AMERICAN ACADEMY OF OPHTHALMOLOGY®

The 12- and 24-Month Effects of Intravitreal Ranibizumab, Aflibercept, and Bevacizumab on Intraocular Pressure

A Network Meta-Analysis

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Topic: To investigate the effect of anti–vascular endothelial growth factor (VEGF) therapy on intraocular pressure (IOP) 12 and 24 months after initiation.

Clinical Relevance: It is unclear whether serial anti-VEGF injections result in sustained IOP increases.

Methods: Randomized controlled trials (RCTs) comparing anti-VEGF agents with each other or with controls for the treatment of neovascular age-related macular degeneration, retinal vein occlusions, or diabetic macular edema were included. Pairwise meta-analysis and Bayesian network meta-analysis examined the proportion of patients whose IOP (1) increased 5 mmHg or more from baseline on consecutive visits, (2) increased 10 mmHg or more from baseline at any visit, (3) was 21 mmHg or more on consecutive visits, (4) was 25 mmHg or more at any visit, (5) was 30 mmHg or more at any visit, (6) prompted initiation of IOP-lowering medications, or (7) increased as per the clinicians' discretion. Grading of Recommendations Assessments, Development, and Evaluations methodology informed the certainty of evidence.

Results: Twenty-six RCTs of 12 522 eyes were included. Aflibercept, bevacizumab, ranibizumab (0.3 mg and 0.5 mg), and noninjection controls were analyzed. Eighty-three of 84 network estimates for comparisons between anti-VEGF agents demonstrated no statistically significant difference (low to moderate certainty of evidence). Ranibizumab 0.5 mg showed higher rates than bevacizumab of IOP measurements of 30 mmHg or more at 12 months (low certainty of evidence). Fifty-three of 56 network estimates for comparisons between anti-VEGF agents and controls demonstrated no statistically significant difference (low to moderate certainty of evidence). Ranibizumab 0.5 mg showed higher rates of consecutive IOP increases of 5 mmHg or more at 24 months (low certainty of evidence) and higher rates of IOP increases as per the clinicians' discretion at 12 and 24 months (low and very low certainty of evidence, respectively). The 95% credible intervals in comparisons without statistically significant effects did not rule out important clinical effects. The certainty of evidence in these comparisons is limited by imprecision.

Conclusion: This network meta-analysis does not show any clear difference in IOP increases 12 and 24 months after treatment initiation between anti-VEGF agents and controls. Imprecision precludes definitive conclusions. *Ophthalmology 2022;129:498-508 © 2021 by the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

Anti–vascular endothelial growth factor (VEGF) injections are the standard of care for the treatment of neovascular age-related macular degeneration (AMD), macular edema resulting from retinal vein occlusions (RVOs), and diabetic macular edema (DME).[1–4] Strong evidence demonstrates that anti-VEGF treatment confers significant benefit to patients with these conditions,[5–7] and as a result, more than 16 million intravitreal anti-VEGF injections were performed globally in 2016.[8] Given the frequency of anti-VEGF intravitreal therapy, understanding the different agents' safety profile is imperative to delivering optimal patient-centered evidence-based care.

The relationship between anti-VEGF injections and intraocular pressure (IOP) elevation has not been elucidated fully.[9] Although transient IOP elevations immediately after injections are an accepted sequela of treatment,[9–12] the data on sustained increases in IOP are conflicting[9]; several studies have demonstrated sustained increases,[13–16] whereas others have demonstrated no increase.[17–19]

