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RESEARCH

Switching to aflibercept 8 mg in neovascular age-related macular degeneration: real-world outcomes according to switch indication

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Abstract

Purpose To evaluate visual and anatomical outcomes after switching to aflibercept 8 mg in eyes with neovascular age-related macular degeneration (nAMD), and to assess outcomes according to the clinical indication for switching.

Methods Multicentre retrospective observational study including 300 eyes with nAMD previously treated with anti-vascular endothelial growth factor therapy and switched to aflibercept 8 mg for non-response (n:74, 24.7%), suboptimal response (n:159, 53.0%), or durability-driven reasons (n:67, 22.3%). Longitudinal data from the 6 months preceding the switch and post-switch visits at 3 and 6 months were analyzed. The primary outcome was change in best-corrected visual acuity (BCVA, ETDRS letters) from the switch visit to the 3-month post-switch visit. Secondary outcomes included changes in central subfield thickness (CST) and retinal fluid status.

Results During the pre-switch period, mean BCVA declined by −1.9 ± 8.2 letters and CST increased. At 3 months after switching, BCVA improved by +2.0 ± 9.2 letters (95% CI, +0.8 to +3.2; $p < 0.01$), with greater gains in eyes switched for non-response (+2.8 ± 12.6 letters). Mean CST decreased by −45.3 ± 79.8 µm (95% CI, −55.4 to −35.2; $p < 0.001$), with corresponding reductions in retinal fluid. Anatomical improvements were more pronounced in eyes switched for non-response, whereas more modest but consistent changes were observed in suboptimal and durability-driven groups. Visual and anatomical outcomes were maintained at 6 months.

Conclusions In previously treated nAMD eyes, switching to aflibercept 8 mg was associated with reversal of pre-switch anatomical worsening, reduction in retinal fluid, and modest visual gains. Greater responses were observed in eyes with inadequate pre-switch disease control, supporting its role as a treatment escalation strategy in clinical practice.

Key messages

What is known

- Aflibercept 8 mg has demonstrated non-inferior visual outcomes with extended dosing intervals compared with standard-dose anti-VEGF therapy in randomized clinical trials, suggesting improved treatment durability in neovascular age-related macular degeneration.

What is new

- In a large multicentre real-world cohort of previously treated nAMD eyes, switching to aflibercept 8 mg was associated with reversal of pre-switch anatomical worsening, significant reduction in retinal fluid, and stable or modestly improved visual acuity up to 6 months.
- Treatment response varied according to the clinical indication for switching, with greater anatomical improvements observed in eyes with inadequate disease control prior to switch, supporting aflibercept 8 mg as a treatment escalation strategy in routine clinical practice.

Extended author information available on the last page of the article

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Keywords Aflibercept 8 mg · Anti-vascular endothelial growth factor therapy · Intravitreal injections · Neovascular age-related macular degeneration · Real-world study · Treatment switch

Introduction

Neovascular age-related macular degeneration (nAMD) remains a leading cause of irreversible central vision loss in older adults and represents a major public health burden in aging populations [1]. The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has fundamentally changed the management of nAMD, allowing stabilization or improvement of visual acuity in a substantial proportion of patients and markedly reducing the risk of severe vision loss [2–6].

However, the long-term effectiveness of anti-VEGF therapy in routine clinical practice is tempered by the need for repeated intravitreal injections and close monitoring over prolonged periods. Even when proactive regimens such as treat-and-extend are adopted, treatment burden remains substantial, and real-world outcomes frequently fall short of those reported in pivotal clinical trials [7, 8]. Persistent or recurrent exudative activity, limited interval extension, and progressive anatomical changes continue to be observed in a relevant proportion of treated eyes, underscoring the need for therapeutic strategies with improved durability [9].

In response to these limitations, longer-acting anti-VEGF approaches have been developed with the aim of sustaining disease control while reducing injection frequency. Aflibercept 8 mg represents a higher-dose formulation delivering a fourfold increase in molar dose compared with the standard 2 mg regimen. This formulation has been associated with prolonged intraocular VEGF suppression and enhanced durability in preclinical and pharmacokinetic evaluations [10, 11].

The clinical efficacy and safety of aflibercept 8 mg have been established in randomized controlled trials. The phase 3 PULSAR trial showed that aflibercept 8 mg administered at 12- or 16-week intervals achieved non-inferior visual outcomes relative to aflibercept 2 mg every 8 weeks, while enabling extended dosing intervals in a substantial proportion of patients with nAMD [12, 13].

