to an agent with a broader mechanism of action may provide additional benefit. The introduction of faricimab, which targets both VEGF-A and angiopoietin-2, represents a significant development in this regard [15–17]. This dual-target approach may help address some of the limitations observed with conventional anti-VEGF monotherapy.

Clinical evidence also supports the rationale for switching. Real-world studies and multicenter analyses have shown that patients with inadequate response to one anti-VEGF agent may experience anatomical improvement, and in some cases visual gain, after switching to another agent [5]. These findings suggest that switching is not merely a theoretical concept, but a practical strategy that can be applied in routine clinical care. Furthermore, variability in treatment response highlights the importance of ongoing assessment and flexibility in management decisions.

In addition to improving efficacy, switching may also play a role in optimizing treatment burden. Some agents offer longer duration of action or allow for extended dosing intervals, which can reduce the frequency of injections and follow-up visits. This is particularly relevant in the context of chronic diseases such as DME, where long-term adherence to treatment is essential. Strategies such as treat-and-extend regimens and individualized dosing schedules further support the use of flexible therapeutic approaches tailored to patient response [16,17].

The decision to switch therapy is typically based on a combination of anatomical and functional criteria. OCT imaging plays a central role in assessing treatment response, allowing clinicians to evaluate changes in retinal thickness and fluid distribution. Functional outcomes, including visual acuity, are also important but may lag behind anatomical improvements. Therefore, a comprehensive assessment of both structural and functional parameters is necessary when considering a change in therapy.

Despite its potential benefits, switching is not without challenges. There is currently no universally accepted definition of treatment failure or standardized protocol for when to switch between agents. Clinical decisions are often based on physician experience and individual patient characteristics. This variability underscores the need for further research to establish clear guidelines and optimize treatment strategies.

In summary, switching between anti-VEGF agents represents a rational and clinically relevant approach in the management of DME, particularly in patients with inadequate response to initial therapy. Differences in drug properties, the complex pathophysiology of the disease, and real-world treatment challenges all support the use of switching as part of an individualized treatment strategy. This approach forms the basis for evaluating the available evidence on outcomes following switching, which is discussed in the following section.

5. Evidence for Switching Between Anti-VEGF Agents

The rationale for switching between anti-VEGF agents in diabetic macular edema (DME) is supported by an increasing body of clinical evidence, including randomized trials, observational studies, and real-world data. These studies suggest that patients with an inadequate response to one anti-VEGF agent may experience anatomical improvement, and in some cases functional benefit, after switching to an alternative therapy.

One of the most relevant sources of evidence comes from real-world and multicenter studies. A large multicenter analysis by Kucukevcilioglu et al. evaluated long-term outcomes in patients treated with ranibizumab, aflibercept, or a combination of both through switching. The study demonstrated that patients who were switched between agents, particularly from ranibizumab to aflibercept, showed significant reductions in central retinal thickness and stabilization or improvement in visual acuity over a 24-month period [5]. These findings support the clinical utility of switching in patients with persistent disease activity.

Similarly, real-world observational studies have highlighted the variability in treatment response and the potential benefits of adapting therapy. Data from clinical practice indicate that many patients do not achieve the same outcomes as those reported in clinical trials, often due to undertreatment or inconsistent follow-up [4,6]. In this context, switching therapy may help optimize outcomes by identifying the most effective agent for a given patient. A systematic review of real-world evidence in Asian populations also demonstrated that treatment patterns and responses vary widely, further emphasizing the need for individualized approaches, including switching strategies [7].

The effectiveness of switching is also supported by studies examining predictive factors of treatment response. Patients with certain baseline characteristics or imaging features may be less likely to respond to a specific anti-VEGF agent, but may still benefit from an alternative therapy [8]. This reinforces the concept that treatment resistance is not absolute, but may be agent-specific.

In addition to switching between conventional anti-VEGF agents, the introduction of newer therapies has expanded the available options for patients with refractory DME. Faricimab, a bispecific antibody targeting both VEGF-A and angiopoietin-2, has been evaluated in large phase 3 clinical trials. The YOSEMITE and RHINE studies demonstrated that faricimab provides visual and anatomical outcomes comparable to aflibercept, with the added advantage of extended dosing intervals in a substantial proportion of patients [16,17]. These results suggest that switching to a therapy with a different mechanism of action may be particularly beneficial in patients who do not respond adequately to traditional anti-VEGF agents.

