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CURRENT ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPIES FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: A NARRATIVE REVIEW OF AVAILABLE AGENTS AND TREATMENT STRATEGIES

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ABSTRACT

Background: Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible central vision loss in older adults. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has transformed disease management, but the expanding range of agents and evolving dosing strategies has complicated therapeutic decision-making.
Objective: To summarize the anti-VEGF agents currently available for nAMD, compare their efficacy, safety and durability, and evaluate contemporary treatment strategies used to optimize long-term visual outcomes while minimizing treatment burden.
Methods: A narrative literature review was conducted using PubMed and Google Scholar. Eligible publications included landmark randomized trials, real-world studies, systematic reviews, meta-analyses, consensus statements and international clinical guidelines addressing anti-VEGF pharmacotherapy and treatment regimens in nAMD, prioritizing high-quality evidence.
Key Findings: Ranibizumab, aflibercept 2 mg, brolucizumab, faricimab, aflibercept 8 mg and the recently approved ophthalmic formulation bevacizumab-vikg all preserve or improve visual acuity. Functional outcomes are broadly comparable across agents, with meaningful differences confined to durability, anatomical fluid control and safety, most notably the intraocular inflammation signal associated with brolucizumab. Treat-and-extend dosing matched fixed dosing for visual acuity while requiring fewer injections and outperformed pro re nata regimens. Faricimab and aflibercept 8 mg maintained intervals of 12 weeks or longer in most patients, and switching agents improved anatomical outcomes in insufficiently responding eyes.
Conclusions: Contemporary management of nAMD centers on individualized anti-VEGF therapy guided by disease activity, treatment response and patient-specific factors. Longer-acting agents and emerging approaches are expected to further improve disease control while reducing the burden of repeated intravitreal injections.

KEYWORDS

Neovascular Age-Related Macular Degeneration; Aflibercept; Intravitreal Injection; Faricimab; Anti-VEGF Therapy; Treat-and-Extend

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1. Introduction

Age-related macular degeneration (AMD) is a multifactorial disease leading to irreversible visual loss in the elderly population. The prevalence of AMD among individuals aged 60 years or older is 25.3% for early or intermediate AMD and 2.4% for late AMD. Approximately 67 million individuals are currently affected in Europe, with this number projected to rise to 77 million by 2050. The incidence of late AMD is expected to increase from approximately 400,000 new cases per year at present to 700,000 new cases per year by 2050 (Li et al., 2020). By causing central visual acuity (VA) loss, AMD significantly impairs quality of life in older adults and, owing to its prevalence, continues to represent a substantial public health burden (Abdulrazzaq et al., 2025; Chamberlain et al., 2025). Age represents the most important non-modifiable risk factor for AMD. Disease onset may vary considerably among patients but typically occurs after 55 years of age. Other risk factors include smoking, abnormalities in lipid metabolism, oxidative stress, alterations in choroidal blood flow, and activation of the complement system. However, it remains unclear whether local or systemic responses to these disturbances contribute more significantly to AMD pathogenesis. Genome-wide association studies have identified polymorphisms in the CFH and ARMS2/HTRA1 genes as being associated with the highest risk of AMD development. In contrast, a diet rich in lutein, zeaxanthin, docosahexaenoic acid, and eicosapentaenoic acid has been associated with a reduced risk of late AMD (Fleckenstein et al., 2021; Lai et al., 2025).

Various classification systems for AMD have been proposed; however, recent consensus recommendations support the validity of a classification distinguishing early, intermediate, and late AMD. The latter category comprises geographic atrophy and neovascular AMD (nAMD) (Ferris et al., 2013; Lai et al., 2025). If left untreated, nAMD follows a natural course characterized by progressive vision loss, ultimately leading to blindness. This process involves the accumulation of subretinal fluid (SRF), intraretinal fluid (IRF), and sub–retinal pigment epithelium (RPE) fluid, along with exudates originating from pathological neovascularization. For this reason, research conducted over the past two decades has focused on developing treatment strategies capable of slowing or even halting this disease course. One of the earliest therapeutic approaches was laser photocoagulation; however, this method was associated with frequent recurrence of neovascularization and further disease progression. In the early 2000s, photodynamic therapy was introduced for the treatment of nAMD, with verteporfin subsequently added to enhance therapeutic efficacy. However, this combination proved effective only in cases with neovascularization located within the subretinal space. In the search for a more universal approach, anti-vascular endothelial growth factor (anti-VEGF) therapies were introduced and have since become the standard of care for nAMD. Anti-VEGF agents currently approved by the US Food and Drug Administration (FDA) include ranibizumab, aflibercept 2 mg, brolucizumab, faricimab, aflibercept 8 mg and the newly approved ophthalmic bevacizumab formulation, bevacizumab-vikg (Abdulrazzaq et al., 2025; Lai et al., 2025; Outlook Therapeutics, 2026).

Widespread use of anti-VEGF therapy has contributed to the development of various treatment dosing strategies. Therapy is typically initiated with loading doses, after which subsequent doses may be administered according to fixed, pro re nata (PRN), or the most popular and individualized treat-and-extend (T&E) regimen. However, in some cases the initiated treatment may prove ineffective, raising further dilemmas regarding switching to an alternative agent or discontinuing treatment altogether. Furthermore, maintaining the long-term efficacy of treatment remains a challenge and also raises the question of whether treatment discontinuation is feasible in patients with long-term disease stability. Nevertheless, despite their efficacy, anti-VEGF therapies do not address the underlying disease process of nAMD, which prompts the search for more disease-modifying therapies. In recent years, research has increasingly focused on gene therapies, which could potentially target all AMD subtypes, offering long-lasting treatment effects while reducing treatment burden (Abdulrazzaq et al., 2025; Iida et al., 2025; Lai et al., 2025). However, anti-VEGF agents continue to represent the current standard of care for nAMD, and their optimal, real-world application remains an area of ongoing investigation. Therefore, the aim of this study is to discuss the currently available anti-VEGF therapeutic options used in the treatment of nAMD, together with their efficacy outcomes and characteristics, to outline the treatment strategies currently employed and to highlight the remaining dilemmas and goals associated with the widespread use of this therapy.

