Intraocular pressure changes and vascular endothelial growth factor inhibitor use in various retinal diseases: long-term outcomes in routine clinical practice: data from the fight retinal blindness! Registry

Pierre-Henry Gabrielle, Vuong Nguyen, Benjamin Wolff, Rohan Essex, Stephanie Young, Adrian Hunt, Chui Ming Gemmy Cheung, Jennifer Arnold, Daniel Barthelmes, Catherine Creuzot-Garcher, et al.

▶ **To cite this version:**

Pierre-Henry Gabrielle, Vuong Nguyen, Benjamin Wolff, Rohan Essex, Stephanie Young, et al.. Intraocular pressure changes and vascular endothelial growth factor inhibitor use in various retinal diseases: long-term outcomes in routine clinical practice: data from the fight retinal blindness! Registry. Ophthalmology Retina, 2020, 4 (9), pp.861-870. 10.1016/j.oret.2020.06.020 . hal-02908021

HAL Id: hal-02908021
https://hal.inrae.fr/hal-02908021

Submitted on 5 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial| 4.0 International License

Version of Record: https://www.sciencedirect.com/science/article/pii/S2468653020302402
Manuscript_b442c97b85a2cd8a100e9a8424913757

Intraocular Pressure Changes and VEGF Inhibitor Use in Various Retinal Diseases: Long-Term Outcomes in Routine Clinical Practice: Data from the Fight Retinal Blindness! Registry

Pierre-Henry Gabrielle, MD[1, 2]; Vuong Nguyen, PhD[2]; Benjamin Wolff, MD[3]; Rohan Essex, MBBS[4]; Stephanie Young, MBBS[5]; Adrian Hunt, MBBS[2]; Chui Ming Gemmy Cheung, MBBS[6]; Jennifer J Arnold, MBBS[7]; Daniel Barthelmes, MD, PhD[2, 8]; Catherine Creuzot-Garcher, MD, PhD[1]; Mark Gillies, MBBS, PhD[2] for the Fight Retinal Blindness! Study Group

[1] Department of Ophthalmology, Dijon University Hospital, Dijon, France
[2] The University of Sydney, Sydney Medical School, Discipline of Ophthalmology, Save Sight Institute, New South Wales, Australia
[3] Private Clinic, Centre Ophtalmologique Maison Rouge, Strasbourg, France
[4] Academic Unit of Ophthalmology, Australian National University, Acton, Australian Capital Territory, Australia
[5] Gladesville Eye Specialists, New South Wales Australia
[6] Singapore National Eye Centre, Singapore, Singapore
[7] Marsden Eye Research, Sydney, Australia
[8] Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Financial Support: The Fight Retinal Blindness! Project is supported by a grant from the Macular Disease Foundation Australia and unrestricted educational grants from Bayer and Novartis.
Conflict of interest: Gillies and Barthelmes are inventors of the software used to collect the data for this analysis
Running head: Intraocular Pressure Changes and VEGF Inhibitors in Retinal Diseases

Corresponding Author/Address for Reprints:
Pierre-Henry Gabrielle, MSc, MD, FEBO
Phone: +61431360231
Email: phgabrielle@gmail.com

This article contains additional online-only material. The following should appear online-only: Figures S1, S2 and S3, Tables S1 and S2 and the acknowledgements.

© 2020 published by Elsevier. This manuscript is made available under the CC BY NC user license
https://creativecommons.org/licenses/by-nc/4.0/

Abstract

Purpose: To report long-term changes in intraocular pressure (IOP) in eyes receiving vascular endothelial growth factor (VEGF) inhibitors for various retinal conditions over 12- and 24-months in routine clinical practice.

Design: Retrospective analysis of data from a prospectively designed observational outcomes registry: the Fight Retinal Blindness! Project.

Participants: Treatment-naïve eyes receiving monotherapy with VEGF inhibitors (ranibizumab [0.5mg], aflibercept [2mg] or bevacizumab [1 mg]) with at least 3 injections, from December 2013 to 31 December 2018 and at least 12 months of follow-up.

Methods: IOP was measured at each clinical visit for all eyes as part of routine practice.

Main Outcome measures: The primary outcome was the mean change in IOP (mmHg) at 12-months. The following secondary IOP outcome measures were investigated at 12 and 24 months: (1) mean change in IOP from baseline and (2) proportion of clinically significant IOP increase defined as an elevation of at least 6 mmHg to an IOP of more than 21 mmHg at any point during the follow-up.

Results: We identified 3429 treatment-naïve eyes (395 bevacizumab, 1138 aflibercept and 1896 ranibizumab) with complete IOP data from 3032 patients with 12 months of follow-up data, of which 2125 (62%) had 24 months of follow-up data. The overall mean [95%CI] IOP change was -0.5 [-0.6, -0.3] mmHg at 12 months and -0.4 [-0.6, -0.3] mmHg at 24 months while the proportion of clinically significant IOP increases were 5.6% and 8.8%. A lower mean IOP change and fewer IOP elevations at 12- and 24-

months was observed in eyes receiving aflibercept than in those receiving bevacizumab and ranibizumab (for both comparison $P \leq 0.01$ at each time point and outcomes). Eyes with pre-existing glaucoma had more IOP increases over 12- and 24-months (OR = 2.2 [1.2, 3.8], $P = 0.012$ and OR = 2.1 [1.1, 3.8], $P = 0.025$, respectively).

Conclusions: Mean IOP did not change significantly from baseline to 12 and 24 months in eyes receiving VEGF inhibitors, while clinically significant IOP elevations occurred in a small proportion of eyes. Aflibercept was associated with fewer clinically significant IOP elevations, whereas eyes with pre-existing glaucoma were at a higher risk.