Emerging real-world data further support the role of switching to newer therapies. Studies evaluating faricimab in routine clinical practice have reported improvements in retinal thickness and visual outcomes in both treatment-naïve and previously treated eyes [19–22]. These findings are particularly relevant for patients who have received multiple prior anti-VEGF injections with limited success, as they suggest that alternative mechanisms of action may overcome resistance to conventional therapy.

It is also important to note that while anatomical improvements are commonly observed following switching, functional outcomes such as visual acuity may be more variable. Some studies report modest visual gains, while others demonstrate stabilization rather than significant improvement. This may be due to irreversible retinal damage in chronic cases, highlighting the importance of early identification of suboptimal response and timely modification of treatment.

Overall, the available evidence supports the use of switching between anti-VEGF agents as a practical and effective strategy in the management of DME. Although the degree of benefit may vary depending on patient characteristics and disease duration, switching can lead to meaningful anatomical improvements and may help optimize long-term outcomes. These findings reinforce the importance of individualized treatment strategies and provide a strong foundation for the incorporation of newer therapies and personalized approaches, which are discussed in the following sections.

Key studies evaluating switching strategies and outcomes in diabetic macular edema are summarized in Table 1.

Table 1. Summary of Key Studies on Switching Anti-VEGF Therapy in Diabetic Macular Edema

Study (Ref)	Study Type	Population	Switch Strategy	Main Findings
Wells et al. [1]	RCT (Protocol T)	DME patients	Comparison (no switch)	Aflibercept superior in worse baseline VA
Bressler et al. [2]	Secondary analysis (RCT)	Persistent DME	Continued same therapy	Persistent edema common despite treatment
Kucukevcilioglu et al. [5]	Real-world multicenter	DME	Ranibizumab → Aflibercept	Improved CRT and VA stabilization
Gurung et al. [8]	Observational	DME	Predictive factors	Response varies based on baseline features
Hussain & Ciulla [9]	Review	Refractory DME	Switching + combination	Switching recommended in non-responders
Sam-Oyerinde et al. [6]	Real-world review	DME	Variable	Undertreatment affects outcomes
Yuen et al. [7]	Systematic review	Asian population	Real-world anti-VEGF	Variable response supports individualization
Wykoff et al. [16]	Phase 3 RCT	DME	Faricimab vs Aflibercept	Non-inferior efficacy, longer durability
Wong et al. [17]	Phase 3 (2-year)	DME	Treat-and-extend	Sustained outcomes with longer intervals
Shimura et al. [18]	Subgroup analysis	DME (Japan)	Faricimab	Consistent efficacy across populations
Khetan et al. [19]	Real-world	DME	Switch to Faricimab	Improved anatomical outcomes
Esteban-Floría et al. [20]	Real-world	Naïve + switch patients	Faricimab	Effective in both groups
Hirakata et al. [21]	Real-world short-term	DME	Faricimab	Early anatomical improvement
Peto et al. [22]	Real-world UK	DME	Faricimab	Reduced treatment burden
Westborg et al. [23]	Cross-sectional	DME	Eligibility for switch	Many patients suitable for switching

Study (Ref)	Study Type	Population	Switch Strategy	Main Findings
Sydnor et al. [27]	Meta-analysis	DME	Multiple agents	All effective, differences exist
Watkins et al. [28]	Network meta-analysis	DME	Focus on Faricimab	Comparable efficacy, longer durability
Nichani et al. [29]	Meta-analysis	Retinal diseases	Faricimab	Safe and effective
Dhoot et al. [31]	RCT analysis	DME	Aflibercept	Functional improvement
Singer et al. [30]	RCT analysis	DME	Ranibizumab	Predictors of response

Abbreviations:
DME – diabetic macular edema; VA – visual acuity; CRT – central retinal thickness; RCT – randomized controlled trial.

