Twelve-month outcomes of intra-vitreal anti-VEGF agents for treatment-naïve neovascular age-related macular degeneration eyes: French data from the fight for retinal blindness! registry

Lolita Lestable, Pierre-Henry Gabrielle, Alain M. Bron, P. Nguyen, Catherine Creuzot Garcher

Twelve-Month Outcomes of Intra-Vitreal Anti-VEGF Agents for Treatment-Naïve Neovascular Age-Related Macular Degeneration Eyes: French Data from the Fight for Retinal Blindness! Registry.

Résultats à 1 an d'un Traitement par Injections Intra-Vitréennes d'Agent Anti-VEGF dans la Dégénérescence Maculaire Liée à l'Age Exsudative Naïve : Données d'une Étude du Registre Fight for Retinal Blindness!.

Anti-VEGF for wet AMD: French Data from Fight for Retinal Blindness! Registry

Lestable L. [1], Gabrielle PH.[1], Bron AM. [1,2], Nguyen P.[3], Creuzot-Garcher C.[1,2]

(1) Service d'Ophtalmologie, CHU de Dijon, France

(2) Eye and Nutrition Research Group, CSGA, UMR1324 INRA, 6265 CNRS, Université Bourgogne Franche-Comté, Dijon, France

(3) The Save Sight Institute, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

Correspondence

Lolita Lestable

Department of Ophthalmology, University-Hospital,

14 rue Paul Gaffarel, 21079 Dijon, France

Tel : +33 (0)380295173, Fax : +33 (0)380293589

E-mail: lolita.lestable@gmail.com ORCHID 0000-0002-3332-8251

Twelve-Month Outcomes of Intra-Vitreal Anti-VEGF Agents for Treatment-Naïve Neovascular Age-Related Macular Degeneration: French Data from the Fight for Retinal Blindness! Registry.

Résultats à 1 an d'un Traitement par Injections Intra-Vitréennes d'Agent Anti-VEGF dans la Dégénérescence Maculaire Liée à l'Age Exsudative Naïve : Données d'une Étude du Registre Fight for Retinal Blindness!.

Summary

Introduction. To describe the one-year functional outcomes of treatment-naïve neovascular age-related macular degeneration (nAMD) treated with anti-VEGF agents at the Dijon University Hospital Ophthalmology Department.

Methods. Real-life interventional study including all treatment-naïve nAMD patients from January 2016 to December 2018 in the Ophthalmology Department of Dijon University Hospital. Data were retrospectively collected from the Fight Retinal Blindness! (FRB!) registry. At baseline, medical history, visual acuity (VA), type of lesion and activity on angiography and optical coherence tomography (OCT), and treatment were recorded. On follow-up, VA, lesion activity and treatment were recorded.

Results. Three-hundred twenty eyes of 259 patients were included, of which 65.6% were female and with a mean age of 80.1 $\pm$ 11.1 years. Mean VA (standard deviation, SD) at baseline was 53.2 ETDRS letters (25.3). All patients received anti-VEGF injections, of which 164 eyes (51.2%), 152 eyes (47.5%) and 4 eyes (1.2%) were treated with aflibercept, ranibizumab and bevacizumab, respectively. A total of 198 eyes of 169 patients completed the 12-month follow-up, with a median (first quartile, third quartile) of 12 visits (10, 13). At

one year (n=198), the overall mean VA gain [95% CI] was +3.3 ETDRS letters [0.7, 5.9] and 173 (87.4%) of the treated eyes did not lose 15 or more letters. We found no statistically significant difference in mean VA gain between aflibercept and ranibizumab.

Conclusion. This real-world study confirmed the efficacy of anti-VEGF agents in nAMD and the feasibility of analyzing data in an international registry.

Key words

Neovascular age-related macular degeneration; Anti-VEGF therapy; Retina

Résumé

Introduction. Décrire les résultats fonctionnels à 1 an des patients atteints de dégénérescence maculaire liée à l'âge exsudative (DMLAe) naïfs traités par anti-VEGF au centre hospitalier universitaire (CHU) de Dijon.

Méthodes. Étude interventionnelle de vraie-vie incluant tous les patients ayant présenté une DMLAe naïve entre janvier 2016 et décembre 2018 au CHU de Dijon. Les données étaient collectées rétrospectivement via le registre Fight for Retinal Blindness! (FRB!). A l'inclusion étaient recueillis : antécédents, acuité visuelle (AV), type et activité du néovaisseau en angiographie et tomographie à cohérence optique (OCT), et traitement introduit. Lors du suivi, AV, activité du néovaisseau et traitement ont été enregistré.

Résultats. Trois cent vingt yeux de 259 patients ont été inclus, 65,6% de femme, d'âge moyen 80,1 $\pm$ 11,1 ans. L'AV moyenne à l'inclusion était de 53,2 lettres ETDRS (25,3). Tous les patients ont bénéficié d'un traitement anti-VEGF, 164 (51,2%) aflibercept, 152 (47,5%) ranibizumab et 4 (1,2%) bevacizumab. Au total, 198 yeux de 169 patients ont completé un suivi de 12 mois avec un nombre médian (1^{e} interquartile ; 3^{e} interquartile) de 12 visites (10 ; 13). A 1 an, le gain moyen [IC 95% ; intervalle de confiance à 95%] d'AV était de +3,3 lettres [0,7 ; 5,9] et 173 des yeux (87,4%) n'ont pas perdu 15 lettres ou plus. Nous n'avons pas retrouvé de différence statistiquement significative entre aflibercept et ranibizumab.