Introduction

Despite the widespread use of vascular endothelial growth factor (VEGF) inhibitors for retinal conditions, such as neovascular age-related macular degeneration (AMD), diabetic macular edema (DME) and macular edema (ME) secondary to retinal vein occlusion (RVO), there are still only limited data on their effect on IOP. It is well known that there is a transient spike in intraocular pressure (IOP) immediately after an injection but this quickly decreases over the next 15 minutes for most patients.[1–3] The degree to which anti-VEGF agent injections contribute to long-term IOP changes is less clear. A large real-world study using the Intelligent Research in Sight (IRIS) registry reported a slight but significant decrease in IOP from baseline in eyes treated with anti-VEGF agents for more than one year compared with control eyes.[4] Moreover, 2.6% of the treated patients had clinically significant, sustained IOP elevations, confirming the results of previous studies.[5–8] Somewhat surprisingly, there were fewer cases of sustained IOP elevations in eyes treated with aflibercept (1.9%) than with those receiving ranibizumab (2.8%) or bevacizumab (2.8%).[4,5] A recent review highlighted the conflicting reports with regards to IOP changes and the risk factors for IOP rises with intravitreal injections of VEGF inhibitors, which may be partially due to variability in methodology and the definition of clinically significant IOP increase between studies.[9] More data are needed on long-term IOP change outcomes and the potential risk factors associated with IOP change in patients treated with VEGF inhibitors. This study aimed to explore changes in IOP in eyes receiving VEGF inhibitors for various retinal conditions over 12- and 24-months in routine clinical practice.

Methods

Design and setting

This was a retrospective analysis of treatment-naïve eyes that had received intravitreal anti-VEGF agents for various retinal diseases in routine clinical practice tracked in the prospectively designed observational database – The Fight Retinal Blindness! Registry.[10] Participants in this analysis included patients from practices in Australia, France, New Zealand, Singapore and Switzerland. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the Southern Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (IRB) (Société Française d'Ophtalmologie IRB), the SingHealth Singapore and the Cantonal Ethics Committee Zurich. All patients gave their informed consent. Informed consent ("opt-in consent") was sought from patients in France, Singapore and Switzerland. Ethics committees in Australia and New Zealand approved the use of "opt-out" patient consent. This study adhered to the tenets of the Declaration of Helsinki and followed the STROBE statements for reporting observational studies.[11]

Data Sources and Measurements

The Fight Retinal Blindness! Registry has several modules that collect data from eyes being treated for neovascular AMD, DME and ME secondary to RVO.[10] Data were obtained prospectively from each clinical visit including IOP measurement (mmHg), treatment given, if any, and ocular adverse events. Demographic characteristics (age and gender), initial diagnosis (AMD, DME or RVO), history of any ocular condition (pre-

existing glaucoma status), and whether the eye received prior treatment (cataract surgery and vitrectomy) were recorded at baseline visit. Treatment decisions, including the choice of drug and injection frequency, were at the discretion of the physician in consultation with the patient, thereby reflecting real-world practice. Data on glaucoma treatment during follow-up such as introduction of IOP-lowering drop, laser or incisional glaucoma surgery were not systematically recorded in any of the three modules.

Patient Selection and Groups

Treatment-naïve eyes that received intravitreal monotherapy of VEGF inhibitors (eyes were excluded if switched or received any other type of intravitreal treatment) with either aflibercept (2mg Eylea, Regeneron Inc/Bayer), bevacizumab (1.25mg Avastin, Genetech Inc/Roche) or ranibizumab (0.5mg Lucentis, Genetech Inc/Novartis) for neovascular AMD, DME or ME secondary to RVO with a minimum of 3 injections and at least one year of follow-up including IOP measurement at least at baseline and 12-months after starting treatment from 1 December 2013 to 31 December 2018 were studied.

Prefilled syringes for administering ranibizumab were approved in early 2015 and global uptake of these prefilled syringes amongst clinicians using ranibizumab increased gradually over time. Prefilled packing was generally adopted in early 2017. To analyze the effect of prefilled vs. non-prefilled syringes on IOP, we analyzed the subset of eyes initially treated with intravitreal ranibizumab injection from 1 January 2017 (*prefilled group*) with those initially treated with intravitreal ranibizumab injection before 1 January

2014 and 1 January 2013 (*non-prefilled group*), thereby allowing 12 and 24 months of follow-up before the start of prefilled packaging, respectively.

Patients were also grouped by the total number of injections received: low (3-4 or 3-9 injections), medium (5-8 or 10-14 injections) and high (≥10 or ≥15 injections) during the 12- and 24-month follow-up periods, respectively. Eyes with pre-existing glaucoma were identified at baseline.

Outcomes

The primary outcome was the adjusted mean change in IOP from baseline to 12 months using a regression model. Secondary outcomes were the proportion of eyes with clinically significant IOP elevation (defined as an IOP increase of at least 6 mmHg from baseline and resulting in an IOP of >21 mmHg in a single event), and predictors of change in IOP and rate of clinically significant IOP elevations during 12- and 24-month follow-up (type of anti-VEGF agent, type of prefilled /non prefilled ranibizumab, number of injections, initial diagnosis, pre-existing glaucoma). Outcomes were analyzed by anti-VEGF agent, number of injections, prefilled/non-prefilled ranibizumab and pre-existing glaucoma status groups as defined above.

Statistical analysis

Descriptive data were summarized using the mean, standard deviation, median, first and third quartiles, and percentages where appropriate. Demographic characteristics were compared between anti-VEGF groups, prefilled groups, and glaucoma groups using ANOVA, Kruskal-Wallis test, t-tests, Wilcoxon rank sum tests, Chi-square tests, or

Fisher's exact tests where appropriate. The mean changes in IOP between subgroups were compared using linear mixed-effects regression models. The proportion of eyes with a clinically significant elevation in IOP was analyzed using logistic mixed-effects regression. The main predictors investigated were type of anti-VEGF agents, type of ranibizumab prefilled/non-prefilled syringes, number of injections, initial diagnosis, pre-existing glaucoma. Regression was adjusted for age, gender, baseline IOP, lens status, and cataract extraction during the follow-up as fixed effects, and nesting of outcomes within practitioners and patients with bilateral disease as random effects. Vitrectomy during the follow-up was not included in the model due to a very low incidence in our cohort. Since it was not mandatory to record IOP in the FRB registry, there was a possibility of bias due to selective reporting of IOP in high risk patients. A sensitivity analysis was done on the cohort of eyes followed by physicians who entered IOP measurement at least 50% of the time during follow-up visits.

A *P*-value of 0.05 was considered statistically significant. *P*-values from pairwise comparisons between anti-VEGF groups were adjusted for using the Holm-Bonferroni correction method. All analyses were conducted using R software version 3.5.3 (http://www.R-project.org/) with the *glmmTMB* package (V0.2.3) for linear mixed-effects and generalized linear mixed-effects regression and the *emmeans* package (V1.3.3) for pairwise comparison of adjusted means.