https://doi.org/10.1016/j.ophtha.2021.11.024
ISSN 0161-6420/21

Multiple theoretical mechanisms have been suggested to explain the potential relationship between anti-VEGF therapy and sustained increases in IOP. These include microparticle obstruction of the trabecular meshwork from medication packing or delivery equipment,[20] inflammatory responses after injection,[21] chronic changes from recurrent microtrauma caused by transient IOP elevations after injection,[22] and decreased aqueous outflow resulting from anti-VEGF inhibition of nitric oxide synthase.[23] It also has been hypothesized that the increase in vitreous volume resulting from intravitreal injections narrows the anterior chamber angle and potentially decreases aqueous humor drainage[24]; however, a recent investigation using anterior segment OCT found no significant differences in angle width associated with the number of intravitreal injections.[25] This investigation did not examine patients with narrow angles, and, thus, a subset of eyes with shallow angles or with nanophthalmos may be at risk of chronic angle closure and may be susceptible to sustained increases in IOP.[24,25] Table S1 (available at www.aaojournal.org) summarizes the current hypotheses for sustained increases in IOP.

Concerns over the potential for sustained IOP increases have prompted investigation into the effects of prophylactic brimonidine plus timolol, acetazolamide, or anterior chamber paracentesis to mitigate the IOP spikes seen after intravitreal injection.[10,11,26] Although these additional interventions can reduce IOP spikes, they are not without the potential for adverse events.[27–29] Moreover, the clinical impact, specifically, the effect of these measures on preventing long-term IOP elevations and even glaucoma, has not been studied.[9] Uncertainty regarding the long-term effects of anti-VEGF therapy on IOP has the potential to affect practice patterns. Although IOP monitoring is recommended in patients receiving anti-VEGF therapy, no consensus exists regarding the timing and frequency of IOP measurements.[30] A better understanding of the effect of anti-VEGF therapy on IOP can help to guide decisions regarding monitoring frequency and glaucoma investigation.

Confounding this issue is that the aging population at risk of exudative retinal vascular conditions developing that require anti-VEGF therapy is also at risk of glaucoma developing.[31] Diabetes also is an independent risk factor for glaucoma, adding to the challenge of determining the effect of anti-VEGF agents for the treatment of DME on sustained increases in IOP.[32]

The lack of consensus is a consequence of the literature predominantly limited to retrospective reviews without control groups and studies using a range of definitions for sustained IOP increases, which limit comparisons across studies. Moreover, current reviews have been descriptive in nature or have focused solely on direct comparisons and thus compare only 2 interventions at a time.[8,9,33,34] These limitations restrict the clinical applications that can be generated from the currently published reviews.[8,9,33]

The complexities associated with this topic necessitate evaluating high-quality randomized controlled trials (RCTs) to elucidate any underlying effect. Given that multiple efficacious anti-VEGF agents are available, network meta-analysis (NMA) is the ideal statistical method for investigating this topic.[35] Network meta-analysis is an extension of classical pairwise meta-analysis that combines all head-to-head comparisons, referred to as direct evidence, with evidence obtained through 1 or more common comparators, known as indirect evidence. Network meta-analysis integrates relevant data while maintaining the strengths of randomization from the individual RCTs. This method of synthesizing information enables comparison of treatments that have not been compared directly by RCTs to help inform decision making.[34–37] Compared with a classic pairwise meta-analysis investigating anti-VEGF agents with control interventions, NMA enables inclusion of additional published trials that compared different anti-VEGF agents solely with each other. By integrating direct and indirect evidence into 1 model, NMA provides more precise effect estimates for the different agents compared with each other and with a control.[34–37]

The focus of the current work was to address the following question: What is the effect of anti-VEGF intravitreal therapy in eyes with neovascular AMD, macular edema resulting from RVO, and DME on IOP 12 and 24 months after initiation?

Methods

Protocol and Registration

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis NMA guidelines.[38] This investigation was registered with the International Prospective Register of Systematic Reviews of Interventions (identifier, CRD42020212791). This study was exempt from ethics approval, as all syntheses were performed utilizing previous clinical trial data for which informed consent and ethics approval had been obtained. This investigation adhered to the tenets of the Declaration of Helsinki.