Beyond the controlled setting of clinical trials, early real-world evidence has begun to emerge, suggesting that aflibercept 8 mg may offer anatomical stabilization and extension of treatment intervals in previously treated nAMD populations. Multicentre observational studies and single-centre series have reported stable visual acuity, reductions in retinal fluid, and a favourable short-term safety profile following transition to aflibercept 8 mg [14–16]. Nevertheless, these reports typically evaluate switched eyes as a single, heterogeneous group and provide limited information on disease behaviour prior to the switch. Detailed characterization of disease activity before switching remains limited in the available literature. Particularly, few studies incorporate longitudinal data from the months preceding the treatment change, a period that is critical for contextualizing anatomical response, treatment burden, and durability under prior anti-VEGF therapy. Moreover, the extent to which different clinical motivations for switching (such as inadequate anatomical response, suboptimal durability, or the pursuit of longer treatment intervals in otherwise controlled eyes) may influence post-switch outcomes remains insufficiently explored.

The present multicentre real-world study was designed to address these gaps by focusing exclusively on previously treated nAMD patients switched to aflibercept 8 mg. Detailed longitudinal data from the six months preceding the switch provide the opportunity to interpret post-switch outcomes in relation to different clinical indications for switching.

Methods

1. Study design and setting

This was a multicentre, observational, real-world study conducted across 9 Italian retina centers (University of Udine, Udine; University of Bari "Aldo Moro", Bari; Polytechnic University of Marche, Ancona; University of Rome Tor Vergata, Rome; IRCCS-Fondazione Bietti, Rome; Catholic University "Sacro Cuore", Rome; Ospedale Generale Regionale F. Miulli, Acquaviva delle Fonti, Bari; University of Turin, Turin; "G. d'Annunzio" University Chieti-Pescara, Chieti). Consecutive patients with nAMD who were switched to intravitreal aflibercept 8 mg as part of routine clinical care between March 2024 and September 2025 were included. Clinical data were collected retrospectively from electronic medical records and standardized data collection forms. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board. Given the retrospective nature of the study, informed consent was obtained or waived according to local regulations governing observational studies based on routinely collected clinical data.

2. Participants

Eligible participants were adults with a diagnosis of nAMD who had received prior intravitreal anti-VEGF therapy and were subsequently switched to aflibercept 8 mg. Eyes were

included if complete demographic information and longitudinal clinical data were available. Specifically, inclusion required availability of (1) baseline demographic and disease characteristics; (2) longitudinal pre-switch data spanning approximately 6 months before switching, including at least two visits with best-corrected visual acuity (BCVA) and optical coherence tomography (OCT); and (3) clinical data at the switch visit corresponding to the first aflibercept 8 mg injection. A post-switch follow-up visit 3 months after switching was prespecified for outcome analyses. Additional post-switch visits, when available, were used for descriptive or exploratory analyses. When both eyes of a patient met eligibility criteria, only one eye was included to avoid within-patient correlation. In such cases, the eye first switched during the study period was selected.

3. Clinical data and imaging

Demographic variables included age and sex. Baseline disease characteristics comprised macular neovascularization (MNV) subtype, eye laterality, disease duration, total number of intravitreal injections before switching, anti-VEGF agent used immediately prior to switching, and the last documented treatment interval. BCVA was recorded at each visit as part of routine clinical assessment. When necessary, BCVA values were converted to approximate ETDRS letter scores using established conversion methods. Spectral-domain or swept-source OCT was performed according to site-specific clinical protocols. Anatomical data were extracted from OCT scans acquired during routine clinical care. Central subfield thickness (CST) values were obtained from automated device measurements, after verification of correct retinal layer segmentation. The presence of intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelium detachment (PED) was recorded by the treating physician at each visit and was documented as binary variables (present or absent).

The decision to perform a loading phase was left to the treating physician and reflected routine clinical practice. A loading phase was defined as the administration of at least three consecutive intravitreal injections within the first 12 weeks following the switch, corresponding to an initial monthly dosing regimen.

4. Classification of switch indication

The clinical indication for switching to aflibercept 8 mg was classified into one of three prespecified categories based on longitudinal clinical and OCT findings during the 3 months preceding the switch, together with the treating physician's documented rationale. To improve reproducibility, predefined operational criteria were applied:

Non-response was defined as persistent/increasing IRF and/or SRF at all available visits during the preceding 3 months, with no meaningful anatomical improvement (defined as a reduction in CST < 10%) and stable or worsening visual acuity (BCVA change ≤ 0 letters), despite ongoing treatment at regular or intensified intervals [17].

Suboptimal response was defined as partial anatomical response under prior anti-VEGF therapy, characterized by a CST reduction ≥ 10% compared with earlier visits but persistent fluid (IRF, SRF, and/or PED) at one or more visits in the preceding 3 months. These eyes typically showed incomplete disease inactivation or fluctuating exudative activity, with stable or mildly improved BCVA [17].

Durability-driven switch was defined as a treatment change performed primarily to extend treatment intervals in eyes with controlled or near-controlled disease. These eyes showed absence of IRF/SRF at the last pre-switch visit, stable CST (variation < 10% over the preceding visits), and stable BCVA, but required relatively short treatment intervals (≤ 8 weeks) to maintain disease control [18].