Results

Study participants

A total of 3429 treatment-naïve eyes (395 bevacizumab, 1138 aflibercept and 1896 ranibizumab) from 3032 patients who received intravitreal monotherapy of VEGF inhibitors for neovascular AMD, DME or ME secondary to RVO with 12 months of IOP follow-up data after starting treatment from 1 December 2013 to 31 December 2018 were identified (from an overall number of 10382 treatment naïve eyes entered in the registry that received anti-VEGF injections from the selected countries involved in this study), of which 2125 (62%) had 24 months of follow-up data. The mean (SD) age overall was 78.1 (10.4) years with 58.7% of women. There were 2901(84.6%) eyes treated for neovascular AMD, 221 (6.4%) eyes for DME and 307 (9%) for ME secondary to RVO. Table 1 summarizes the baseline characteristics in each of the groups. Eyes receiving ranibizumab were significantly older than those receiving aflibercept and bevacizumab (mean 74.3 *vs.* 76.4 vs. 79.9 years for bevacizumab, aflibercept and ranibizumab, respectively; $P < 0.01$) and had a higher proportion of female patients (51.3% *vs.* 54.8% vs. 63.0% for bevacizumab, aflibercept and ranibizumab, respectively; $P < 0.01$). The overall proportions of eyes in each group of total number of injections received were 10.2% (350 eyes) and 8.2% (175 eyes) in the low group, 46% (1578) and 44.8% (951) in the medium group and 43.8% (1501) and 47% (999) in the high group at 12 and 24 months of treatment, respectively. The proportion of eyes that had cataract surgery was 3.7% (107 eyes) and 6.3% (181 eyes) over 12- and 24-months of follow-up.

Intraocular pressure change outcomes

Baseline mean (SD) IOP was 14.4 (3.8) mmHg overall, 14.9 (3.6) for bevacizumab, 14.4 (4.0) for aflibercept, and 14.4 (3.6) for ranibizumab. The overall mean [95%CI] IOP change at 12- and 24-months was -0.5 [-0.6, -0.3] mmHg ($P < 0.01$) and -0.4 [-0.6, -0.3] mmHg ($P < 0.01$), respectively. Figure 1 reports the adjusted mean IOP change at 12- and 24-months by type of VEGF inhibitors, number of injections, initial diagnosis and pre-existing glaucoma status. Eyes receiving aflibercept had significantly greater IOP reduction (adjusted mean [95% CI]) at 12- and 24-months (-1.3 [-1.6, -1.1] and -1.3 [-1.7, -1.0] mmHg, respectively) than bevacizumab (0.0 [-0.4, 0.4], $P < 0.01$ and 0.0 [-0.6, 0.6], $P < 0.01$, respectively) and ranibizumab (0.0 [-0.2, 0.2], P < 0.01 and -0.1 [-0.4, 0.2], P < 0.01, respectively). There was no difference between bevacizumab and ranibizumab at 12 and 24 months. There was also a significant trend for eyes with neovascular AMD (-0.5 [-0.7, 0.3]) and pre-existing glaucoma (-1 [-1.5, 0.4]) to be associated with a greater adjusted mean reduction in IOP at 12 months than eyes with RVO (+0.2 [-0.3, 0.6], $P = 0.010$) or pre-existing glaucoma (-0.4 [-0.3, 0.6], $P = 0.043$), respectively.

Clinically significant intraocular pressure elevation outcomes

The overall proportion of clinically significant IOP elevations was 5.6% (193 eyes) at 12 months and 8.8% (186 eyes) at 24 months. Figure 2 describes the adjusted proportion of clinically significant IOP elevations during 12 and 24 months of follow-up by type of VEGF inhibitors, number of injections, initial diagnosis and pre-existing glaucoma status. Clinically significant IOP elevations during 12 and 24 months follow-up were less likely to occur in aflibercept-treated eyes (reference subgroup) than eyes treated with bevacizumab (OR = 2.2 [1.2, 4.0], $P = 0.015$ and OR = 2.7 [1.4, 5.0], $P < 0.01$,

respectively) or ranibizumab (OR = 2.8 [1.8, 4.1], $P < 0.01$ and OR = 2.6 [1.7, 4.0], $P < 0.01$, respectively) (Table 2). The rates of clinically significant elevated IOP were 2.4% and 3.9% in the aflibercept group, 5.2% and 9.7% in the bevacizumab group and 6.4% and 9.4% in the ranibizumab group during 12- and 24-months follow-up, respectively (Figure 2). RVO treated eyes tended to be significantly more at risk of IOP elevations during the first 12 months of follow-up than eyes treated for AMD (OR = 1.9 [1.1, 3.1], $P = 0.039$), though this association was not statistically significant at 24 months. Glaucomatous eyes were more likely to have an IOP elevation during both 12- and 24-months follow-up (OR = 2.2 [1.2, 3.8], $P = 0.012$ and OR = 2.1 [1.1, 3.8], $P = 0.025$, respectively) with an adjusted rate of 2.1% and 11.0% when treated with aflibercept, 14.1% and 23% with bevacizumab, and 14.7% and 23.0% with ranibizumab. There was a trend for an increasing rate of IOP elevations with more injections during both one and two-years of follow-up, however, this was not statistically significant (Figure 2).

Intraocular pressure change outcomes by type of ranibizumab syringe

There was no statistically significant difference in the adjusted mean (95% CI) IOP change at 12- and 24-months between the two types of ranibizumab syringe (-0.1 [-0.4, 0.2] and -0.2 [-0.7, 0.4] for non-prefilled syringe vs. 0.1 [-0.3, 0.5] and 0.7 [-0.3, 1.6] for prefilled syringe, P = 0.34 and P = 0.11, respectively) (Figure 3A and 3B). Nor did we find a significant association with the type of syringe and clinically significant IOP elevation (Table 2; Figure 3C). There was no significant variation at 12 and 24 months in the adjusted mean IOP change from baseline ($P = 0.39$ and 0.87, respectively) and rate of IOP elevations ($P = 0.81$ and 0.75, respectively) by year of treatment initiation.

