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# Anti-VEGF Therapy in Diabetic Retinopathy: A Synthesis of Efficacy, Durability, and a Clinical Decision-Making Framework in the Context of Developing Countries

**Mohammad Aulia Molid Ogest Putra Calisanie[1], Ramzi Amin[2], Petty Purwanita[3].**
[1]Universitas Sriwijaya, Palembang, Indonesia, calisanie@fk.unsri.ac.id
[2]Universitas Sriwijaya, Palembang, Indonesia, ramzi.amin26@gmail.com
[3]Universitas Sriwijaya, Palembang, Indonesia, pettypurwanita@yahoo.com

Corresponding Author: calisanie@fk.unsri.ac.id[1]

**Abstract:** Diabetic retinopathy is a leading cause of preventable blindness in working-age populations, with vascular endothelial growth factor (VEGF) playing a central role in its progression. This critical narrative review aims to synthesize comparative evidence on the efficacy and durability of anti-VEGF agents and to formulate a contextual clinical decision-making framework for developing countries, particularly Indonesia. A literature search through PubMed/MEDLINE, Google Scholar, and ClinicalTrials.gov identified 143 articles; after stepwise screening with qualitative appraisal based on study design, sample size, and clinical relevance, 40 articles were included. Findings show that aflibercept demonstrated meaningful superiority in patients with poor baseline visual acuity of 20/50 or worse (approximately 2.7 ETDRS letters compared to bevacizumab, PROTOCOL T), while all three major agents yielded comparable outcomes at better baseline vision. Faricimab offered clinical durability up to 16 weeks in 53% of patients (YOSEMITE/RHINE). Approximately 30 to 40% of patients exhibit inadequate response, classifiable as primary non-response or secondary loss of response, each carrying distinct therapeutic implications. Optimal agent selection requires stratification by baseline visual acuity, durability profile, and cost-effectiveness considerations within Indonesia's National Health Insurance (JKN) system. Prospective research in the Indonesian population remains an urgent priority.

***Keyword:*** *Diabetic Retinopathy, Anti-VEGF, Diabetic Macular Edema, Treatment Durability, Developing Countries*

***Indonesian Abstract:*** *Retinopati diabetik merupakan penyebab utama kebutaan yang dapat dicegah pada usia produktif, dengan peran sentral vascular endothelial growth factor (VEGF) dalam progresinya. Tinjauan naratif kritis ini bertujuan mensintesis bukti komparatif efikasi dan durabilitas agen anti-VEGF serta merumuskan kerangka pengambilan keputusan klinis yang kontekstual untuk negara berkembang, khususnya Indonesia. Penelusuran literatur melalui PubMed/MEDLINE, Google Scholar, dan ClinicalTrials.gov mengidentifikasi 143 artikel; setelah penyaringan bertahap dengan evaluasi kualitatif berbasis desain studi, ukuran sampel, dan relevansi klinis, sebanyak 40 artikel dimasukkan dalam analisis akhir. Temuan menunjukkan bahwa aflibercept memberikan keunggulan*

*bermakna pada pasien dengan tajam penglihatan awal 20/50 atau lebih buruk (selisih sekitar 2,7 huruf ETDRS dibandingkan bevacizumab, PROTOCOL T), sementara ketiga agen utama memberikan hasil sebanding pada kondisi awal yang lebih baik. Faricimab menawarkan durabilitas klinis hingga 16 minggu pada 53% pasien (YOSEMITE/RHINE). Sekitar 30 hingga 40% pasien mengalami respons tidak adekuat yang dapat diklasifikasikan sebagai primary non-response atau secondary loss of response, masing-masing dengan implikasi terapeutik yang berbeda. Pemilihan agen optimal memerlukan stratifikasi berbasis tajam penglihatan awal, profil durabilitas, dan pertimbangan cost-effectiveness dalam sistem Jaminan Kesehatan Nasional Indonesia. Penelitian prospektif berbasis populasi Indonesia merupakan prioritas yang mendesak.*

**Keywords:** Retinopati Diabetik, Anti-VEGF, Edema Makula Diabetik, Durabilitas Terapi, Negara Berkembang

## INTRODUCTION

Diabetes mellitus (DM) is one of the greatest global health challenges of this century. The International Diabetes Federation (IDF) estimated that approximately 537 million adults were living with DM in 2021, a figure projected to reach 783 million by 2045 (International Diabetes Federation, 2021). Indonesia ranks fifth worldwide in the number of people living with DM (Kemenkes RI, 2018).

Diabetic retinopathy (DR) is a leading cause of preventable blindness among working-age populations (Teo et al., 2021). Globally, an estim_—ated one-third of all people with DM develop some degree of DR, and about one-third of these are at risk of vision-threatening disease (VTDR) (Yau et al., 2012). This burden carries inseparable medical, social, and economic dimensions.

Anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the management of DR over the past two decades. Several large phase III clinical trials, namely RISE, RIDE, PROTOCOL T, VIVID, VISTA, YOSEMITE, and RHINE, have consistently demonstrated the superiority of anti-VEGF over laser photocoagulation in improving visual acuity (Nguyen et al., 2012; Gross et al., 2015). However, this consensus conceals a number of important clinical tensions.

