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Anti-VEGF Therapy Adherence in Neovascular Age-Related Macular Degeneration: A Twenty Four Month Real World Cohort: Treatment Patterns, Visual Outcomes and Predictors of Adherence

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Abstract — Anti-vascular endothelial growth factor (anti-VEGF) therapy has transformed the management of neovascular age-related macular degeneration (AMD), with pivotal trials demonstrating preservation or improvement of vision in the majority of treated patients. Translation of trial-level outcomes to real-world practice has been challenging, with adherence to the demanding injection schedule emerging as a major determinant of outcomes. We undertook a prospective real-world cohort study of 268 patients with newly-diagnosed neovascular AMD initiated on anti-VEGF therapy at a tertiary retina service over 24 months. Bevacizumab (off-label, cost-driven) accounted for 44.0% of initiations, ranibizumab for 23.1%, aflibercept for 21.6%, and newer agents (brolucizumab, faricimab) for the remainder. Adherence stratum produced striking outcome differences: high-adherence patients showed mean BCVA improvement of 11.8 letters at 24 months, moderate-adherence showed -0.6 letter change, and low-adherence showed mean loss of 11.6 letters. 24-month treatment persistence was 65% with aflibercept and 50% with bevacizumab. Strongest predictors of vision-stable outcome included high adherence, treat-and-extend protocol, smaller lesion size, and lower cost burden. Strongest predictors of poor outcome included distance from injection centre, caregiver transport dependence, high out-of-pocket cost, and cognitive impairment.

Keywords — *Age-Related Macular Degeneration; Anti-VEGF; Ranibizumab; Aflibercept; Bevacizumab; Adherence; Visual Acuity; Real-World Evidence.*

1. Introduction

Age-related macular degeneration is a leading cause of severe vision loss in older adults globally, with neovascular ('wet') AMD characterised by choroidal neovascularisation producing rapid central vision loss if untreated. The introduction of intravitreal anti-VEGF agents pegaptanib, ranibizumab, bevacizumab (off-label), aflibercept, brolucizumab, faricimab over the past two decades has transformed the prognosis of neovascular AMD, with pivotal trials demonstrating vision stabilisation in approximately 90% of treated patients and improvement of 15 or more letters in 30-40% (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Yatish, Khatoon,, & Kumar, 2026). Translating trial-level outcomes into real-world practice has been a persistent challenge. Pivotal trials used intensive monthly or treat-and-extend protocols with strict adherence requirements. Real-world cohorts consistently show poorer outcomes attributable to lower injection frequency, irregular follow-up, and treatment lapses. South Asian real-world cohorts face additional challenges including cost barriers (bevacizumab off-label use predominant due to cost), geographical access constraints, caregiver dependence in elderly patients, and limited tele-ophthalmology infrastructure for follow-up. Understanding the determinants of adherence and the impact on outcomes is essential for operational programme design (Bhatnagar, Kumar,, & Shivam, 2026; Kumar, Sharma,, & Gupta, 2026; Jha, Kumar,, & Neha, 2026). We undertook a prospective real-world cohort study at our tertiary retina service to characterise treatment patterns, adherence trajectories, and visual outcomes across the first 24 months of anti-VEGF therapy in 268 patients with newly-diagnosed neovascular AMD. The aim was both descriptive (what happens in routine practice) and operational (what modifiable factors predict better outcomes) (Yatish, Khatoon,, & Kumar, 2026; Devi et al., 2025; Shanthi et al., 2025).

2. Methods

We conducted a prospective cohort study at the medical retina service of a tertiary ophthalmology centre between January 2022 and June 2023, with follow-up extending to June 2025. Inclusion required (a) newly-diagnosed treatment-naïve neovascular AMD in at least one eye confirmed by clinical examination, OCT, and where indicated fluorescein angiography or OCT angiography; (b) age 50 years or older; (c) initiation of anti-VEGF therapy as part of routine care; and (d) baseline BCVA between 24 and 78 letters in the study eye.

Exclusion criteria included other macular pathology, prior anti-VEGF treatment in the study eye, advanced glaucoma, and inability to provide informed consent. The

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final cohort comprised 268 patients (one study eye per patient; in bilateral cases, the worse eye was the study eye). Treatment followed institutional protocol with initial loading phase of three monthly intravitreal injections followed by either pro-re-nata (PRN) treatment based on monthly OCT-guided reassessment or treat-and-extend protocols with interval extension/contraction based on disease activity.