Discussion

We used the FRB! observational outcomes database to explore the effect of intravitreal VEGF inhibitors on long-term IOP change in treatment naïve eyes for various exudative retinal diseases in routine clinical practice. The overall mean IOP at 12- and 24-months slightly decreased in our cohort, which corroborates recent results.[4,8] Interestingly, eyes treated with aflibercept had significantly greater adjusted mean reduction in IOP than bevacizumab and ranibizumab at 12 and 24 months. This finding was previously reported in a secondary analysis of intraocular pressure outcomes in the VIEW 1 and 2 study that compared aflibercept (2mg q4, 2mg q8, 0.5mg q4) with ranibizumab (0.3mg q4) for neovascular AMD.[5] This statistically significant difference seen in our study is minor and may not be clinically relevant.

The outcomes of clinically significant IOP elevation (increase of at least 6 mmHg from baseline and resulting in an IOP of > 21 mmHg in a single event) are of more clinical interest. Our overall rate of 5.6% at 12 months is higher than the 2.8% rate of elevated IOP of the IRIS registry study and 3.4% by the study of Adelman *et al.*.[4,7] This difference may be explained by the stricter definition of IOP elevation (proportion of eyes with a baseline IOP ≤ 21 mmHg that had an IOP rise of at least 6 mmHg which resulted in an IOP greater than 21 mmHg at 2 consecutive visits) for the former study and the exclusion of glaucoma patients at baseline for the latter, who are possibly more at risk of IOP elevations. An exploratory *ad hoc* analysis of DRCRnet studies assessing IOP change between ranibizumab versus focal/grid laser for DME through 3 years found similar rates of IOP elevations with 5.7% at one year and a cumulative incidence of 9.5% at 3 years in the ranibizumab group, though their definition was also different

(same criteria at 2 consecutive visits or initiation/augmentation of IOP-lowering drug). The rate of elevated IOP reported in VIEW 1 and 2, defined as IOP > 21 mmHg at 2 consecutive visits, was in keeping with our results with 5.2% vs. 2.5 % vs. 2.4% vs. 1.5% at one year and 8.4% vs 3.2% vs. 4.2% vs. 2.7% at 2 years for ranibizumab, aflibercept 2q4, 2q8 and 0.5q4, respectively.[5]

The pathophysiological process underlying sustained IOP elevations following treatment with VEGF inhibitors has not been identified, although several etiologies have been proposed. It may be related to a decrease in aqueous outflow by chronic mechanical damage to the trabecular meshwork from repeated injection-related IOP spikes or direct toxicity of VEGF inhibitors itself or obstruction due to accumulation of protein aggregates or silicone droplets, or even trabecular meshwork constriction mediated by inhibition of nitric oxide synthesis.[6,12–14]

We found that aflibercept-treated eyes were consistently less likely to have IOP elevations than bevacizumab- and ranibizumab-treated eyes during the follow-up, which is consistent with the analyses in VIEW 1 and 2.[5] Freund *et al.* proposed that accumulation of protein aggregates might be greater with ranibizumab compared to aflibercept or that repeated ranibizumab injections lead to progressive trabeculitis secondary to an endotoxin inflammatory response caused by a different manufacturing process involving Escherichia coli bacteria compared with Chinese hamster ovary cells for aflibercept.[5] However, bevacizumab is produced with similar production processes as aflibercept, and we found a similar consistent rate of IOP elevations between bevacizumab and ranibizumab, which does not support this theory. Ranibizumab and bevacizumab bind to all VEGF-A isoforms, while aflibercept can trap VEGF-A, VEGF-B

290 and placental growth factor (PlGF).[15] PlGF only acts on pathological angiogenesis and
291 inflammation and is not involved in physiological angiogenic processes.[16–18] Anti-VEGF
292 agents may lead to drug resistance due to an angiogenic rescue program with up-
293 regulation of other growth factors such as PlGF.[17–19] Repeated injections of ranibizumab
294 and bevacizumab may induce a progressive inflammatory response secondary to
295 upregulation of intraocular PlGF levels, which make those eyes more at risk of
296 inflammatory-related IOP elevations than aflibercept, which possibly controls this
297 deleterious upregulation.

298 No previous studies in the literature have assessed the impact of syringe
299 packaging on IOP outcomes. Our study tried to address this question with a sub-
300 analysis of the ranibizumab cohort. Our finding reported no significant difference in IOP
301 outcomes between the prefilled and non-prefilled syringe period. This is not consistent
302 with the theory that droplets of silicone oil, applied to lubricate the components of insulin
303 syringe used for bevacizumab or non-prefilled ranibizumab packing, play a role in IOP
304 elevations.[12,14] This finding needs to be confirmed in further studies.

305 It has been reported that increased frequency and number of injections may raise
306 the risk of IOP elevations.[4,20,21] There was a trend for an increasing rate of elevated IOP
307 with a higher number of injections in the present study, although this was not statistically
308 significant; there are conflicting reports on this topic.[22,23]

309 Eyes with pre-existing glaucoma were more at risk of clinically significant IOP
310 elevation during the follow-up, which is also consistent with previous reports.[4,24,25]
311 Bergen *et al.* recently reported that PlGF aqueous levels were elevated in glaucomatous
312 patients.[17] The consistently increased rate of IOP elevations in bevacizumab and

313 ranibizumab treated eyes compared to aflibercept in the glaucomatous subgroup
314 emphasizes a possible involvement of PlGF in the pathophysiology of IOP elevation in
315 eyes treated with VEGF inhibitors.
316 This study has several strengths and limitations. Observational studies provide
317 data that represent the ability of a drug to achieve its intended purpose in the real world.
318 Our data are representative of a wide variety of real-world international practices.
319 Though there is variability in the quality of data in observational studies, the FRB!
320 system includes quality assurance measures that eliminate out of range and missing
321 data.[10] Well-designed observational studies may not systematically overestimate the
322 effect of treatment as randomized clinical trials may.[26] The limitations of the study are,
323 first, no specific protocol for IOP measurements was defined so there may be variability
324 in methodology, frequency and timing of IOP measurements between practitioners and
325 over time. We did not record which instrument was used to record the IOP, so we were
326 unable to adjust for this in our analysis. We included nesting of outcomes within
327 practitioners in our models to help control for these effects but there may still be biases,
328 particularly if practitioners used different instruments within the same clinic. We also
329 performed a sensitivity analysis on the cohort of eyes followed by physicians who
330 entered IOP measurements at ≥ 50% follow-up visits to account for possible bias
331 caused by doctors who might only enter IOP measurements for at-risk cases. This did
332 not modify the main findings of the primary analysis (see supplemental material)
333 (available at http://www.aaojournal.org). Second, the baseline diagnosis of glaucoma
334 may vary between practitioners, however our data are consistent with previous reports
335 showing that eyes with pre-existing glaucoma are more at risk of IOP elevations.[4] Third,