The main unresolved gap is not merely a shortage of Indonesian-language literature, but concerns three more substantive dimensions. First, there is no existing synthesis oriented toward clinical decision-making that takes into account the comparative differences among agent profiles. Second, a wide gulf exists between efficacy in controlled clinical trials, which use tertiary populations, strict injection protocols, and intensive follow-up, and effectiveness in the real world, where adherence, access to care, and patient comorbidity profiles differ considerably. Third, almost no therapeutic framework explicitly considers the context of Indonesia's National Health Insurance (Jaminan Kesehatan Nasional, JKN) system in agent selection.

This critical narrative review was undertaken to address these three gaps by analytically synthesizing current evidence and formulating it into a clinical decision-making framework applicable across different levels of healthcare facilities.

This review was designed to comparatively examine the efficacy and durability of individual anti-VEGF agents along with the limits of their interpretation, to examine the factors that influence treatment response and how these factors translate into a clinical decision-making framework, and to discuss how contextual considerations, particularly Indonesia's JKN system and limited access to health services, influence rational anti-VEGF agent selection.

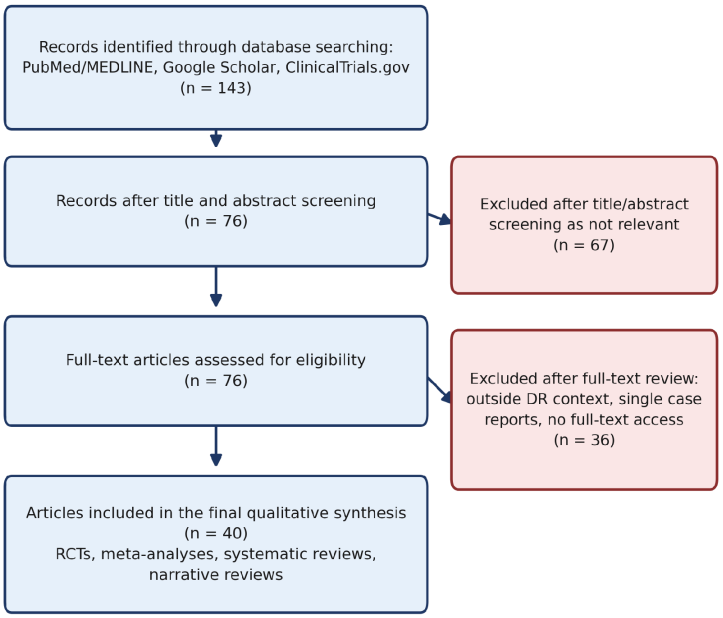
## METHODS

This review was conducted through a literature search using PubMed/MEDLINE, Google Scholar, and ClinicalTrials.gov. The search was performed in January 2026 using combinations of the keywords "anti-VEGF therapy," "diabetic retinopathy," "diabetic macular edema," "aflibercept," "faricimab," "treatment durability," "real-world evidence," and "developing countries," combined using Boolean AND/OR operators.

Inclusion criteria comprised articles published between 2012 and 2024, in English or Indonesian, encompassing relevant Randomized Controlled Trials (RCTs), meta-analyses, systematic reviews, and narrative reviews. Foundational studies published before 2012 with high methodological impact were retained. Articles outside the context of DR, single case reports, and literature without full-text access were excluded.

Each study was appraised qualitatively across three dimensions. First, study design, with phase III RCTs assigned the highest weight of evidence, followed by meta-analyses and systematic reviews. Second, sample size and follow-up duration as indicators of the reliability of effect estimates. Third, clinical relevance, considering whether the study population and protocol could be generalized to real-world conditions in Indonesia. Studies with phase III RCT and meta-analysis designs were prioritized in the synthesis, while observational studies and narrative reviews were used as supporting data on context and real-world evidence. A narrative review design was chosen given the high heterogeneity across studies, which makes quantitative synthesis through meta-analysis inappropriate. The literature selection flow is presented in Figure 1.

***Figure 1. Literature Selection Flow Diagram (Adapted from PRISMA)***




## RESULTS AND DISCUSSION

### Definition and Classification of Diabetic Retinopathy

Diabetic retinopathy is a chronic microvascular complication of DM that progressively involves the retinal vasculature (Cheung et al., 2010). The most widely used classification is the ETDRS system, which divides DR into mild, moderate, and severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Center-involved DME (CI-DME) with reduced visual acuity is the primary indication for anti-VEGF therapy (Wilkinson et al., 2003; American Academy of Ophthalmology, 2020).

It is important to understand that this classification is not merely a taxonomy but a direct therapeutic guide. The transition from severe NPDR to PDR marks a critical point of change in management, while the presence of CI-DME, regardless of DR stage, is the primary trigger for initiating anti-VEGF therapy according to AAO and EURETINA consensus (American Academy of Ophthalmology, 2020; Schmidt-Erfurth et al., 2017).

**Pathogenesis of Diabetic Retinopathy and the Role of VEGF**

The pathogenesis of DR involves activation of the polyol and hexosamine pathways, protein kinase C (PKC), and accumulation of advanced glycation end-products (AGEs), which converge on dysfunction of endothelial cells, pericytes, and Müller cells (Stitt et al., 2016). Pericyte loss is the earliest histopathological finding, causing disruption of the blood-retinal barrier (BRB) that underlies the formation of DME (Hammes et al., 2002). Notably, neurodegenerative and microvascular changes in the retina appear to precede clinically detectable DR: a cross-sectional study in Indonesian patients with type 2 diabetes but no clinical retinopathy found measurable thinning of the retinal neural layers together with reduced contrast sensitivity, suggesting that subclinical retinal injury begins well before conventional fundoscopic signs of DR emerge (Amin et al., 2026b).