Eligibility Criteria

We included data from RCTs of patients 18 years of age or older who received anti-VEGF injections for the treatment of neovascular AMD, RVO, or DME. Studies were included if they compared different anti-VEGF agents with each other or with a control; ranibizumab, bevacizumab, and aflibercept were the only anti-VEGFs examined because they represent the treatments used most commonly in clinical practice. Laser therapy, photodynamic therapy, observation, and sham injections were considered appropriate control treatments. Only studies reporting at least 1 of the outcomes of interest were included. Studies were included if they were conducted for a minimum of 12 months and if the published report was written in the English language.

Studies were excluded if patients crossed over to receive a different treatment during the study and did not evaluate outcomes based on whether the patient crossed over. Studies also were excluded if they compared an anti-VEGF agent solely with a steroid given the known potential effect of steroids on IOP[39,40]; however, if studies compared multiple interventions, one of which was a steroid, the nonsteroid groups were included.

Information Sources and Search

Searches of Ovid MEDLINE, Ovid Embase, Cochrane Library, PubMed, Web of Science, and the Cumulative Index to Nursing

and Allied Health Literature were performed on April 20, 2020, and were updated on January 5, 2021. The search strategy is shown in the Appendix (available at www.aaojournal.org). Reference lists from included articles also were hand searched to identify additional relevant studies.

Study Selection

The results from all databases searched were compiled, and the abstracts were screened independently by 2 initial reviewers (K.N. and G.S.S.) to determine which articles would receive a full-text review. Reviewers were masked to each other's decisions. Disagreements were resolved through discussion. The eligibility criteria to receive full-text review were the correct population, intervention, and control. The correct outcome was determined through full-text review. Covidence (Melbourne, Australia) was used to compile abstracts and track triage decisions.

Data Collection

All information was extracted independently in duplicate by 2 reviewers (K.N. and G.S.S.) using a standardized pilot-tested data collection form. Reviewers collected data pertaining to the study design, patient demographics, and outcomes. Information was collected from published manuscripts, published data sets, and unpublished data obtained from corresponding authors. Disagreements were resolved through discussion. Any unclear information from the published manuscripts was clarified with the corresponding author or sponsoring pharmaceutical company.

Data Items

Extracted data for the study design included the study title, journal of publication, year of publication, indication for treatment, as well as dosing and frequency of treatment. Extracted data for patient information included the number of participants, the age of the participants, and ocular comorbidities.

Outcome information included the proportion of patients at 12 and 24 months whose IOP before injection (1) increased by 5 mmHg or more compared with baseline on consecutive visits, (2) increased by 10 mmHg or more at any visit compared with baseline, (3) was 21 mmHg or more on consecutive visits, (4) was 25 mmHg or more at any visit, (5) was 30 mmHg or more at any visit, (6) prompted initiation of IOP-lowering medications, and (7) increased as per the clinicians' discretion without providing a specific definition. This final outcome captured data from RCTs that reported rates of IOP increases without a prespecified threshold but rather at the discretion of the investigator.

Risk of Bias

For each eligible trial, 2 review authors (K.N. and G.S.S.) assessed the risk of bias using the Cochrane Risk of Bias Tool for Systematic Reviews version 1[41] across the following domains: random sequence generation, allocation concealment, selective reporting, masking of participants and personnel, masking of outcome assessment, incomplete outcome data, and other biases. Each domain was rated as having a low, high, or unclear risk of bias. Disagreements were resolved through discussion. We rated trials as having a high risk of bias overall if more than 1 domain was rated as having a high risk of bias or if more than 2 domains were deemed to have an unclear risk of bias.

Statistical Analysis

We evaluated direct comparisons for each outcome at 12 and 24 months. Pairwise meta-analyses were performed on Cochrane Review Manager version 5.4 software via random-effects modeling using the DerSimonian and Laird method to estimate odds ratios (OR) and corresponding 95% confidence intervals (CIs). We assessed heterogeneity between RCTs for each direct comparison with visual inspection of forest plots and the I^2 statistic. Heterogeneity of 0% to 40% was classified as "might not be important," heterogeneity of 30% to 60% was classified as moderate, heterogeneity of 50% to 90% was classified as substantial, and heterogeneity of 75% to 100% was classified as considerable.