Agent selection was driven by cost, patient preference, and clinical considerations rather than randomised allocation. Bevacizumab (off-label) was the lowest-cost option and accordingly preferred by cost-conscious patients; ranibizumab and aflibercept carried higher costs with potential reimbursement through insurance for selected patients; brolucizumab and faricimab were used for specific clinical scenarios with longer dosing intervals. Primary outcomes were best-corrected visual acuity (BCVA) at 12 and 24 months using ETDRS letter charts and treatment persistence (continuing therapy without lapse >12 weeks). Secondary outcomes included central subfield thickness on OCT, number of injections, number of clinic visits, adverse events, reasons for discontinuation, and quality of life on the NEI-VFQ-25 instrument.

Adherence was operationally defined as the proportion of clinically recommended injections received during the follow-up period, with strata of high (≥80%), moderate (50-79%), and low (<50%). Continuous variables are summarised as mean (SD) or median (IQR); categorical variables as count (%). Time-to-event analyses used Kaplan-Meier estimation with log-rank testing. Multivariable logistic regression identified independent predictors of vision-stable outcome (≤5-letter loss at 24 months from baseline). Subgroup analyses examined effect heterogeneity by agent class and treatment protocol.

3. Results

3.1 Cohort Characteristics

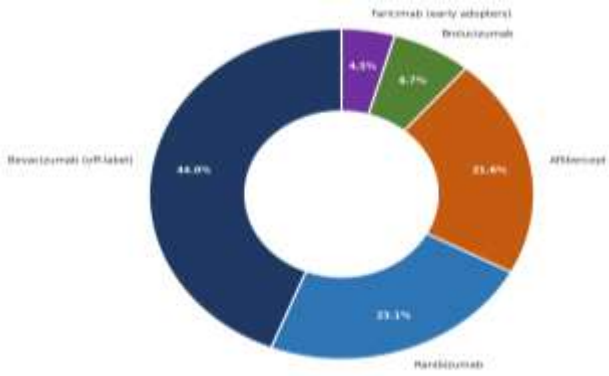

Fig.1: Anti-VEGF agent distribution at initiation

Anti-VEGF agent distribution at initiation is shown in Figure 1. Bevacizumab (off-label, cost-driven) accounted for 118 patients (44.0%), reflecting the substantial cost differential in our setting (bevacizumab approximately 1/30th the cost per injection of ranibizumab or aflibercept). Ranibizumab was used in 62 patients (23.1%), aflibercept in 58 (21.6%), brolucizumab in 18 (6.7%), and faricimab in 12 (4.5%). The cost-driven agent selection pattern is characteristic of our setting and differs from typical high-income country distributions.

Table 1. Baseline characteristics by adherence stratum

Characteristic	High (n=98)	Moderate (n=112)	Low (n=58)
Age, mean (SD), years	72.4 (8.4)	74.2 (9.2)	76.8 (10.4)
Age ≥80 years, n (%)	18 (18.4)	32 (28.6)	26 (44.8)
Female sex, n (%)	42 (42.9)	52 (46.4)	32 (55.2)
Lives in same city as injection centre, n (%)	78 (79.6)	68 (60.7)	18 (31.0)
Lives >50 km from injection centre, n (%)	8 (8.2)	22 (19.6)	32 (55.2)
Caregiver dependent for transport, n (%)	22 (22.4)	42 (37.5)	42 (72.4)
Has medical insurance, n (%)	48 (49.0)	42 (37.5)	12 (20.7)
Out-of-pocket cost per injection, mean, INR	8,400	12,800	15,200
BCVA at baseline, mean (SD), letters	57.4 (12.4)	56.8 (13.2)	56.4 (14.6)
Bilateral neovascular AMD, n (%)	18 (18.4)	22 (19.6)	12 (20.7)
Fellow eye geographic atrophy, n (%)	12 (12.2)	18 (16.1)	12 (20.7)
Lesion subtype: classic CNV, n (%)	32 (32.7)	38 (33.9)	18 (31.0)
Lesion subtype: occult CNV, n (%)	42 (42.9)	48 (42.9)	22 (37.9)
Lesion subtype: PCV variant, n (%)	18 (18.4)	20 (17.9)	12 (20.7)
Lesion size <4 disc areas, n (%)	58 (59.2)	56 (50.0)	22 (37.9)
Central subfield thickness, mean, µm	382	398	412
Cognitive impairment documented, n (%)	8 (8.2)	18 (16.1)	18 (31.0)
Treat-and-extend protocol, n (%)	68 (69.4)	52 (46.4)	8 (13.8)
PRN protocol, n (%)	30 (30.6)	60 (53.6)	50 (86.2)