6. Emerging Therapies and the Role of Faricimab

The development of newer therapeutic agents has significantly expanded the treatment landscape for diabetic macular edema (DME), particularly in patients with suboptimal response to conventional anti-VEGF therapy. Among these, faricimab represents a major advancement due to its dual mechanism of action, targeting both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2). This approach addresses multiple pathways involved in the pathophysiology of DME and may provide improved vascular stability and longer-lasting therapeutic effects [15,16].

Unlike traditional anti-VEGF agents that focus solely on VEGF inhibition, faricimab simultaneously modulates the Ang/Tie2 signaling pathway. Angiopoietin-2 plays a role in vascular destabilization and inflammation, contributing to increased vascular permeability and disease progression. By inhibiting both VEGF-A and Ang-2, faricimab offers a broader therapeutic approach, which may be particularly beneficial in patients who do not respond adequately to single-pathway inhibition [15,16].

The efficacy and safety of faricimab have been evaluated in large phase 3 clinical trials, including the YOSEMITE and RHINE studies. These randomized, double-masked trials demonstrated that faricimab provides visual acuity gains and reductions in central retinal thickness comparable to aflibercept, a widely used anti-VEGF agent [16]. Importantly, a significant proportion of patients treated with faricimab were able to achieve extended dosing intervals of up to 12 or 16 weeks while maintaining disease control [16,17]. This represents a meaningful reduction in treatment burden and is a key advantage in long-term disease management.

Longer-term data further support the durability of faricimab. Two-year results from the YOSEMITE and RHINE trials confirmed sustained efficacy and safety, with continued visual and anatomical benefits and consistent dosing intervals in many patients [17]. Subgroup analyses have also demonstrated that these outcomes are reproducible across different populations, including regional cohorts, suggesting broad applicability in clinical practice [18].

In addition to randomized trial data, real-world studies provide valuable insights into the effectiveness of faricimab in routine clinical settings. Several recent studies have evaluated its use in both treatment-naïve patients and those previously treated with other anti-VEGF agents. These studies report improvements in retinal thickness and stabilization or modest gains in visual acuity following initiation of faricimab therapy [19–21]. Importantly, patients who had previously demonstrated inadequate response to other anti-VEGF agents also showed favorable anatomical responses after switching to faricimab, supporting its role as an alternative option in refractory cases.

Real-world evidence also highlights the potential of faricimab to reduce treatment burden. Studies have shown that many patients can be managed with fewer injections and longer intervals between treatments compared to traditional anti-VEGF regimens [22]. This is particularly relevant in clinical practice, where adherence to frequent injection schedules can be challenging. The ability to maintain disease control with fewer visits may improve patient compliance and overall treatment outcomes.

Another important aspect is patient selection. Not all patients may require switching to newer agents, and the decision should be based on individual response and disease characteristics. However, the availability of therapies such as faricimab provides clinicians with additional flexibility in managing complex or refractory cases. Furthermore, real-world analyses suggest that a substantial proportion of patients currently treated with conventional anti-VEGF agents may be eligible for switching to faricimab based on clinical criteria [23].

Overall, emerging therapies such as faricimab represent an important step forward in the management of DME. By targeting multiple pathways and offering extended dosing intervals, these agents address some of the key limitations of traditional anti-VEGF therapy. Their role is particularly relevant in the context of switching strategies, where they provide an effective alternative for patients with inadequate response or high treatment burden. As more real-world data become available, the integration of these therapies into individualized treatment algorithms is likely to play an increasingly important role in optimizing patient outcomes.

7. Comparative Evidence and Meta-Analyses

In addition to individual clinical trials and real-world studies, comparative analyses and meta-analyses provide a broader perspective on the relative efficacy and safety of different anti-VEGF agents in diabetic macular edema (DME). These studies are particularly valuable in the context of switching strategies, as they synthesize data across multiple trials and patient populations, helping to identify consistent patterns of response.

Several systematic reviews and network meta-analyses have compared the efficacy of commonly used anti-VEGF agents, including ranibizumab, aflibercept, bevacizumab, and more recently, newer agents such as faricimab. Overall, these analyses confirm that anti-VEGF therapy is effective in improving both visual acuity and anatomical outcomes in DME, although differences between agents may exist depending on baseline patient characteristics and study design [27,28].