A random-effect Bayesian NMA was performed for each outcome at 12 and 24 months. All analyses were performed in R software version 4.0.3 (The R Project) using the gemtc, rjags, and dmetar packages. Estimates were obtained using the Markov chains Monte Carlo method with noninformative priors. Five thousand initial iterations were used as adaptation, followed by 100 000 iterations for calculation of ORs and their corresponding 95% credible intervals (CrIs). Convergence was assessed via the Brooks–Gelman–Rubin statistic.[42] We used node-splitting models to assess local incoherence and consistency of results from direct and indirect evidence and to obtain indirect estimates.[43]

Quality Assessment

We appraised the geometry of the networks for each outcome separately at 12 and 24 months. Transitivity was assessed by comparing baseline characteristics and treatment comparisons across studies. For each outcome at 12 and 24 months, the certainty of evidence was evaluated using the Grading of Recommendations Assessments, Development, and Evaluations (GRADE) approach for NMA. For each direct estimate, the risk of bias, inconsistency, indirectness, and publication bias were assessed. For each indirect estimate, intransitivity was assessed; this rating was incorporated with the lowest rating from the 2 direct comparisons forming the most dominant first-order loop to determine the certainty of the indirect evidence. At the network level, incoherence and imprecision were assessed, and these ratings were incorporated with the rating for either the direct or indirect estimate to determine a final rating for the network estimate. The rating for the indirect estimate was not incorporated into the rating of the network estimate if the certainty of the direct evidence was high and the contribution of the direct evidence to the network estimate was at least as great as that of the indirect evidence. Ultimately, the certainty of evidence for each network estimate was graded as high, moderate, low, or very low.[44,45]

Subgroup Analyses

Subgroup analyses were performed excluding studies with an overall high risk of bias, as well as for each of the disease types.

Results

Study Selection

Figure 1 reports the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for study analysis. Fifteen thousand three hundred thirty-four articles were identified through electronic literature searches, 5579 of which remained after removal of duplicates. A total of 411 articles proceeded to full-text screening. The NMA analyzed data from 26 RCTs that included 12 522 eyes; these data include 22 individual RCTs,[46–66] 1 study reporting pooled IOP results from 2 similarly designed RCTs,[67] and 1 post hoc IOP review of 2 similarly designed RCTs.[16] The mean age of patients was 68.3 years, and 49.2% of included patients were men. Table 1 reports the characteristics of all selected studies. The specific anti-VEGF agents and doses

