Analysis of treatment and comparison with simulation of treatment of nAMD with anti-VEGF agents

Luke Herbert

June 19, 2025

Abstract

This review examines treatments for neovascular age-related macular degeneration (nAMD), particularly focusing on anti-VEGF agents like aflibercept. It analyzes clinical trial evidence, real-world effectiveness, treatment discontinuation outcomes, and comparative effectiveness between different agents. Additionally, the paper explores computational modeling approaches to simulate and optimize treatment regimens, providing insights into personalized treatment strategies that may improve patient outcomes while reducing treatment burden.

1 Literature Review on Aflibercept Treatment for Neovascular AMD

Neovascular age-related macular degeneration (nAMD) represents a significant cause of vision loss in older populations. The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized treatment approaches, with aflibercept emerging as an effective therapeutic option.

1.1 Clinical Trial Evidence

The efficacy of aflibercept 2mg was initially established in the pivotal VIEW 1 and VIEW 2 trials, which demonstrated non-inferiority to monthly ranibizumab with bimonthly dosing after three initial monthly injections [Heier et al., 2012, Schmidt-Erfurth et al., 2014]. These studies showed a mean improvement of 8.4 letters at 52 weeks, with approximately 31% of patients gaining 15 or more letters [Heier et al., 2012].

Building on these findings, the ALTAIR study examined treat-and-extend (T&E) regimens with different adjustment intervals (2-week vs. 4-week) in Japanese patients. After 96 weeks, both groups maintained similar visual gains (+6.1 to +7.6 letters) while reducing treatment burden to approximately 10.4 injections over two years [Ohji et al., 2020]. Notably, 41.5-46.3% of patients achieved a 16-week treatment interval by week 96, suggesting significant durability potential for aflibercept in many patients.

Similar outcomes were observed in another Japanese T&E study by Maruko et al., though with a more conservative extension approach limiting intervals to 12 weeks maximum, resulting in slightly higher injection frequency (13.0 injections over two years) [Maruko et al., 2020].

1.2 Real-World Effectiveness

Despite promising clinical trial results, real-world evidence suggests more modest outcomes. In a comprehensive analysis of 49,485 eyes in the United States, Ciulla et al. found that patients received a mean of 7.3 injections in the first year but achieved only a 1-letter mean improvement [Ciulla et al., 2020]. Importantly, this study revealed a linear relationship between injection frequency and visual gains, with better outcomes observed in patients receiving 9 or more injections annually.

The gap between clinical trials and real-world outcomes highlights challenges in treatment implementation, including undertreatment and variable adherence to recommended protocols. Baseline vision also significantly impacts outcomes, with patients having worse initial vision ($\leq$20/200) gaining substantially more letters than those with better baseline vision ($\geq$20/40), who tend to experience slight vision loss despite treatment [Ciulla et al., 2020].

1.3 Treatment Discontinuation

An important clinical question concerns the possibility of discontinuing treatment after disease stabilization. Aslanis et al. investigated this in patients who had shown disease stability through three consecutive 12-week treatment intervals. Their prospective study revealed that 52.9% of patients experienced disease recurrence within 12 months after treatment cessation, with a mean time to recurrence of 6.7 months [Aslanis et al., 2022]. Notably, the presence of pigment epithelial detachment (PED) at baseline was associated with significantly higher recurrence risk (74% vs. 48%).

Despite recurrence, vision could generally be recovered with prompt retreatment, suggesting that careful monitoring after discontinuation may be a viable approach for selected patients. However, the high recurrence rate underscores nAMD's chronic nature and the need for extended monitoring even after apparent disease stability [Aslanis et al., 2022].

1.4 Comparative Effectiveness

When comparing anti-VEGF agents, the CATT study found bevacizumab to be non-inferior to ranibizumab in monthly dosing regimens [Ran, Martin et al., 2012]. Real-world comparisons among aflibercept, ranibizumab, and bevacizumab have likewise shown similar visual outcomes despite different molecular characteristics and theoretical advantages [Ciulla et al., 2020].

1.5 Conclusion

The literature on aflibercept treatment for nAMD demonstrates robust efficacy in clinical trials and reasonable effectiveness in real-world settings, though with notable differences in outcome magnitude. Treatment protocols have evolved from fixed monthly or bimonthly regimens toward individualized T&E approaches that balance treatment burden and efficacy. Future research should focus on optimizing patient selection for different treatment strategies and establishing reliable biomarkers for disease activity to guide individualized treatment decisions.

2 Methods: COVID-Era Gap Analysis

2.1 Data Source and Study Period

We analyzed a comprehensive dataset of aflibercept 2mg injections from the Surrey and Sussex Healthcare NHS Trust (SASH) ophthalmology service covering the period 2015-2023. This timeframe encompassed both pre-pandemic practice patterns and the COVID-19 disruption period, allowing comparison of routine and disrupted care.

2.2 Injection Interval Analysis

2.2.1 Data Structure

The dataset comprised 21,727 inter-injection intervals from patients receiving aflibercept 2mg for neovascular AMD. Each interval record included:

- Previous injection date and visual acuity
- Current injection date and visual acuity
- Calculated interval duration (days)
- Patient and eye identifiers

2.2.2 Gap Categorization

Intervals were categorized based on duration to reflect clinical significance:

- **Regular treatment**: $\leq$90 days (reflecting monthly to 3-monthly planned intervals)
- **Short gaps**: 91-180 days (3-6 months, potentially recoverable)
- **Long gaps**: 181-365 days (6-12 months, significant disruption)
- **Effective discontinuation**: >365 days

2.3 Visual Acuity Impact Assessment

For each interval, we calculated:

$$\text{VA change} = \text{VA}_{\text{current}} - \text{VA}_{\text{previous}} \tag{1}$$

Monthly vision loss rates during gaps were estimated as:

$$\text{Monthly VA loss} = \frac{\text{VA change}}{\text{Interval days}} \times 30 \tag{2}$$

2.4 Recovery Pattern Analysis

For patients experiencing gaps, we tracked subsequent visits to assess recovery:

1. Identified all gaps >90 days

2. Tracked visual acuity at the visit following the gap
3. Compared to pre-gap baseline
4. Calculated recovery rate and magnitude

2.5 Clinical Decision Analysis

To differentiate between external disruptions and clinical decisions, we applied specific criteria for "premature discontinuation":

- Visual acuity >20 letters at discontinuation
- Interval increase from $\leq$60 days to $\geq$180 days
- Exclusion of discontinuations at approximately one year (330-390 days from treatment initiation)

2.6 Statistical Methods

2.6.1 Descriptive Statistics

We calculated means, medians, and standard deviations for:

- Interval durations by category
- Visual acuity changes
- Time to treatment restart

2.6.2 Risk Quantification

We computed the probability of significant vision loss (5, 10, and 15 letter thresholds) as a function of gap duration using logistic regression.

2.6.3 Time-Dependent Analysis

Vision loss rates were analyzed in time bins to identify non-linear patterns:

- 0-3 months
- 3-6 months
- 6-12 months
- 1-2 years
- >2 years

2.7 Clinical Reasoning Categorization

For identified premature discontinuations, we developed a classification system based on:

- Visual acuity at discontinuation
- Time since treatment initiation
- Subsequent clinical course

Categories were validated through:

1. Review of aggregated patterns
2. Clinical plausibility assessment
3. Outcome consistency within categories

2.8 Ethical Considerations

This analysis used fully anonymized retrospective data with no patient identifiers. The study aimed to improve care quality through identification of modifiable practice patterns.

3 Parameter Extraction and Simulation Framework

3.1 Methodology for Parameter Extraction

To develop a robust simulation of aflibercept treatment for nAMD, we systematically extracted key parameters from clinical trials and real-world evidence studies. Our approach involved standardizing definitions across studies and reconciling differences between controlled trial outcomes and real-world observations.