Conclusion. Cette étude de vraie-vie confirme l'efficacité des anti-VEGF dans la DMLAe et la faisabilité de traiter des donnés dans un registre international.

Mots Clés

Dégénérescence maculaire liée à l'âge exsudative ; Anti-VEGF ; Rétine

Introduction

Age-related macular degeneration (AMD) is one of the leading causes of visual deficiency after 50 years in industrialized countries [1]. The neovascular form may concern about 10 to 15% of all patients suffering from AMD, representing 1.7 million in North America and a significant public health issue. Current anti-vascular endothelial growth factor (VEGF) agent intravitreal therapies (IVT), such as ranibizumab and aflibercept, proved their effectiveness in neovascular age-related macular degeneration (nAMD) controlled phase 3 clinical trials [2–7]. International guidelines recommend these anti-VEGF agents as first-line therapy for nAMD [8].

However, significant visual loss still affects a sizeable proportion of patients treated with anti-VEGF agents. The MARINA study (Minimally Classic/Occult Trial of the Anti VEGF Antibody Ranibizumab in the treatment of neovascular AMD) [2] and the ANCHOR study (Anti VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) [4] found a loss of vision about 15 letters or more in 8% to 10% of eyes at 2 years. Similarly, 4.9% to 6.3% of eyes developed a loss of vision of 15 letters or more in the VIEW 1 and 2 studies (VEGF trap-eye: Investigation of efficacy and safety in the wet AMD studies) at two years [9]. Identifying treated eyes with severe visual loss may assist physicians in subsequent treatment decision and guiding patient's expectation.

Real-world studies constitute an essential step to confirm the anti-VEGF agents' effectiveness in nAMD. Indeed, many patients treated for nAMD in the general practice may not meet the inclusion criteria of clinical trials. International database, like the Fight Retinal Blindness! (FRB!), the retinal disease web platform from the Save Sight registries, allows clinicians in any routine medical centre to follow-up their patients and collect data for worldwide study in the meantime. Our study aimed to describe the one-year functional

outcome of treatment-naïve eyes presenting with nAMD and treated with anti-VEGF agents using data incorporated in the FRB! registry.

Methods

Design and setting

This interventional study was conducted in the Department of Ophthalmology at Dijon University Hospital (France) using data retrospectively collected. All patients have been tracked in the FRB! database, which has already been described elsewhere [10,11]. Data were collected from contributing practitioners in the Ophthalmology Department at Dijon University Hospital using the FRB! system. The physician determined the type of anti-VEGF agents and visit agenda in consultation with the patient, which reflects real-world practice. The treatment regimens available for selection were monthly, Pro Re Nata (PRN) and treat and extend (T&E). The research described adhered to the tenets of the Declaration of Helsinki. The FRB! database is compliant with the International Consortium for Healthcare Outcome Measures (ICHOM) [12].

Study population and groups

Treatment-naïve eyes receiving anti-VEGF agent monotherapy for nAMD from January 1, 2016, to December 31, 2018, were included. Eyes were analyzed by treatment group by the drug chosen at the first injection. Eyes completing 12 months of follow-up were considered for analysis. Noncompleters were defined as eyes not completing 12 months of follow-up as of May 1, 2019, thus allowing at least three months for a follow-up visit to occur after the end of the 12-month observation period. Switchers were defined as eyes receiving at least two injections of the other anti-VEGF agent before completing 12 months of follow-up. For completers, the most recent VA reading within the 12 months was defined as the VA at 12 months. The last observation carried forward (LOCF) method was used for analysis, which included completers and noncompleters.

Study Measurements

At the baseline visit, the FRB! system collected clinical history of the patient, such as age, gender, ophthalmologic history conditions and previous treatment or surgery, the type and size of choroidal neovascular membrane (CNV) lesion (occult, predominantly classic, minimally classic, retinal angiomatous proliferation (RAP), idiopathic polypoidal choroidal vasculopathy (IPCV)) defined by the fundus fluorescein angiography, optical coherence tomography (OCT) characteristics, such as atrophy, fibrosis and pigmented epithelium detachment (PED) profile, and the choice of anti-VEGF drug. VA was measured in letters with an ETDRS (Early Treatment Diabetic Retinopathy Study) chart. The follow-up visits reported VA, activity of the CNV on OCT (defined by the presence of subretinal or intraretinal fluid) or fundus ophthalmoscopy (defined by the presence of hemorrhage), treatment choice, adverse event occurred and other treatment affecting visual acuity since the previous visit (such as cataract surgery,YAG capsulotomy, retinal laser).

Study outcome

The primary study outcome was the mean change in VA at one year in treatment-naïve eyes receiving anti-VEGF IVT for nAMD. Secondary outcomes were the median inactivation time and the baseline predictive factors of vision loss.

Statistical Analysis

Categorical variables were expressed as number (%) and continuous variables as mean and standard deviation (SD) or mean and 95% confidence interval [95% CI] or median and interquartile range (IQR) as appropriate. Student *t*-test, Chi-square and Wilcoxon rank-sum test were used to compare baseline group characteristics when appropriate. Locally weighted scatterplot smoothing (LOESS) regression curve were used to compare visual acuity at one year for treatment naïve eyes completing 12 months of follow up, grouped by

initial received treatment. Kaplan Meier survival curve were used to analyzed time from baseline visit to the first inactive grading of lesion activity grouped by initial given treatment. The predictors of VA loss were evaluated by univariate analysis using student t-test, Wilcoxon rank-sum test and Fisher's exact test, as appropriate. P-values of less than 0.05 were considered statistically significant.