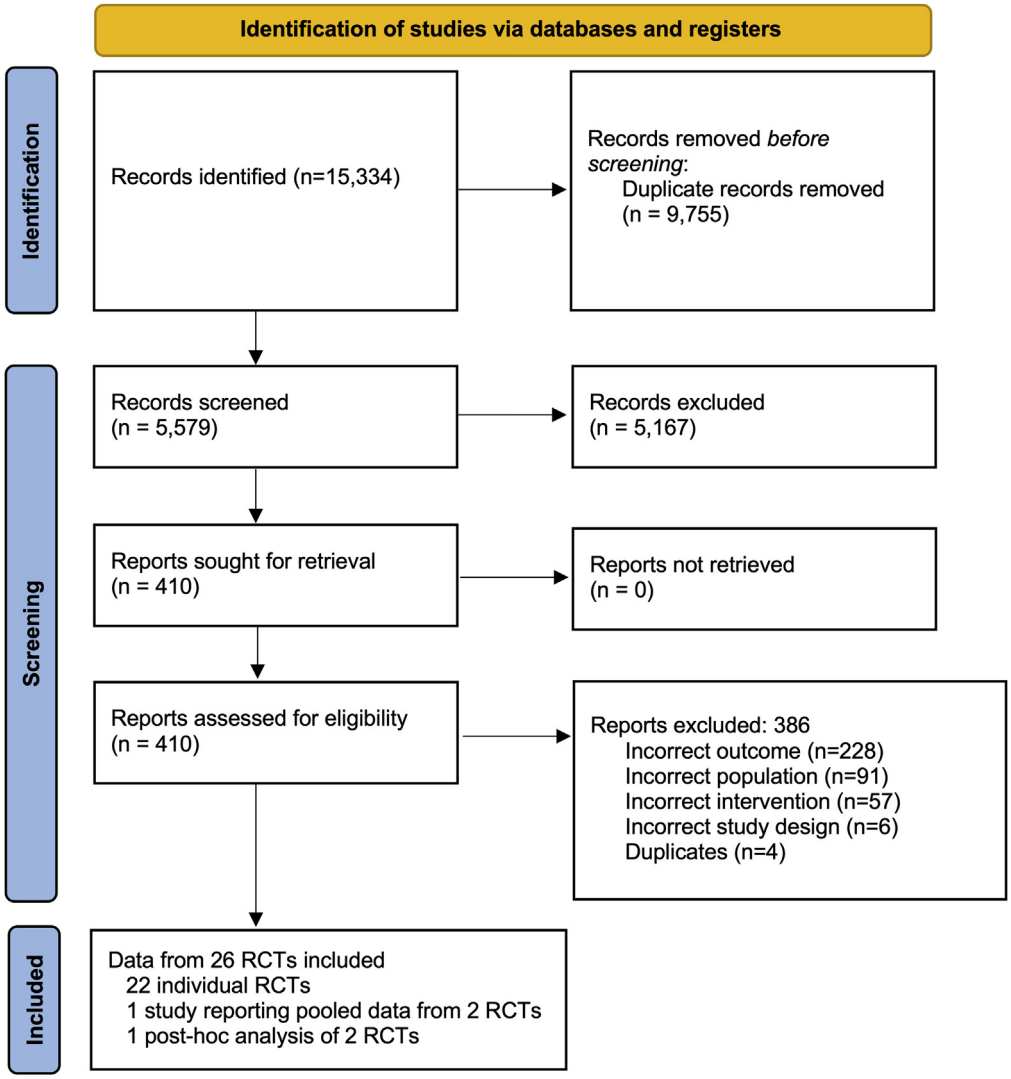

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram showing the study selection process. RCT = randomized controlled trial.

included are as follows: aflibercept, 2.0 mg; bevacizumab, 1.25 mg; and ranibizumab, 0.3 mg and 0.5 mg. Other doses of these agents were not analyzed because of insufficient data. Eight of the included RCTs provided relevant outcome data at both 12 and 24 months, 10 RCTs provided relevant outcome data at only 12 months, and 8 RCTs provided relevant outcome data at only 24 months. Ten of the RCTs evaluated treatments in patients with neovascular AMD, 4 in patients with RVOs and 12 in patients with DME. Table S2 (available at www.aaojournal.org) reports the number of studies with data at 12 and 24 months for the outcomes of interest. Table S3 (available at www.aaojournal.org) reports which studies provided data for each outcome at 12 and 24 months. Nineteen studies compared 2 interventions, and 7 studies compared 3 interventions. The data from the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration trials reported the number of patients experiencing consecutive IOP increases of 6 mmHg or more compared with baseline rather than 5 mmHg or more. As a result, the level of evidence for comparisons involving these data was downgraded because of indirectness among outcomes. All other studies reported outcomes exactly as defined by this review.

Network Structure and Geometry

Figure S1 (available at www.aaojournal.org) demonstrates the network plot of the treatment comparisons at 12 and 24 months. Direct comparisons are indicated by lines with the thickness corresponding to the number of studies.