A network meta-analysis by Sydnor et al. evaluated the comparative efficacy and safety of multiple anti-VEGF agents and demonstrated that while all agents provide significant benefit, certain drugs may offer advantages in specific clinical scenarios, such as greater visual gains or improved anatomical outcomes [27]. These findings support the concept that treatment selection should be individualized and that switching between agents may be appropriate when optimal outcomes are not achieved.

Similarly, a systematic review and network meta-analysis by Watkins et al. focused on faricimab and demonstrated comparable efficacy to established anti-VEGF agents, with the added benefit of increased durability and extended dosing intervals [28]. This reinforces the potential role of faricimab not only as a first-line therapy but also as an alternative in patients requiring a switch due to inadequate response or treatment burden.

Meta-analyses evaluating the broader use of faricimab across multiple retinal diseases, including DME, further support its safety and efficacy profile. Nichani et al. reported that faricimab is associated with significant improvements in both visual and anatomical outcomes, with a safety profile comparable to other anti-VEGF agents [29]. These findings are consistent with those observed in randomized trials and real-world studies, strengthening the evidence base for its use in clinical practice.

Importantly, comparative studies also highlight that differences between agents are often modest, and that patient-specific factors play a major role in determining outcomes. This variability reinforces the importance of ongoing monitoring and the flexibility to modify treatment strategies, including switching between agents when necessary. Rather than a one-size-fits-all approach, the management of DME increasingly relies on personalized treatment algorithms that take into account both clinical response and patient preferences.

Overall, evidence from meta-analyses supports the effectiveness of anti-VEGF therapy while emphasizing the nuanced differences between agents. These findings provide further justification for switching strategies in selected patients and underscore the importance of individualized treatment approaches in optimizing outcomes in DME.

8. Clinical Implications

The findings presented in this review have important implications for clinical practice in the management of diabetic macular edema (DME). While anti-VEGF therapy remains the cornerstone of treatment, the variability in patient response highlights the need for a more individualized approach to care.

One of the key clinical considerations is the early identification of suboptimal responders. Persistent macular edema, limited visual acuity improvement, or the need for frequent injections without sustained

benefit should prompt clinicians to reassess the treatment strategy. Evidence suggests that continuing the same therapy in the presence of inadequate response may lead to prolonged disease activity and potentially irreversible retinal damage [2,8]. Therefore, timely modification of treatment, including switching between anti-VEGF agents, is essential for optimizing outcomes.

Switching therapy should be considered as part of a structured, patient-centered approach. Although there is no universally accepted definition of treatment failure, many clinicians rely on a combination of anatomical and functional criteria, including OCT findings and visual acuity changes. Regular monitoring with imaging plays a crucial role in guiding these decisions and allows for early detection of persistent or recurrent disease activity.

The availability of multiple anti-VEGF agents provides flexibility in treatment selection. Differences in pharmacologic properties and mechanisms of action support the rationale for switching in selected patients. In particular, newer agents such as faricimab offer additional therapeutic options, especially in cases where conventional anti-VEGF therapy has been insufficient [15–17]. The potential for extended dosing intervals also makes these agents attractive in reducing treatment burden.

Treatment burden remains a significant challenge in the long-term management of DME. Frequent intravitreal injections and clinic visits can negatively impact patient adherence and overall outcomes. Real-world studies have consistently shown that patients often receive fewer injections than recommended in clinical trials, leading to suboptimal results [4,6]. Strategies that reduce injection frequency while maintaining efficacy, including treat-and-extend regimens and the use of longer-acting agents, are therefore highly relevant in clinical practice.

In addition, patient-specific factors must be considered when making treatment decisions. Comorbidities, access to healthcare, socioeconomic factors, and patient preferences all influence adherence and outcomes. In certain populations, such as those in low- and middle-income settings, barriers to care may further complicate treatment delivery, making flexible and individualized approaches even more important [6].

Overall, switching between anti-VEGF agents represents a practical and evidence-based strategy that can be integrated into routine clinical care. By tailoring treatment to individual patient response and leveraging newer therapeutic options, clinicians can improve both anatomical and functional outcomes while addressing the challenges associated with long-term disease management.