Although predefined criteria were applied, classification retained a degree of clinical judgment, reflecting real-world decision-making in routine practice.

5. Outcomes and study timepoints

The primary outcome was change in BCVA from the switch visit to the 3-month post-switch visit. Secondary outcomes included changes in CST and in the presence of IRF, SRF, and PED. Additional secondary analyses evaluated functional and anatomical outcomes at the 6-month post-switch visit. Descriptive analyses further characterized disease activity during the pre-switch period.

To ensure consistent temporal alignment across centres, prespecified time windows were applied. The switch visit was defined as the visit at which the first aflibercept 8 mg injection was administered.

The pre-switch period was defined as the 6 months preceding the switch visit.

The 3-month post-switch visit was defined as the visit closest to 90 days after the switch (± 15 days).

The 6-month post-switch visit was defined as the visit closest to 180 days after the switch (± 30 days).

6. Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median (interquartile range), as appropriate, while categorical variables were reported as counts and percentages.

Changes in continuous outcomes, including BCVA and CST, were evaluated using paired comparisons between

predefined timepoints (6-month pre-switch visit, switch visit, 3-month post-switch visit, and 6-month post-switch visit). Corresponding mean changes and 95% confidence intervals were calculated. Comparisons between groups were performed using Student's t-test or Mann–Whitney U test for continuous variables, and one-way ANOVA or Kruskal–Wallis test for comparisons across multiple groups, as appropriate. Categorical variables were compared using chi-square or Fisher's exact test, while paired categorical comparisons across timepoints were performed using the McNemar test. Normality of data distribution was assessed using the Shapiro–Wilk test. Multivariable regression analyses were performed to identify clinical and anatomical factors associated with functional (BCVA change) and anatomical (CST change) outcomes at the 3-month post-switch visit. Covariates included BCVA or CST at the switch visit, switch indication category, macular neovascularization subtype, presence of IRF, SRF, or PED at the switch visit, subfoveal atrophy, macular fibrosis, prior anti-VEGF agent, and treatment centre. All analyses were considered exploratory in nature, and statistical significance was interpreted cautiously in light of the observational study design. To address heterogeneity in prior anti-VEGF exposure, a sensitivity analysis was performed by repeating the primary functional and anatomical outcome analyses in the subgroup of eyes switched directly from aflibercept 2 mg. Statistical analyses were performed using IBM SPSS Statistics, version 29 (IBM Corp., Armonk, NY, USA).

Results

1. Study population and baseline characteristics

A total of 300 eyes from 300 patients with nAMD were included in the analysis. All included eyes had complete demographic, functional, and imaging data available for the 6-month pre-switch period, the switch visit, and the 3- and 6-month post-switch visits. During the follow-up period, the mean number of aflibercept 8 mg injections administered was 3.3 ± 1.3. At the 6-month post-switch visit, the mean treatment interval was 9.4 ± 3.7 weeks, with 57.7% of eyes achieving an interval of 12 weeks or longer. Baseline demographic and clinical characteristics at the switch visit are summarized in Table 1. Type 1 MNV was the most frequent subtype, accounting for 181 eyes (60.3%), followed by Type 2 in 51 eyes (17.0%), polypoidal choroidal vasculopathy in 32 eyes (10.7%), mixed MNV in 20 eyes (6.7%), and Type 3 in 16 eyes (5.3%). Subfoveal retinal pigment epithelium atrophy was present in 78 eyes (26.0%), while subretinal macular fibrosis was observed in 104 eyes (34.7%). The primary indication for switching was suboptimal response in 53% of eyes, non-response in 24.7%, and a durability-driven strategy in 22.3%. A loading phase with aflibercept 8 mg was performed in 156 eyes (52.0%), while 144 eyes (48.0%) did not receive a loading phase.

Table 1 Baseline demographic and clinical characteristics at the switch visit

Characteristic (mean ± SD; median [IQR] unless otherwise specified)	Value
Age, years	78.2 ± 7.6; 79 [73–84]
Female sex, *n* (%)	159 (53.0)
Disease duration, months	30.1 ± 24.6; 27 [13–48]
Total anti-VEGF injections before switch	13.9 ± 8.1; 12 [7–19]
Anti-VEGF injections in prior 6 months	3.5 ± 1.1; 3 [2–6]
BCVA at switch visit, ETDRS letters	60.1 ± 19.5; 65 [50–75]
CST at switch visit, µm	314.1 ± 120.9; 289 [232–370]
Intraretinal fluid present, n (%)	150 (50.0)
Subretinal fluid present, n (%)	164 (54.7)
Pigment epithelium detachment present, n (%)	206 (68.7)
Last anti-VEGF agent before switch, *n* (%)	
– Aflibercept 2 mg	226 (75.3)
– Bevacizumab	47 (15.7)
– Faricimab	20 (6.7)
– Brolucizumab	5 (1.7)
– Ranibizumab	2 (0.7)
Last treatment interval before switch, *n* (%)	
– q4 weeks	88 (29.3)
– q6 weeks	30 (10.0)
– q8 weeks	114 (38.0)
– q10 weeks	8 (2.7)
– q12 weeks	46 (15.3)
– q16 weeks	14 (4.7)
Switch indication, *n* (%)	
– Non-response	74 (24.7)
– Suboptimal response	159 (53.0)
– Durability-driven switch	67 (22.3)