pseudo-phakic status at baseline may have been underreported since the rate reported seemed to be relatively low. We have attempted to control for the influence of lens status on IOP outcomes by adjusting the statistical analysis for baseline lens status and cataract extraction during the follow-up. Fourth, data on baseline subtype and severity of glaucoma and management of elevated IOP during follow-up such as addition or introduction of IOP-lowering drops, laser or incisional glaucoma surgery, were not monitored. We were unable to address the influence of these factors on the results. Fifth, the definition of clinically significant IOP elevation was based on a single event. While it may have overestimated the results, we preferred a single event definition due to the absence of data on glaucoma treatment during follow-up. Sixth, we did not assess the influence of IOP change outcomes on the onset of glaucoma and the anatomical and functional progression of glaucoma. Seventh, we were not able to include fellow eye data as a control for our results. Fellow eyes have a basic rate of IOP rises.[4,8] However, our results are in keeping with the literature and the absence of control does not influence our finding regarding predictors of IOP changes and elevations.

In conclusion, our study found aflibercept reduces IOP slightly from baseline to 12 and 24 months compared to bevacizumab and ranibizumab, though this difference was not clinically significant. Of more clinical interest, clinically significant IOP elevations occurred in a small proportion of eyes receiving VEGF inhibitors. Aflibercept was associated with fewer clinically significant IOP elevations, whereas eyes with pre-existing glaucoma were at a higher risk. Aflibercept may be safer than bevacizumab or

ranibizumab in eyes with glaucomatous optic neuropathy or ocular hypertension that develop exudative retinal disease.

References

1. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 2012;119:1175–1183.
2. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. Am J Ophthalmol 2008;146:930-934.e1.
3. Lee JW, Park H, Choi JH, et al. Short-term changes of intraocular pressure and ocular perfusion pressure after intravitreal injection of bevacizumab or ranibizumab. BMC Ophthalmol 2016;16:69.
4. Atchison EA, Wood KM, Mattox CG, et al. The Real-World Effect of Intravitreous Anti-Vascular Endothelial Growth Factor Drugs on Intraocular Pressure: An Analysis Using the IRIS Registry. Ophthalmology 2018;125:676–682.
5. Freund KB, Hoang QV, Saroj N, Thompson D. Intraocular Pressure in Patients with Neovascular Age-Related Macular Degeneration Receiving Intravitreal Aflibercept or Ranibizumab. Ophthalmology 2015;122:1802–1810.
6. Bakri SJ, Moshfeghi DM, Francom S, et al. Intraocular pressure in eyes receiving monthly ranibizumab in 2 pivotal age-related macular degeneration clinical trials. Ophthalmology 2014;121:1102–1108.
7. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. J Ocul Pharmacol Ther 2010;26:105–110.
8. Bressler SB, Almukhtar T, Bhorade A, et al. Repeated intravitreous ranibizumab injections for diabetic macular edema and the risk of sustained elevation of intraocular pressure or the need for ocular hypotensive treatment. JAMA Ophthalmol 2015;133:589–597.
9. Hoguet A, Chen PP, Junk AK, et al. The Effect of Anti-Vascular Endothelial Growth Factor Agents on Intraocular Pressure and Glaucoma: A Report by the American Academy of Ophthalmology. Ophthalmology 2019;126:611–622.
11. Gillies MC, Walton R, Liong J, et al. Efficient capture of high-quality data on outcomes of treatment for macular diseases: the fight retinal blindness! Project. Retina 2014;34:188–195.
11. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–349.
13. Bakri SJ, Ekdawi NS. Intravitreal silicone oil droplets after intravitreal drug injections. Retina 2008;28:996–1001.
13. Morshedi RG, Ricca AM, Wirostko BM. Ocular Hypertension Following Intravitreal Antivascular Endothelial Growth Factor Therapy: Review of the Literature and Possible Role of Nitric Oxide. J Glaucoma 2016;25:291–300.
14. Liu L, Ammar DA, Ross LA, et al. Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: effects of long-term storage and product mishandling. Invest Ophthalmol Vis Sci 2011;52:1023–1034.
1. Fogli S, Del Re M, Rofi E, et al. Clinical pharmacology of intravitreal anti-VEGF drugs. Eye 2018;32:1010–1020.
16. Carmeliet P, Moons L, Luttun A, et al. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med 2001;7:575–583.
17. Bergen T, Jonckx B, Hollanders K, et al. Inhibition of placental growth factor improves