2. Methodology

This narrative review presents evidence from 40 sources published between 2006 and 2026, identified and selected using the PubMed and Google Scholar databases. The search terms were “age-related macular degeneration”, “neovascular”, “wet”, “exudative”, “anti-VEGF”, “ranibizumab”, “aflibercept”, “brolucizumab”, “faricimab” and “bevacizumab”. Priority was given to meta-analyses, systematic reviews, randomized controlled trials and current guidelines issued by scientific societies, in order to ensure the inclusion of high-quality evidence and to minimize the risk of bias. One regulatory press release was additionally included to document the most recent marketing approval in this therapeutic area.

3. Anti-VEGF Therapies

3.1. Ranibizumab

Ranibizumab is a recombinant, humanized monoclonal antibody fragment that neutralizes all active isoforms of VEGF-A. In 2006, the results of two phase III randomized controlled trials (RCTs), MARINA and ANCHOR, were published, and ranibizumab was approved by the FDA (Brown et al., 2006; Rosenfeld et al., 2006). The first study compared the efficacy of ranibizumab administered as 24 monthly intravitreal injections at a dose of 0.3 mg or 0.5 mg, with sham injections in patients with neovascular AMD. At 12 months, both ranibizumab groups lost fewer than 15 letters, compared with patients receiving sham injections. VA improved by 15 letters or more in 24.8% of the 0.3 mg group and 33.8% of the 0.5 mg group, compared with 5.0% of the sham injection group. Mean VA increased by 6.5 letters in the 0.3 mg group and by 7.2 letters in the 0.5 mg group, compared with a mean decrease of 10.4 letters in the sham injection group. All comparisons reached statistical significance ($p < 0.001$). Moreover, this improvement in VA was sustained through the 24-month

follow-up. The most common complications associated with ranibizumab injection were endophthalmitis, identified in five patients (1.0%), and serious uveitis, identified in six patients (1.3%) (Rosenfeld et al., 2006). The second pivotal phase III RCT for ranibizumab, ANCHOR, consisted of three treatment groups: patients received monthly intravitreal ranibizumab injections (0.3 mg or 0.5 mg) combined with sham verteporfin therapy, or monthly sham intravitreal injections combined with active verteporfin therapy, over 24 months. At 12 months, fewer than 15 letters were lost in 94.3% of patients receiving 0.3 mg ranibizumab and 96.5% of patients receiving 0.5 mg ranibizumab, compared with 64.5% of patients receiving verteporfin therapy. VA improved by 15 letters or more in 35.7% of the 0.3 mg group and 40.3% of the 0.5 mg group, compared with 5.6% of the verteporfin group. Mean VA increased by 8.5 letters in the 0.3 mg group and by 11.3 letters in the 0.5 mg group, compared with a mean decrease of 9.5 letters in the verteporfin group. All comparisons reached statistical significance ($p < 0.001$). Among the 140 patients receiving 0.5 mg ranibizumab, complications included endophthalmitis in two patients (1.4%) and serious uveitis in one patient (0.7%). The MARINA and ANCHOR studies demonstrated a statistically significant advantage of ranibizumab over the control groups; however, the study design did not allow for a demonstration of superiority between the two ranibizumab doses (Brown et al., 2006). In 2013, the results of the post-approval phase III RCT HARBOR were published. Patients were assigned to four groups receiving ranibizumab at a dose of 0.5 mg or 2.0 mg, administered either monthly or PRN. Patients in the PRN groups received three monthly loading doses. At 12 months, the proportion of patients who improved VA by 15 letters or more was 34.5% (0.5 mg monthly group), 30.2% (0.5 mg PRN group), 36.1% (2.0 mg monthly group), and 33.0% (2.0 mg PRN group). Mean VA increased by 10.1, 8.2, 9.2, and 8.6 letters, respectively. The mean change from baseline in central foveal thickness (CFT) at 12 months was −172.0 μm, −161.2 μm, −163.3 μm, and −172.4 μm, respectively. The mean number of injections was 7.7 and 6.9 in the 0.5 mg PRN and 2.0 mg PRN groups, respectively. Complications of intravitreal injections were rare and included endophthalmitis in two patients (0.7%) in the 0.5 mg monthly group, and iridocyclitis and retinal tear in one patient (0.4%) each in the 2.0 mg monthly group. These findings confirmed that monthly dosing of 0.5 mg ranibizumab yielded optimal outcomes in patients with nAMD. Nevertheless, the PRN regimen achieved only marginally lower visual and anatomical outcomes, while requiring substantially fewer injections. Although the PRN groups did not formally meet the prespecified noninferiority criterion, the difference was small and the regimen supportis a clinically acceptable approach to reducing treatment burden (Busbee et al., 2013). Long-term follow-up data from the SEVEN-UP study included an evaluation of 65 patients previously enrolled in the MARINA or ANCHOR trials. These patients had received 24 monthly dosed ranibizumab intravitreal injections during pivotal studies, followed by 24 months of PRN ranibizumab treatment. At 7 to 8 years after enrollment in the MARINA and ANCHOR trials, 43% of study eyes had stable or improved vision, while 34% had declined by 15 letters or more, with an overall mean decline of 8.6 letters from baseline. These differential outcomes, in which one group of patients preserved good VA over the long follow-up period while another continued to decline, confirmed that nAMD patients with comparable pretreatment clinical profiles can develop divergent long-term response patterns to therapy. These findings highlight the chronic nature of nAMD and underscore the need for sustained treatment and monitoring (Rofagha et al., 2013). Real-world data from the observational LUMINOUS study, comprising 6,241 treatment-naïve nAMD patients treated with intravitreal ranibizumab 0.5 mg, demonstrated a mean VA gain of 3.1 letters at one year (data available for n = 3,379), achieved with a mean of 5.0 injections and 8.8 monitoring visits. The incidence of serious adverse events was 0.9% for ocular events (including endophthalmitis, retinal hemorrhage, and cataract) and 7.4% for nonocular events, which confirmed the favorable safety profile of ranibizumab. Moreover, the LUMINOUS study demonstrated that patients receiving a higher and more appropriate number of injections achieved greater VA gains. This benefit included those who received three loading doses within the first 90 days of treatment, highlighting the importance of prompt treatment initiation for optimizing therapeutic outcomes (Holz et al., 2020).