BCVA best corrected visual acuity, *CST* central subfield thickness, *ETDRS* early treatment diabetic retinopathy study, *IQR* interquartile range, *n* number; qX = dosing interval of X weeks, *SD* standard deviation, *VEGF* vascular endothelial growth factor

2. Functional outcomes

Functional outcomes over time are reported in Table 2 and Fig. 1. At the 6-month pre-switch visit, mean BCVA was 62.0 ± 19.0 ETDRS letters. From the 6-month pre-switch visit to the switch visit, mean BCVA decreased to 60.1 ± 19.5 letters, corresponding to a mean change of − 1.9 ± 8.2 letters.

Table 2 Functional and anatomical parameters over time

Outcome	Pre-switch (−6 months)	Switch visit (baseline)	Change from pre-switch	3-month post-switch	Change from switch (3 months)	6-month post-switch	Change from switch (6 months)
BCVA overall mean ± SD	62.0 ± 19.0	60.1 ± 19.5	−1.9 ± 8.2	62.1 ± 20.1	+2.0 ± 9.2	62.1 ± 20.2	+2.0 ± 8.9
Non-response	63.6 ± 16.4	60.0 ± 18.6	−3.6 ± 9.5	62.8 ± 17.9	+2.8 ± 12.6	63.0 ± 18.0	+3.0 ± 13.1
Suboptimal response	59.4 ± 21.4	57.7 ± 21.3	−1.6 ± 8.3	59.5 ± 22.1	+1.8 ± 7.1	59.1 ± 22.4	+1.4 ± 6.8
Durability-driven switch	66.4 ± 13.9	65.8 ± 14.4	−0.6 ± 6.2	67.4 ± 16.1	+1.6 ± 9.4	68.0 ± 15.0	+2.3 ± 7.7
CST overall, mean ± SD	298.1 ± 109.0	314.1 ± 120.9	+16.0 ± 99.5	268.9 ± 85.0	−45.3 ± 79.8	269.7 ± 89.1	−44.4 ± 87.5
Non-response	341.5 ± 120.9	389.2 ± 154.0	+47.7 ± 131.7	295.6 ± 105.2	−93.6 ± 104.6	297.1 ± 102.7	−92.1 ± 114.5
Suboptimal response	284.9 ± 104.1	289.7 ± 93.1	+4.8 ± 93.6	260.2 ± 76.5	−29.5 ± 62.4	261.8 ± 86.5	−27.9 ± 73.1
Durability-driven switch	281.2 ± 94.5	288.7 ± 103.7	+7.5 ± 56.8	259.6 ± 73.8	−29.1 ± 62.7	257.7 ± 72.8	−31.0 ± 63.5
IRF present, n (%)	138 (46.0)	150 (50.0)	+12 (+4.0%)	32 (10.7)	−118 (−39.3%)	76 (25.3)	−74 (−24.7%)
SRF present, n (%)	152 (50.7)	164 (54.7)	+12 (+4.0%)	62 (20.7)	−102 (−34.0%)	76 (25.3)	−88 (−29.4%)
PED present, n (%)	196 (65.3)	206 (68.7)	+10 (+3.4%)	170 (56.7)	−36 (−12.0%)	179 (59.7)	−27 (−9.0%)

BCVA best corrected visual acuity, *CST* central subfield thickness, *IRF* intraretinal fluid, *n* number, *PED* pigment epithelium detachment, *SD* standard deviation, *SRF* subretinal fluid; Changes in fluid presence are expressed as absolute differences in number of eyes and corresponding percentage-point changes