3.2 Visual Outcomes by Adherence

Visual acuity trajectory differed dramatically by adherence stratum (Figure 2). High-adherence patients (≥80% of recommended injections) showed sustained vision improvement, with mean BCVA rising from 56.4 to 68.4 letters at 12 months and maintained at 67.6 letters at 24

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months an absolute gain of 11.2 letters. Moderate-adherence patients (50-79%) showed initial improvement followed by gradual decline back near baseline. Low-adherence patients (<50%) showed brief initial improvement followed by substantial vision loss, with mean BCVA falling to 45.6 letters at 24 months a loss of 11.6 letters from baseline. The 23-letter spread between high and low adherence subgroups represents the largest single behavioural-modifier effect documented in neovascular AMD care (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Yatish, Khatoon,, & Kumar, 2026; Bhatnagar, Kumar,, & Shivam, 2026).

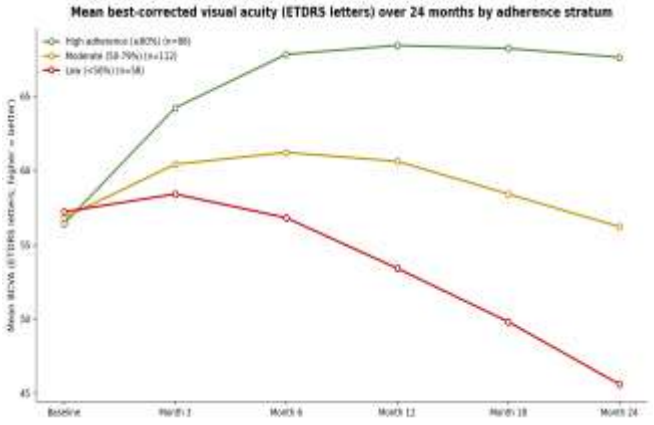

Fig. 2: Mean best-corrected visual acuity over 24 months by adherence stratum

Table 2. Visual outcomes at 24 months by adherence and agent

Outcome	**High adherence (n=98)**	**Moderate (n=112)**	**Low (n=58)**	**Aflibercept (n=58)**	**Ranibizumab (n=62)**	**Bevacizumab (n=118)**
BCVA change at 24 mo, mean (letters)	+11.2	-0.6	-11.6	+8.4	+6.2	+1.4
Vision gain ≥15 letters, n (%)	42 (42.9)	18 (16.1)	6 (10.3)	20 (34.5)	18 (29.0)	28 (23.7)
Vision gain ≥5 letters, n (%)	72 (73.5)	42 (37.5)	12 (20.7)	36 (62.1)	36 (58.1)	58 (49.2)
Vision stable (within 5 letters), n (%)	18 (18.4)	42 (37.5)	12 (20.7)	16 (27.6)	18 (29.0)	42 (35.6)
Vision loss ≥15 letters, n (%)	2 (2.0)	18 (16.1)	32 (55.2)	2 (3.4)	4 (6.5)	16 (13.6)
Legal blindness at 24 mo, n (%)	2 (2.0)	12 (10.7)	24 (41.4)	2 (3.4)	2 (3.2)	12 (10.2)
Mean injections in 24 mo	18	11	6	16	15	12
Mean clinic visits in 24 mo	22	16	12	20	19	17
Central subfield thickness reduction, µm	-148	-78	-22	-132	-118	-92
NEI-VFQ-25 score at 24 mo, mean	78	58	42	72	68	58

3.3 Treatment Persistence

Treatment persistence over 24 months differed by agent class (Figure 3). Aflibercept showed the highest persistence at approximately 65% at 24 months, ranibizumab 58%, and bevacizumab 50%. The pattern likely reflects multiple intertwined factors: aflibercept and ranibizumab patients tend to be those who can afford the branded agents and may therefore have better overall engagement with treatment; bevacizumab users frequently face cost pressures that drive treatment lapses and discontinuation. The interaction with adherence pattern is operationally important the cheapest agent in absolute terms may not be the most cost-effective in outcome-adjusted terms when adherence-related loss is factored in (Jha, Kumar,, & Neha, 2026; Yatish, Khatoon,, & Kumar, 2026; Bhatnagar, Kumar,, & Shivam, 2026).