9. Limitations of Available Evidence

Despite the growing body of literature supporting switching strategies in DME, several limitations should be acknowledged. First, a significant proportion of the available evidence is derived from retrospective studies and real-world analyses, which may be subject to selection bias and variability in treatment protocols. Unlike randomized controlled trials, these studies often lack standardized criteria for defining treatment response and switching.

Second, there is considerable heterogeneity in study design, patient populations, and outcome measures across the literature. Differences in baseline characteristics, duration of disease, prior treatments, and follow-up periods make direct comparisons between studies challenging. This variability limits the ability to draw definitive conclusions regarding the optimal timing and criteria for switching therapy.

Another important limitation is the lack of consensus on the definition of treatment failure or inadequate response. In clinical practice, decisions to switch therapy are often based on physician judgment rather than standardized guidelines. This highlights the need for more clearly defined criteria to guide clinical decision-making and improve consistency across studies.

Furthermore, while newer agents such as faricimab have shown promising results, long-term real-world data remain limited. Although clinical trials provide robust evidence of efficacy and safety, their controlled environments may not fully reflect routine clinical practice. Ongoing studies and post-marketing data will be essential to better understand the long-term outcomes and safety profiles of these therapies.

Finally, functional outcomes such as visual acuity do not always correlate directly with anatomical improvements. In patients with chronic DME, irreversible retinal damage may limit the potential for visual recovery, even when anatomical resolution is achieved. This underscores the importance of early intervention and timely modification of treatment strategies.

10. Conclusions

Anti-VEGF therapy has transformed the management of diabetic macular edema, providing significant improvements in visual and anatomical outcomes. However, a substantial proportion of patients exhibit incomplete or suboptimal responses, highlighting the need for alternative treatment strategies.

Switching between anti-VEGF agents represents a rational and clinically relevant approach in patients with inadequate response to initial therapy. Differences in pharmacologic properties, mechanisms of action, and individual patient characteristics support the use of switching as part of an individualized treatment strategy. Evidence from clinical trials, real-world studies, and meta-analyses demonstrates that switching can lead to meaningful anatomical improvements and may help optimize long-term outcomes.

The emergence of newer therapies, particularly faricimab, has further expanded the therapeutic landscape by offering dual-pathway inhibition and extended dosing intervals. These advances provide additional options for patients with refractory disease and may help address some of the limitations associated with traditional anti-VEGF therapy.

Despite these advances, important challenges remain, including variability in treatment response, high treatment burden, and the lack of standardized guidelines for switching. Future research should focus on identifying predictive biomarkers, establishing clear criteria for treatment modification, and evaluating long-term outcomes in real-world settings.

In conclusion, the management of DME is evolving toward a more personalized approach, in which treatment decisions are guided by individual patient response and disease characteristics. Within this framework, switching between anti-VEGF agents plays a key role in optimizing therapeutic outcomes and improving patient care.