Results

Study participants

We identified 320 treatment-naïve eyes of 259 patients, starting with either aflibercept, bevacizumab or ranibizumab IVT, between January 1st 2016 and December 31st 2018. One hundred ninety-eight eyes of 169 patients completed the 12 months follow-up. The baseline characteristics of the study groups are described in Table 1. All patient received at least one anti-VEGF agent, as first-line therapy, 111 eyes (56.1%) had aflibercept, 85 eyes (42.9%) had ranibizumab and 2 eyes (1.0%) had bevacizumab. Few patients were treated with multiple agents during the follow-up, 2 eyes (1.8%) switched from aflibercept to ranibizumab and 3 eyes (3.5%) switched from ranibizumab to aflibercept. Mean baseline VA (standard deviation, SD) did not differ significantly between ranibizumab-treated and aflibercept-treated eyes nor did other characteristics between the two populations.

Visual acuity outcomes

Regarding visual acuity, for all completers the mean VA gain [95% confidence interval, 95% CI] in our study was 4.7 letters [2.5, 6.8] at 3 months and 3.3 [0.7, 5.9] after 12 months of follow up whatever the treatment. There was no significant difference highlighted in our study between aflibercept and ranibizumab. At one year, 173 eyes among 198 completing a 12 month follow-up (87.4%) did not present a vision loss of 15 letters or more. In the aflibercept group, the mean visual acuity gain was 1.9 letters [-1.7, 1.5] versus 4.8 [1.0, 8.7] in the ranibizumab group. For aflibercept treated eyes, mean visual acuity at one year was 55.3 letters (24.4) versus 56.7 (26.0) at baseline visit. For ranibizumab patients, mean visual acuity after one year of follow-up was 56.3 (26.9) versus 57.4 (25.3) initially. Table 2 resume outcomes at 3 and 12 months for treatment-naïve eyes completing a 12-month follow-up grouped by initial treatment. Figure 1 describes the locally weighted scatterplot smoothing

(LOESS) regression curve of mean visual acuity at 12 months, grouped according to the initial treatment. In Figure 2, the detailed visual outcomes at 3 and 12 months are displayed globally and separately for each module.

Time to inactivated status

The median injection number (first quartile Q1, third quartile Q3) for each eye was 8 (5.0, 10.8). The median time to inactivity was 97 days (87, 200) for all eyes, 94 days (85, 191) for aflibercept, and 98 days (90, 218) for ranibizumab. The median injections until inactivity was 3 injections (3, 6). There was no significant statistical difference between aflibercept and ranibizumab. Figure 3 shows the Kaplan-Meier survival curve for the time until the first inactive grading of lesion activity grouped by the initial treatment.

Mean treatment interval

During the first three months, the mean treatment interval between 2 injections for 92.4% of eyes were every four weeks. Whatever the treatment regimen, from month fourth to month twelve, 27.7% of eyes stayed with a mean injection interval of 4 weeks, while 33.8 % were treated every 6 weeks and 24.6% every 8 weeks.

Characteristics associated with poor visual outcome

Table 3 describes the characteristics associated with a visual loss of 15 letters or more at 12 months. After one year of follow-up, 24 eyes (12.6%) presented a visual loss of 15 letters or more. Subretinal fibrosis (P = 0.016) on OCT at 12 months was associated significantly with a poor visual outcome.

Visual acuity after cataract extraction

Seventeen eyes underwent cataract surgery during our study, the mean VA acuity before and after surgery was 53.7 (19.3) and 61.6 (22.2) letters, respectively. The mean VA gain represented 7.9 letters [3.9, 11.8].

Discussion

This retrospective study provides new data on the functional outcome of nAMD treatment-naïve eyes treated with anti-VEGF agents IVT in real-life clinical practice.

Overall, the mean VA improved significantly by +3.3 letters [0.7, 5.9] over the first 12 months with a median time of 97 days (87, 200) until the first inactivated status of the CNV lesion for all eyes, after a median of 3 injections (3, 6). There was no significant difference of functional outcomes between the two mains anti-VEGF agents worldly used for nAMD, ranibizumab and aflibercept. As already shown in previous studies, these findings confirmed that VEGF inhibitors achieve excellent outcomes for nAMD in real-world practice. Gillies M.C. *et al.* found a mean VA gain of +4.7 letters and a median time to inactivation of lesion of 194 days after 12 months of prospective follow-up, using the FRB! Database [13]. One might explain their better functional outcomes compared to our study since they used principally a T&E regimen, which showed to give better functional results compared to PRN regimen in nAMD [14–16]. Furthermore, our study reported similar functional results as compared to the French LUMIERE study with a mean VA gain of 3.2 letters [17]. Similarly, in another study of the FRB! study group, they did not find any significant difference of functional outcomes between aflibercept and ranibizumab with a mean VA gain of 3.7 letters for ranibizumab-treated eyes and 4.3 for aflibercept-treated eyes [11]. Additionally, another observational study reported similar VA improvement after 12 months in naive-eyes [18]. Our data emphasize that the two mains anti-VEGF agents have similar functional outcomes and time to inactivation delay in nAMD [3,11].

Furthermore, these results confirmed that real-world clinical studies achieve inferior visual outcome compared with phase 3 clinical trials. Indeed in MARINA and ANCHOR

studies, the mean gain at 12 months for ranibizumab-treated eyes was respectively +7.2 and +11.3 letters [2,4].