VEGF-A plays a central role as a mediator of vascular permeability and pathological angiogenesis via VEGFR-1 and VEGFR-2 (Ferrara et al., 2003). Vitreous VEGF levels correlate directly with DR severity and increase ICAM-1 expression, which amplifies the inflammatory response (Aiello et al., 1994; Joussen et al., 2004). Understanding this pathway explains why VEGF inhibition is a rational intervention, while also explaining why not all patients respond optimally, given the contribution of non-VEGF inflammatory cytokines that remain unaddressed.

**Conceptualizing Durability and the Efficacy versus Effectiveness Framework**

Durability in the context of anti-VEGF therapy refers to two interrelated but distinct dimensions. Pharmacological durability reflects an agent's ability to maintain adequate intravitreal VEGF suppression based on its molecular half-life. Clinical durability, which is more relevant in practice, refers to an agent's ability to sustain therapeutic effect such that injection intervals can be extended without losing anatomical control (increased central subfield thickness [CST] on OCT) or functional control (decreased best-corrected visual acuity [BCVA]). Faricimab, through its dual inhibition of VEGF-A and Ang-2, achieves clinical durability of up to 16 weeks in 53% of patients, currently the longest interval available clinically (Wykoff et al., 2022).

The distinction between efficacy (outcomes in controlled clinical trials) and effectiveness (real-world outcomes) is key to interpreting anti-VEGF evidence (Krentz et al., 2022). Trials such as PROTOCOL T operate under ideal conditions, namely a strictly selected tertiary population, consistent injection protocols, multidisciplinary teams, and intensive follow-up. These conditions differ substantially from the reality of eye clinics in Indonesia, where access is limited, cost is a barrier, follow-up adherence varies, and OCT capacity is not evenly distributed. This efficacy-effectiveness gap must be an explicit consideration in agent selection, not merely a matter of pursuing the best trial figures, but rather choosing the strategy that is most robust under real-world conditions.

**Anti-VEGF Agents: Mechanism of Action and Comparative Profile**

There are currently four anti-VEGF agents relevant to DR and DME, each with a distinct molecular structure and pharmacokinetic profile. The full comparative profile is presented in Table 1.

Ranibizumab (Lucentis®) is a Fab fragment developed specifically for intraocular use, neutralizing all active VEGF-A isoforms. Its small size allows optimal retinal penetration (Ferrara et al., 2006).

Bevacizumab (Avastin®) is used off-label, with an efficacy profile comparable to other agents in populations with good baseline VA, along with a cost advantage that cannot be ignored in the context of Indonesia's JKN system (Wells et al., 2015).

Aflibercept (Eylea®), acting as a decoy receptor, binds VEGF-A, VEGF-B, and PlGF with an in vitro affinity approximately 10 times higher than ranibizumab (Papadopoulos et al., 2012). Although the clinical relevance of this difference in affinity remains debated at therapeutic concentrations that already exceed receptor saturation, its clinical benefit in the subgroup with poor baseline VA has been consistently demonstrated.

Faricimab (Vabysmo®) is the first bispecific antibody to simultaneously inhibit VEGF-A and Ang-2, enabling dual-pathway control of vascular permeability beyond VEGF inhibition alone (Wykoff et al., 2022).

**Indications and Administration Protocols**

Anti-VEGF is indicated as first-line therapy for CI-DME with reduced visual acuity, according to AAO and EURETINA consensus (Schmidt-Erfurth et al., 2017). Protocols generally begin with a loading phase of 3 to 6 monthly injections, followed by treat-and-extend (T&E) or pro re nata (PRN) maintenance based on BCVA and CST response on OCT (Wells et al., 2016).

For high-risk PDR with neovascularization of the disc (NVD) covering 35% or more of the disc area, neovascularization elsewhere (NVE) accompanied by vitreous hemorrhage, or traction complications, a combination of panretinal photocoagulation (PRP) with anti-VEGF, or vitrectomy with preoperative anti-VEGF, remains recommended according to AAO guidelines (Gross et al., 2018).

**Anti-VEGF Efficacy in DME: Synthesis of Evidence**

The evidence base for anti-VEGF use in DME originates from a series of phase III RCTs that successfully transformed the management paradigm. The RISE and RIDE studies demonstrated a mean BCVA improvement of 10.9 to 12.5 ETDRS letters in the ranibizumab group compared with 2.6 to 2.9 letters in controls at year three (Nguyen et al., 2012). This difference exceeds the minimal clinically important difference (MCID) threshold of 5 letters, so its functional relevance to daily activities can be clinically justified.

PROTOCOL T is the most influential comparative study, evaluating all three agents head-to-head. Its key finding was that aflibercept's superiority is context-specific, being clinically meaningful only in patients with baseline VA of 20/50 or worse (6/15 meters), with a difference of approximately 2.7 letters compared with bevacizumab, but not significantly different at baseline VA of 20/40 or better (6/12 meters) (Wells et al., 2015). This finding supports a VA-based stratification approach as a practical algorithm for therapy selection, rather than a universal agent preference.