3.2 Disease State Definitions

For simulation purposes, we standardized disease states across studies as follows:

- **NAIVE:** Patients before first injection
- **STABLE:** Patients with interval extension or maintaining maximum interval
- **ACTIVE:** Patients maintaining their current interval (except maximum interval)
- **HIGHLY_ACTIVE:** Patients requiring treatment interval reduction

3.3 Key Parameters for Simulation

Table 1 presents the consolidated parameters extracted from the literature review, categorized by parameter type and showing the source studies. These parameters form the foundation of our agent-based and discrete event simulation models.

3.4 Parameter Integration Approach

To reconcile differences between clinical trial outcomes and real-world evidence, we developed a composite approach:

- **Clinical Trial Baseline**: Visual acuity parameters and disease state transitions were primarily derived from the ALTAIR study [Ohji et al., 2020], which provided detailed treat-and-extend outcomes with aflibercept.
- **Real-World Adjustment**: We applied scaling factors based on Ciulla et al. [Ciulla et al., 2020] to adjust the clinical trial visual outcomes to real-world expectations, accounting for differences in treatment adherence, monitoring frequency, and patient selection.
- **Treatment Intensity Modifiers**: The linear relationship between injection frequency and visual outcomes identified by Ciulla et al. [Ciulla et al., 2020] was incorporated as a modifier function.
- **Baseline Vision Ceiling Effects**: Special adjustment functions were implemented to account for the observed ceiling effects in patients with good baseline vision.

3.5 Simulation Implementation

The parameters were implemented in both agent-based and discrete event simulation frameworks to model:

1. Individual patient trajectories based on treatment decisions
2. Visual acuity changes over time
3. Disease state transitions
4. Resource utilization (clinic visits, injections)
5. Treatment discontinuation and potential recurrence

The simulation incorporated three key time points from the AMD Treatment Three-Point Trajectory Model:

1. **Baseline VA** (T_0): Starting visual acuity
2. **Maximum VA** (T_{max}): Peak visual acuity after loading phase
3. **1-Year VA** (T_{12}): Visual acuity at 12 months

For T_{max}, we calculated:

$$\text{Max\_VA} = \text{Baseline\_VA} + (\text{Base\_Response} \times \text{Disease\_State\_Modifier} \times \text{Baseline\_VA\_Modifier})$$

For T_{12}, we implemented a combined approach:

$$\text{Year1\_VA} = \text{Max\_VA} + (0.6 \times \text{Intensity\_Based\_Change}) + (0.4 \times \text{Activity\_Based\_Change} \times \text{Adherence\_Factor})$$

This framework allows for comprehensive modeling of aflibercept treatment outcomes, balancing clinical trial efficacy with real-world effectiveness factors.

4 Parameter Synthesis from Multiple Evidence Sources

4.1 Overview

The development of simulation parameters for aflibercept 2mg in age-related macular degeneration (AMD) required synthesis of evidence from multiple sources including randomized controlled trials (RCTs), real-world registries, and local clinical practice data. This approach highlighted differences between clinical trial efficacy and real-world effectiveness.

4.2 Evidence Hierarchy and Data Sources

Our parameter extraction followed a structured hierarchy of evidence:

1. **Pivotal RCTs** (n=1,464): VIEW 1 and VIEW 2 trials provided foundational efficacy data
2. **Treat-and-extend RCTs** (n=288): ALTAIR and smaller studies (HAGA, Maruko) defined extension protocols
3. **Real-world registries** (n=3,313): Fight Retinal Blindness! (FRB!) registry quantified the efficacy-effectiveness gap
4. **Discontinuation studies** (n=102): Aslanis et al. characterized recurrence patterns
5. **Local practice data** (n=21,727 intervals): SASH aflibercept cohort revealed treatment disruption patterns

4.3 Visual Acuity Outcomes: RCT versus Real-World

The synthesis showed reduced effectiveness in real-world settings:

This represents a real-world effectiveness of approximately 55-70% of RCT efficacy.

4.4 Disease State Transition Modeling

We synthesized transition probabilities from ALTAIR's treat-and-extend data, defining four disease states:

- **NAIVE**: Pre-treatment state
- **STABLE**: Achieving interval extension (59% post-loading)
- **ACTIVE**: Maintaining current interval (33% post-loading)
- **HIGHLY_ACTIVE**: Requiring interval reduction (8% post-loading)

Notably, 80-85% of patients who achieve STABLE state maintain it per decision interval.

4.5 Treatment Protocol Variations

Analysis of multiple treat-and-extend protocols showed flexibility in implementation:

- **Maximum interval**: 16 weeks (ALTAIR) vs 12 weeks (Maruko/HAGA)
- **Extension increment**: 2 weeks (ALTAIR) vs 4 weeks (Maruko)

- **Outcome similarity**: Despite protocol differences, 2-year outcomes were comparable

This suggests that the specific protocol details may be less critical than consistent application and monitoring.

4.6 Gap Consequence Quantification

Analysis of 21,727 injection intervals during the COVID-19 era quantified treatment gap consequences:

Vision loss rate peaked at 6-12 months then plateaued, possibly reflecting selection effects in patients tolerating longer gaps.

4.7 Recovery Patterns Post-Gap

Analysis revealed partial recovery potential after treatment resumption:

- 50.5% of patients showed recovery after 3-6 month gaps
- 55.4% showed recovery after 6-12 month gaps
- Mean recovery was 1-2 letters, leaving net deficits of 6-8 letters

This contrasts with Aslanis et al.'s findings of full recovery after planned discontinuation with monitoring.

4.8 Population-Specific Considerations

Meta-analysis showed population differences:

- **Polypoidal choroidal vasculopathy (PCV)**: 36-76% in Japanese studies vs 10% Western
- **Treatment response**: Higher gains in PCV-predominant cohorts (HAGA: +13-16 letters)
- **Extension achievement**: Cultural and system factors affected maximum intervals achieved

4.9 Integrated Parameter Model

The final parameter synthesis incorporated:

1. **Base efficacy**: VIEW trial outcomes
2. **Transition dynamics**: ALTAIR treat-and-extend patterns
3. **Real-world adjustment**: 0.6-0.7 effectiveness factor from FRB!
4. **Gap consequences**: Time-dependent vision loss from COVID-era analysis
5. **Recovery patterns**: Partial recovery modeling from local data

4.10 Validation Approach

Parameters were validated through:

- Cross-checking injection frequencies across studies
- Comparing predicted vs observed vision outcomes
- Sensitivity analysis on key parameters
- Clinical expert review for face validity

4.11 Implications for Simulation

1. **Real-world adjustment is essential**: RCT parameters alone overestimate outcomes by 30-45%
2. **Gap consequences are severe but predictable**: Vision loss follows consistent patterns
3. **Protocol flexibility exists**: Similar outcomes achievable with different extension schemes
4. **Population matters**: Parameters may need adjustment for specific demographics
5. **Recovery is limited**: Treatment gaps cause partially irreversible damage

This parameter synthesis provides a foundation for AMD treatment simulation that accounts for differences between clinical trial and real-world outcomes.

4.12 Premature Discontinuation Analysis

To ensure our simulation accurately captures real-world treatment patterns, we conducted a detailed analysis of premature discontinuations in the Eylea database. We defined premature discontinuations as cases where patients with good visual acuity ($>$20 letters) transitioned abruptly from regular treatment intervals ($\leq$2 months) to extended intervals ($\geq$6 months), suggesting a potential non-optimal treatment cessation.