REFERENCES

1. Wells, J. A., Glassman, A. R., Ayala, A. R., Jampol, L. M., Bressler, N. M., Bressler, S. B., Brucker, A. J., Ferris, F. L., Hampton, G. R., Jhaveri, C., Melia, M., Beck, R. W., & Diabetic Retinopathy Clinical Research Network. (2016). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology, 123*(6), 1351–1359. https://doi.org/10.1016/j.ophtha.2016.02.022
2. Bressler, N. M., Beaulieu, W. T., Glassman, A. R., Blinder, K. J., Bressler, S. B., Jampol, L. M., Melia, M., Wells, J. A., III, & Diabetic Retinopathy Clinical Research Network. (2018). Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: A secondary analysis of a randomized clinical trial. *JAMA Ophthalmology, 136*(3), 257–269. https://doi.org/10.1001/jamaophthalmol.2017.6565
3. Campochiaro, P. A., Brown, D. M., Pearson, A., Ciulla, T., Boyer, D., Holz, F. G., Tolentino, M., Gupta, A., Duarte, L., Madreperla, S., Gonder, J., Kapik, B., Billman, K., Kane, F. E., & FAME Study Group. (2011). Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology, 118*(4), 626–635.e2. https://doi.org/10.1016/j.ophtha.2010.12.028
4. Blinder, K. J., Dugel, P. U., Chen, S., Jumper, J. M., Walt, J. G., Hollander, D. A., & Scott, L. C. (2017). Anti-VEGF treatment of diabetic macular edema in clinical practice: Effectiveness and patterns of use (ECHO Study Report 1). *Clinical Ophthalmology, 11*, 393–401. https://doi.org/10.2147/OPTH.S128509
5. Kucukevcilioglu, M., Yeşiltaş, Y. S., Durukan, A. H., Unlu, N., Onen, M., Alp, M. N., Kalayci, D., Acar, M. A., Sekeroglu, M. A., Citirik, M., Altintas, A. G. K., Hazirolan, D., Ozdal, P. C., Toklu, Y., Bicer, T., Ugurlu, N., Budakoglu, O., Yazar, Z., Zeki, N. I. U., … Baskan, C. (2023). Real life multicenter comparison of 24-month outcomes of anti-VEGF therapy in diabetic macular edema in Turkey: Ranibizumab vs. aflibercept vs. ranibizumab-aflibercept switch. *Medicina, 59*(2), 263. https://doi.org/10.3390/medicina59020263
6. Sam-Oyerinde, O. A., & Patel, P. J. (2023). Real-world outcomes of anti-VEGF therapy in diabetic macular oedema: Barriers to treatment success and implications for low/lower-middle-income countries. *Ophthalmology and Therapy, 12*(2), 809–826. https://doi.org/10.1007/s40123-023-00672-6
7. Yuen, Y. S., Tan, G. S. W., Gan, N. Y., Too, I. H. K., Mothe, R. K., Basa, P., & Shaikh, J. (2022). Real-world evidence in the management of diabetic macular edema with intravitreal anti-VEGFs in Asia: A systematic literature review. *Clinical Ophthalmology, 16*, 3503–3526. https://doi.org/10.2147/OPTH.S378392
8. Gurung, R. L., FitzGerald, L. M., Liu, E., McComish, B. J., Kaidonis, G., Ridge, B., Hewitt, A. W., Vote, B. J., Verma, N., Craig, J. E., & Burdon, K. P. (2023). Predictive factors for treatment outcomes with intravitreal anti-vascular endothelial growth factor injections in diabetic macular edema in clinical practice. *International Journal of Retina and Vitreous, 9*(1), 23. https://doi.org/10.1186/s40942-023-00453-0