Risk of Bias

The summary of the risk of bias assessments across all included studies is illustrated in Figure S2 (available at www.aaojournal.org). Most studies showed a low risk of bias in all domains, 3 studies showed unclear risks of selection bias, 7 studies showed high risks of performance bias, 1 study showed a high risk of detection bias, 1 study showed a high risk of

Table 1. Baseline Characteristics of Included Studies

Study No.	Primary Author	Trial Name	Year Published	Disease	Interventions	No. of Eyes	Mean Age (yrs)	No. of Men (%)
1	Baker	Protocol V	2019	DME	A	226	59	131 (58)
					C	336	60	307 (64)
2	Brown	ANCHOR	2009	AMD	R3	140	77	73 (52)
					R5	140	76	75 (54)
					C	93	79	42 (45)
3	DRCR Network Writing Committee	Protocol I	2010	DME	R5	375	62	212 (57)
					C	293	63	170 (58)
4	Regillo	PIER	2008	AMD	R3	60	79	26 (43)
					R5	61	79	28 (46)
					C	63	78	20 (32)
5 and 6	Freund	VIEW 1 and 2	2015	AMD	R5	595	76	254 (43)
					A	1219	76	498 (41)
7	Schmidt-Erfuth	EXCITE	2011	AMD	R3	235	75	99 (42)
					R5	118	76	45 (38)
8	Scott	SCORE2	2018	RVO	A	159	69	86 (54)
					B	134	69	80 (60)
9	Wei	BLOSSOM	2020	RVO	R5	190	57	89 (47)
					C	26	57	15 (58)
10	Wells	Protocol T	2016	DME	A	224	60	114 (51)
					B	218	62	115 (53)
					R3	218	60	124 (57)
11	Berger	RESPOND	2015	DME	R5	148	61	89 (60)
					C	74	63	43 (58)
12	Michaelides	BOLT	2010	DME	B	42	65	30 (71)
					C	38	64	25 (66)
13	Bakri	MARINA	2006	AMD	R3	238	77	79 (33.2)
					R5	240	77	85 (35.7)
					C	238	77	88 (36.2)
14	Chakravarthy	IVAN	2013	AMD	R5	314	78	129 (41)
					B	296	78	115 (39)
15	Boyer	RISE	2012	DME	R3	125	62	73 (58)
					R5	125	63	65 (52)
					C	127	62	74 (58)
16	Boyer	RIDE	2012	DME	R3	125	63	73 (58)
					R5	127	62	80 (63)
					C	130	64	66 (51)
17	Gillies	RIVAL	2019	AMD	R5	142	77	70 (49)
					A	139	79	63 (45)
18	Brown	VISTA	2015	DME	A	307	63	167 (54)
					C	154	62	78 (52)
19	Brown	VIVID	2015	DME	A	271	63	171 (63)
					C	133	64	78 (59)
20	Hykin	LEAVO	2019	RVO	R5	155	69.2	85 (55)
					A	154	68.7	94 (61)
					B	154	69.3	86 (56)
21	Mitchell	RESTORE	2011	DME	R5	235	63	143 (61)
					C	110	64	58 (52)
22	Ishibashi	REVEAL	2015	DME	R5	265	61	148 (56)
					C	128	62	75 (57)
23	ClinicalTria ls.gov	SALT	N/A	AMD	R5	353	77	143 (41)
					A	354	78	136 (38)
24	Li	REFINE	2019	DME	R5	307	59	139 (45)
					C	77	59	38 (49)
25	Tadayoni	BRIGHTER	2017	RVO	R5	363	66	189 (52)
					C	26	67	30 (46)
26	CATT Team	CATT	2011	AMD	R5	599	79	231 (39)
					B	586	80	222 (38)