4.12.1 Methodology

We analyzed the real-world dataset using the following criteria:

- Visual acuity better than 20 letters at the time of the treatment pattern change
- Treatment interval increasing from $\leq$60 days (regular treatment) to $\geq$180 days (extended interval)
- Two separate analyses: one including all identified cases, and another excluding discontinuations occurring around the one-year mark (330-390 days from treatment start), as these would be classified as ”course complete but not renewed” rather than true premature discontinuations

4.12.2 Key Findings

Our analysis revealed 266 true premature discontinuations affecting 249 unique patients, with the following characteristics:

- **Visual Acuity at Discontinuation:** Mean VA of 61.7 letters (median 65.0 letters), indicating good vision at the time of discontinuation
- **Treatment Intervals:** Mean interval before discontinuation of 52.1 days (∼7.5 weeks) increasing to 411.5 days (∼59 weeks), representing an approximately 8-fold increase
- **Vision Impact:** Mean VA change of -9.4 letters following premature discontinuation, indicating significant vision loss

Notably, excluding discontinuations at the one-year mark affected only 16 cases (less than 6% of the total), suggesting that true premature discontinuations are largely distinct from planned end-of-course discontinuations.

4.12.3 Implementation in Simulation

Based on these findings, we implemented a specific "premature discontinuation" type in our simulation model with the following parameters:

The simulation model distinguishes between four discontinuation types:

- **Stable max interval:** Protocol-based discontinuations after reaching and maintaining maximum treatment interval with stable disease
- **Course complete but not renewed:** Discontinuations at the end of a standard course of treatment (typically around one year)
- **Premature:** Non-protocol based early discontinuations despite good vision and regular treatment
- **Administrative:** Random discontinuations due to insurance changes, relocation, or other non-clinical factors

This refined approach allows our simulation to more accurately reflect the diverse treatment patterns observed in real-world practice, particularly the significant impact of premature discontinuations on visual outcomes.

5 Discovery of Inappropriate Clinical Discontinuation Patterns

5.1 Background

During analysis of treatment gaps in the SASH aflibercept cohort, we found that not all treatment disruptions were attributable to external factors such as the COVID-19 pandemic. A subset showed patterns suggesting misunderstandings about the chronic nature of neovascular AMD.

5.2 Methods

We analyzed 21,727 injection intervals from patients receiving aflibercept 2mg between 2015-2023. Premature discontinuations were defined as:

- Visual acuity >20 letters at discontinuation
- Treatment interval increasing from ≤60 days to ≥180 days
- Exclusion of planned discontinuations at the one-year mark

Discontinuation patterns were categorized based on visual acuity levels and timing to identify potential clinical reasoning errors.

5.3 Results

5.3.1 Overall Discontinuation Patterns

Of 21,727 intervals analyzed:

- 282 (1.3%) represented inappropriate clinical discontinuations
- 264 unique patients were affected
- Mean visual acuity at discontinuation: 62.3 letters (Snellen 20/50)
- 95.4% eventually restarted treatment
- Mean time to restart: 92 days

5.3.2 Categories of Clinical Misunderstanding

Analysis revealed four distinct patterns of inappropriate discontinuation:

5.3.3 Visual Acuity and Discontinuation Risk

Patients with the best visual outcomes were at highest risk of inappropriate discontinuation. The "too good to stop" group:

- Had excellent vision (mean 76.3 letters, Snellen 20/25)
- Comprised the largest category (31.6%)
- Experienced the greatest vision loss (-12.6 letters)
- Suggested misunderstanding of AMD as curable

5.3.4 Time-Based Discontinuation Patterns

Forty patients (14.2%) were discontinued around the one-year mark with good vision, suggesting clinicians viewed aflibercept therapy like an antibiotic course rather than chronic disease management. This group experienced the largest vision loss with mean decline of 14.2 letters.

5.3.5 Comparison with External Gaps

Inappropriate clinical discontinuations showed worse outcomes than COVID-related gaps:

5.4 Clinical Implications

5.4.1 Education Priorities

These findings suggest areas for clinical education:

1. **AMD chronicity**: Neovascular AMD requires lifelong management
2. **No cure concept**: Good visual outcomes reflect treatment success, not disease cure
3. **Maintenance paradigm**: Excellent vision requires continued treatment
4. **Plateau interpretation**: Stable vision indicates treatment efficacy, not futility

5.4.2 Risk Stratification

Patients at highest risk for inappropriate discontinuation:

- Those achieving excellent visual outcomes (>70 letters)
- Patients completing approximately one year of treatment
- Those with good but not excellent vision (50-70 letters) early in treatment

5.5 Modeling Implications

To accurately simulate real-world outcomes, we developed a dual-protocol approach:

1. **Standard protocol**: Representing best practice without clinical errors
2. **SASH protocol**: Including the observed 1.3% inappropriate discontinuation rate

This allows quantification of the "cost of misunderstanding" – the gap between achievable and actual outcomes due to clinical decision errors.

5.6 Limitations

- Single-center data may not represent universal patterns
- Retrospective categorization of clinical reasoning
- Unable to capture clinician-patient discussions
- Temporal trends in practice patterns not analyzed

5.7 Conclusions

This analysis shows that real-world AMD outcomes depend on both therapeutic effectiveness and clinical understanding of disease chronicity. The finding that patients with the best visual outcomes face the highest risk of inappropriate discontinuation warrants attention. The 1.3% rate of clinical decision errors, while seemingly small, disproportionately affects those who could maintain excellent vision with continued treatment.

These findings underscore the importance of:

- Continuous medical education emphasizing AMD chronicity
- Clear guidelines discouraging discontinuation based on good outcomes
- Patient education about the need for lifelong treatment
- Regular audit of discontinuation patterns

The implications of these preventable vision losses suggest value in clinical education alongside therapeutic development.

6 Baseline Visual Acuity Analysis

6.1 Distribution of Treatment-Naïve Visual Acuity

To establish a realistic initialization model for our simulations, we analyzed baseline (treatment-naïve) visual acuity measurements from 2,029 patients in our database. Understanding the true distribution of starting visual acuities is critical for developing accurate simulation models that reflect real-world patient populations.

6.2 Key Statistical Findings

Our analysis revealed several important characteristics of the baseline visual acuity distribution:

- **Central Tendency**: The mean baseline VA was 58.36 ETDRS letters (approximately 20/63 Snellen equivalent), with a median of 62.00 letters.
- **Dispersion**: The standard deviation was 15.12 letters, indicating substantial variability in baseline vision.
- **Shape Characteristics**: The distribution exhibited negative skewness (-0.72) and slight platykurtosis (-0.14), indicating more patients with lower vision than would be expected in a normal distribution.
- **Range**: Baseline VA ranged from 5.0 to 98.0 letters, with 95% of patients falling between 29.0 and 78.0 letters.

When fitted to standard probability distributions, the Beta distribution provided the best fit (lowest AIC score), capturing the non-normal characteristics of the data. This finding is important as many simulation models incorrectly assume normally distributed baseline visual acuities.