In our study, 12.6% of eyes presented a loss of vision of 15 letters or more. In the MARINA and ANCHOR pivotal phase III trials, 5.5% and 3.6% of ranibizumab treated eyes respectively had lost 15 letters of VA by one year [2,4]. In the CATT study, 9.2% of patients treated with ranibizumab or aflibercept presented 15 letters or more visual loss at two years [6]. The monthly regimen used in these pivotal studies, which is rarely used in routine practice, can be an explanation of the lower rate of VA loss in these trials. The FRB! study group reported 11.0% and 22.9% of eyes losing 15 letters or more at two years and five years in a real-world clinical dataset, respectively, which is more in agreement with our data [19].

Regarding factors contributing to poor visual outcome for nAMD naive-treated patients, older age at baseline seems to be associated with visual loss but was not statistically significant in our univariate analysis. (P=0.051). Indeed, age > 80 was found as a risk factor independently associated with poor visual outcome in Chu Luan Nguyen *et al.* FRB! study.[19] Rosenfeld *et al.* evaluated the risk of vision loss in MARINA and ANCHOR trials and found an increased risk of visual loss with age [20]. However, age was not significantly associated with a sustained VA loss at two years in a post-hoc analysis of the CATT study [21]. CNV lesion size has been identified as a risk factor of vision loss in several studies. In Chu Luan Nguyen *et al.* FRB! study, a median greatest linear dimension > 2500µm (measured on fluorescein angiography) represented a risk factor of poor visual outcome in multivariable analysis [19]. Furthermore Rosenfeld *et al.* and Ying *et al.* identified larger neovascular baseline lesion size as significant for poor visual outcome in MARINA and ANCHOR trials and in CATT study, respectively [20,22]. Although CNV lesion size at baseline

seems to be larger for patients presenting VA loss of 15 letters or more in our study, it was not significantly associated in our univariate analysis. Additionally, we found that subfoveal fibrosis was associated with VA loss at 12 months. In another long term observational study using FRB! database, geographic atrophy and subretinal fibrosis were thought to be the long term VA loss cause for 37% and 31% of eyes presenting a loss of 10 letters or more, respectively [23]. Surprisingly, geographic atrophy and worse baseline VA were not associated with VA loss of 15 letters or more in this study, as compared to other studies [22,24]. Unfortunately, multivariate analysis was not possible due to a low number of eyes with a visual loss of 15 letters or more in our cohort.

Regarding cataract surgery performed on nAMD treated eyes, we found a mean VA gain of 7.9 [3.9, 11.8] letters following the intervention. In a retrospective matched case-control study using FRB! Database, Daien *et al.* found a mean VA gain of 10.6 letters [7.8, 13.2] in nAMD treated eyes after cataract surgery and no evidence of an association between cataract surgery and CNV lesion activity [25].

We acknowledge several limitations in our study. First, Subjective criteria like activity or lesion type in FRB! database might not be graded uniformly since they were reported by the treating physicians rather than a centralized reading centre. Although this determination seemed to have lower internal validity than phase 3 clinical trials, it is still meaningful since it represents how this clinically relevant diagnosis is made in real-world practice. Second, case selection and treatment regimens may be different from those of clinical trials and among different ophthalmologist. Third, high noncompletion rates are common in retrospective studies, and this study was not an exception because 38% of eyes did not complete the 12 months follow-up during the study period. Reasons for noncompletions, when noticed, were

patient declining further treatment or medical condition making treatment and follow-up impossible.

This study emphasizes the importance of real-world studies and the usefulness of an extensive international database like the FRB! project. Undoubtedly, they provide real value of ophthalmologic routine treatment follow-up and appear essential to compare practice and cohort characteristics between centres.

In conclusion, real-world studies are determinant to provide information on the clinical outcomes of new treatments in routine clinical practice as compared to clinical trials. The efficacity of anti-VEGF agents in nAMD described in our study is reasonably good. Further research would be warranted to determine long term functional outcome of eyes with persistent activity or VA loss.

Disclosure of interest

The authors declare that they have no competing interest.

REFERENCES

[1] Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA 2004;291:1900–1.

[2] Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.

[3] Sarwar S, Clearfield E, Soliman MK, Sadiq MA, Baldwin AJ, Hanout M, et al. Aflibercept for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2016;2:CD011346.

[4] Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009;116:57-65.e5.

[5] CATT Research Group, Martin DF, Maguire MG, Ying G, Grunwald JE, Fine SL, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–1908.

[6] Martin DF, Maguire MG, Fine SL, Ying G, Jaffe GJ, Grunwald JE, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–98.

[7] Traynor K. Aflibercept approved for macular degeneration. Am J Health Syst Pharm 2012;69:6–6.

[8] Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, et al. Guidelines for the management of neovascular age-related macular degeneration by the european society of retina specialists (euretina). Br J Ophthalmol 2014;98:1144–67.

[9] Schmidt-Erfurth U, Kaiser PK, Korobelnik J-F, Brown DM, Chong V, Nguyen QD, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six–week results of the VIEW studies. Ophthalmology 2014;121:193–201.

[10] Gillies MC, Walton R, Liong J, Arnold JJ, McAllister I, Morlet N, et al. Efficient capture of high-quality data on outcomes of treatment for macular diseases: the fight retinal blindness! Project. Retina 2014;34:188–95.

[11] Gillies MC, Nguyen V, Daien V, Arnold JJ, Morlet N, Barthelmes D. Twelve-Month Outcomes of Ranibizumab vs. Aflibercept for Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 2016;123:2545–53.