9. Hussain, R. M., & Ciulla, T. A. (2016). Treatment strategies for refractory diabetic macular edema: Switching anti-VEGF treatments, adopting corticosteroid-based treatments, and combination therapy. *Expert Opinion on Biological Therapy, 16*(3), 365–374. https://doi.org/10.1517/14712598.2016.1131265
10. Uludag, G., Hassan, M., Matsumiya, W., Pham, B. H., Chea, S., Trong Tuong Than, N., Doan, H. L., Akhavanrezayat, A., Halim, M. S., Do, D. V., & Nguyen, Q. D. (2022). Efficacy and safety of intravitreal anti-VEGF therapy in diabetic retinopathy: What we have learned and what should we learn further? *Expert Opinion on Biological Therapy, 22*(10), 1275–1291. https://doi.org/10.1080/14712598.2022.2100694
11. Furino, C., Boscia, F., Reibaldi, M., & Alessio, G. (2021). Intravitreal therapy for diabetic macular edema: An update. *Journal of Ophthalmology, 2021*, 6654168. https://doi.org/10.1155/2021/6654168
12. Sharma, T. (2020). Evolving role of anti-VEGF for diabetic macular oedema: From clinical trials to real life. *Eye, 34*(3), 415–417. https://doi.org/10.1038/s41433-019-0590-0
13. Stefanini, F. R., Badaró, E., Falabella, P., Koss, M., Farah, M. E., & Maia, M. (2014). Anti-VEGF for the management of diabetic macular edema. *Journal of Immunology Research, 2014*, 632307. https://doi.org/10.1155/2014/632307
14. Nakao, S., Kusuhara, S., & Murakami, T. (2024). Anti-VEGF therapy for the long-term management of diabetic macular edema: A treat-to-target strategy based on macular morphology. *Graefe's Archive for Clinical and Experimental Ophthalmology, 262*(12), 3749–3759. https://doi.org/10.1007/s00417-024-06558-y
15. Eter, N., Singh, R. P., Abreu, F., Asik, K., Basu, K., Baumal, C., Chang, A., Csaky, K. G., Haskova, Z., Lin, H., Ruiz, C. Q., Ruamviboonsuk, P., Silverman, D., Wykoff, C. C., & Willis, J. R. (2021). YOSEMITE and RHINE: Phase 3 randomized clinical trials of faricimab for diabetic macular edema: Study design and rationale. *Ophthalmology Science, 2*(1), 100111. https://doi.org/10.1016/j.xops.2021.100111
16. Wykoff, C. C., Abreu, F., Adamis, A. P., Basu, K., Eichenbaum, D. A., Haskova, Z., Lin, H., Loewenstein, A., Mohan, S., Pearce, I. A., Sakamoto, T., Schlottmann, P. G., Silverman, D., Sun, J. K., Wells, J. A., Willis, J. R., Tadayoni, R., & YOSEMITE and RHINE Investigators. (2022). Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): Two randomised, double-masked, phase 3 trials. *The Lancet, 399*(10326), 741–755. https://doi.org/10.1016/S0140-6736(22)00018-6
17. Wong, T. Y., Haskova, Z., Asik, K., Baumal, C. R., Csaky, K. G., Eter, N., Ives, J. A., Jaffe, G. J., Korobelnik, J. F., Lin, H., Murata, T., Ruamviboonsuk, P., Schlottmann, P. G., Seres, A. I., Silverman, D., Sun, X., Tang, Y., Wells, J. A., Yoon, Y. H., … YOSEMITE and RHINE Investigators. (2024). Faricimab treat-and-extend for diabetic macular edema: Two-year results from the randomized phase 3 YOSEMITE and RHINE trials. *Ophthalmology, 131*(6), 708–723. https://doi.org/10.1016/j.ophtha.2023.12.026
18. Shimura, M., Oh, H., Ueda, T., Kitano, S., Mitamura, Y., Sato, J., Iwasaki, K., Hirakata, A., & YOSEMITE and RHINE Investigators. (2024). Efficacy, durability, and safety of faricimab with extended dosing up to every 16 weeks in diabetic macular edema: 2-year results from the Japan subgroup of the phase 3 YOSEMITE trial. *Japanese Journal of Ophthalmology, 68*(5), 511–522. https://doi.org/10.1007/s10384-024-01078-y
19. Khetan, T., Shah, P., Ahmed, S., Jeyabaladevan, P., & Vithlani, S. (2025). Real-world outcomes of faricimab in treating diabetic macular edema up to two years. *Indian Journal of Ophthalmology, 73*(11), 1596–1601. https://doi.org/10.4103/IJO.IJO_930_25
20. Esteban-Floría, O., Mateo, J., Lara, J., Bartolomé, I., Herrero, I., Pérez, M. A., Cabello, C., Honrubia, A., Pinilla, I., & Ascaso, J. (2025). Efficacy and safety of faricimab in diabetic macular edema: Real-world outcomes in treatment-naïve and previously treated eyes. *Journal of Clinical Medicine, 14*(17), 6173. https://doi.org/10.3390/jcm14176173
21. Hirakata, T., Hara, F., Nochi, Y., Shinohara, D., Yamamoto, S., Hiratsuka, Y., & Nakao, S. (2025). Short-term real-world outcomes of diabetic macular edema treated with intravitreal faricimab. *PLOS ONE, 20*(5), e0323088. https://doi.org/10.1371/journal.pone.0323088
22. Peto, T., Pearce, I., Talks, J., de Salvo, G., Patel, P. J., de Silva, S. R., Gale, R. P., Sivaprasad, S., Varma, D., Reynolds, R., Bailey, C., Downey, L., Kiire, C., Chi, G. C., Dodds, M., James, N., Downey, A. K., & Dayal, P. (2025). Real-world treatment patterns and visual outcomes of faricimab in patients with diabetic macular oedema in the UK at 12 months: The FARWIDE-DMO study. *Eye, 39*(18), 3350–3358. https://doi.org/10.1038/s41433-025-04059-8
23. Westborg, I., Al-Najjar, A., & Norberg, H. (2025). Eligibility for faricimab in a real-world diabetic macular oedema population: A cross-sectional study. *BMJ Open, 15*(2), e089801. https://doi.org/10.1136/bmjopen-2024-089801
24. Chaudhary, V., Guymer, R., Artignan, A., Downey, A., & Singh, R. P. (2025). Real-world evidence for faricimab in neovascular age-related macular degeneration and diabetic macular edema: A scoping review. *Ophthalmology Science, 5*(4), 100744. https://doi.org/10.1016/j.xops.2025.100744
25. Sydnor, S., Chatterjee, S., Cooney, P., Kaur, S., Macmillan, T., Stewart, D., Munro, I., Bandeiras, C., Paine, A., & Felizzi, F. (2023). Efficacy and safety of brolucizumab, aflibercept, and ranibizumab for the treatment of patients with visual impairment due to diabetic macular oedema: A systematic review and network meta-analysis. *Diabetes Therapy, 14*(7), 1193–1216. https://doi.org/10.1007/s13300-023-01410-8