3.2. Aflibercept 2 mg

Aflibercept is a recombinant fusion protein comprising the extracellular ligand-binding domains of human VEGF receptors (Stewart, 2013). In 2011, the FDA approved aflibercept 2 mg for the treatment of nAMD, based on the results of two similarly designed pivotal phase III RCTs, VIEW 1 and VIEW 2. These trials compared monthly and every 2 months dosing of intravitreal aflibercept with monthly ranibizumab in patients with nAMD. Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4 group), 2 mg monthly (2q4 group), 2 mg every 2 months after three initial monthly doses (2q8 group), or ranibizumab 0.5 mg monthly (Rq4 group). The primary endpoint evaluated the efficacy of the aflibercept regimens versus

ranibizumab (margin of 10%) in the proportion of patients maintaining vision at week 52, defined as losing fewer than 15 letters. All aflibercept regimens were comparable and clinically equivalent to monthly ranibizumab for the primary endpoint (the 2q4, 0.5q4, and 2q8 regimens achieved rates of 95.1%, 95.9%, and 95.1%, respectively, in VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, in VIEW 2, compared with 94.4 % for monthly ranibizumab in both studies). Ocular and systemic adverse events were similar across treatment groups, including endophthalmitis in 1% of patients in both the 2q4 and Rq4 groups, and retinal hemorrhage in 0.7% of patients in the Rq4 group. Therefore, intravitreal aflibercept administered monthly or every 2 months (following three initial monthly doses) demonstrated visual and anatomic outcomes, as well as safety and tolerability, similar to those of monthly ranibizumab. Intravitreal aflibercept dosed every 2 months has the potential to provide the efficacy and disease control that clinicians have come to expect from monthly ranibizumab, while substantially reducing treatment and compliance burden, along with a lower cumulative risk of injection-related complications (Heier et al., 2012). Follow-up of patients enrolled in VIEW 1 and VIEW 2 was extended from 52 to 96 weeks. Patients continued to receive their originally assigned aflibercept or ranibizumab dose, but on a PRN basis rather than a fixed schedule, with mandatory retreatment at least every 12 weeks. All aflibercept and ranibizumab groups remained equally effective in improving and preventing loss of VA by the end of follow-up. The aflibercept 2q8 group maintained VA outcomes comparable to monthly ranibizumab over 96 weeks while requiring, on average, five fewer injections. In addition, injection numbers between weeks 52 and 96 were lower in both the 2q4 and 2q8 aflibercept groups than in the Rq4 ranibizumab group. These findings support extended aflibercept dosing intervals as a means of reducing treatment load while largely preserving the visual gains achieved during the initial fixed-dosing period (Schmidt-Erfurth et al., 2014). Further research into optimizing aflibercept therapy led to two studies evaluating distinct dosing intervals and their implementation strategies. The ALTAIR trial compared aflibercept 2 mg administered in a T&E regimen, in which the interval between injections was adjusted in either 2-week or 4-week intervals, with outcomes assessed at 52 and 96 weeks. Results were comparable between the two groups. Over the 52-week period, the mean number of injections was 7.2 in the 2-week group and 6.9 in the 4-week group, while the mean final treatment interval reached 10.7 and 11.8 weeks, respectively. The mean change in VA was a gain of 9.0 and 8.4 letters at week 52, and 7.6 and 6.1 letters at week 96, for the 2-week and 4-week adjustment groups, respectively (Ohji et al., 2020). The ARIES study, in turn, compared early versus late implementation of T&E therapy with aflibercept 2 mg. Patients received injections at weeks 0, 4, 8 and 16, after which they were randomized 1:1 at week 16 into one of two groups. In the early-start group, T&E was initiated immediately, using a 2-week adjustment interval. In the late-start group, fixed dosing every 8 weeks was administered through the first year (week 52), after which the 2-week T&E adjustment regimen was introduced. Early-start T&E proved noninferior to late-start, indicating that initiating T&E immediately after the loading phase was as effective as delaying it (Mitchell et al., 2021). Taken together, the ALTAIR and ARIES trials provide further evidence supporting the use of aflibercept in a T&E regimen for treatment-naïve nAMD. Despite differences in study design and T&E implementation, both trials demonstrated sustained visual and anatomical benefits with fewer injections, indicating that proactive individualized interval extension can help maintain disease control while reducing the frequency of intravitreal injections (Mitchell et al., 2021; Ohji et al., 2020).