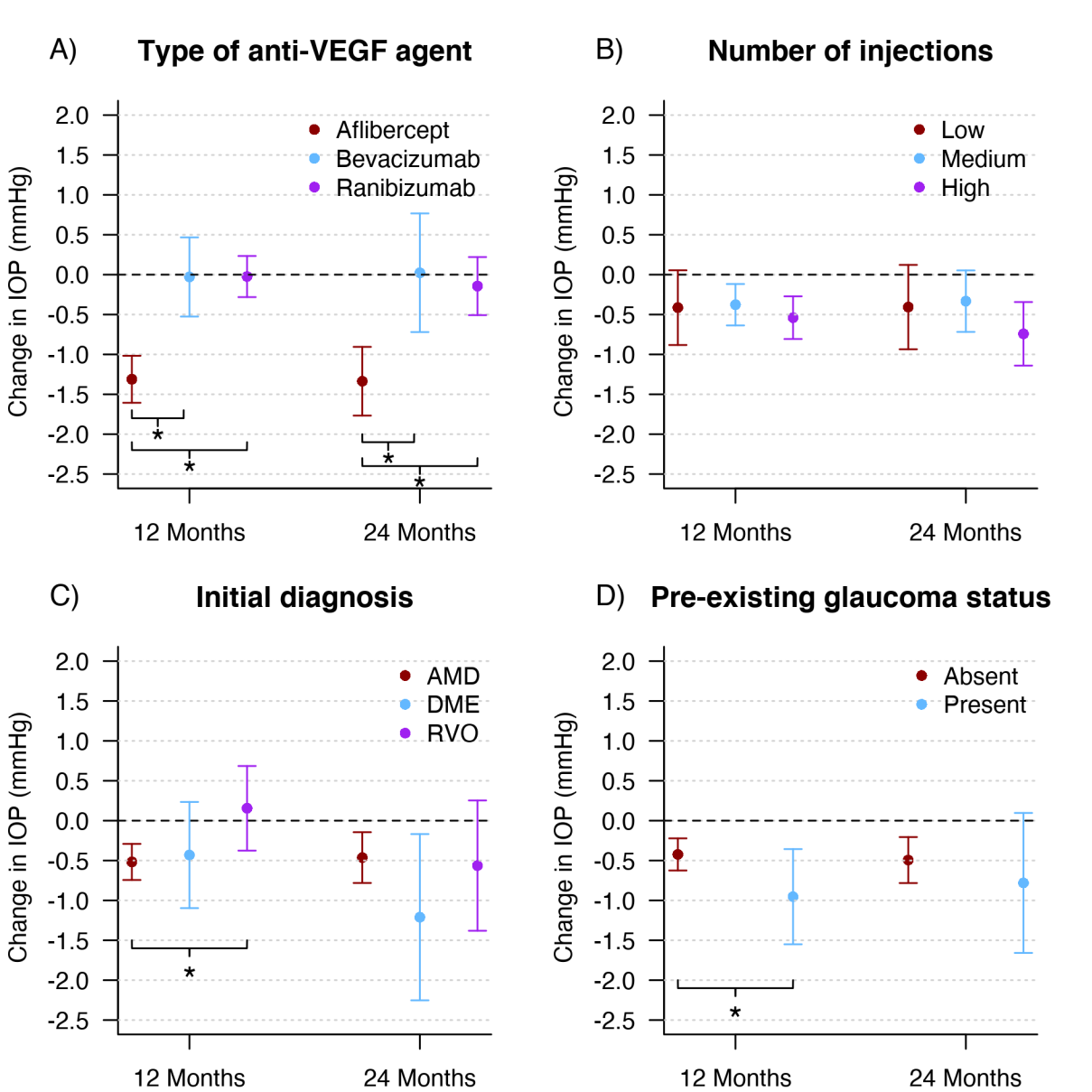
surgical outcome of glaucoma surgery. J Cell Mol Med 2013;17:1632–1643.
18. Van Bergen T, Etienne I, Cunningham F, et al. The role of placental growth factor (PlGF) and its receptor system in retinal vascular diseases. Progress in Retinal and Eye Research 2019;69:116–136.
19. Batchelor TT, Sorensen AG, di Tomaso E, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007;11:83–95.
20. Mathalone N, Arodi-Golan A, Sar S, et al. Sustained elevation of intraocular pressure after intravitreal injections of bevacizumab in eyes with neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2012;250:1435–1440.
21. Hoang QV, Mendonca LS, Della Torre KE, et al. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. Ophthalmology 2012;119:321–326.
22. Choi DY, Ortube MC, McCannel CA, et al. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. Retina 2011;31:1028–1035.
23. Knip MM, Välimäki J. Effects of pegaptanib injections on intraocular pressure with and without anterior chamber paracentesis: a prospective study. Acta Ophthalmol 2012;90:254–258.
24. Boyer DS, Goldbaum M, Leys AM, et al. Effect of pegaptanib sodium 0.3 mg intravitreal injections (Macugen) in intraocular pressure: posthoc analysis from V.I.S.I.O.N. study. Br J Ophthalmol 2014;98:1543–1546.
25. Kim YJ, Sung KR, Lee KS, et al. Long-term effects of multiple intravitreal antivascular endothelial growth factor injections on intraocular pressure. Am J Ophthalmol 2014;157:1266-1271.e1.
26. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–1892.

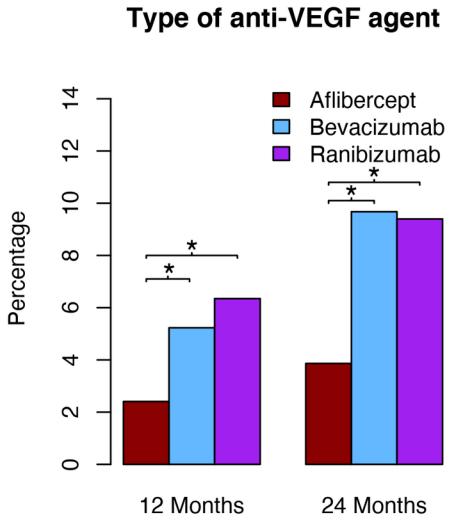
Figures legends

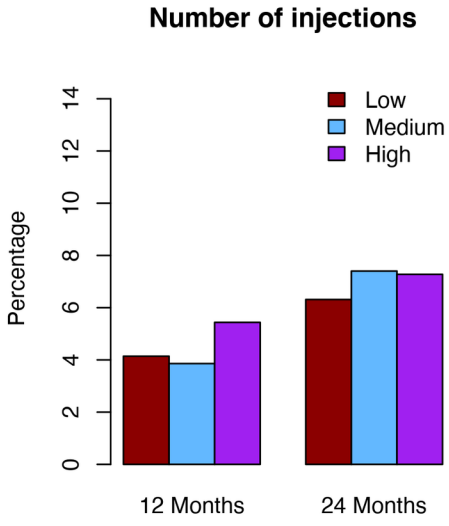
Figure 1. Adjusted change in intraocular pressure from baseline until 12- and 24-month follow-up visits by A) type of VEGF inhibitors, B) number of injections, C) initial diagnosis, and D) pre-existing glaucoma status.

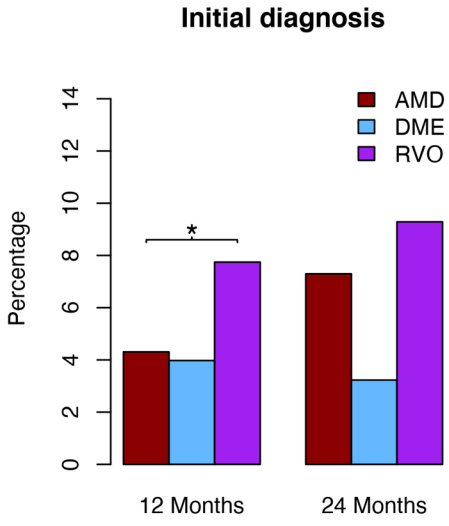
Figure 2. Adjusted proportion of clinically significant intraocular pressure elevations during the 12- and 24-month follow-up by A) type of VEGF inhibitors, B) number of injections, C) initial diagnosis, and D) pre-existing glaucoma status.