[12] Rodrigues IA, Sprinkhuizen SM, Barthelmes D, Blumenkranz M, Cheung G, Haller J, et al. Defining a minimum set of standardized patient-centered outcome measures for macular degeneration. Am J Ophthalmol 2016;168:1–12.

[13] Gillies MC, Walton R, Simpson JM, Arnold JJ, Guymer RH, McAllister IL, et al. Prospective audit of exudative age-related macular degeneration: 12-month outcomes in treatment-naïve eyes. Invest Ophthalmol Vis Sci 2013;54:5754–60.

[14] Augsburger M, Sarra G-M, Imesch P. Treat and extend versus pro re nata regimens of ranibizumab and aflibercept in neovascular age-related macular degeneration: a comparative study. Graefes Arch Clin Exp Ophthalmol 2019. Epub ahead of print

[15] Hatz K, Prünte C. Treat and extend versus pro re nata regimens of ranibizumab in neovascular age-related macular degeneration: a comparative 12 month study. Acta Ophthalmol 2017;95:e67–72.

[16] Chin-Yee D, Eck T, Fowler S, Hardi A, Apte RS. A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration. Br J Ophthalmol 2016;100:914–7.

[17] Cohen SY, Mimoun G, Oubraham H, Zourdani A, Malbrel C, Queré S, et al. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. Retina 2013;33:474–81.
[18] Holz FG, Tadayoni R, Beatty S, Berger A, Cereda MG, Cortez R, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol 2015;99:220–6.
[19] Nguyen CL, Gillies MC, Nguyen V, Daien V, Cohn A, Banerjee G, et al. Characterization of poor visual outcomes of neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents. Ophthalmology 2019;126:735–42.
[20] Rosenfeld PJ, Shapiro H, Tuomi L, Webster M, Elledge J, Blodi B. Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. Ophthalmology 2011;118:523–30.
[21] Ying G, Kim BJ, Maguire MG, Huang J, Daniel E, Jaffe GJ, et al. Sustained visual acuity loss in the comparison of age-related macular degeneration treatments trials. JAMA Ophthalmol 2014;132:915–21.
[22] Ying G, Huang J, Maguire MG, Jaffe GJ, Grunwald JE, Toth C, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2013;120:122–9.
[23] Gillies MC, Campain A, Barthelmes D, Simpson JM, Arnold JJ, Guymer RH, et al. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. Ophthalmology 2015;122:1837–45.
[24] Westborg I, Albrecht S, Rosso A. Risk for low visual acuity after 1 and 2 years of treatment with ranibizumab or bevacizumab for patients with neovascular age-related macular degeneration. Retina 2017;37:2035–46.
[25] Daien V, Nguyen V, Morlet N, Arnold JJ, Essex RW, Young S, et al. Outcomes and Predictive Factors After Cataract Surgery in Patients With Neovascular Age-related Macular Degeneration. The Fight Retinal Blindness! Project. Am J Ophthalmol 2018;190:50–7.

Table 1. Demographic characteristics at baseline for all eyes and eyes completing a 12-month follow-up treated for neovascular age-related macular degeneration.

	All eyes	12-Month completers [d]	Aflibercept completers	Ranibizumab completers	*P*-value
Eyes	320	198	111 (56.1%)	85 (42.9%)	
Patients	259	169	95	76	
Gender (female) [a]	65.6%	64.5%	64.2%	65.8%	0.760
Age (years) [b]	80.1 (11.1)	79.1 (11.7)	80.0 (8.9)	77.9 (14.7)	0.244
VA, (ETDRS letters) [b]	53.2 (25.3)	52.3 (25.8)	53.4 (25.4)	51.5 (26.3)	0.603
VA ≤ 35 letters [a]	25.3%	27.8%	26.1%	28.2%	0.867
VA ≥ 70 letters [a]	36.9%	37.4%	36.9%	38.8%	0.903
Lesion size, µm [c]	840 (420, 1310)	930 (500, 1500)	930 (560, 1500)	875 (400, 1500)	0.365
Angiographic lesion type [a]					
Occult	111 (34.7%)	73 (36.9%)	42 (37.8%)	31 (36.5%)	0.946
Minimally Classic	26 (8.1%)	16 (8.1%)	8 (7.2%)	8 (9.4%)	
Predominantly Classic	79 (24.7%)	55 (27.8%)	31 (27.9%)	24 (28.2%)	
IPCV	5 (1.6%)	3 (1.5%)	1 (0.9%)	2 (2.4%)	
RAP	21 (6.6%)	12 (6.1%)	8 (7.2%)	4 (4.7%)	
Not done	76 (23.8%)	38 (19.2%)	20 (18%)	16 (18.8%)	
Initial injection type [a]					
Bevacizumab	4 (1.2%)	2 (1.0%)			
Aflibercept	164 (51.2%)	111 (56.1%)			
Ranibizumab	152 (47.5%)	85 (42.9%)			

VA: visual acuity; µm: micrometer; ETDRS: Early Treatment Diabetic Retinopathy Study; IPCV: idiopathic polypoidal choroidal vasculopathy; RAP: retinal angiomatous proliferation

[a] Categorical variables are expressed as number (%)

[b] Continuous variables are expressed as mean (standard deviation)

[c] Continuous variables are expressed as median (Q1: first quartile, Q3: third quartile)

[d] 2 (1%) eyes completing a twelve-month follow-up were treated with Bevacizumab

Table 2. Outcomes at 3 and 12 months for treatment-naïve eyes completing a 12-month follow-up grouped by initial treatment.