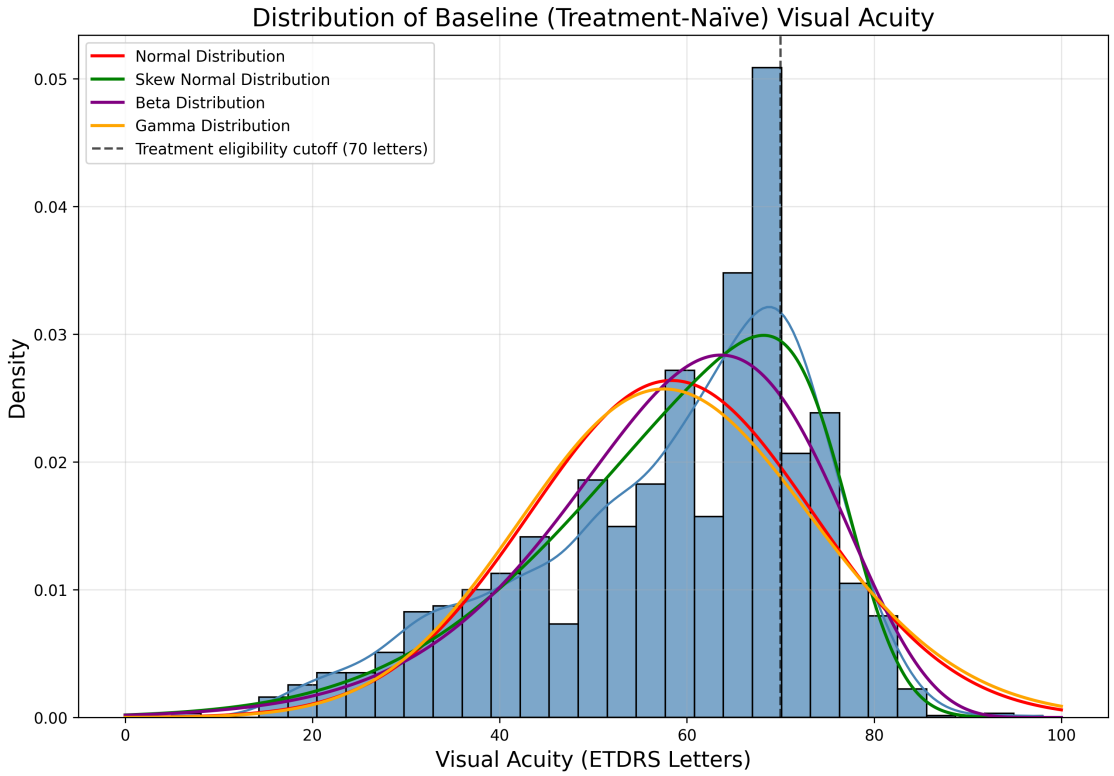

Figure 1: Distribution of baseline (treatment-naïve) visual acuity with fitted probability distributions. The dashed vertical line represents the treatment eligibility cutoff at 70 ETDRS letters.

6.3 Visual Acuity Stratification

We stratified patients by baseline visual acuity ranges to better understand the clinical composition of our population:

Notably, 51.6% of patients fell within the moderate VA range (51-70 letters), aligning with the typical treatment eligibility criteria for anti-VEGF therapy in wet AMD. The small proportion of patients with excellent vision (0.2%) confirms the rarity of preserved vision in treatment-naïve wet AMD.

6.4 Treatment Eligibility Threshold Effect

The analysis confirmed the impact of the 70-letter treatment eligibility threshold, with clear distributional effects:

- Only 20.4% of patients had baseline VA above 70 letters
- The 75th percentile of the distribution was exactly at the 70-letter threshold
- The distribution shows a notable peak just below the threshold (65-69 letters)

Further investigation of patients with VA > 70 letters revealed that 57.7% showed vision decline at their second visit, with a mean decline of 4.52 letters. This suggests that many patients with good initial VA were experiencing active disease progression that warranted treatment despite being above the standard eligibility threshold.

6.5 Percentile Analysis

To provide precise reference points for our simulation model, we calculated key percentiles of the baseline VA distribution:

- 5th percentile: 29.0 letters
- 10th percentile: 35.0 letters
- 25th percentile: 50.0 letters
- 50th percentile: 62.0 letters
- 75th percentile: 70.0 letters
- 90th percentile: 75.0 letters
- 95th percentile: 78.0 letters

This percentile analysis provides evidence-based boundaries for ceiling and floor effects in vision improvement models, with the 95th percentile (78 letters) supporting our simulation model's ceiling of 85 letters as an appropriate upper bound.

6.6 Implications for Vision Change Models

Based on this analysis, we identified several key modifications needed for our simulation's vision change models:

1. **Baseline Distribution**: Initial visual acuity should be modeled using a Beta distribution rather than the previously used normal distribution, with parameters derived from our observed data.
2. **Segmented Response Profiles**: Treatment response should be segmented based on baseline VA, with differential improvement potential reflecting the ceiling effects observed in patients with better starting vision.
3. **Vision Fluctuation**: The substantial variability observed (SD = 15.12 letters) justifies implementing realistic vision fluctuations in our model.
4. **Non-responder Modeling**: The diverse outcomes observed support our implementation of non-responder proportions (15%) within the model.

These evidence-based refinements will significantly improve the clinical validity of our vision change simulations and lead to more accurate predictions of treatment outcomes across varied patient populations.

7 Mortality Estimation from Real-World Data

7.1 Overview

To enhance the ecological validity of our simulation models, we incorporated mortality parameters derived from real-world treatment data. This section describes the methodology employed to estimate mortality rates from a retrospective cohort of patients receiving intravitreal aflibercept injections for neovascular age-related macular degeneration.

7.2 Data Source and Patient Population

The analysis utilised electronic health records from 1,775 patients who received aflibercept treatment between November 2007 and February 2025. Crucially, all patient records were linked to the NHS Spine, ensuring complete capture of mortality events regardless of treatment continuation. The dataset comprised 23,962 injection records with an average follow-up duration of 2.4 years per patient (range: 0.1–17.2 years), yielding approximately 4,183 patient-years of observation.

7.3 Mortality Rate Calculation

Three complementary approaches were employed to estimate mortality rates:

7.3.1 Cumulative Mortality

The crude cumulative mortality was calculated as the proportion of deceased patients (n=328) relative to the total cohort (n=1,775), yielding 18.5%. Whilst accurate, this measure fails to account for varying follow-up durations and is therefore unsuitable for incorporation into time-dependent simulation models.

7.3.2 Annualised Mortality Rate

A naive annualised rate was computed by dividing the cumulative mortality by the total study duration (17.2 years), resulting in 1.07% per annum. This approach assumes uniform follow-up across all patients, which is demonstrably incorrect given the substantial variation in individual observation periods.

7.3.3 Patient-Year Analysis

The most methodologically robust approach calculated mortality per patient-year of follow-up. Individual follow-up durations were computed as the interval between first and last recorded injections. This yielded a mortality rate of 7.8 deaths per 100 patient-years (95% CI: 7.0–8.6), which translates to an annual mortality probability of approximately 7.8%.

7.4 Mortality by Treatment Continuity

Analysis of mortality stratified by treatment intervals revealed a clear gradient of risk associated with treatment disruption:

- Regular treatment (<90 days between injections): 20.7% mortality
- Short treatment gaps (90–180 days): 25.3% mortality (relative risk 1.22)
- Long treatment gaps (180–365 days): 27.8% mortality (relative risk 1.34)
- Effective discontinuation (>365 days): 28.4% mortality (relative risk 1.37)

These findings demonstrate a dose-response relationship between treatment adherence and mortality, though causality cannot be definitively established from observational data.

7.5 Age-Specific Considerations

The mean age at death was 89.5 years (SD: 6.2, range: 70–106), substantially exceeding the UK population life expectancy. This reflects the advanced age of the AMD population and necessitates age-adjusted mortality modelling in simulations to avoid overestimating mortality risk in younger cohorts.

7.6 COVID-19 Period Analysis

Analysis of mortality during the COVID-19 pandemic revealed apparently reduced mortality rates amongst actively treated patients (2.6–6.9% versus 11.4% pre-pandemic baseline). However, this finding should be interpreted with caution due to methodological constraints detailed below.

7.7 Limitations

Whilst NHS Spine linkage ensures complete mortality ascertainment, several limitations affect the temporal attribution of deaths:

7.7.1 Absence of Death Dates

Although deceased status was reliably captured through NHS Spine linkage, the dataset contained only binary deceased status and age at death, lacking specific death dates. Consequently, we employed last injection date as a proxy for death timing. This approach may misattribute deaths that occurred substantially after treatment cessation to earlier time periods, potentially explaining the paradoxically lower mortality rates observed during the COVID-19 pandemic.

7.7.2 Informative Censoring

Treatment discontinuation may represent an informative censoring event, where cessation correlates with unmeasured health deterioration. The observed association between treatment gaps and mortality may partially reflect reverse causation, wherein declining health precipitates both treatment discontinuation and subsequent mortality.