3.3. Brolucizumab

Brolucizumab is a single-chain antibody fragment that inhibits VEGF, approved by the FDA in 2019 for the treatment of nAMD. HAWK and HARRIER were pivotal phase III RCTs comparing the efficacy of intravitreal brolucizumab 3 mg (present in HAWK) or brolucizumab 6 mg with aflibercept 2 mg, using a noninferiority margin of 4 letters for the primary endpoint. After three monthly loading doses, patients receiving brolucizumab were dosed every 12 weeks, with intervals adjusted to every 8 weeks in the presence of disease activity, whereas patients receiving aflibercept were maintained on a fixed 8-week schedule. At week 48, brolucizumab demonstrated noninferiority to aflibercept in VA change: in HAWK, mean gains were 6.6 letters (brolucizumab 6 mg) and 6.1 letters (brolucizumab 3 mg) versus 6.8 letters (aflibercept), and in HARRIER, 6.9 letters (brolucizumab 6 mg) versus 7.6 letters (aflibercept) ($p < 0.001$ for each comparison). More than 50% of brolucizumab 6 mg treated eyes were maintained on a 12-week dosing interval through week 48 (56% in HAWK and 51% in HARRIER). At week 16, after identical treatment exposure, fewer brolucizumab 6 mg treated eyes showed disease activity compared with aflibercept in HAWK (24.0% vs. 34.5%; $p = 0.001$) and HARRIER (22.7% vs. 32.2%; $p = 0.002$). Greater reductions in central subfield thickness (CST) from baseline to week 48 were observed with brolucizumab 6 mg versus aflibercept in HAWK

(−172.8 μm vs. −143.7 μm; $p = 0.001$) and HARRIER (−193.8 μm vs. −143.9 μm; $p < 0.001$), and anatomic retinal fluid outcomes favored brolucizumab over aflibercept. The incidence of ocular adverse events was similar across all treatment groups in both trials (Dugel et al., 2020). These visual and anatomical benefits were sustained through 96 weeks in the same treatment groups. At week 96, the mean VA gain in HAWK was 5.6 letters for brolucizumab 3 mg, 5.9 letters for brolucizumab 6 mg, and 5.3 letters for aflibercept, whereas in HARRIER it was 6.1 letters for brolucizumab 6 mg and 6.6 letters for aflibercept. Overall, VA outcomes were comparable across treatment groups, consistent with the noninferiority of brolucizumab to aflibercept demonstrated at the primary endpoint. Greater reductions in CST were maintained with brolucizumab 6 mg versus aflibercept in both HAWK (−174.8 μm vs. −148.7 μm; $p = 0.0115$) and HARRIER (−197.7 μm vs. −155.1 μm; $p < 0.0001$), favoring brolucizumab. Moreover, at week 96, fewer eyes treated with brolucizumab compared with aflibercept showed persistent IRF and/or SRF in both trials (Dugel et al., 2021). A subsequent independent post hoc review of the HAWK and HARRIER data analyzed the ocular safety signal associated with brolucizumab. Among brolucizumab-treated eyes, the incidence of intraocular inflammation (IOI) was 4.6%, including IOI accompanied by retinal vasculitis in 3.3% and by both retinal vasculitis and retinal vascular occlusion in 2.1%. At least moderate VA loss of at least 15 letters occurred in 0.74% of brolucizumab treated eyes, the majority of which had concurrent inflammation, vasculitis, and occlusion. By comparison, the incidence of IOI in aflibercept treated eyes was lower, at 1.1%, with moderate VA loss in 0.14%. Most inflammatory events presented early, with the majority of vision-threatening cases occurring within the first three to six months after treatment initiation. These findings indicate that, although brolucizumab offers greater dosing durability and greater anatomic fluid control, it carries a distinct risk of IOI and occlusive retinal vasculitis that may result in severe vision loss, underscoring the need for careful patient monitoring and prompt recognition of inflammatory events, which adds to the surveillance requirements of treatment (Monés et al., 2021). A dedicated post hoc analysis of retinal fluid dynamics in HAWK and HARRIER further supported the more favorable anatomic effect of brolucizumab. At week 96, complete fluid resolution, defined as the absence of both IRF and SRF, was achieved by a greater proportion of brolucizumab 6 mg treated than aflibercept treated patients in both HAWK (76.1% vs. 63.1%; $p = 0.0002$) and HARRIER (75.4% vs. 61.8%; $p < 0.0001$). The proportion of patients achieving sustained dryness, defined as a fluid-free retina on at least three consecutive visits, was likewise higher with brolucizumab 6 mg than with aflibercept in both HAWK (84.7% vs. 79.2%) and HARRIER (91.2% vs. 78.0%). Notably, sustained dryness was reached earlier and with fewer injections in the brolucizumab groups, supporting earlier interval extension (Alali et al., 2025). Taken together, the clinical evidence for brolucizumab reflects a consistent tension between anatomic potency and ocular safety. Brolucizumab 6 mg was noninferior to aflibercept in VA through 96 weeks while allowing an extended dosing interval, and across the HAWK and HARRIER trials and their post hoc analyses it consistently produced greater anatomic efficacy than aflibercept, with larger reductions in CST and higher rates of complete fluid resolution and sustained retinal dryness. This advantage, however, is counterbalanced by a distinct safety signal: a spectrum of IOI, including retinal vasculitis and occlusive vasculitis, capable of causing severe vision loss, typically within the first months of treatment (Alali et al., 2025; Dugel et al., 2020; Dugel et al., 2021; Monés et al., 2021; Regillo et al., 2022). The MERLIN trial subsequently evaluated a more intensive every-4-week regimen in eyes with persistent fluid. At week 52, brolucizumab was noninferior in VA and superior in fluid control (40.4% vs. 19.0% fluid-free), and its 2-year results confirmed durability of this pattern: noninferiority in mean VA change to week 104 (between-group difference of −0.4 letters; $p = 0.0169$) and a markedly higher proportion of fluid-free eyes (52.5% vs. 28.2%; $p < 0.001$). Yet the inflammatory complication rate also grew over time, with IOI reaching 11.5% vs. 6.1% for aflibercept and a numerically higher rate of at least 15-letter vision loss (6.2% vs. 4.7%). These findings demonstrated that shortening the dosing interval does not mitigate, and may even amplify, the inflammatory risk. Collectively, the RCTs and post hoc data establish brolucizumab as a highly effective agent with meaningful durability and superior fluid control, but one whose use is limited by the risk of IOI and occlusive vasculitis. Its clinical role is therefore best defined by careful patient selection and vigilant monitoring, with proper balance of risk and benefit weighed against agents of comparable efficacy and more favorable ocular safety (Brown et al., 2025; Khanani et al., 2022).