	All Completers	Aflibercept	Ranibizumab	*P*-values
Eyes	198	111	85	
Baseline VA (ETDRS letters) [a]	52.3 (25.8)	53.4 (25.4)	51.5 (26.3)	
3 Months Outcomes				
VA (ETDRS letters) [a]	56.9 (25.6)	56.7 (26)	57.4 (25.3)	
VA change [b]	4.7 [2.5, 6.8]	3.3 [0.2, 6.3]	5.9 [3.1, 8.7]	
Without 15 letters loss [c]	182 (91.9%)	97 (87.4%)	83 (97.6%)	
12 Month Outcomes				
VA (ETDRS letters) [a]	55.6 (26.7)	55.3 (26.4)	56.3 (26.9)	0.788
VA change [b]	3.3 [0.7, 5.9]	1.9 [-1.7, 5.4]	4.8 [1.0, 8.7]	0.256
Without 15 letters loss [c]	173 (87.4%)	94 (84.7%)	78 (91.8%)	0.201
Injections [d]	8 (5, 10.8)	8 (6, 10)	8 (4, 11)	0.662
Visits [d]	12 (10, 13)	12 (10, 13)	11 (9, 13)	0.698
Switched [c]	5 (2.5%)	2 (1.8%)	3 (3.5%)	0.620

VA: visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study

[a] Continuous variables are expressed mean (standard deviation)

[b] Continuous variables are expressed mean [95%, Confidence Interval]

[c] Categorical variables are expressed as number (%)

[d] Continuous variables are expressed as median (Q1: first quartile, Q3: third quartile)

Table 3. Characteristics associated with a visual loss of 15 letters or more at 12 months.

	VA loss ≥15 letters	No VA loss ≥15 letters [d]	*P*-value [c]
Eyes	24	172	
Gender (female) [a]	65.2%	65.2%	1.000
Age (years) [b]	82.8 (9.3)	78.5 (12)	0.051
Baseline VA (ETDRS letters) [b]	52.1 (21.9)	52.7 (26.3)	0.906
Lesion size, µm [c]	1495 (957.5, 1687.5)	870 (440, 1370)	0.067
Angiographic lesion type [a]			
Occult	7 (29.2%)	66 (38.4%)	
Minimally Classic	0 (0%)	16 (9.3%)	
Predominantly Classic	11 (45.8%)	44 (25.6%)	0.237
Other	2 (8.4%)	13 (7.6%)	
Initial injection [a]			
Aflibercept	**17 (70.8%)**	**94 (54.7%)**	**0.201**
Ranibizumab	**7 (29.2%)**	**78 (45.3%)**	
Geographic atrophy at 12 months [a]			
Not present	4 (16.7%)	58 (33.7%)	
Subfoveal	20 (83.3%)	106 (61.6%)	0.147
Extrafoveal	0 (0%)	8 (4.7%)	
Subretinal fibrosis at 12 months [a]			
Not present	7 (29.2%)	91 (52.9%)	
Subfoveal	17 (70.8%)	68 (39.5%)	**0.016**
Extrafoveal	0 (0%)	13 (7.6%)	

VA: Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; µm: micrometer

[a] Categorical variables are expressed as number (%)

[b] Continuous variables are expressed mean (standard deviation)

[c] *P* value calculated from univariable analysis, those reaching statistical significance are in bold

[d] 2 eyes completing a 12-month follow-up treated with Bevacizumab were not included in this analysis