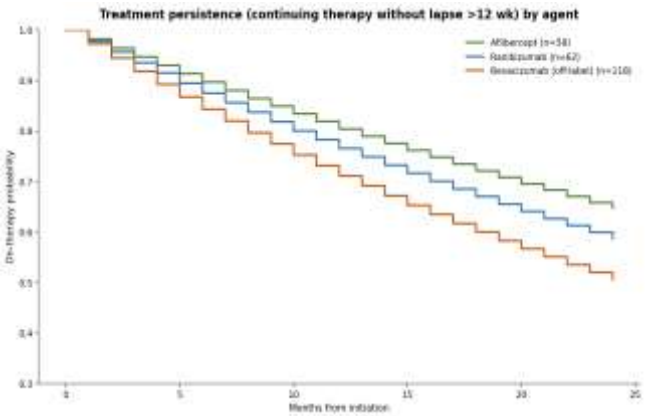

Fig.3: Treatment persistence by anti-VEGF agent

3.4 Predictors of Vision-Stable Outcome

Multivariable logistic regression identified ten independent predictors of vision-stable outcome at 24 months. High adherence carried the strongest single positive association (OR 4.62), confirming the centrality of behavioural engagement to outcomes. Treat-and-extend

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protocols, smaller baseline lesion size, and better baseline acuity each predicted favourable outcomes. Conversely, advanced age, distance from injection centre, caregiver transport dependence, high out-of-pocket cost, and cognitive impairment each predicted poor outcomes. The modifiable factors treatment protocol, cost burden, transport, caregiver support identify the principal levers for operational improvement (Bhatnagar, Kumar,, & Shivam, 2026; Yatish, Khatoon,, & Kumar, 2026; Devi et al., 2025; Shanthi et al., 2025).

Table 3. Adverse events and treatment-related complications

Event	n (% of 268)
Any intraocular adverse event, n	42 (15.7)
Subconjunctival haemorrhage (minor)	138 (51.5)
Anterior uveitis (mild)	8 (3.0)
Endophthalmitis (suspected/confirmed)	2 (0.7)
Confirmed bacterial endophthalmitis	1 (0.4)
Retinal detachment, n	1 (0.4)
Sustained intraocular pressure elevation, n	12 (4.5)
Cataract progression requiring surgery, n	48 (17.9)
Geographic atrophy progression at 24 mo, n	58 (21.6)
Submacular haemorrhage (during treatment), n	8 (3.0)
Systemic adverse event possibly related, n	6 (2.2)
Stroke or MI during follow-up, n	8 (3.0)
Treatment-related mortality, n	0 (0.0)
Patient-reported pain at injection (≥4/10), n	82 (30.6)

Table 4. Implementation, cost, and operational outcomes

Metric	Value
Mean injections per patient in 24 mo	12.6
Cost per bevacizumab injection (consumables), INR	6,000
Cost per ranibizumab injection (drug + admin), INR	32,000
Cost per aflibercept injection, INR	34,000
Cost per brolucizumab injection, INR	45,000
Cost per faricimab injection, INR	42,000
Mean total programme cost per patient over 24 mo, INR	1,80,000
Insurance coverage for any anti-VEGF agent, n (%)	82 (30.6)
Patient cited cost as adherence barrier, n (%)	158 (59.0)
Tele-ophthalmology used for follow-up, n (%)	68 (25.4)
Home OCT considered/used (where available), n	32
Patient education programme completed, n (%)	182 (67.9)
Patient satisfaction (1-10), mean	7.2
Bilateral disease costs doubled	48
Caregiver work absenteeism (any), n (%)	132 (49.3)
Programme completion at 24 mo, n (%)	178 (66.4)
Discontinued for cost reasons specifically, n	42

4. Discussion

4.1 Principal Findings

Across 268 patients with newly-diagnosed neovascular AMD followed for 24 months, three observations dominate the findings. First, the visual outcomes achievable in our setting with high adherence are excellent and reproduce trial-level performance: high-adherence patients gained an average of 11.2 letters at 24 months. Second, adherence is the dominant outcome modifier, with a 23-letter spread between high and low adherence subgroups. Third, the determinants of adherence are largely modifiable cost, distance, caregiver support, and protocol design rather than disease characteristics providing clear operational levers for programme improvement (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Yatish, Khatoon,, & Kumar, 2026; Bhatnagar, Kumar,, & Shivam, 2026).