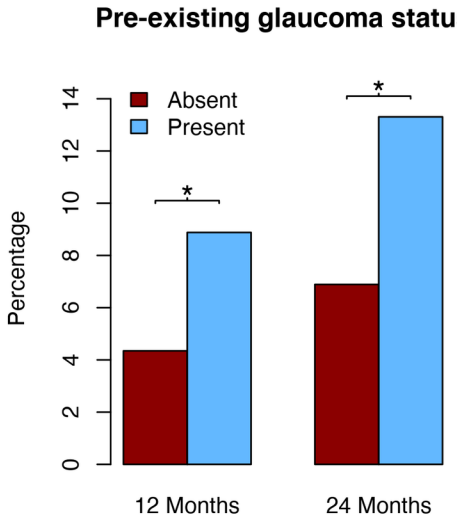
Figure 3. Adjusted change in intraocular pressure from baseline (A and B) and adjusted proportion of clinically significant intraocular pressure elevations (C) by year of treatment initiation at 12- and 24-months for eyes treated with ranibizumab


A)
Type of anti-VEGF agent
Change in IOP (mmHg)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
Aflibercept
Bevacizumab
Ranibizumab
*
*
*
*
12 Months
24 Months
B)
Number of injections
Change in IOP (mmHg)
Low
Medium
High
12 Months
24 Months
C)
Initial diagnosis
Change in IOP (mmHg)
AMD
DME
RVO
*
12 Months
24 Months
D)
Pre-existing glaucoma status
Change in IOP (mmHg)
Absent
Present
*
12 Months
24 Months


Type of anti-VEGF agent
Aflibercept
Bevacizumab
Ranibizumab
Percentage
0
2
4
6
8
10
12
14
*
*
*
*
12 Months
24 Months


Number of injections
Low
Medium
High
Percentage
0
2
4
6
8
10
12
14
12 Months
24 Months


Initial diagnosis
AMD
DME
RVO
Percentage
0
2
4
6
8
10
12
14
*
12 Months
24 Months


Pre-existing glaucoma status
Absent
Present
Percentage
0
2
4
6
8
10
12
14
*
*
12 Months
24 Months

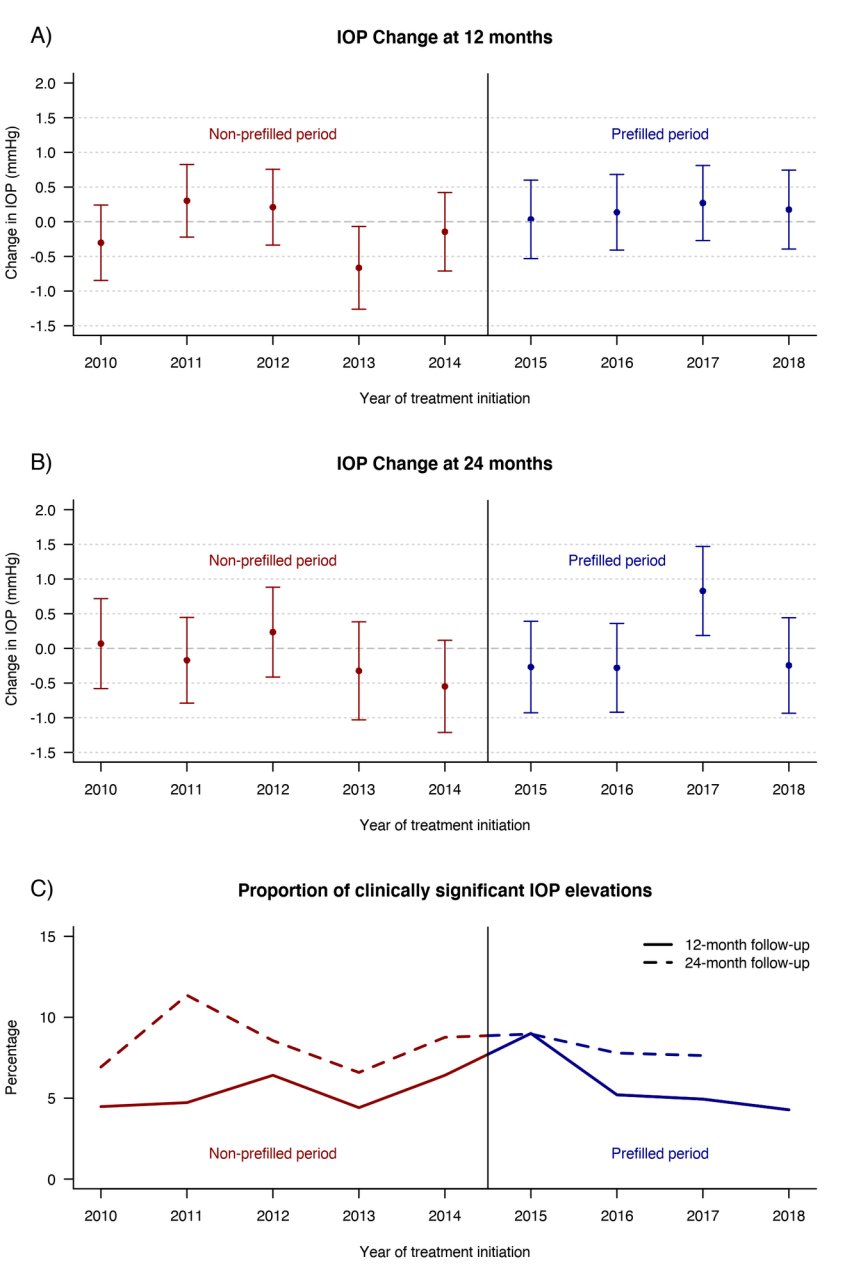

A)
IOP Change at 12 months
Change in IOP (mmHg)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Non-prefilled period
Prefilled period
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year of treatment initiation
B)
IOP Change at 24 months
Change in IOP (mmHg)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Non-prefilled period
Prefilled period
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year of treatment initiation
C)
Proportion of clinically significant IOP elevations
Percentage
15
10
5
0
12-month follow-up
24-month follow-up
Non-prefilled period
Prefilled period
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year of treatment initiation

Table 1. Baseline demographic characteristics of eyes grouped by type of VEGF inhibitor, type of syringe and pre-existing glaucoma status.