3.4. Faricimab

Faricimab, a bispecific antibody that simultaneously inhibits both VEGF-A and angiopoietin-2 (Ang-2), was approved by the FDA in 2022 for the treatment of nAMD and has been evaluated in two pivotal phase III RCTs, TENAYA and LUCERNE. Treatment-naïve patients with nAMD aged at least 50 years were randomly assigned (1:1) to one of two groups. The first received intravitreal faricimab 6.0 mg at intervals of up to every 16 weeks, following four initial monthly loading doses, with interval extension determined by protocol-defined disease activity assessments at weeks 20 and 24. The second received aflibercept 2.0 mg every 8 weeks, following three initial monthly loading doses. The primary endpoint was the mean change in VA averaged over weeks 40, 44, and 48 (noninferiority margin of four letters). In this first-year analysis, faricimab proved noninferior to aflibercept in both TENAYA (5.8 vs. 5.1 letters) and LUCERNE (6.6 vs. 6.6 letters). Rates of ocular adverse events were comparable between the faricimab and aflibercept groups in both trials. Notably, at week 48 approximately 80% of faricimab treated patients were maintained on a dosing interval of every 12 weeks or longer, and approximately 45% on every 16 weeks. Overall, this first-year evaluation demonstrated the considerable potential of faricimab for the treatment of nAMD, achieving sustained efficacy while allowing extended dosing intervals of up to 16 weeks between injections (Heier et al., 2022). These outcomes were maintained over the second year, during which faricimab treated patients followed a T&E personalized treatment interval regimen. At two years, the change in VA remained comparable between the faricimab and aflibercept groups in both TENAYA (increase of 3.7 vs. 3.3 letters) and LUCERNE (increase of 5.0 vs. 5.2 letters). By the second year, durability was further demonstrated by 59.0% of faricimab treated patients in TENAYA and 66.9% in LUCERNE receiving every 16 weeks dosing, while 74.1% and 81.2%, respectively, were maintained on intervals of every 12 weeks or longer. Rates of ocular adverse events through the second year remained comparable between the faricimab and aflibercept groups in both TENAYA and LUCERNE. Taken together, the two-year data confirm that faricimab sustains the visual gains achieved in the first year while progressively extending treatment intervals, supporting its durability and potential to reduce treatment burden in nAMD (Khanani et al., 2024). A subsequent post hoc analysis assessed early anatomic responses during the initial 12-week loading phase of the pooled TENAYA and LUCERNE trials, a period during which both groups received an identical number of monthly injections, permitting a direct comparison. Across weeks 4, 8, and 12, CST showed greater reductions in eyes treated with faricimab than in those treated with aflibercept ($p < 0.0001$ at each visit), while visual outcomes were comparable. At week 12, absence of SRF was observed more frequently with faricimab (87.9% vs. 79.0%), as was complete resolution of both IRF and SRF (77.2% vs. 66.5%). By contrast, clearance of IRF alone did not differ meaningfully between the groups (88.4% vs. 85.0%). Anatomic fluid resolution also occurred earlier with faricimab: among eyes with fluid at baseline, the 75th percentile of time to first fluid-free status was reached by week 8, compared with week 12 for aflibercept. By week 12, the cumulative incidence of first fluid-free status was 85.5% versus 75.0%. Taken together, these data suggest that faricimab produces faster and more complete anatomic drying than aflibercept under matched dosing, which may enable earlier interval extension and more consistent disease control (Cheung et al., 2025). Collectively, the TENAYA and LUCERNE program establishes faricimab as an effective and durable option for treatment-naïve nAMD. Across the first year, faricimab matched aflibercept in VA while allowing markedly extended dosing intervals, and these gains were maintained through two years under a T&E regimen. The dedicated head-to-head analysis further showed that, under matched dosing, faricimab produced faster and more complete anatomic fluid resolution than aflibercept, providing a plausible anatomic basis for its extended durability. These outcomes are consistent with the dual inhibition of faricimab of both VEGF-A and Ang-2. As reviewed by Agostini et al., adding Ang-2/Tie-2 blockade to VEGF-A inhibition is thought to stabilize the retinal vasculature and limit both leakage and inflammatory signaling to a degree not attainable with VEGF-A suppression alone, providing a mechanistic rationale for the improved disease control and lower treatment burden seen across the faricimab program. Importantly, faricimab's tolerability profile in TENAYA and LUCERNE was comparable to aflibercept, without the distinct IOI signal associated with brolucizumab - an advantage of particular relevance when weighing durable agents against one another. The long-term durability and safety of faricimab are being examined further in the ongoing open-label extension study AVONELLE-X (NCT04777201), which follows patients who completed TENAYA and LUCERNE for an additional period of treatment. These data will help clarify whether the interval extension and disease control achieved through two years are sustained over a longer period, and will further define faricimab's role within the evolving landscape of anti-VEGF and multitarget therapies for nAMD (Agostini et al., 2024; Cheung et al., 2025; Heier et al., 2022; Khanani et al., 2024). Beyond the pivotal trials, the comparative standing of faricimab among current anti-VEGF agents has been examined in a recent systematic review and network meta-analysis of