A = aflibercept 2.0 mg; AMD = age-related macular degeneration; ANCHOR = Anti-vascular endothelial growth factor Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; B = bevacizumab 1.25 mg; BLOSSOM = Ranibizumab Intravitreal Injections Versus Sham Control in Patients with Branch Retinal Vein Occlusion; BOLT = Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema; BRIGHTER = Efficacy and Saftey of Ranibizumab With or Without Laser in Coparison to Laser in Branch Retinal Vein Occlusion; CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; C = control; DME = diabetic macular edema; DRCR = Diabetic Retinopathy Clinical Research;

R5 = ranibizumab 0.5 mg; EXCITE = Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration; IVAN = Inhibition of VEGF in Age-Related Choroidal Neovascularization; LEAVO = Lucentis, Eylea, Avastin in Vein Occlusion Study; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PIER study = A **P**hase IIIb, Multicenter, Randomized, Double-Masked, Sham **I**njection-Controlled Study of the **E**fficacy and Safety of **R**anibizumab in Subjects with Subfoveal Choroidal Neovascularization [CNV] with or without Classic CNV Secondary to Age-Related Macular Degeneration R3 = ranibizumab 0.3 mg; REFINE = Efficacy and Safety of Ranibizumab 0.5mg in Chinese Patients with Visual Impairment Due to Diabetic Macular Edema; RESPOND = Efficacy/Safety of Ranibizumab Monotherapy or With Laser Versus Laser Monotherapy in DME; REVEAL = Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema; RIDE = Ranibizumab Injection in Subjects with Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus; RISE = Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus; RIVAL = The Development of Macular Atrophy in Patients with Neovascular Age-Related Macular Degeneration: A Comparison of Ranibizumab and Aflibercept; RVO = retinal vein occlusion; SALT = Efficacy of Ranibizumab PRN Treatment Compared to Aflibercept Bimonthly Intravitreal Injections on Retinal Thicknes Stability in Patients With Wet AMD; SCORE2 = Study of Comparative Treatments for Retinal Vein Occlusion 2; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; VISTA = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema; VIVID = Intravitreal Aflibercept Injection in Vision Impairment due to DME; RESTORE study = A 12 Month Core Study to Assess the Efficacy and Safety of Ranibizumab in Patients with Visual Impairment Due to Diabetic Macular Edema and a 24 Month Open-label Extension Study

reporting bias, and 6 studies showed a high risk of other bias. Overall, 5 studies were graded as having high risks of bias: 1 as an unclear risk of bias and the remainder as having low risks of bias.

Pairwise Meta-analysis

Table S4 (available at www.aaojournal.org) presents the detailed results of all pairwise meta-analysis and heterogeneity estimates for direct comparisons across all outcomes. Four and 12 significant comparisons at 12 and 24 months, respectively, were available. At 12 months, 39 outcomes (56%) had 1 direct comparison, 28 outcomes (40%) had 0 direct comparisons, 2 outcomes (3%) had 2 direct comparisons, and 1 outcome (1%) had 5 direct comparisons. At 24 months, 51 outcomes (73%) had 1 direct comparison, 9 outcomes (13%) had 2 direct comparisons, 9 outcomes (13%) had 0 direct comparisons, and 1 outcome (1%) had 3 direct comparisons.

NMA

Table S5 (available at www.aaojournal.org) presents the results of the NMA with the corresponding assessment of inconsistency for each outcome at 12 and 24 months. Forest plots for each outcome are displayed in Figure S3 (available at www.aaojournal.org). All simulations showed adequate convergence, as demonstrated in Table S6 (available at www.aaojournal.org).