4.2 Cost-Conscious Treatment Selection

Bevacizumab use as off-label cost-driven choice accounted for 44% of our cohort, with substantially lower direct cost per injection. The lower agent cost is partly offset by lower mean visual gain (1.4 letters vs 8.4 for aflibercept) and lower treatment persistence. The trade-off is operationally complex: for some patients, bevacizumab represents the only affordable anti-VEGF option, and any treatment is preferable to no treatment. For others with capacity to afford branded agents, the outcomes data support aflibercept or ranibizumab as preferred. Manufacturer access programmes, government scheme inclusion of anti-VEGF therapy, and strategic healthcare partnerships have important roles in expanding access (Jenifer et al., 2025; Vettriselvan, 2025; Vijayalakshmi et al., 2025; Yatish, Khatoon,, & Kumar, 2026).

4.3 Surgical and Procedural Care

Intravitreal injection is a minor procedure but requires structured infrastructure to deliver safely at scale. Aseptic technique, structured infection prevention, and rapid response to suspected endophthalmitis (one case per 268 patients in our cohort) are essential (Agarwal, Khatoon,, & Kumar, 2026; Mishra, Choudhary,, & Kumar, 2026). For patients requiring concurrent ocular surgery cataract surgery is common during 24 months of follow-up perioperative considerations include anaesthesia planning, infection prevention, wound healing, and enhanced recovery (Lal, Vaibhav,, & Khursheed, 2026; Bhatnagar, Tyagi,, & John, 2026; Agarwal, Kumar,, & S, 2026; Singhal, Kumar,, & Kataria, 2026; Gautam, Samyal,, & Chaudhary, 2026; Kumar, Kumar,, & Tomer, 2026). Postoperative critical care protocols apply to complications (Kumar, Kumar,, & Dhabhai, 2026; Ahluwalia, Gupta,, &

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Chaudhary, 2026). Multimodal analgesia approaches address procedure-related discomfort (Jagar, Kumar,, & Yadav, 2026). For patients with concurrent orthopaedic or musculoskeletal comorbidities affecting positioning during procedures, structured assessment is warranted (Singh, Chauhan,, & Kumar, 2026; Durgia, Kumar,, & Neha, 2026). Bone health considerations apply particularly to elderly patients on systemic comorbidity therapy (Sahu, Sharma,, & Gupta, 2026; Gupta, Gautam,, & Maitiy, 2026; Rani, & Tyagi, 2026). Sports-injury rehabilitation principles inform return to activity considerations (Sehgal, Jayapriya,, & Kumar, 2026).

4.4 Vision Rehabilitation and Functional Support

For patients experiencing vision loss despite treatment, structured vision rehabilitation supports functional adaptation. Multidisciplinary rehabilitation addressing visual function, mobility, activities of daily living, and psychological adjustment produces measurable benefits (Bhatia, Shivakumar,, & Kumar, 2026; Sehgal, Jayapriya,, & Kumar, 2026; Lodha, Sharma,, & Saraswat, 2026; Venice et al., 2026). Adaptive devices and assistive technology including magnification aids, audio interfaces, and home modifications support independence (Natarajan et al., 2026). Advanced prosthetic and motion-control technologies inform broader rehabilitation philosophy (Pavithra et al., 2026; Suresh et al., 2026). Virtual reality applications offer specific value for low-vision rehabilitation and patient education (Vinodh, & Subramani, 2026). Psychological support for vision loss is essential particularly in patients facing geographic atrophy progression or bilateral disease (Sharma, Sharma,, & Tyagi, 2026; Aumose, & Raj, 2026). Self-leadership and emotional intelligence approaches support adaptation (Mustafa et al., 2026; Zahoor et al., 2025). For elderly patients facing vision loss, structured social support and community programmes provide important resources (Ashifa, 2022; Rasi, & Ashifa, 2019; Natarajan et al., 2026).