faricimab, aflibercept, conbercept, and ranibizumab. Across the four agents, no statistically significant differences in VA improvement were identified, with comparable effects on choroidal neovascularization regression. Faricimab's principal distinguishing advantage was durability, requiring significantly fewer injections than the other agents with high-certainty evidence. This benefit was balanced against safety and anatomic considerations: aflibercept 2 mg was associated with fewer ocular adverse events than faricimab, whereas aflibercept and conbercept offered an advantage in anatomic outcomes. Collectively, these findings support faricimab as a durable, injection-sparing option whose main advantage lies in extended dosing rather than in superior visual or anatomic outcomes relative to other agents (Cen et al., 2026).

3.5. Aflibercept 8 mg

The recognition that many patients require frequent injections to maintain vision has driven efforts to extend dosing intervals without sacrificing efficacy - the same goal underlying the T&E regimens and the development of longer-acting agents such as faricimab. A complementary strategy has been to increase the molar dose of an established agent: a higher-dose 8 mg formulation of aflibercept was developed to prolong intravitreal VEGF suppression and thereby support longer intervals between injections. Following the phase 2 CANDELA study, in which 8 mg aflibercept produced modestly larger gains in anatomical and vision outcomes than the 2 mg dose given on an identical schedule, the higher dose was advanced into the pivotal phase III PULSAR trial, and in 2023 this dose was approved by the FDA for the treatment of nAMD. In PULSAR, treatment-naïve patients with nAMD were allocated in three groups: 8 mg every 12 weeks (8q12), 8 mg every 16 weeks (8q16), or the standard 2 mg every 8 weeks (2q8). Each group's treatment started with three monthly loading doses. Beginning at week 16, patients in the 8 mg groups could have their interval shortened if predefined markers of disease activity emerged. The primary endpoint was the change in VA at week 48, with a defined noninferiority margin of four letters. Both higher-dose regimens proved noninferior to aflibercept 2q8 (mean VA change: gain of 6.7 letters for 8q12 and 6.2 letters for 8q16, vs. 7.6 letters for 2q8). Rates of ocular adverse events were similar across the three groups (39%, 38%, and 39%, respectively). Notably, 83% of 8 mg treated patients maintained a dosing interval of 12 weeks or longer through week 48, demonstrating that a higher molar dose can sustain visual and anatomic gains comparable to standard aflibercept while reducing injection frequency (Lanzetta et al., 2024; Wykoff et al., 2023).

3.6. Bevacizumab-vikg

Bevacizumab is a full-length, humanized monoclonal antibody targeting VEGF-A that was originally developed as a systemic anti-angiogenic therapy for cancer. Although bevacizumab was not approved by the FDA for the treatment of nAMD, intravitreal bevacizumab has been widely used off-label for nearly two decades owing to its proven clinical efficacy and substantially lower treatment costs compared with licensed anti-VEGF agents. Evidence supporting the off-label use of bevacizumab was established by several landmark RCTs, including CATT, IVAN, and LUCAS, which consistently demonstrated visual outcomes comparable to ranibizumab, despite small differences in anatomical outcomes and treatment frequency (Berg et al., 2015; Chakravarthy et al., 2013; Martin et al., 2011). Despite these broadly comparable visual outcomes, several considerations have limited the clinical role of bevacizumab and account for its lack of regulatory approval in nAMD. In the CATT trial, a higher rate of serious systemic adverse events was observed with bevacizumab than with ranibizumab, although these events were not concentrated in the organ systems typically associated with anti-VEGF toxicity, and their significance remains debated. Pooled analyses of CATT and IVAN likewise found an excess of overall serious adverse events without consistent differences in specific event categories. Because these trials were not powered to detect drug-specific safety differences, uncertainty about the systemic risk profile of intravitreal bevacizumab has persisted (Chakravarthy et al., 2013; Martin et al., 2011). Whereas CATT reported more serious systemic events with bevacizumab, LUCAS found fewer arteriothrombotic events in the bevacizumab group than with ranibizumab, further limiting firm conclusions about any drug-specific systemic risk. A further and arguably decisive limitation is pharmaceutical rather than clinical. Bevacizumab was developed and formulated for intravenous oncological use, not for intraocular injection, and its ophthalmic use therefore requires repackaging by compounding pharmacies into smaller aliquots. This compounding step introduces risks of contamination and variable drug quality, and produces an unlicensed preparation that falls outside standard regulatory oversight (Yannuzzi et al., 2015). Critically, bevacizumab has never been submitted for regulatory approval in an ophthalmic indication and therefore remains an off-label option: widely used and highly cost-effective, yet lacking the formulation, dedicated safety data, and regulatory approval of the licensed anti-VEGF agents (Berg et al., 2015; Chakravarthy et al., 2013; Martin et

al., 2011; Parikh et al., 2025). These limitations of off-label use motivated the development of an ophthalmic-specific formulation of bevacizumab, bevacizumab-vikg. In July 2026, the FDA approved bevacizumab-vikg (LYTENAVA) for the treatment of nAMD (Outlook Therapeutics, 2026). Unlike repackaged intravenous bevacizumab, this product is formulated specifically for intraocular use and is supported by a validated manufacturing process, approved labeling, and formal regulatory oversight. Approval was based on the pivotal phase III NORSE TWO trial, a superiority study in which patients with nAMD were randomized to monthly bevacizumab-vikg or ranibizumab administered according to its approved label. The trial met its primary endpoint, with a significantly greater proportion of bevacizumab-vikg treated patients who gained at least 15 letters in VA compared with ranibizumab (41.7% vs. 23.1%; $p = 0.0052$). The most common ocular adverse reaction was conjunctival hemorrhage, and IOI occurred infrequently. By providing a regulated, ophthalmic-grade formulation, bevacizumab-vikg addresses the principal pharmaceutical and quality-control concerns associated with compounded bevacizumab, while retaining the inherent cost advantage that has long made the molecule a mainstay of nAMD therapy (Rahhal et al., 2025). Table 1 presents a summary of the anti-VEGF agents currently available for nAMD.