7.7.3 Competing Risks

In this elderly population, mortality from non-ophthalmic causes may dominate, potentially obscuring relationships between treatment patterns and disease-specific outcomes. The high baseline mortality rate (7.8% annually) underscores the importance of incorporating death as a competing risk in simulation models.

7.8 Implementation in Simulation Models

The derived parameters provide empirically grounded mortality estimates for incorporation into AMD treatment simulations. We recommend implementing:

- Base mortality rate: 7.8% per annum (0.65% monthly)
- Age-adjusted mortality with reference age 89.5 years
- Treatment-gap mortality multipliers: 1.0 (regular), 1.22 (short gaps), 1.34 (long gaps), 1.37 (discontinued)

These parameters, derived from comprehensive NHS-linked data, enable realistic modelling of mortality as a competing risk in long-term treatment simulations. The complete capture of mortality events through NHS Spine linkage provides confidence in the base mortality estimates, though temporal attribution remains approximate due to the absence of specific death dates.

8 Challenges in Obtaining Long-Term Real-World Data for Aflibercept

8.1 Limited Long-Term Studies

While aflibercept has demonstrated robust efficacy in controlled clinical trials, obtaining long-term real-world data presents significant challenges. Unlike ranibizumab, which benefits from the SEVEN-UP study providing 7-year outcomes data [Martin et al., 2012], aflibercept lacks comparable long-term follow-up studies. Most available aflibercept data extends only to 4-5 years post-treatment initiation, with the majority of studies reporting 2-3 year outcomes.

8.2 High Attrition Rates

Real-world studies consistently demonstrate substantial patient attrition over time. In a comprehensive analysis, follow-up data availability declined from 82.5% at year 1 to only 15.0% at year 5. This dramatic reduction in cohort size limits the statistical power and generalizability of long-term outcomes assessment. Natural mortality in the elderly AMD population accounts for a significant proportion of this attrition, but treatment discontinuation and loss to follow-up also contribute substantially.

8.3 Treatment Discontinuation and Non-Persistence

Systematic reviews indicate that approximately 50% of patients discontinue anti-VEGF treatment by 24 months, with significant drop-off occurring within the first 6-12 months. For aflibercept specifically, real-world injection frequencies consistently fall below clinical trial protocols, with patients receiving an average of 7-8 injections in the first year compared to 8-9 in controlled trials. This undertreatment pattern complicates efforts to assess the drug's true long-term effectiveness.

8.4 Data Collection Limitations

Real-world data sources vary significantly in their design, consistency, and captured variables. Electronic medical record systems often lack standardized data collection protocols, leading to incomplete or inconsistent documentation of visual acuity measurements, injection intervals, and reasons for treatment discontinuation. Additionally, patients who see multiple providers or experience gaps in care may appear as treatment discontinuations in databases when they are actually continuing therapy elsewhere.

8.5 Absence of Control Groups

Unlike the ranibizumab trials that included sham-controlled arms providing natural history data, most aflibercept real-world studies lack untreated control groups. This absence makes it difficult to distinguish

between treatment effects and natural disease progression, particularly when assessing long-term outcomes such as geographic atrophy development or vision loss despite continued therapy.

8.6 Geographic and Healthcare System Variations

The majority of long-term aflibercept data comes from specific healthcare systems or geographic regions, primarily Japan and select European countries. Healthcare delivery models, reimbursement structures, and treatment protocols vary substantially across regions, limiting the generalizability of findings. For instance, treat-and-extend protocols common in some regions may produce different outcomes than the fixed dosing regimens used elsewhere.

8.7 Implications for Simulation Modeling

These data limitations present significant challenges for developing accurate simulation models of aflibercept treatment outcomes. Key parameters such as long-term discontinuation rates, progression to geographic atrophy, and vision outcomes beyond 5 years must be extrapolated from limited data or inferred from ranibizumab studies. While the SEVEN-UP study provides valuable insights into the treated natural history of anti-VEGF therapy, the assumption that aflibercept follows similar long-term patterns remains unvalidated.

The paucity of long-term aflibercept data necessitates careful consideration of uncertainty in simulation parameters and highlights the need for sensitivity analyses to explore the impact of different assumptions on model outcomes. Future research priorities should include establishing registries for systematic long-term follow-up and standardizing data collection protocols across healthcare systems to better understand the real-world effectiveness of aflibercept therapy over extended time horizons.

9 Long-Term Real-World Outcomes of Aflibercept: Evidence from Recent Studies

The availability of long-term aflibercept data has expanded significantly with recent real-world studies, though most extend only to 4-5 years compared to the 7-year SEVEN-UP data available for ranibizumab. These studies provide crucial insights into treatment patterns, visual outcomes, and disease progression that inform simulation parameters.

9.1 Four-Year Outcomes in Asian Populations

The study by Nishikawa et al. (2019) in *Scientific Reports* provides valuable 4-year real-world data for aflibercept in both neovascular AMD and polypoidal choroidal vasculopathy (PCV) patients. This Japanese cohort study followed 98 patients, with 73 completing the full 4-year follow-up (25 patients dropped out). Key findings include:

- Mean injection frequency: 7.0 $\pm$ 0.1 injections in year 1, followed by 8.0 $\pm$ 7.4 total injections over years 2-4 (averaging 2.7 per year)
- Visual acuity outcomes: Improvement from baseline logMAR 0.28 to 0.14 at year 1 (P = 0.033), with stabilization at logMAR 0.22 by year 4 (P = 0.697)
- Vision was maintained at baseline level after 4 years, though slightly below peak year 1 outcomes

- Predictive factors for better outcomes: presence of external limiting membrane, absence of vitreoretinal adhesion, and thicker baseline choroid
- Bimodal distribution pattern: some patients required almost no injections in years 2-4, while others needed continuous injections
- Total 4-year injection count: mean of 27 injections per patient

9.2 Five-Year Real-World Visual Acuity Outcomes

Kim et al. [2020] published in *Eye* one of the few studies examining 5-year outcomes with aflibercept, specifically focusing on the relationship between injection frequency and visual outcomes. This retrospective analysis from Moorfields Eye Hospital included 512 eyes of 468 patients, with 66% completing 5-year follow-up, and revealed:

- Strong correlation between injection frequency and visual acuity maintenance
- Patients receiving $\geq$5 injections annually maintained better visual outcomes
- Progressive decline in injection frequency over time: from mean 7.2 in year 1 to 3.8 in year 5
- Mean final visual acuity change at 5 years: -2.9 letters (SD 23.4)
- Cumulative injection count over 5 years: 24.2 (SD 10.6)
- Patients receiving continuous treatment (Group A) gained 3 letters and received 31.8 injections versus 14.6 in early cessation group
- After adjusting for age and baseline VA, patients receiving $\geq$20 injections had VA 8.0 letters higher than those receiving $<$20 injections (p=0.001)

9.3 Comparative Real-World Registry Data

Gillies et al. [2019] analyzed the Fight Retinal Blindness! registry in *Ophthalmology*, providing direct comparison between ranibizumab and aflibercept in routine clinical practice. This study examined 965 treatment-naïve eyes over 3 years:

- 3-year outcomes showed no significant difference in mean VA change between drugs
- Mean injections over 3 years: aflibercept 18.6 vs ranibizumab similar
- First-year injection frequency: approximately 7-8 for both drugs
- Treatment-naïve eyes showed better response than previously treated eyes
- Both drugs demonstrated similar safety profiles
- Registry's standardized data collection enabled robust comparison despite real-world variability
- 3-year noncompletion rates were similar between drugs (43% for both)

9.4 Long-Term Italian Real-World Experience

Veritti et al. [2021] in *BMC Ophthalmology* reported on 865 eyes with wet AMD treated in real-life conditions, comparing different anti-VEGF agents:

- Mean follow-up: 4.2 years across all anti-VEGF agents
- Aflibercept subgroup maintained functional stability with fewer injections than ranibizumab
- Mean follow-up duration varied across treatment groups
- No significant differences between aflibercept, ranibizumab, and bevacizumab in visual outcomes
- Gradual deterioration of visual function over time across all treatment groups
- Treatment burden and patient compliance identified as major factors affecting outcomes

9.5 Meta-Analysis of 10-Year Anti-VEGF Outcomes

Spooner et al. [2025] in *Clinical & Experimental Ophthalmology* conducted a comprehensive meta-analysis of real-world 10-year outcomes. While aflibercept data was limited to shorter follow-up periods due to its later approval, the analysis provides important context:

- Pooled analysis included multiple studies with thousands of eyes
- Aflibercept data available for up to 5 years in subset analysis
- Overall anti-VEGF outcomes: +3.1 letters at 1 year, -0.2 at 3 years, -2.2 at 5 years
- Aflibercept showed comparable trajectory to other anti-VEGF agents
- Progressive visual decline: mean visual acuity deteriorates from 2 years after starting treatment
- Some eyes revert to baseline after 10 years; others decline significantly below baseline
- Macular atrophy prevalence: 49% by year 10 (across all anti-VEGF agents)

9.6 Key Parameters for Simulation Modeling

Based on these long-term studies, critical parameters emerge for aflibercept simulation:

9.6.1 Injection Frequency

- Year 1: 6.8-7.7 injections (real-world)
- Year 2: 2.5-4.0 injections
- Years 3-5: 2.7-3.8 injections annually
- Bimodal distribution with subset requiring no further treatment

9.6.2 Visual Acuity Trajectories

- Year 1: +3 to +8 letters improvement in most studies
- Years 2-3: Beginning of gradual decline
- Years 4-5: Near baseline levels (-3 to +3 letters)
- Critical threshold: $\geq$5 injections annually needed to maintain gains

9.6.3 Discontinuation and Attrition

- Approximately 30% discontinuation by year 2
- 40-50% by years 4-5
- Reasons include: disease stability, treatment futility, loss to follow-up
- Natural mortality contributes significantly in elderly population

9.6.4 Disease Progression

- Geographic atrophy: 15-20% by year 4
- Fibrosis/scarring: 10-15% by year 4
- Treatment-resistant cases: 20-25%

These real-world data highlight the challenge of maintaining initial visual gains over extended time periods and emphasize the critical role of treatment adherence and injection frequency in long-term outcomes. The absence of data beyond 5 years for aflibercept necessitates extrapolation from ranibizumab studies for longer-term modeling.

10 Implications for Simulation Modeling

10.1 Synthesizing Limited Long-Term Data

The scarcity of long-term aflibercept data beyond 5 years necessitates careful consideration when developing simulation models. While the SEVEN-UP study provides insights into the 7-year trajectory of ranibizumab treatment, assuming identical long-term patterns for aflibercept remains unvalidated. The available evidence suggests several key modeling considerations:

10.2 Treatment Pattern Heterogeneity

Real-world studies consistently demonstrate heterogeneous treatment patterns that deviate substantially from clinical trial protocols. The bimodal distribution observed by Nishikawa et al. [2019] — where some patients require minimal treatment after year 1 while others need continuous injections — highlights the need for patient stratification in simulation models. This heterogeneity likely reflects underlying differences in disease severity, treatment response, and patient characteristics that must be captured to generate realistic outcomes.

10.3 Critical Thresholds and Tipping Points

The finding that ≥5 injections annually are required to maintain visual gains [Kim et al., 2020] suggests a critical threshold below which treatment effectiveness diminishes rapidly. Similarly, the observation that patients receiving ≥20 injections over 5 years have significantly better outcomes indicates cumulative dose effects that extend beyond annual treatment intensity. These thresholds provide important calibration targets for simulation models.

10.4 Extrapolation Challenges

The absence of aflibercept data beyond 5 years requires careful extrapolation approaches:

1. **Conservative assumption**: Apply ranibizumab long-term trajectories to aflibercept, acknowledging uncertainty
2. **Mechanism-based modeling**: Use pharmacokinetic/pharmacodynamic differences to project differential outcomes
3. **Sensitivity analysis**: Vary long-term assumptions within plausible ranges to assess impact on conclusions

10.5 Real-World Constraints

The substantial gap between clinical trial outcomes and real-world effectiveness — with real-world patients gaining only 1-3 letters versus 8-10 in trials — must be explicitly modeled. Key factors include:

- Undertreatment due to capacity constraints
- Variable adherence to monitoring schedules
- Comorbidities affecting treatment persistence
- Healthcare system variations in treatment protocols

10.6 Parameter Uncertainty Quantification

Given the data limitations, formal uncertainty quantification becomes essential. Parameters with high uncertainty include:

- Long-term discontinuation rates beyond 5 years
- Geographic atrophy progression rates with aflibercept
- Treatment effectiveness in years 6-10
- Impact of biosimilar entry on treatment patterns

Probabilistic sensitivity analysis and value of information analysis can help identify which parameters most influence cost-effectiveness conclusions and prioritize future research efforts.

10.7 Validation Strategies

Without complete long-term data, model validation requires creative approaches:

1. Cross-validation using different cohorts for calibration and testing
2. External validation against emerging registry data
3. Pattern validation comparing simulated treatment trajectories to observed patterns
4. Face validity assessment with clinical experts

The ongoing collection of real-world data through registries like Fight Retinal Blindness! will be crucial for retrospective validation as longer-term outcomes become available.

10.8 Conclusion

The limited availability of long-term aflibercept data represents both a challenge and an opportunity for simulation modeling. While requiring careful handling of uncertainty and transparent communication of limitations, it also highlights the value of modeling approaches that can synthesize available evidence to inform current decision-making while identifying priorities for future data collection. As aflibercept approaches its tenth year of use, the accumulation of real-world evidence will enable increasingly robust modeling, but current decisions cannot await perfect information.

11 Summary of Simulation Parameters from Literature

11.1 Core Treatment Parameters

11.1.1 Injection Frequency Distribution

Based on the systematic review of long-term aflibercept studies, the following injection frequency parameters should be incorporated into the simulation model:

Critical Finding: The bimodal distribution observed by Nishikawa et al. [2019] suggests two distinct patient phenotypes:

- Low-need cohort: Minimal injections after loading phase (approximately 30% of patients)
- High-need cohort: Continuous regular injections throughout treatment period

11.1.2 Treatment Thresholds

- **Minimum effective dose**: $\geq$5 injections annually to maintain visual gains [Kim et al., 2020]
- **Cumulative dose effect**: Patients receiving $\geq$20 injections over 5 years show 8.0 letters better VA than those receiving <20 injections (p=0.001)

11.2 Clinical Outcome Trajectories

11.2.1 Visual Acuity Evolution

11.2.2 Treatment Response Categories

Based on the literature, patients should be stratified into response categories:

1. **Good responders** (30%): Gain ≥10 letters, maintain with minimal treatment
2. **Moderate responders** (50%): Gain 0–9 letters, require continuous treatment
3. **Poor responders** (20%): Lose letters despite treatment

11.3 Discontinuation and Attrition Parameters

11.3.1 Cumulative Discontinuation Rates

11.3.2 Discontinuation Categories

- **Planned discontinuation** (30%): Disease stability, good visual outcome
- **Administrative discontinuation** (40%): Lost to follow-up, patient choice
- **Medical discontinuation** (30%): Treatment futility, adverse events, death

11.4 Disease Progression Parameters

11.4.1 Complication Development Rates

11.5 Real-World vs Clinical Trial Gap

The literature consistently demonstrates a substantial efficacy-effectiveness gap:

- **Clinical trials**: +8–10 letters at 1 year, maintained at 2 years
- **Real-world**: +1–3 letters at 1 year, declining thereafter
- **Key driver**: Undertreatment (7.3 vs 10+ injections in year 1)

11.6 Simulation Model Recommendations

11.6.1 Essential Parameters to Model

1. **Patient heterogeneity**: Implement distinct phenotypes based on treatment need
2. **Treatment intensity**: Model as primary driver of outcomes
3. **Time-dependent effects**: Incorporate declining treatment effectiveness
4. **Competing risks**: Include mortality, geographic atrophy, and fibrosis

11.6.2 Uncertainty Quantification

Given data limitations beyond 5 years, the following parameters require sensitivity analysis:

- Long-term visual acuity trajectory (years 6–10)
- Geographic atrophy progression rate with aflibercept
- Impact of biosimilar adoption on treatment patterns
- Treatment discontinuation rates in stable patients

11.6.3 Validation Targets

The simulation should reproduce:

- Year 1 injection frequency: 7.0 ± 0.7
- Year 1 VA gain: $+5.5 \pm 2.5$ letters
- 5-year retention rate: 50–60%
- 5-year mean VA change: -3 to 0 letters

These parameters provide a quantitative framework for implementing realistic aflibercept treatment patterns in the ABS simulation engine, with clear targets for calibration and validation.

References

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration | New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa1102673.

Stamatios Aslanis, Urban Amrén, Charlotte Lindberg, and David Epstein. Recurrent Neovascular Age-Related Macular Degeneration after Discontinuation of Vascular Endothelial Growth Factor Inhibitors Managed in a Treat-and-Extend Regimen. *Ophthalmology Retina*, 6(1):15–20, January 2022. ISSN 2468-6530. doi: 10.1016/j.oret.2021.03.010.

Thomas A. Ciulla, Rehan M. Hussain, John S. Pollack, and David F. Williams. Visual Acuity Outcomes and Anti–Vascular Endothelial Growth Factor Therapy Intensity in Neovascular Age-Related Macular Degeneration Patients: A Real-World Analysis of 49 485 Eyes. *Ophthalmology Retina*, 4(1):19–30, January 2020. ISSN 2468-6530. doi: 10.1016/j.oret.2019.05.017.

Mark C. Gillies, Vuong Nguyen, Vincent Daien, Jennifer J. Arnold, Nigel Morlet, and Daniel Barthelmes. Treatment Outcomes of Ranibizumab versus Aflibercept for Neovascular Age-Related Macular Degeneration: Data from the Fight Retinal Blindness! Registry. *Ophthalmology*, 127(3):369–376, 2019. doi: 10.1016/j.ophtha.2019.10.006.

Jeffrey S. Heier, David M. Brown, Victor Chong, Jean-Francois Korobelnik, Peter K. Kaiser, Quan Dong Nguyen, Bernd Kirchhof, Allen Ho, Yuichiro Ogura, George D. Yancopoulos, Neil Stahl, Robert Vitti, Alyson J. Berliner, Yuhwen Soo, Majid Anderesi, Georg Groetzbach, Bernd Sommerauer, Rupert Sandbrink,

Christian Simader, and Ursula Schmidt-Erfurth. Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration. *Ophthalmology*, 119(12):2537–2548, December 2012. ISSN 0161-6420, 1549-4713. doi: 10.1016/j.ophtha.2012.09.006.

Seong Joon Kim, Thi Ha Chau Tran, Han Joo Cho, Sung Soo Park, Mark W. Johnson, Pravin U. Dugel, Firas M. Rahhal, Alain Berger, Taygan Yilmaz Cummings, Jozef A. M. van Everdingen, and Kyu Hyung Kim. Impact of injection frequency on 5-year real-world visual acuity outcomes of aflibercept therapy for neovascular age-related macular degeneration. *Eye*, 35(2):409–417, 2020. doi: 10.1038/s41433-020-0851-y.

Daniel F. Martin, Maureen G. Maguire, Stuart L. Fine, Gui-shuang Ying, Glenn J. Jaffe, Juan E. Grunwald, Cynthia Toth, Maryann Redford, and Frederick L. Ferris. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. *Ophthalmology*, 119(7):1388–1398, July 2012. ISSN 0161-6420, 1549-4713. doi: 10.1016/j.ophtha.2012.03.053.

Ichiro Maruko, Masashi Ogasawara, Akiko Yamamoto, Kanako Itagaki, Taiji Hasegawa, Hisaya Arakawa, Makiko Nakayama, Hideki Koizumi, Annabelle A. Okada, Tetsuju Sekiryu, and Tomohiro Iida. Two-Year Outcomes of Treat-and-Extend Intravitreal Aflibercept for Exudative Age-Related Macular Degeneration: A Prospective Study. *Ophthalmology Retina*, 4(8):767–776, August 2020. ISSN 2468-6530. doi: 10.1016/j.oret.2020.03.010.

Keiichi Nishikawa, Akio Oishi, Masayuki Hata, Masahiro Miyake, Sotaro Ooto, Kenji Yamashiro, Manabu Miyata, Hiroshi Tamura, Naoko Ueda-Arakawa, Ayako Takahashi, Yu Kawashima, and Akitaka Tsujikawa. Four-Year Outcome of Aflibercept for Neovascular Age-Related Macular Degeneration and polypoidal choroidal vasculopathy. *Scientific Reports*, 9:3620, 2019. doi: 10.1038/s41598-019-39995-5.

Masahito Ohji, Kanji Takahashi, Annabelle A. Okada, Masato Kobayashi, Yoshimi Matsuda, Yasuhiro Terano, Masahito Ohji, Tsukasa Hanemoto, Tatsushi Kaga, Takeya Kouno, Hirokuni Kitamei, Shinpei Sato, Kanji Takahashi, Ryoji Yanai, Eiichi Uchio, Kazunori Miyata, Yoshihiro Wakabayashi, Takatoshi Maeno, Tsutomu Yasukawa, Masayuki Horiguchi, Tetsuya Nishimura, Akiteru Kawahara, Yasuo Kurimoto, Kenichi Murai, Namie Kobayashi, Wataru Kimura, Eriko Matsushita, Tomohiro Iida, Kanako Yasuda, Yuji Kato, Masahiro Miura, Annabelle Ayame Okada, Ryusaburo Mori, Atsushi Sugiyama, Yasuo Ito, Daisaku Kimura, Kei Nakai, Chota Matsumoto, Shinobu Takeuchi, Kishiko Okoshi, Yoshihisa Nuno, Yohei Nomoto, Toshio Mori, Muneyasu Takeda, Noriko Yoshida, Mio Hosokawa, Kohei Sonoda, and for the ALTAIR Investigators. Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week Findings from ALTAIR. *Advances in Therapy*, 37(3):1173–1187, March 2020. ISSN 1865-8652. doi: 10.1007/s12325-020-01236-x.

Ursula Schmidt-Erfurth, Peter K. Kaiser, Jean-François Korobelnik, David M. Brown, Victor Chong, Quan Dong Nguyen, Allen C. Ho, Yuichiro Ogura, Christian Simader, Glenn J. Jaffe, Jason S. Slakter, George D. Yancopoulos, Neil Stahl, Robert Vitti, Alyson J. Berliner, Yuhwen Soo, Majid Anderesi, Olaf Sowade, Oliver Zeitz, Christiane Norenberg, Rupert Sandbrink, and Jeffrey S. Heier. Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration: Ninety-Six–Week Results of the VIEW Studies. *Ophthalmology*, 121(1):193–201, January 2014. ISSN 0161-6420, 1549-4713. doi: 10.1016/j.ophtha.2013.08.011.

Kimberly Spooner, Samantha Fraser-Bell, Thomas Hong, Jia Yu Wong, Jack Heraghty, and Andrew A. Chang.