4.5 Comorbidity and Multidisciplinary Care

Neovascular AMD patients are typically elderly with substantial comorbidity burden. Multimorbidity-aware management is essential to optimise overall health alongside vision outcomes (Kumar, Sharma,, & Gupta, 2026; Yatish, Khatoon,, & Kumar, 2026). Cognitive impairment documented in 17% of our cohort and particularly common in low-adherence patients warrants structured assessment and support (Sharma, Sharma,, & Tyagi, 2026). Cardiovascular and metabolic comorbidities require ongoing management, with anti-VEGF therapy considered safe in most cardiovascular contexts. Biomarker-based risk stratification informs individualised management (Kumar, Gautam,, & Maitiy, 2026). Chronic disease prevention principles apply to broad health maintenance (Yatish, Khatoon,, & Kumar, 2026). Patient education programmes that address both disease understanding and behavioural strategies for adherence produce measurable benefits (Vettriselvan, Ramya, et al., 2026; Catherine, Gupta, Gopi,, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine,, & Velmurugan, 2025).

4.6 Digital Health and Implementation

Digital health tools offer substantial promise for neovascular AMD care. Patient-facing apps for appointment scheduling, symptom monitoring, and home Amsler grid testing support engagement (Deepa et al., 2026; Catherine, Gupta, Gopi,, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine,, & Velmurugan, 2025). Wearable monitoring with home OCT emerging as a feasible technology could transform follow-up by enabling between-injection monitoring (Deepa et al., 2026). Tele-ophthalmology consultation reduces travel burden and frequency of in-person visits (Vijayalakshmi et al., 2025; Vinodh, Subramani, & Vettriselvan, 2026). AI-supported decision tools assist with OCT interpretation, treatment timing decisions, and risk stratification (Devi et al., 2025; Shanthi et al., 2025; Jha, Kumar,, & Neha, 2026). Digital twin frameworks model individual disease trajectories (Subramani, Chillagattu, et al., 2026; Pradeepa et al., 2026). Cyber-physical infrastructure supports cold-chain logistics for anti-VEGF agents (Catherine, Nasrin Sulthana, et al., 2026). Educational infrastructure for training ophthalmologists, optometrists, and primary care providers in AMD recognition and management is essential (Vinodh, Subramani,, & Vettriselvan, 2026; Bhatnagar, Tyagi,, & John, 2026). AI ethics and governance frameworks address algorithmic fairness particularly for elderly patients with limited digital literacy (Selvi et al., 2026). Mindful technology use is important given the often-limited digital literacy of elderly patients (Vettriselvan, Velmurugan, et al., 2025). Quality improvement methodology supports systematic outcome improvement (Bhatnagar, Kumar,, & Shivam, 2026). Strategic healthcare partnerships extend service reach (Vettriselvan, 2025; Vijayalakshmi et al., 2025; Jenifer et al., 2025).

4.7 Limitations

Limitations include the non-randomised design with potential confounding by agent selection (agent choice correlates strongly with cost and adherence characteristics); the single-centre tertiary setting which over-represents complex cases; the 24-month follow-up which captures most early outcomes but does not address very-long-term vision trajectories particularly for geographic atrophy progression; and the limited representation of newer agents (brolucizumab, faricimab) in our cohort. Selection bias

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toward patients who initiate treatment may under-represent the broader population of those who are diagnosed but cannot access therapy.

5. Conclusion

Anti-VEGF therapy for neovascular AMD in this real-world cohort produced excellent visual outcomes when adherence was high (mean gain of 11.2 letters at 24 months) but substantial vision loss when adherence was low (mean loss of 11.6 letters). The 23-letter spread between adherence strata represents the dominant outcome modifier in real-world practice. Strongest predictors of vision-stable outcome included high adherence, treat-and-extend protocols, smaller lesion size, lower cost burden, shorter distance from injection centre, and adequate caregiver support. The modifiable determinants identify principal operational levers including cost-reduction programmes, decentralised injection capacity, structured transport support, tele-ophthalmology follow-up, and structured patient education.

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