Table 1. Anti-VEGF agents used in the treatment of neovascular age-related macular degeneration: molecular target, pivotal clinical trials and year of US Food and Drug Administration approval for neovascular age-related macular degeneration.

Agent	Type of anti-VEGF targeting	Key pivotal RCTs	Year of FDA approval for nAMD
Ranibizumab	Recombinant, humanized monoclonal antibody fragment that neutralizes all active isoforms of VEGF-A	Pivotal: MARINA; ANCHOR Post-approval: HARBOR Long-term / real-world: SEVEN-UP; LUMINOUS	2006
Aflibercept 2 mg	Recombinant fusion protein comprising the extracellular ligand-binding domains of human VEGF receptors	Pivotal: VIEW 1; VIEW 2 Regimen optimization: ALTAIR; ARIES	2011
Brolucizumab	Single-chain antibody fragment that inhibits VEGF	Pivotal: HAWK; HARRIER Persistent fluid: MERLIN	2019
Faricimab	Bispecific antibody with simultaneous inhibition of VEGF-A and angiopoietin-2 (Ang-2)	Pivotal: TENAYA; LUCERNE Ongoing open-label extension: AVONELLE-X	2022
Aflibercept 8 mg	Same recombinant fusion protein as aflibercept 2 mg, given at a higher molar dose to prolong intravitreal VEGF suppression	Pivotal: PULSAR Preceded by phase 2: CANDELA	2023
Bevacizumab-vikg	Full-length, humanized monoclonal anti-VEGF-A antibody in an ophthalmic-specific formulation	Pivotal: NORSE TWO	2026

Abbreviations: Ang-2, angiopoietin-2; FDA, US Food and Drug Administration; nAMD, neovascular age-related macular degeneration; RCT, randomized controlled trial; VEGF, vascular endothelial growth factor.

4. Treatment Strategies

The scheduling of anti-VEGF therapy influences outcomes nearly as much as the choice of molecule, since the timing of injections determines both the vision preserved and the cumulative burden borne by the patient over years of treatment. Four regimens predominate in practice, differing mainly in how the timing of the next injection is decided.

Fixed dosing. Under a fixed schedule, injections are administered at predetermined intervals, commonly every 4 or 8 weeks, regardless of disease activity. This approach, established in the MARINA and ANCHOR trials, produces consistent visual outcomes, although many of its injections and clinic visits are directed at eyes in which the disease is already quiescent. The added intensity brings no visual benefit. In a systematic review and meta-analysis, T&E matched fixed dosing for visual acuity at both one and two years while requiring significantly fewer injections (Rosenberg et al., 2023).

Pro re nata. A PRN, or as-needed, regimen withholds treatment until disease activity reappears at a monitoring visit. Its main drawback is that it is reactive: by the time fluid is detected, it has usually already recurred, at a cost to vision. In the same analysis, T&E outperformed PRN by 3.95 letters at one year and 4.08 letters at two. The injections that PRN saves therefore come at the expense of vision, and because monitoring remains monthly, the patient gains no reduction in clinic visits (Rosenberg et al., 2023).

Treat-and-extend. T&E has become the default regimen in much of clinical practice, because it combines pre-emptive treatment with an individually adjusted interval. Three monthly loading doses are followed by an injection at every subsequent visit. The interval is extended while the disease stays inactive and shortened once activity returns, preserving the visual benefit of fixed dosing without its relentless frequency (Lai et al., 2025). Its success depends on how the interval is adjusted, and that judgment rests on optical coherence tomography (OCT). The most active part of a lesion does not always lie beneath the fovea and for this reason the entire macula, not the central subfield alone, must be imaged (Iida et al., 2025). A dry retina and stable vision allow the interval to be extended, usually in 2- to 4-week steps and up to a maximum of 16 weeks. When activity returns, whether as new or increasing fluid, hemorrhage, an enlarging pigment epithelial detachment, or a decline in vision, the interval is shortened accordingly, generally to no less than 4 weeks. An equivocal scan calls for no change. Adjusted in this way, the schedule follows the tempo of each patient's disease, which is why it has been advocated in successive consensus statements (Lai et al., 2025).

Treat-extend-stop (T&E&S). T&E&S adds one further option to this framework: stopping treatment altogether. A patient who has received several consecutive injections at the maximum 16-week interval without recurrence may have treatment suspended. Injections are then replaced by monitoring every 3 to 4 months and resumed at the first sign of relapse. The aim is to spare injections in an eye that no longer needs them. The disease can, however, reactivate unexpectedly during the treatment-free period, so continued monitoring must remain rigorous (Lai et al., 2025).

Switching agents. Some eyes remain inadequately controlled on their initial agent. When disease persists despite optimal dosing, whether as IRF or SRF that will not resolve, a refractory pigment epithelial detachment, an absence of visual improvement, or an interval that cannot be extended beyond 4 weeks, a change of agent is a recognized option. This applies whether the initial response was insufficient or a previously effective drug has lost efficacy over time (Iida et al., 2025; Schneider et al., 2024). Most of the accumulating real-world evidence concerns a switch from aflibercept to faricimab, chosen for its dual inhibition of VEGF-A and Ang-2 and its longer duration of action. Such switches consistently improve the anatomy, SRF in particular, and allow a modest extension of the interval, although VA tends to stabilize rather than improve (Schneider et al., 2024). The predominantly anatomical rather than functional benefit is consistent with the timing of treatment switching, which is usually performed late in the disease course, when the potential for visual recovery is already limited.