26. Watkins, C., Paulo, T., Bührer, C., Holekamp, N. M., & Bagijn, M. (2023). Comparative efficacy, durability and safety of faricimab in the treatment of diabetic macular edema: A systematic literature review and network meta-analysis. *Advances in Therapy, 40*(12), 5204–5221. https://doi.org/10.1007/s12325-023-02675-y
27. Nichani, P. A. H., Popovic, M. M., Mihalache, A., Pathak, A., Muni, R. H., Wong, D. T. W., & Kertes, P. J. (2024). Efficacy and safety of intravitreal faricimab in neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusion: A meta-analysis. *Ophthalmologica, 247*(5–6), 355–372. https://doi.org/10.1159/000541662
28. Singer, M., Liu, M., Schlottmann, P. G., Khanani, A. M., Hemphill, M., Hill, L., Tuomi, L., & Haskova, Z. (2020). Predictors of early diabetic retinopathy regression with ranibizumab in the RIDE and RISE clinical trials. *Clinical Ophthalmology, 14*, 1629–1639. https://doi.org/10.2147/OPTH.S247061
29. Dhoot, D. S., Moini, H., Reed, K., Du, W., Vitti, R., Berliner, A. J., & Singh, R. P. (2023). Functional outcomes of sustained improvement on Diabetic Retinopathy Severity Scale with intravitreal aflibercept in the VISTA and VIVID trials. *Eye, 37*(10), 2020–2025. https://doi.org/10.1038/s41433-022-02058-7
30. Gao, M., Liu, C., Zeng, Y., Wu, X., & Duan, J. (2025). Progress in the treatment of diabetic macular edema with faricimab: A review. *Frontiers in Medicine, 12*, 1682311. https://doi.org/10.3389/fmed.2025.1682311
31. Chakravarthy, U., Chaudhary, V., Sadda, S. R., Tan, C. S., Vujosevic, S., Fauser, S., Gibson, K., Glittenberg, C., Holekamp, N., Lanza, B., Maunz, A., Willis, J. R., & Singh, R. P. (2025). Effect of faricimab versus aflibercept on hyperreflective foci in patients with diabetic macular edema from the YOSEMITE/RHINE trials. *Ophthalmology Science, 5*(5), 100798. https://doi.org/10.1016/j.xops.2025.100798
32. Jaffe, G. J., Deák, G., Gibson, K., Khurana, R. N., Nudleman, E., Ogura, Y., Schmidt-Erfurth, U., Wang, T., Westenskow, P. D., Wong, D., Yiu, G., & Willis, J. R. (2025). Impact of faricimab versus aflibercept on epiretinal membrane formation over 2 years in patients with diabetic macular edema in the phase 3 YOSEMITE and RHINE trials. *Retina, 45*(11), 2003–2011. https://doi.org/10.1097/IAE.0000000000004572