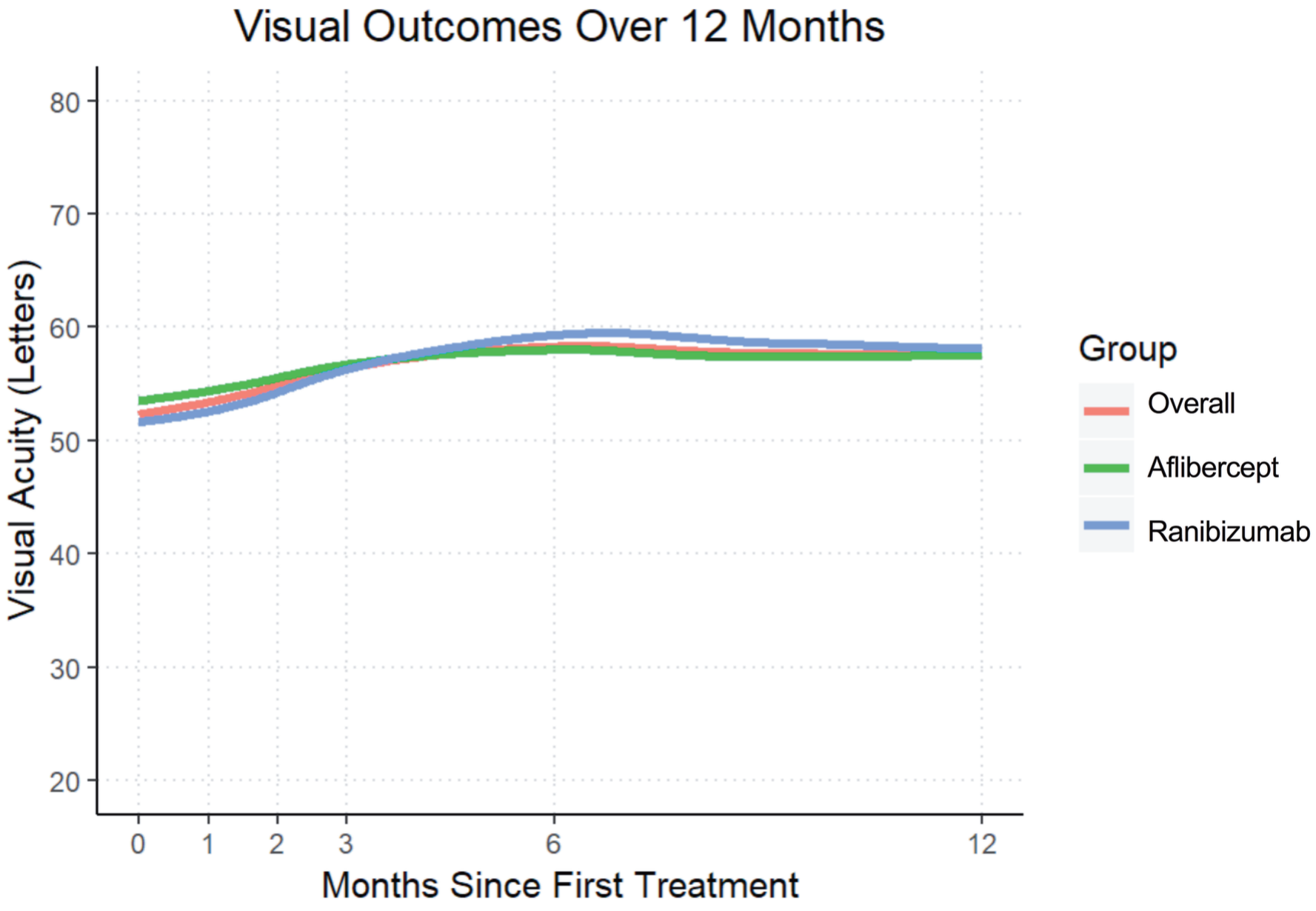
Caption page

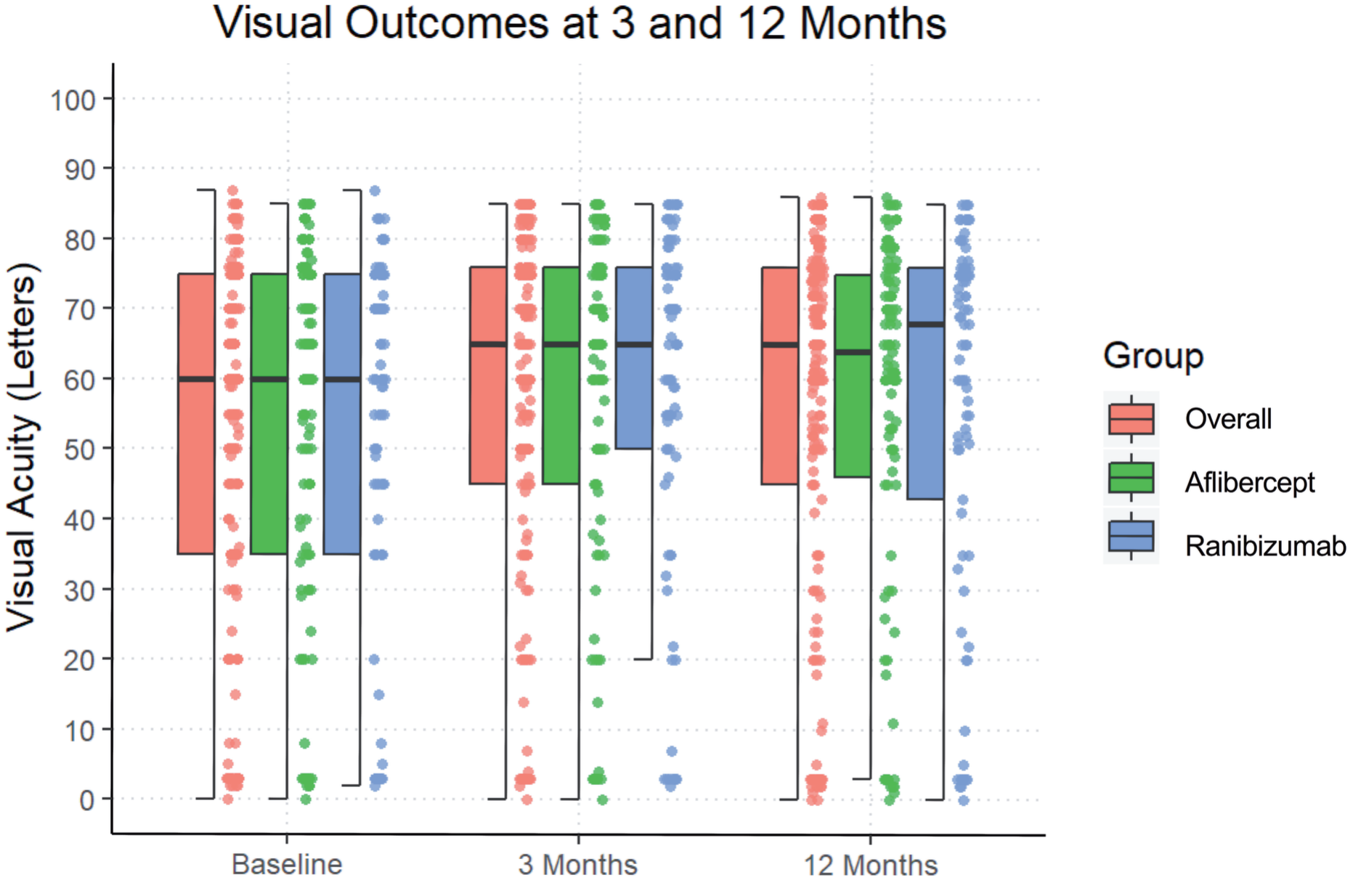
Figure 1. Locally weighted scatterplot smoothing (LOESS) regression curves of mean visual acuity for treatment-naïve eyes completing a 12-month follow-up grouped by initial treatment.