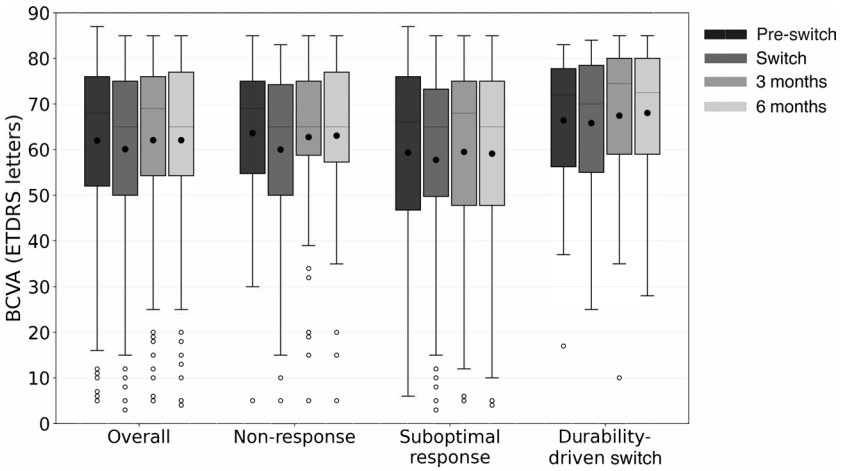

Fig. 1 Distribution of best-corrected visual acuity (BCVA, ETDRS letters) across study timepoints according to switch indication. Boxplots illustrate BCVA at the pre-switch (−6 months), switch (baseline), 3-month post-switch, and 6-month post-switch visits in the overall cohort and in eyes switched for non-response, suboptimal response, or durability-driven reasons. Boxes represent the interquartile range, whiskers indicate 1.5 × the interquartile range, open circles denote outliers, and black dots indicate mean values

At the 3-month post-switch visit, mean BCVA improved to 62.1 ± 20.1 letters, corresponding to a mean gain of +2.0 ± 9.2 letters relative to the switch visit (95% CI, +0.8 to +3.2; $p < 0.01$). At the 6-month post-switch visit, mean BCVA was 62.1 ± 20.2 letters, corresponding to a mean change of +2.0 ± 8.9 letters versus the switch visit (95% CI, +0.8 to +3.1; $p < 0.01$).

When stratified by switch indication, eyes switched for non-response exhibited the largest mean BCVA gains, with increases of +2.8 ± 12.6 letters at the 3-month post-switch visit and +3.0 ± 13.1 letters at the 6-month post-switch visit. Eyes switched for suboptimal response and those switched for durability-driven reasons showed comparable functional trajectories, characterized by modest but sustained BCVA improvements after switching (+1.8 ± 7.1 and +1.6 ± 9.4 letters at 3 months, respectively; $p < 0.01$). These gains were maintained at 6 months (+1.4 ± 6.8 and +2.3 ± 7.7 letters, respectively; $p < 0.01$).

When outcomes were analyzed according to loading phase strategy, the distribution of switch indications differed significantly between groups ($p < 0.001$): eyes receiving a loading phase were more frequently switched for non-response (36.5% vs 11.8%) or suboptimal response (53.8% vs 52.1%), whereas eyes not receiving a loading phase were more often switched for durability-driven reasons (36.1% vs 9.6%). In the overall comparison, eyes treated with a loading phase showed a greater BCVA improvement at the 3-month post-switch visit compared with those without (+3.4 ± 9.1 vs +0.5 ± 9.1 letters; $p = 0.006$). When stratified by switch indication, the functional benefit associated with the loading

phase was most evident in eyes switched for suboptimal response (+3.6±6.8 vs −0.2±6.8 letters; $p<0.001$). A similar trend was observed in eyes switched for non-response (+4.1±12.4 vs −1.6±12.4 letters; $p=0.10$). In contrast, no significant difference was observed in eyes switched for durability-driven reasons (−0.5±9.3 vs +2.2±9.3 letters; $p=0.33$).

3. Anatomic outcomes

Anatomical outcomes are summarized in Table 2 and Fig. 2. At the 6-month pre-switch visit, mean CST was 298.1±109.0 µm. From the 6-month pre-switch visit to the switch visit, mean CST increased to 314.1±120.9 µm, corresponding to a mean change of +16.0±99.5 µm. At the 3-month post-switch visit, mean CST decreased to 268.9±85.0 µm, representing a mean reduction of −45.3±79.8 µm relative to the switch visit (95% CI, −55.4 to −35.2; $p<0.001$). At the 6-month post-switch visit, mean CST was 269.7±89.1 µm, corresponding to a mean change of −44.4±87.5 µm versus the switch visit (95% CI, −55.6 to −33.4; $p<0.001$). When stratified by switch indication, eyes switched for non-response exhibited the largest anatomical improvements, with mean CST reductions of −93.6±104.6 µm at the 3-month post-switch visit and −92.1±114.5 µm at the 6-month post-switch visit. Eyes switched for suboptimal response and those switched for durability-driven reasons showed more modest but consistent CST reductions after switching, with mean changes of −29.5±62.4 µm and −29.1±62.7 µm at 3 months, respectively. These reductions were maintained at 6 months (−27.9±73.1 µm and −31.0±63.5 µm, respectively), with comparable anatomical trajectories between these two subgroups. The proportion of eyes with IRF and SRF decreased after switching. Detailed changes in individual fluid compartments (IRF, SRF, and PED) across timepoints are reported in Table 2 and illustrated in Fig. 3.