	Overall	Type of anti-VEGF inhibitors			Type of syringe [a]		Pre-existing glaucoma status	
		Bevacizumab	Aflibercept	Ranibizumab	Prefilled	Non-prefilled	Present	Absent
Eyes	3429	395	1138	1896	318	1104	184	3245
Patients	3032	380	1015	1688	293	990	177	2871
Females, n (%)	1779 (58.7%)	195 (51.3%)	556 (54.8%)	1064 (63%)	199 (67.9%)	617 (62.3%)	98 (55.4%)	1691 (58.9%)
Age, mean y (SD)	78.1 (10.4)	74.3 (11.2)	76.4 (11.1)	79.9 (9.4)	80.2 (10.3)	79.6 (8.7)	80.1 (9.1)	78 (10.4)
Intraocular pressure, mean mmHg (SD)	14.4 (3.8)	14.9 (3.6)	14.4 (4.0)	14.4 (3.6)	13.5 (3.4)	14.8 (3.7)	15.2 (5.2)	14.4 (3.7)
Lens status, n phakic (%)	2895 (84.4%)	357 (90.4%)	917 (80.6%)	1621 (85.5%)	230 (72.3%)	1002 (90.8%)	116 (63%)	2779 (85.6%)
Initial diagnosis, n (%)								
Neovascular age-related macular degeneration	2901 (84.6%)	284 (71.9%)	898 (78.9%)	1719 (90.7%)	288 (90.6%)	1026 (92.9%)	132 (71.7%)	2769 (85.3%)
Diabetic macular edema	221 (6.4%)	24 (6.1%)	130 (11.4%)	67 (3.5%)	11 (3.5%)	34 (3.1%)	6 (3.3%)	215 (6.6%)
Macular edema secondary to RVO	307 (9.0%)	87 (22.0%)	110 (9.7%)	110 (5.8%)	19 (6%)	44 (4%)	46 (25.0%)	261 (8.0%)
History of glaucoma, n (%)	184 (5.4%)	12 (3.0%)	70 (6.2%)	102 (5.4%)	18 (5.7%)	61 (5.5%)	184 (100.0%)	0 (0%)

VEGF, Vascular endothelial growth factor; RVO, Retinal vein occlusion.

[a] Cohort of eyes treated with ranibizumab: eyes initially treated from 1 January 2017 were defined as the prefilled syringe group and those initially treated before 1 January 2014 and 1 January 2013 were defined as the prefilled syringe group, thereby allowing 12 and 24 months of follow-up before the start of prefilled packaging in January 2015, respectively.

Table 2. Odds ratios from univariate and multivariate logistic regression for clinically significant IOP elevation at 12 and 24 months.

Subgroup (Reference subgroup)	12 months follow-up				24 months follow-up			
	Clinically significant IOP elevation				Clinically significant IOP elevation			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
By type of anti-VEGF drug (aflibercept)[a]								
Bevacizumab	2.37 (1.34, 4.18)	**<0.01**	2.24 (1.24, 4.04)	**<0.01**[c]	2.81 (1.54, 5.12)	**<0.01**	2.66 (1.42, 4.98)	**<0.01**[d]
Ranibizumab	2.30 (1.56, 3.39)		2.75 (1.82, 4.14)		2.38 (1.57, 3.60)		2.58 (1.68, 3.96)	
By type of ranibizumab syringe (non-prefilled)[b]								
Prefilled	0.76 (0.41, 1.42)	0.39	0.93 (0.49, 1.79)	0.83	0.61 (0.27, 1.37)	0.23	0.79 (0.34, 1.87)	0.60
By number of injections (low)[a]								
Medium	0.83 (0.49, 1.41)	0.07	0.93 (0.54, 1.60)	0.09	0.99 (0.64, 1.54)	0.95	1.19 (0.75, 1.88)	0.75
High	1.21 (0.72, 2.03)		1.33 (0.77, 2.28)		1.05 (0.67, 1.63)		1.16 (0.73, 1.85)	
By Initial diagnosis (neovascular AMD)[a]								
Diabetic macular edema	1.19 (0.65, 2.19)	**<0.01**	0.92 (0.45, 1.87)	**0.039**[e]	0.65 (0.28, 1.54)	**0.034**	0.42 (0.16, 1.11)	0.07
Macular edema secondary to RVO	2.39 (1.53, 3.74)		1.86 (1.13, 3.09)		1.85 (1.11, 3.09)		1.30 (0.73, 2.31)	
By pre-existing glaucoma status (absent) [a]								
Glaucoma	2.25 (1.34, 3.78)	**<0.01**	2.15 (1.23, 3.75)	**0.012**	2.21 (1.26, 3.88)	**<0.01**	2.07 (1.13, 3.81)	**0.025**

OR, odds ratio; AMD, age-related macular degeneration; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor.

Number of injections groups were defined as low if 3-4 injections during the first year or 3-9 injections during two years of follow-up, medium if 5-8 injections during first year or 10-14 injections during two years of follow-up and high if at least 10 injections during the first year or at least 15 injections during two years of follow-up.

[a] Multivariate model included type of anti-VEGF agent, age, gender, lens status, cataract extraction during the follow-up, baseline IOP, frequency of injection, history of glaucoma.

[b] Multivariate model included type of ranibizumab syringe, age, gender, lens status, cataract extraction during the follow-up, baseline IOP, frequency of injection, history of glaucoma.

Pairwise comparison with Holm-Bonferroni adjustment for multiple comparisons

[c] Aflibercept vs. Bevacizumab (P = 0.015); Aflibercept vs. Ranibizumab (P < 0.01); Bevacizumab vs. Ranibizumab (P = 0.44)

[d] Aflibercept vs. Bevacizumab (P < 0.01); Aflibercept vs. Ranibizumab (P < 0.01); Bevacizumab vs. Ranibizumab (P = 0.91)

[e] neovascular AMD vs. DME (*P* = 0.82); neovascular AMD vs. RVO (*P* = 0.046); DME vs. RVO (*P* = 0.13).