However, the PROTOCOL T findings must be read with several critical caveats. First, the study population comprised strictly selected tertiary-care patients with routine OCT access and an intensive injection protocol that does not reflect everyday practice in many Indonesian facilities. Second, the 2.7-letter difference, although exceeding the MCID, remains at the threshold of clinical significance and may not be subjectively detectable by patients. Third, at year two, the between-group difference narrowed further (Wells et al., 2016), raising the question of whether aflibercept's initial superiority is sustained in the long term across all patients. The conclusion is clear: aflibercept is the biologically stronger choice for poor baseline VA, but there is insufficient clinical justification to make it a universal agent

replacing bevacizumab in populations with good baseline VA within resource-limited systems.

The YOSEMITE and RHINE studies demonstrated that faricimab is non-inferior to aflibercept in improving BCVA, with notable clinical durability, as 53% of T&E patients achieved a 16-week interval (Wykoff et al., 2022). The direct implication is not merely patient convenience but a reduction in system burden, cumulative procedural risk, and long-term costs relevant to the chronic management of DR.

**Anti-VEGF Efficacy in PDR**

PROTOCOL S demonstrated that ranibizumab is non-inferior to PRP in preserving visual acuity, with the additional advantage of less visual field loss and lower incidence of DME (Gross et al., 2015). Nonetheless, critical interpretation remains necessary, because at 5-year follow-up, 41% of patients in the ranibizumab group required PRP as rescue therapy (Gross et al., 2018), revealing a high dependence on continuity of treatment that cannot always be guaranteed.

In the Indonesian context, with variable access and follow-up adherence, the effectiveness of anti-VEGF for PDR is inversely related to the risk of loss to follow-up. In settings with a high risk of loss to follow-up, PRP is pragmatically superior to anti-VEGF monotherapy, not because of higher efficacy in clinical trials, but because its effect is more persistent with a far smaller number of procedures required. Clinicians working in facilities with limited access need to explicitly position PRP as the primary option for PDR cases, rather than as a "fallback" when anti-VEGF is unavailable.

PROTOCOL W demonstrated that prophylactic aflibercept significantly reduces progression to VTDR in severe NPDR through early PDR without CI-DME (Wykoff et al., 2021). The clinical value of this finding lies not only in the evidence of effectiveness but also in the as-yet-unanswered question of which subgroup benefits the most. Without a validated predictive biomarker, a universal prophylactic approach risks exposing patients to an injection burden they may not need. Clinicians must resist extrapolating the PROTOCOL W findings as justification for routine anti-VEGF therapy in all patients with severe NPDR, as this extrapolation is not supported by current evidence.

**Comparative Efficacy Across Agents: Comparative Synthesis**

A recent meta-analysis (Cochrane, 2023) confirmed that, in the general DME population without VA stratification, the difference in efficacy among the major agents is not clinically meaningful (Virgili et al., 2023). This finding strengthens the argument that agent selection should be based on clinical stratification rather than a universal agent preference.

From a durability perspective, the development of faricimab represents genuine progress in reducing injection burden without sacrificing efficacy (Wykoff et al., 2022). Meanwhile, the increasing global availability of ranibizumab and aflibercept biosimilars opens opportunities for improved accessibility in Indonesia, although long-term efficacy and safety data in Asian populations still require further evaluation.

Data from Indonesia and Southeast Asia remain very limited (Krentz et al., 2022). Available international observational studies consistently show outcomes lower than those of controlled clinical trials, confirming the efficacy-effectiveness gap discussed earlier. This gap represents the most urgent evidence gap to be filled through local research; recent Indonesian cross-sectional studies on retinal neurovascular changes in diabetes (Amin et al., 2026a, 2026b) represent early steps in that direction, though prospective, treatment-outcome data remain lacking.

***Table 1. Comparison of the Profiles of the Main Anti-VEGF Agents for Diabetic Retinopathy***

| Parameter | Ranibizumab | Bevacizumab | Aflibercept | Faricimab |
|---|---|---|---|---|
| Registration status (DR/DME) | On-label | Off-label | On-label | On-label |

| | | | | |
|---|---|---|---|---|
| Main pivotal trials | RISE, RIDE | PROTOCOL T | VIVID, VISTA, PROTOCOL T | YOSEMITE, RHINE |
| BCVA improvement (ETDRS letters) | +10.9–12.5 | Comparable to ranibizumab* | +12.5 (superior at baseline VA ≤20/50) | Non-inferior vs aflibercept |
| Inhibition mechanism | Anti-VEGF-A (all isoforms) | Anti-VEGF-A (all isoforms) | Anti-VEGF-A, -B, PlGF (decoy receptor) | Anti-VEGF-A + Ang-2 (bispecific) |
| Maximum T&E interval | 12 weeks | 12 weeks | 16 weeks | 16 weeks (53% of patients) |
| Main advantage | Excellent intraocular safety profile | Lowest cost; relevant for JKN/BPJS | Optimal efficacy at poor baseline VA | Longest durability; dual-pathway |
| Limitations | Higher cost than bevacizumab | Off-label status; no official intraocular indication | High cost; RWE data still limited | Long-term data beyond 3 years still developing |
| Availability in Indonesia | Limited / high price | Widely available; used under BPJS | Available; high price | Very limited |

**In patients with baseline VA ≥20/40; bevacizumab is non-inferior. BCVA: best-corrected visual acuity; T&E: treat-and-extend; VA: visual acuity; RWE: real-world evidence; PlGF: placental growth factor; Ang-2: angiopoietin-2; CST: central subfield thickness.*

**Treatment Response: Classification and Clinical Implications**

The phenomenon of inadequate response to anti-VEGF, experienced by approximately 30 to 40% of patients, requires a more structured approach than mere description. Clinically, this pattern can be classified into two distinct categories with different therapeutic implications.