4. Multivariable analyses

After multivariable adjustment, the presence of IRF and SRF at the switch visit were independently associated with a smaller BCVA gain at the 3-month post-switch visit (IRF: β −2.70 letters, $P=0.017$; SRF: β −3.52 letters, $P=0.006$), whereas PED was not. Higher BCVA at the switch visit predicted a smaller subsequent BCVA change (β −0.084 letters per letter; $P=0.029$). Fibrosis, subfoveal atrophy, and MNV subtype were not associated with BCVA change. In the morphological model, CST at the switch visit was the strongest predictor of CST reduction (β −0.519 µm per µm; $p<0.001$), while fluid status at the switch visit, MNV subtype, fibrosis, and subfoveal atrophy were not independently associated with CST change (all $p\geq0.08$).

5. Sensitivity analysis

A sensitivity analysis restricted to eyes switched directly from aflibercept 2 mg ($n=226$, 75.3%) yielded results consistent with those of the overall cohort. Within this subgroup, switch indications were distributed as follows: suboptimal response in 125 eyes (55.3%), durability-driven reasons in 54 eyes (23.9%), and non-response in 47 eyes (20.8%). Mean BCVA changed by +1.8±8.9 letters at 3 months and +1.9±8.7 letters at 6 months after switching (both $p<0.01$). Mean CST decreased by −42.8±78.3 µm at 3 months and −42.0±86.5 µm at 6 months (both $p<0.001$). The pattern of differential responses across switch indications was maintained in this subgroup.

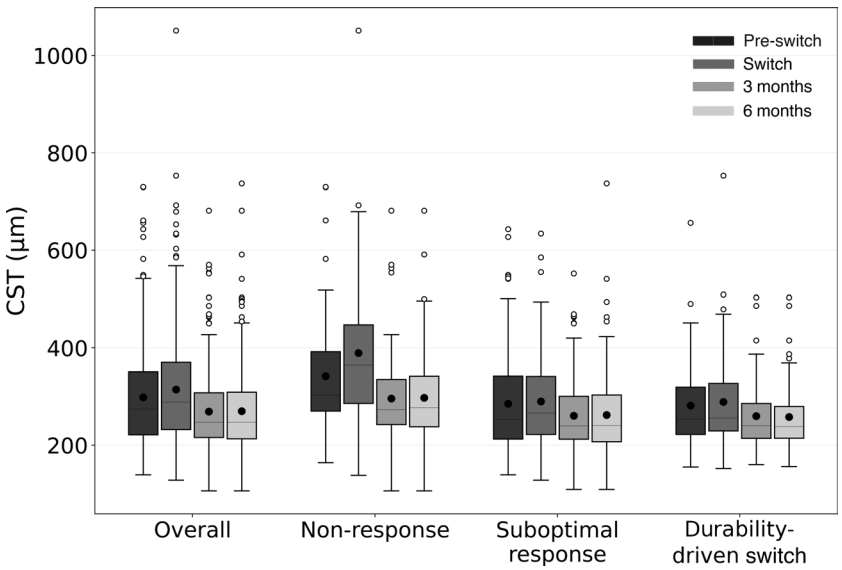

Fig. 2 Distribution of central subfield thickness (CST, µm) across study timepoints according to switch indication. Boxplots illustrate CST at the pre-switch (−6 months), switch (baseline), 3-month post-switch, and 6-month post-switch visits in the overall cohort and in eyes switched for non-response, suboptimal response, or durability-driven reasons. Boxes represent the interquartile range, whiskers indicate 1.5 × the interquartile range, open circles denote outliers, and black dots indicate mean values