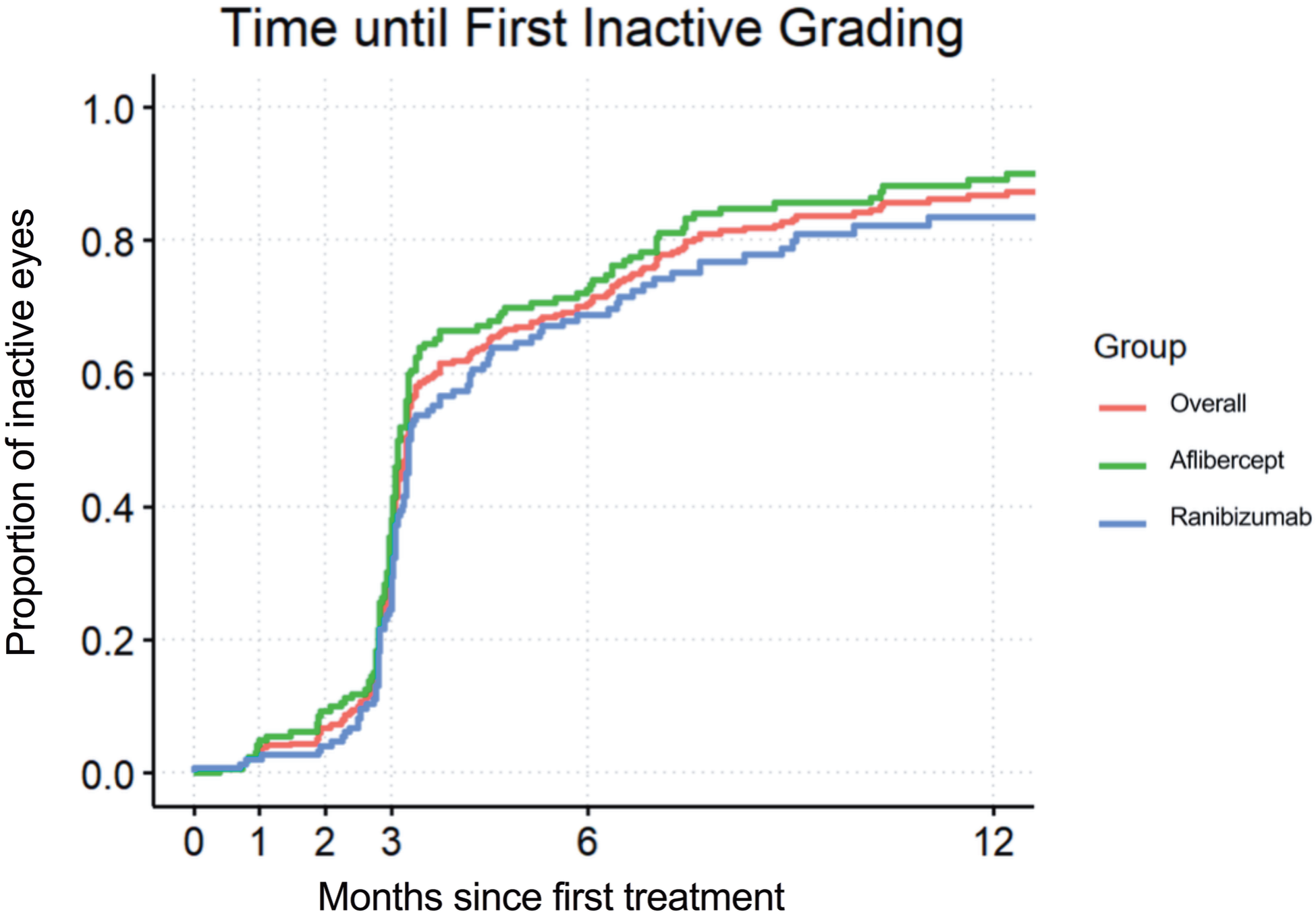
Figure 2. Hybrid boxplot showing the distribution of visual acuity at baseline vs. 3 and 12 months for treatment-naïve eyes completing a 12-month follow-up grouped by initial treatment.

Whiskers represent the 25^{th} and 75^{th} percentiles plus or minus the interquartile range. Each dot represents the visual acuity for a single eye.

Figure 3. Kaplan-Meier survival curves for time until first inactive grading of lesion activity grouped by initial treatment. The median (Q1, Q3) time to inactivity was 97 days (87, 200) for all eyes, 94 days (85, 191) for Aflibercept, and 98 days (90, 218) for Ranibizumab. The median (Q1, Q3) injections until inactivity was 3 injections (3, 6).


Visual Outcomes Over 12 Months
Visual Acuity (Letters)
80
70
60
50
40
30
20
0
1
2
3
6
12
Months Since First Treatment
Group
Overall
Aflibercept
Ranibizumab


Visual Outcomes at 3 and 12 Months
Visual Acuity (Letters)
100
90
80
70
60
50
40
30
20
10
0
Baseline
3 Months
12 Months
Group
Overall
Aflibercept
Ranibizumab


Time until First Inactive Grading
Proportion of inactive eyes
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
6
12
Months since first treatment
Group
Overall
Aflibercept
Ranibizumab