Primary non-response is defined as the failure of anatomical response (no meaningful decrease in CST on OCT) and/or functional response (no meaningful improvement in BCVA) after at least three adequate loading injections. This condition indicates that VEGF may not be the dominant mediator in that patient. Comprehensive evaluation should include three elements: confirming diagnostic accuracy and excluding a tractional component on OCT examination, identifying the degree of retinal ischemia through fundus fluorescein angiography, and considering the contribution of non-VEGF inflammatory cytokines. Optical coherence tomography angiography (OCTA) offers a complementary, non-invasive means of quantifying macular ischemia: an Indonesian cross-sectional OCTA study found that a larger foveal avascular zone (FAZ) diameter was associated with poorer best-corrected visual acuity in diabetic retinopathy, supporting FAZ measurement as a practical adjunct when ischemia is suspected as a driver of non-response (Amin et al., 2026a). In this group, switching to combination therapy with an intravitreal corticosteroid (dexamethasone implant) or evaluation for vitrectomy is more relevant than simply switching anti-VEGF agents (Boyer et al., 2014; Bressler et al., 2016).

Secondary loss of response refers to a condition in which a patient shows a good initial response but gradually loses control over time. This phenomenon may reflect three possibilities: tachyphylaxis, or reduced sensitivity to the same agent; the development of compensatory angiogenesis mechanisms via non-VEGF pathways; or worsening of the underlying disease due to uncontrolled hyperglycemia. Therapeutic approaches in this group include re-titration of the T&E interval, switching to an agent with a different mechanism, such as from a single VEGF inhibitor to faricimab, which simultaneously inhibits Ang-2, or the addition of intravitreal steroid (Wykoff et al., 2022; Bressler et al., 2016).

This classification is not merely academic, as it directly determines the next step, whether switching agents, adding therapy, or proceeding to surgical evaluation. This decision must be made based on the documented response pattern, not on the duration of therapy alone.

## Clinical Decision-Making in the Context of Indonesia's National Health Insurance (JKN)

Within Indonesia's JKN system, a cost-effectiveness approach becomes a determinant that cannot be ignored. Bevacizumab, although off-label for intraocular indications, remains rational as first-line therapy in CI-DME patients with baseline VA of 20/40 or better, where its efficacy is equivalent to other agents. The use of aflibercept or ranibizumab can be medically justified in the subgroup with a specific indication, namely baseline VA of 20/50 or worse, but this decision must be communicated transparently during informed consent, including its long-term cost implications.

Faricimab, with its longest durability profile, holds unique potential value in systems with limited visit capacity. Reducing the average of 8 to 10 injections per year to 3 to 4 injections per year in patients who respond well directly reduces system burden, transportation costs, and the risk of dropping out of follow-up. In remote areas of Indonesia, where the distance to a facility with intravitreal injection capability can reach hundreds of kilometers, this consideration carries real clinical value.

Procedural complications such as endophthalmitis (0.02 to 0.05% per injection) and transient elevation of intraocular pressure (IOP) (3 to 11%) must be communicated in cumulative terms. In a patient requiring 100 injections over a lifetime, the cumulative risk of endophthalmitis reaches 2 to 5%. This is not intended to undermine confidence in the therapy, but to promote informed and transparent decision-making (Fileta et al., 2014).

## Therapeutic Developments: Relevance for the Future

The Port Delivery System (PDS) with ranibizumab offers sustained release via a refillable intraocular implant (Campochiaro et al., 2019), while AAV-based gene therapy, including the 4D-150 program that simultaneously inhibits VEGF-A and PDGF-B, opens the potential for a transformative single-dose intervention (Khanani et al., 2024). Artificial intelligence (AI) is increasingly playing a role in predicting treatment response based on OCT characteristics, with the potential to guide individualized agent selection before therapy begins (Gulshan et al., 2016). These three innovations move in a single direction, namely from repeated therapy toward fewer, more precise, and more individualized interventions, directly relevant to the Indonesian context with its high follow-up burden. However, the direct implications of these three innovations for everyday clinical decision-making remain limited to date, as gene therapy has not yet broadly entered phase III trials for DR, PDS is not yet available in Indonesia, and predictive AI algorithms have not been validated in Southeast Asian populations. Indonesian clinicians still need to make decisions based on currently available agents and current evidence.

## Proposed Clinical Decision Framework

Based on the synthesis of evidence presented above, the following clinical decision-making framework is proposed. This framework is not a substitute for official guidelines, but rather a clinical reasoning aid that integrates current evidence with contextual considerations of care delivery in Indonesia. A summary is presented in Table 2.