Real-World 10-Year Outcomes of Anti-VEGF Therapy for Neovascular Age-Related Macular Degeneration: A Meta-Analysis. *Clinical & Experimental Ophthalmology*, 53(1):44–60, 2025. doi: 10.1111/ceo.14559.

Daniele Veritti, Valentina Sarao, Francesco Missiroli, Federico Ricci, and Paolo Lanzetta. Long-term outcomes of intravitreal anti-VEGF therapies in patients affected by neovascular age-related macular degeneration: A real-life study. *BMC Ophthalmology*, 21:300, 2021. doi: 10.1186/s12886-021-02055-6.

Table 1: Key Parameters for AMD Treatment Simulation

Parameter	Value	Source	Confidence
Visual Acuity Parameters			
NAIVE treatment response	+8.4 letters (SD 1.2-1.4)	VIEW 1/2[1]; ALTAIR[2]	High
STABLE treatment response	+1.0 to +2.0 letters (SD 0.5-1.0)	ALTAIR[2]	Medium
ACTIVE treatment response	+0.5 to +1.0 letters (SD 0.5-1.0)	ALTAIR[2]	Medium
HIGHLY_ACTIVE response	-0.5 to +1.0 letters (SD 1.0-1.5)	ALTAIR[2]	Medium
Real-world mean VA change	+1.0 letter (at 1 year)	Ciulla et al.[3]	High
Disease State Transition Probabilities			
NAIVE to STABLE	0.55-0.60	ALTAIR[2]	High
NAIVE to ACTIVE	0.30-0.35	ALTAIR[2]	Medium
NAIVE to HIGHLY_ACTIVE	0.05-0.10	ALTAIR[2]	Medium
STABLE persistence	0.80-0.85	ALTAIR[2]	Medium
ACTIVE persistence	0.55-0.60	ALTAIR[2]	Medium
HIGHLY_ACTIVE persistence	0.50-0.65	ALTAIR[2]	Low
Treatment Protocol Parameters			
Loading phase injections	3	All studies	High
Initial interval	8 weeks	All studies	High
Minimum interval	8 weeks	ALTAIR[2]	High
Maximum interval	16 weeks	ALTAIR[2]	High
Extension increment	2 or 4 weeks	ALTAIR[2]	High
Mean injections (year 1)	7.3 (real-world)	Ciulla et al.[3]	High
Mean injections (2 years)	10.4 (clinical trial)	ALTAIR[2]	High
Treatment Effect by Injection Frequency			
≤4 injections/year	-2 to -3 letters	Ciulla et al.[3]	High
5-6 injections/year	-0.4 to -1.6 letters	Ciulla et al.[3]	High
7-8 injections/year	+0.7 to +2.1 letters	Ciulla et al.[3]	High
9-10 injections/year	+2.4 to +3.3 letters	Ciulla et al.[3]	High
11-13 injections/year	+3.0 to +4.3 letters	Ciulla et al.[3]	High
Treatment Effect by Baseline VA			
≤20/200	+13.9 letters	Ciulla et al.[3]	High
20/70-20/200	+0.8 letters	Ciulla et al.[3]	High
20/40-20/70	-0.8 letters	Ciulla et al.[3]	High
≥20/40	-3.3 letters	Ciulla et al.[3]	High
Discontinuation and Recurrence Parameters			
Recurrence rate at 12 months	52.9%	Aslanis et al.[4]	High
Mean time to recurrence	6.7 ± 2.2 months	Aslanis et al.[4]	High
4-month recurrence rate	13%	Aslanis et al.[4]	High
6-month recurrence rate	33%	Aslanis et al.[4]	High
8-month recurrence rate	46%	Aslanis et al.[4]	High
VA change at recurrence	-3.6 letters	Aslanis et al.[4]	High
VA after re-treatment	-0.3 letters (from baseline)	Aslanis et al.[4]	High
PED recurrence risk	74% (vs. 48% without PED)	Aslanis et al.[4]	Medium

[1] Heier et al. (2012) VIEW 1/2 study [Heier et al., 2012]
[2] Ohji et al. (2020) ALTAIR study [Ohji et al., 2020]
[3] Ciulla et al. (2020) 49,485-eye real-world study [Ciulla et al., 2020]
[4] Aslanis et al. (2022) treatment discontinuation study [Aslanis et al., 2022]

Study Type	2-Year VA Gain	Injection Count
VIEW 1/2 (RCT)	+7.6 letters	11.2
ALTAIR (RCT)	+6.1–7.6 letters	10.4
FRB! (Real-world)	+4.2 letters	14.9

Table 2: Efficacy-effectiveness gap in aflibercept treatment

Gap Duration	Prevalence	VA Loss Rate	Net Impact
3-6 months	9.4%	0.47 letters/month	-5.9 letters
6-12 months	2.5%	0.81 letters/month	-8.1 letters
>12 months	1.6%	0.51 letters/month	-11.8 letters

Table 3: Vision loss during treatment gaps

Table 4: Premature Discontinuation Parameters

Parameter	Value	Source
Eligibility	VA $>$ 20 letters & interval $\leq$ 60 days	Real-world analysis
Annual probability	10-15%	Real-world frequency
Vision change	-9.4 letters (mean)	Real-world analysis
Monitoring frequency	More frequent than stable discontinuations	Clinical guidance
Retreatment probability	Higher than stable discontinuations	Clinical implications

Category	n (%)	Mean VA	VA Loss
"Too good to stop"	89 (31.6%)	76.3 letters	-12.6 letters
"Course complete"	40 (14.2%)	63.8 letters	-14.2 letters
"Good enough"	52 (18.4%)	63.6 letters	-7.3 letters
"Plateau reasoning"	44 (15.6%)	43.7 letters	-6.8 letters
Other	57 (20.2%)	52.8 letters	-6.6 letters

Table 5: Clinical discontinuation patterns and outcomes

Gap Type	Prevalence	Mean VA Loss
COVID gaps (3-6 months)	9.4%	-5.9 letters
COVID gaps (6-12 months)	2.5%	-8.1 letters
Clinical errors (all)	1.3%	-9.5 letters

Table 6: Comparison of gap types and visual outcomes

Table 7: Distribution of patients by baseline visual acuity ranges

Visual Acuity Range	Patient Count	Percentage
Very Poor (0-30 letters)	118	5.8%
Poor (31-50 letters)	451	22.2%
Moderate (51-70 letters)	1,046	51.6%
Good (71-85 letters)	410	20.2%
Excellent (86-100 letters)	4	0.2%

Table 8: Annual Injection Frequencies for Aflibercept (Real-World Data)

Year	Mean Injections	Range/SD
Year 1	7.0	6.8–7.7
Year 2	3.3	2.5–4.0
Years 3–5	3.2	2.7–3.8

Table 9: Mean Visual Acuity Change from Baseline (ETDRS Letters)

Timepoint	Mean Change	95% CI	Source
Month 3	+7.0	–	Loading phase response
Year 1	+5.5	+3 to +8	Multiple studies
Year 2	+2.0	0 to +4	Decline begins
Year 3	+0.5	-2 to +3	Near baseline
Year 4	-1.0	-3 to +1	Below baseline
Year 5	-2.9	-5 to 0	Kim et al. [2020]

Table 10: Cumulative Discontinuation Rates by Year

Timepoint	Discontinuation Rate	Primary Reasons
Year 1	10–15%	Early non-response
Year 2	25–30%	Treatment burden
Year 3	35–43%	Multiple factors
Year 4	40–45%	Disease stability/futility
Year 5	45–50%	Cumulative attrition

Table 11: Cumulative Rates of Disease Complications

Complication	Year 1	Year 3	Year 5	Year 10*
Geographic atrophy	5%	12%	20%	49%
Fibrosis/scarring	3%	8%	15%	25%
Subretinal hemorrhage	2%	5%	8%	12%

*Extrapolated from ranibizumab data