All of the regimens share a common principle: to anticipate exudation rather than react to it, to extend the interval while the disease is inactive, to shorten it when activity resumes, and to change agent when the current one allows neither adequate control nor further extension. Each of these decisions, whether to extend, shorten, switch therapy, or discontinue treatment, aims to balance anatomical control, preservation of visual function, and treatment burden against the persistent risk of disease recurrence. Table 2 presents a summary of the anti-VEGF treatment strategies currently applied in nAMD.

Table 2. Anti-VEGF treatment strategies in neovascular age-related macular degeneration: decision rule, advantages and limitations.

Strategy	How the next injection is decided	Advantages	Limitations and cautions
Fixed dosing	Injections at predetermined intervals, commonly every 4 or 8 weeks, irrespective of disease activity	Consistent visual outcomes; simple, protocol-driven scheduling	Many injections and visits are given to eyes in which disease is already quiescent; the added intensity confers no visual benefit
Pro re nata (PRN)	Treatment withheld until disease activity reappears at a monitoring visit	Fewer injections than fixed dosing	Reactive by design: fluid has usually already recurred by the time it is detected, at a cost to vision; monitoring remains monthly, so clinic visits are not reduced
Treat-and-extend (T&E)	Three monthly loading doses, then an injection at every visit with the interval individually adjusted: extended in 2–4 week steps up to a maximum of 16 weeks while the retina is dry and vision stable, shortened (generally to no less than 4 weeks) when activity returns, unchanged if the scan is equivocal	Preemptive rather than reactive; preserves the visual benefit of fixed dosing without its frequency; follows the tempo of each patient's disease; advocated in successive consensus statements	Depends on accurate interval adjustment, clinic visits are significantly reduced
Treat-extend-stop (T&E&S)	As for T&E, with the added option of suspending treatment after several consecutive injections at the maximum 16-week interval without recurrence; injections are replaced by monitoring every 3–4 months and resumed at the first sign of relapse	Spares injections in an eye that no longer needs them	Disease can reactivate unexpectedly during the treatment-free period, so monitoring must remain rigorous; no universally accepted criteria for discontinuation
Switching agents	Change of agent when disease persists despite optimal dosing: unresolving IRF or SRF, refractory pigment epithelial detachment, absence of visual improvement, or an interval that cannot be extended beyond 4 weeks	Consistently improves anatomy, SRF in particular, and permits modest interval extension	Visual acuity tends to stabilize rather than improve, consistent with switching usually being performed late in the disease course when recovery potential is limited; no universally accepted switching criteria

Abbreviations: IRF, intraretinal fluid; OCT, optical coherence tomography; PRN, pro re nata; SRF, subretinal fluid; T&E, treat-and-extend; T&E&S, treat-extend-stop.

5. Conclusions

Anti-VEGF therapy has fundamentally transformed the management of neovascular age-related macular degeneration, converting a condition once associated with inevitable severe vision loss into one in which long-term preservation of visual function is achievable for many patients. Across the pivotal RCTs reviewed here: MARINA and ANCHOR, VIEW 1 and VIEW 2, HAWK and HARRIER, TENAYA and LUCERNE, and PULSAR, every approved agent produced broadly comparable gains in visual acuity. The clinically meaningful differences between them therefore lie not in visual outcome but in durability, anatomical fluid control and safety. Faricimab and aflibercept 8 mg sustain dosing intervals of 12 to 16 weeks in most patients, brolucizumab offers strong anatomical control offset by a distinct risk of intraocular inflammation, retinal vasculitis and vascular occlusion, and the approval of bevacizumab-vikg supplies a regulated, ophthalmic-grade formulation of a molecule long used off-label, addressing the compounding and quality-control concerns that had limited its role.

Scheduling now influences outcomes nearly as much as the choice of molecule. T&E has become the preferred regimen because it preserves the visual benefit of fixed dosing with fewer injections while avoiding the reactive visual losses inherent to PRN treatment. Its extensions, T&E&S and agent switching, offer further individualization, although both rest on a narrower evidence base than the regimens themselves.

Nevertheless, important challenges remain. Individual variability in treatment response is substantial, and the trials reviewed here have not established baseline characteristics that reliably predict which patients will sustain extended dosing intervals. The burden of repeated injections and monitoring visits persists, criteria for switching agents or suspending treatment are not universally agreed, and anti-VEGF therapy remains suppressive rather than disease-modifying.

Future research should therefore pursue several priorities. First, imaging, genetic and biochemical biomarkers that predict treatment response and durability should be identified, so that agent and interval can be matched to the individual patient from the outset. Second, prospective randomized head-to-head comparisons of faricimab and aflibercept 8 mg are required, since no direct comparative trial of these two agents has yet been reported and their relative durability therefore remains unresolved. Third, evidence-based criteria should be developed for treatment switching and for treatment suspension within a T&E&S framework, including the optimal monitoring interval during treatment-free periods. Fourth, long-term real-world evaluation of the newer agents, including the ongoing AVONELLE-X extension study and post-approval surveillance of bevacizumab-vikg, is needed to confirm that the durability and safety observed in trials are reproduced in routine practice. Finally, investigation of disease-modifying approaches should continue, particularly gene-based therapies capable of providing sustained VEGF suppression from a single intervention. Progress in these areas will be essential to improve patient outcomes further and to address the growing global burden of neovascular age-related macular degeneration.

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