***Table 2. Proposed Clinical Decision Framework: Anti-VEGF Agent Selection in Diabetic Retinopathy in the Context of a Developing Country***

| Clinical Condition | Preferred Agent | Alternative | Clinical Notes |
|---|---|---|---|
| CI-DME, baseline VA ≤20/50 (6/15 m) | Aflibercept | Faricimab (if visit burden is a priority) | Aflibercept superiority demonstrated in this subgroup (PROTOCOL T). Evaluate ischemic and tractional components. |
| CI-DME, baseline VA ≥20/40 (6/12 m) | Bevacizumab (JKN first line) | Ranibizumab or aflibercept | Efficacy of the three agents is equivalent. Bevacizumab |

| | | | |
|---|---|---|---|
| | | | is rational from a cost-effectiveness standpoint within Indonesia's JKN system. |
| PDR without CI-DME (severe NPDR to early PDR) | PRP or anti-VEGF (situational) | Combined PRP + anti-VEGF in high-risk PDR | In follow-up-limited settings, PRP is more persistent with fewer procedures. Prophylactic anti-VEGF (PROTOCOL W) is promising but still requires patient selection. |
| Primary non-responder (fails ≥3 loading injections) | Diagnostic re-evaluation | Agent switching or addition of intravitreal steroid | Consider tractional component (OCT), severe ischemia, or non-VEGF inflammatory contribution. Dexamethasone implant combination may be considered. |
| Secondary loss of response (initially effective, then declines) | Shorten injection interval → T&E re-titration | Switching to an agent with longer durability (faricimab) | Evaluate tachyphylaxis versus progression of underlying disease. Consider changes in intravitreal cytokine composition over time. |
| High visit burden / long distance to facility | Faricimab (interval up to 16 weeks) | Aflibercept T&E | Relevant for patients in remote areas of Indonesia. Also consider PRP for PDR when reliable injection access is uncertain. |

*CI-DME: center-involved diabetic macular edema; JKN: Jaminan Kesehatan Nasional (National Health Insurance); PRP: panretinal photocoagulation; PDR: proliferative diabetic retinopathy; T&E: treat-and-extend; OCT: optical coherence tomography; IOP: intraocular pressure.*

It is important to emphasize that this framework is designed as a living framework, meaning it must be updated as real-world data from the Indonesian population become available and as regulations governing access to new agents within the JKN formulary evolve.

**Novelty**

The principal contribution of this review lies in three elements not previously found integrated within the existing literature. First, the integration of VA-based stratification, the concept of clinical versus pharmacological durability, and the efficacy-effectiveness framework into a single coherent clinical decision-making framework. Second, the classification of poor responders into primary non-response and secondary loss of response, each with a distinct follow-up algorithm, a framing not previously made explicit in prior Indonesian-language reviews. Third, the contextualization of the entire framework within the reality of Indonesia's JKN system yields recommendations directly applicable by clinicians across different levels of care, from class III referral hospitals (FKRTL) to tertiary referral centers.

## CONCLUSIONS AND RECOMMENDATIONS

**Conclusion**

This review explicitly addresses the three research questions posed. First, evidence from phase III RCTs consistently demonstrates the superiority of anti-VEGF over laser therapy. Aflibercept's superiority is context-specific at baseline VA ≤20/50; all three agents yield comparable outcomes at better baseline vision. Faricimab offers the longest clinical durability currently available. Second, baseline VA stratification is the primary determinant of

agent selection. The poor-responder phenomenon needs to be classified as either primary non-response or secondary loss of response, as each demands a different therapeutic strategy. Third, within Indonesia's JKN system, bevacizumab remains rational as first-line therapy for the majority of DME patients with good baseline VA, while aflibercept is specifically indicated for poor baseline VA. The substantial efficacy-effectiveness gap and the absence of local Indonesian data are limitations that should drive a national prospective research agenda.

**Limitations**

As a literature review, this study carries a potential for selection bias compared with a systematic review conducted under a full PRISMA protocol. Heterogeneity in study populations, treatment protocols, and outcome definitions across studies limits direct comparison. Nearly all of the evidence used originates from clinical trials conducted in developed countries with optimal access to health care, so generalization to the Indonesian population requires proportional caution. The absence of real-world data from Indonesia is a substantial limitation and, at the same time, the most urgent research agenda.

**Recommendations**

Anti-VEGF agent selection should be based on baseline VA stratification, a durability profile matched to patient needs, and cost-effectiveness considerations within the JKN system. Development of a national Indonesian DR registry is a concrete first step toward a genuine local evidence base and should become a shared priority among professional associations, academic institutions, and regulators.

**Author Contributions**

Conceptualization, literature search and selection, data analysis and synthesis, and original draft preparation through to the final manuscript: Mohammad Aulia Molid Ogest Putra Calisanie. The first author also carried out critical revision of the scientific content and approved the final version of the manuscript. Academic supervision, conceptual direction, and critical review of manuscript content to ensure scientific accuracy and clinical relevance: Ramzi Amin. Final approval of the manuscript for publication: Petty Purwanita. All authors have read and agreed to the published version of the manuscript.

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**Conflict of Interest**

The authors declare that there are no conflicts of interest, financial or non-financial, related to the research, authorship, and/or publication of this article.