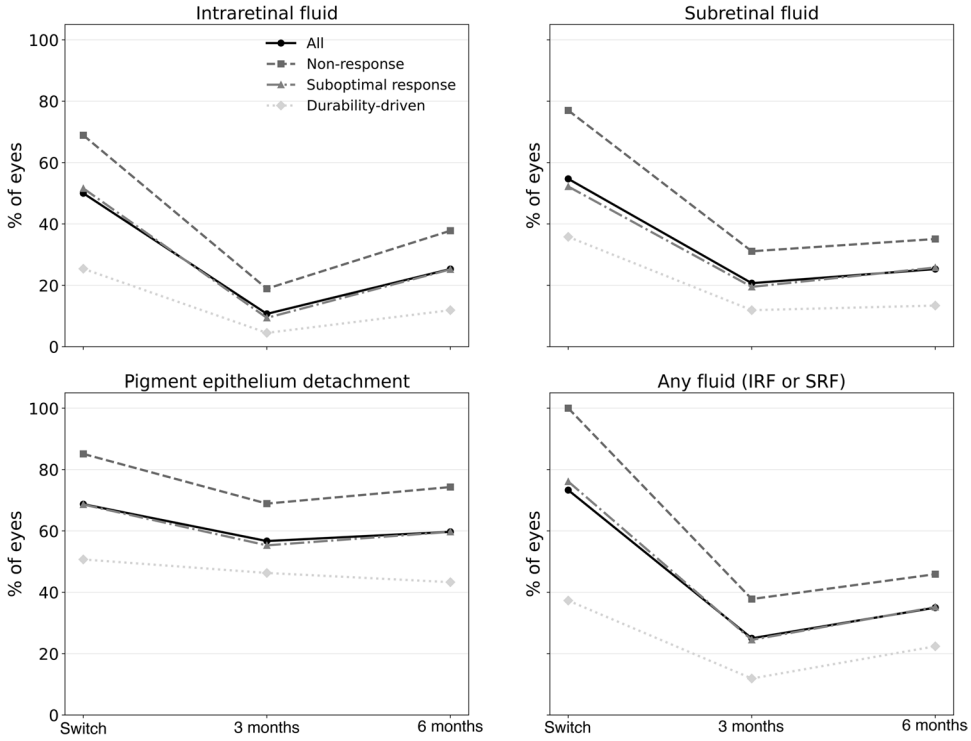

Fig. 3 Temporal evolution of retinal fluid compartments according to switch indication. Line plots illustrate the percentage of eyes with intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachment (PED), and any fluid (IRF or SRF) at the switch (baseline), 3-month post-switch, and 6-month post-switch visits in the overall cohort and stratified by switch indication (non-response, suboptimal response, and durability-driven). Values represent the proportion of eyes with the specified fluid compartment at each timepoint

6. Safety

No treatment-related serious adverse events, including intraocular inflammation or endophthalmitis, were recorded during the study period.

Discussion

In this real-world study, switching to aflibercept 8 mg was associated with meaningful anatomical improvement accompanied by a visual gain in a large, clinically diverse but predominantly treatment-experienced and challenging cohort of eyes with nAMD. Importantly, the observed decline in BCVA and increase in CST during the pre-switch period indicate that a substantial proportion of eyes represented a clinically challenging subgroup with insufficient disease control under prior anti-VEGF therapy. This selection pattern is inherent to switch studies in routine practice and should be considered when interpreting post-switch outcomes. Therefore, the cohort reflects real-world clinical decision-making, where treatment escalation is typically considered in eyes with evidence of disease instability or insufficient response. Within this context, a central finding of this study is the capacity of aflibercept 8 mg to counteract a documented trajectory of anatomical worsening in eyes switched for non-response or suboptimal response. In these subgroups, progressive increases in CST during the months preceding the switch, together with persistent or increasing retinal fluid, indicated insufficient disease control under prior treatment regimens. Following initiation of aflibercept 8 mg, anatomical outcomes improved and were subsequently maintained throughout follow-up, effectively offsetting the pre-switch deterioration. This pattern indicates that the observed post-switch changes reflect not only anatomical improvement, but also a modification of a previously progressive or unstable disease course.

These findings are broadly consistent with prior real-world studies of aflibercept 8 mg in switched nAMD populations, which have generally reported anatomical improvement with limited functional gains [13–16, 19]. However, most of these reports focused exclusively on post-switch outcomes, without accounting for the disease trajectory preceding treatment escalation. By anchoring post-switch responses to a clearly defined pre-switch course, the present analysis strengthens interpretation of treatment effects, helps contextualize post-switch changes and mitigates the risk of over-attributing regression toward the mean to treatment escalation.

At the functional level, visual acuity remained largely stable across the cohort, with modest gains observed during follow-up. This finding is consistent with expectations in switched populations characterized by relatively preserved baseline BCVA and long-standing disease. In such eyes, ceiling effects and irreversible structural damage—including macular fibrosis or atrophy—are likely to limit the potential for substantial visual improvement despite effective anatomical control. Within this context, maintenance

of visual acuity, particularly in eyes showing deterioration prior to switching, represents a clinically relevant outcome. Of note, in eyes switched for inadequate response, a complete loading phase was associated with greater BCVA gains. However, this finding should be interpreted with caution. The loading phase resulted in shorter injection intervals during the early post-switch period, and therefore the greater functional improvement observed in this subgroup may reflect, at least in part, the effect of increased injection frequency rather than the pharmacological effect of switching to aflibercept 8 mg alone.

Eyes switched primarily for durability-related reasons represent a distinct clinical phenotype within the cohort. At the time of switching, these eyes were generally under apparent anatomical control, with treatment escalation driven by the goal of extending dosing intervals and reducing treatment burden. Despite relative functional stability at baseline, this subgroup showed a small but consistent improvement in BCVA following the switch. Although modest in magnitude, this finding suggests that functional optimization may still be observed even in eyes considered well controlled. Similar signals have been reported sporadically in smaller real-world series [13, 19–21], but remain insufficiently explored in larger cohorts.