## REFERENCES


Adamis, A. P., Aiello, L. P., & D'Amato, R. A. (1999). Angiogenesis and ophthalmic disease. Angiogenesis, 3(1), 9–14. https://doi.org/10.1023/a:1009004700358

Aiello, L. P., Avery, R. L., Arrigg, P. G., Keyt, B. A., Jampel, H. D., Shah, S. T., et al. (1994). Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy. New England Journal of Medicine, 331(22), 1480–1487. https://doi.org/10.1056/NEJM199412013312203

American Academy of Ophthalmology. (2020). Diabetic retinopathy preferred practice pattern. Ophthalmology, 127(1), 66–145. https://doi.org/10.1016/j.ophtha.2019.09.025

Amin, R., Pratama, R., Purwanita, P., & Calisanie, M. A. M. O. P. (2026a). Association of foveal avascular zone diameter with best-corrected visual acuity in diabetic retinopathy: A cross-sectional optical coherence tomography angiography study. Bioscmed, 10(8), 2764–2776. https://bioscmed.com/index.php/bsm/article/view/1659

Amin, R., Rahayu, R., Purwanita, P., & Calisanie, M. A. M. O. P. (2026b). Retinal neural layer thickness and contrast sensitivity in type 2 diabetes without clinical retinopathy: A cross-sectional study. Bioscmed, 10(7), 2637–2648. https://bioscmed.com/index.php/bsm/article/view/1660

Boyer, D. S., Yoon, Y. H., Belfort, R., Jr., Bandello, F., Maturi, R. K., Augustin, A. J., et al. (2014). Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in diabetic macular edema. Ophthalmology, 121(10), 1904–1914. https://doi.org/10.1016/j.ophtha.2014.04.024

Bressler, S. B., Glassman, A. R., Almukhtar, T., Bressler, N. M., Ferris, F. L., Googe, J. M., et al. (2016). Five-year outcomes of ranibizumab with prompt or deferred laser versus laser or triamcinolone plus deferred ranibizumab for diabetic macular edema. American Journal of Ophthalmology, 164, 57–68. https://doi.org/10.1016/j.ajo.2015.12.025

Brownlee, M. (2005). The pathobiology of diabetic complications: A unifying mechanism. Diabetes, 54(6), 1615–1625. https://doi.org/10.2337/diabetes.54.6.1615

Campochiaro, P. A., Marcus, D. M., Awh, C. C., Regillo, C., Adamis, A. P., Bantseev, V., et al. (2019). The port delivery system with ranibizumab for neovascular age-related macular degeneration: Results from the randomized phase 2 Ladder clinical trial. Ophthalmology, 126(8), 1141–1154. https://doi.org/10.1016/j.ophtha.2019.03.036

Cheung, N., Mitchell, P., & Wong, T. Y. (2010). Diabetic retinopathy. Lancet, 376(9735), 124–136. https://doi.org/10.1016/S0140-6736(09)62124-3

Diabetic Retinopathy Clinical Research Network. (2014). Relationship of retinal thickness to diabetic retinopathy severity in eyes without center-involved diabetic macular edema. Retina, 34(9), 1742–1749. https://doi.org/10.1097/IAE.0000000000000151

Early Treatment Diabetic Retinopathy Study Research Group. (1985). Photocoagulation for diabetic macular edema: ETDRS report number 1. Archives of Ophthalmology, 103(12), 1796–1806. https://doi.org/10.1001/archopht.1985.01050120030015

Early Treatment Diabetic Retinopathy Study Research Group. (1991). Grading diabetic retinopathy from stereoscopic color fundus photographs: ETDRS report number 10. Ophthalmology, 98(5, Suppl.), 786–806. https://doi.org/10.1016/s0161-6420(13)38012-9

Ferrara, N., Gerber, H. P., & LeCouter, J. (2003). The biology of VEGF and its receptors. Nature Medicine, 9(6), 669–676. https://doi.org/10.1038/nm0603-669

Ferrara, N., Damico, L., Shams, N., Lowman, H., & Kim, R. (2006). Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina, 26(8), 859–870. https://doi.org/10.1097/01.iae.0000242842.14624.e7

Fileta, J. B., Scott, I. U., & Flynn, H. W., Jr. (2014). Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmic Surgery, Lasers and Imaging Retina, 45(2), 143–149. https://doi.org/10.3928/23258160-20140306-08

Gross, J. G., Glassman, A. R., Jampol, L. M., Inusah, S., Aiello, L. P., Antoszyk, A. N., et al. (2015). Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy. JAMA, 314(20), 2137–2146. https://doi.org/10.1001/jama.2015.15217

Gross, J. G., Glassman, A. R., Liu, D., Sun, J. K., Antoszyk, A. N., Baker, C. W., et al. (2018). Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for

proliferative diabetic retinopathy (PROTOCOL S). JAMA Ophthalmology, 136(10), 1138–1148. https://doi.org/10.1001/jamaophthalmol.2018.3255

Gulshan, V., Peng, L., Coram, M., Stumpe, M. C., Wu, D., Narayanaswamy, A., et al. (2016). Development and validation of a deep learning algorithm for detection of diabetic retinopathy. JAMA, 316(22), 2402–2410. https://doi.org/10.1001/jama.2016.17216

Hammes, H. P., Lin, J., Renner, O., Shani, M., Lundqvist, A., Betsholtz, C., et al. (2002). Pericytes and the pathogenesis of diabetic retinopathy. Diabetes, 51(10), 3107–3112. https://doi.org/10.2337/diabetes.51.10.3107

International Diabetes Federation. (2021). IDF diabetes atlas (10th ed.). International Diabetes Federation. https://doi.org/10.1016/j.diabres.2021.109119

Joussen, A. M., Poulaki, V., Le, M. L., Koizumi, K., Esser, C., Janicki, H., et al. (2004). A central role for inflammation in the pathogenesis of diabetic retinopathy. FASEB Journal, 18(12), 1450–1452. https://doi.org/10.1096/fj.03-1476fje

Kemenkes RI. (2018). Riset kesehatan dasar (Riskesdas) 2018. Badan Penelitian dan Pengembangan Kesehatan. https://doi.org/10.22435/bpk.v46i1.372

Khanani, A. M., Kothari, A., Warwick, A., Chien, J. L., Westenskow, P. D., Bhatt, N., et al. (2024). PRISM: Phase 1/2 study of 4D-150 intravitreal gene therapy for diabetic macular edema. Ophthalmology Retina. Advance online publication. https://doi.org/10.1016/j.oret.2024.01.020

Korobelnik, J. F., Do, D. V., Schmidt-Erfurth, U., Boyer, D. S., Holz, F. G., Heier, J. S., et al. (2014). Intravitreal aflibercept for diabetic macular edema. Ophthalmology, 121(11), 2247–2254. https://doi.org/10.1016/j.ophtha.2014.05.006

Korobelnik, J. F., Do, D. V., Schmidt-Erfurth, U., Boyer, D. S., Holz, F. G., Heier, J. S., et al. (2016). Intravitreal aflibercept for diabetic macular edema (VIVID-DME and VISTA-DME): Two-year results. Ophthalmology, 123(7), 1521–1529. https://doi.org/10.1016/j.ophtha.2016.03.008

Krentz, T., Bhatt, N., & Hussain, R. M. (2022). Real-world outcomes of anti-VEGF therapy for diabetic macular edema: A systematic review. Clinical Ophthalmology, 16, 1263–1276. https://doi.org/10.2147/OPTH.S356500

Mitchell, P., Bandello, F., Schmidt-Erfurth, U., Lang, G. E., Massin, P., Schlingemann, R. O., et al. (2011). The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology, 118(4), 615–625. https://doi.org/10.1016/j.ophtha.2011.01.031

Nguyen, Q. D., Brown, D. M., Marcus, D. M., Boyer, D. S., Patel, S., Feiner, L., et al. (2012). Ranibizumab for diabetic macular edema: Results from two phase III randomized trials, RISE and RIDE. Ophthalmology, 119(4), 789–801. https://doi.org/10.1016/j.ophtha.2011.12.039

Papadopoulos, N., Martin, J., Ruan, Q., Rafique, A., Rosconi, M. P., Shi, E., et al. (2012). Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis, 15(2), 171–185. https://doi.org/10.1007/s10456-011-9249-6

Pokroy, R., Desai, U. R., Du Toit, N., & Morrison, J. C. (2011). Bevacizumab prior to vitrectomy for diabetic tractional retinal detachment. Eye, 25(8), 989–997. https://doi.org/10.1038/eye.2011.100

Schmidt-Erfurth, U., Garcia-Arumi, J., Bandello, F., Berg, K., Chakravarthy, U., Gerendas, B. S., et al. (2017). Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica, 237(4), 185–222. https://doi.org/10.1159/000458539

Stitt, A. W., Curtis, T. M., Chen, M., Medina, R. J., McKay, G. J., Jenkins, A., et al. (2016). The progress in understanding and treatment of diabetic retinopathy. Progress in Retinal and Eye Research, 51, 156–186. https://doi.org/10.1016/j.preteyeres.2015.08.001

Teo, Z. L., Tham, Y. C., Yu, M., Chee, M. L., Rim, T. H., Cheung, N., et al. (2021). Global prevalence of diabetic retinopathy and projection of burden through 2045. Ophthalmology, 128(11), 1580–1591. https://doi.org/10.1016/j.ophtha.2021.04.019

Virgili, G., Parravano, M., Evans, J. R., Gordon, I., & Lucenteforte, E. (2023). Anti-vascular endothelial growth factor for diabetic macular oedema: A network meta-analysis. Cochrane Database of Systematic Reviews, 2023(10), Article CD007419. https://doi.org/10.1002/14651858.CD007419.pub7

Wells, J. A., Glassman, A. R., Ayala, A. R., Jampol, L. M., Aiello, L. P., Antoszyk, A. N., et al. (2015). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. New England Journal of Medicine, 372(13), 1193–1203. https://doi.org/10.1056/NEJMoa1414264

Wells, J. A., Glassman, A. R., Ayala, A. R., Jampol, L. M., Bressler, N. M., Bressler, S. B., et al. (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

Wilkinson, C. P., Ferris, F. L., III, Klein, R. E., Lee, P. P., Agardh, C. D., Davis, M., et al. (2003). Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology, 110(9), 1677–1682. https://doi.org/10.1016/S0161-6420(03)00475-5

Wykoff, C. C., Abreu, F., Adamis, A. P., Basu, K., Eichenbaum, D. A., Haskova, Z., et al. (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). Lancet, 399(10326), 741–755. https://doi.org/10.1016/S0140-6736(22)00018-6

Wykoff, C. C., Bhatt, N. P., Brown, D. M., Boyer, D., Brown, K., Cunningham, M. A., et al. (2021). Efficacy and safety of intravitreal aflibercept in eyes with moderately severe to severe nonproliferative diabetic retinopathy (PROTOCOL W). JAMA Ophthalmology, 139(7), 701–712. https://doi.org/10.1001/jamaophthalmol.2021.0606

Yau, J. W., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T., et al. (2012). Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care, 35(3), 556–564. https://doi.org/10.2337/dc11-1909