Analysis of individual retinal fluid compartments further clarifies the treatment response. The marked reduction in proportion of eyes with IRF and SRF following the switch is consistent with evidence from both pivotal trials and real-world studies of aflibercept 8 mg, supporting its enhanced potency and durability [13, 22–25]. In contrast, PED followed a more variable and frequently persistent course and was not independently associated with functional outcomes. This differential behaviour is consistent with established pathophysiological models in which IRF and SRF more directly reflect VEGF-driven exudation, whereas PED likely represents more complex or structurally established disease features with limited short-term functional relevance [26].

Several limitations of this study should be acknowledged. First, the retrospective design and the absence of an active-comparator control group limit causal inference. Therefore, the observed post-switch changes cannot be attributed solely to aflibercept 8 mg and should be interpreted as outcomes of a real-world treatment-change strategy. In particular, the longitudinal pre-switch period provides useful clinical context for interpreting post-switch outcomes, but it does not replace a parallel control group. Second, treatment regimens were not standardized and reflected routine clinical decision-making. Post-switch treatment intervals were individualized according to physician judgment and disease activity. Accordingly, durability outcomes should be interpreted in light of the non-standardized treatment schedules and the potential influence of physician preference and local practice patterns. In particular, the classification of switch indication and the decision to perform a loading phase were left to the treating physician, potentially introducing variability across centres. The comparison between eyes receiving a loading phase and those without should therefore be interpreted with caution, as these groups differed in baseline characteristics and switch indications, raising the possibility of selection bias. Third, the relatively short follow-up limits conclusions regarding long-term durability and visual outcomes. Finally, anatomical assessment was based on central subfield thickness and qualitative evaluation of retinal fluid, without quantitative volumetric analysis, and OCT data were derived from routine clinical interpretation rather than centralized reading, which may have introduced additional variability. Nonetheless, the relatively large sample size and inclusion of a broad spectrum of clinical phenotypes support the external validity and real-world relevance of the findings.

In conclusion, in a large and heterogeneous real-world cohort of switched nAMD eyes, aflibercept 8 mg was associated with reversal of pre-switch anatomical deterioration, sustained reduction in retinal fluid, and overall visual stability with modest functional gains. The differential responses observed across switch indications highlight the importance of individualized treatment strategies and realistic expectation setting. These findings complement existing trial and real-world evidence and support the role of aflibercept 8 mg as a treatment escalation option in contemporary nAMD management.

Author contributions Daniele Veritti, Valentina Sarao, Marco Lupidi and Paolo Lanzetta contributed to the study conception and design. All authors performed material preparation and data collection. Analysis was performed by Daniele Veritti and Valentina Sarao. The first draft of the manuscript was written by Daniele Veritti, and all authors commented on previous versions. All authors read and approved the final manuscript.

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Data availability The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The study adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Boards of the participating centres according to national regulations governing retrospective observational studies based on routinely collected clinical data.

Consent to participate Due to the retrospective nature of the study, informed consent was obtained or waived according to local institutional requirements.

Consent for publication Not applicable.

Competing interests Daniele Veritti: consultant for Bayer, Hofmann La Roche; Valentina Sarao: consultant for Bayer, I-Care, Hofmann La Roche; Pasquale Viggiano: consultant for Abbvie, Bayer, Bausch and Lomb, Hofmann La Roche, Novartis and Zeiss; Mariacristina Parravano: consultant for Abbvie, Bayer, Hofmann La Roche, Novartis, Zeiss; Enrico Borrelli: consultant/advisor for Abbvie, Bayer, EyePharma, Hofmann La Roche, Novartis, Zeiss. Francesco Boscia: consultant for Alcon, Abbvie, Bayer, Bausch and Lomb, Hofmann La Roche, Novartis and Zeiss. Michele Reibaldi: consultant for Abbvie, Bayer, Hofmann La Roche, Novartis, Zeiss; Monica Varano: consultant for Abbvie, Bayer, Novartis; Paolo Lanzetta: consultant for Aerie, Allergan, Annexon, Apellis, Bausch & Lomb, Bayer, Biogen, Boehringer Ingelheim, EyeBio, Genentech, I-Care, Novartis, Ocular Therapeutix, Outlook Therapeutics, and Hofmann La Roche. Marco Lupidi, Marco Lombardo, Giacomo Boscia, Lisa Toto, Asia Amelia Martin, Alba Chiara Termite, Giulia Ribezzi, Enrico Nacciarriti, Eleni Nikolopoulou Gisotti, Giovanni Neri, Cesare Persavalli, Claudia Fossataro, Maria Cristina Savastano, Cesare Mariotti, Rodolfo Mastropasqua, Federico Ricci, Alfonso Savastano, Stanislao Rizzo: none. Enrico Borrelli is a member of the journal's Editorial Board but had no role in the peer review or editorial decision-making process for this manuscript.

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