When evaluating comparisons between anti-VEGF agents, 83 of 84 network estimates demonstrated no statistically significant difference between groups (low to moderate certainty of evidence). Ranibizumab 0.5 mg showed higher rates of IOP measurements of 30 mmHg or more at 12 months than bevacizumab (OR, 91; 95% CrI, 1.1−28 000; low certainty of evidence). The 95% CI of comparisons with no statistically significant effect included potentially clinically relevant effects, and, thus, the certainty of evidence for each of these comparisons was downrated by 1 or 2 levels for imprecision (Table S7, available at www.aaojournal.org).[45,68,69]

For comparisons between anti-VEGF agents and control interventions, 53 of 56 network estimates demonstrated no statistically significant difference between groups (low to moderate certainty of evidence). Ranibizumab 0.5 mg showed higher rates of consecutive IOP increases of 5 mmHg or more at 24 months (OR, 1.5; 95% CrI, 1.1−2.2; low certainty of evidence) and higher rates of IOP increases as per the clinicians' discretion at 12 months (OR, 6.0; 95% CrI, 1.8−71; low certainty of evidence) and at 24 months (OR, 4.1; 95% CrI, 1.3−24; very low certainty of evidence). As with the comparisons between anti-VEGF agents, the 95% CI of comparisons between agents and control interventions with no statistically significant difference included potentially clinically relevant effects. Consequently, the certainty of evidence for each of these comparisons was downrated by 1 or 2 levels for imprecision (Table S7).

Exploration for Local Inconsistency

The results of the node-splitting analyses are summarized in Table S5, and the full node-splitting analyses are shown in Figure S4. The node-splitting assessment of inconsistency revealed incoherence in 3 comparisons ($P < 0.05$): aflibercept compared with bevacizumab for the outcome of rate of IOP measurements of 30 mmHg or more at 24 months ($P = 0.039$), aflibercept compared with ranibizumab 0.5 mg regarding rate of increased IOP of 10 mmHg or more compared with baseline at 24 months ($P = 0.043$), and ranibizumab 0.5 mg compared with control when evaluating the rates of IOP of 30 mmHg or more at 24 months ($P = 0.039$).

Subgroup Analyses

Subgroup analyses excluding all studies deemed to have a high risk of bias as well as for the different disease types were performed for each outcome at 12 and 24 months. Table S8 (available at www.aaojournal.org) displays the detailed results. Limited data precluded network estimates for many outcomes when examining patients treated for AMD at 12 months, as well as for RVOs at 12 and 24 months. Higher rates in IOP increases as per the clinicians' discretion were found when comparing ranibizumab 0.5 mg with a control intervention for patients with DME and when excluding studies with a high risk of bias. No other significant differences were found across outcomes at both 12 and 24 months across all groups.

Discussion

Summary of Evidence

The effects of anti-VEGF injections on IOP were evaluated at 12 and 24 months using an NMA of data derived from RCTs. We used a partially contextualized framework, GRADE's proposed approach to drawing conclusions from NMA, and summarized our results in Figure 2.[69] Table S8 displays the NMA results sorted based on GRADE certainty of evidence and effect estimates for the comparisons between anti-VEGF agents and control interventions at 12 and 24 months.

Five examined outcomes were defined precisely and were standardized across all trials: the rate of IOP consecutive increases of 5 mmHg or more compared with baseline, consecutive IOP measurements of 21 mmHg or more, IOP increases of 10 mmHg or more compared with baseline, IOP

Intervention	12 Month Outcomes						
	Consecutive IOP increases ≥ 5 compared to baseline	IOP increases ≥ 10 compared to baseline	Consecutive IOP measurements ≥ 21	IOP measurements ≥ 25	IOP measurements ≥ 30	Initiation of IOP lowering drops	Increases in IOP as per the clinicians' discretion
	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Aflibercept	1.2 (0.65 to 2.6)	2.5 (0.58 to 11)	0.87 (0.38 to 2.1)	0.80 (0.30 to 2.0)	0.47 (0.010 to 9.5)	3.2 (0.61 to 20)	2.7 (0.51 to 29)
Bevacizumab	0.98 (0.35 to 3.0)	1.4 (0.24 to 9.5)	0.90 (0.24 to 3.6)	0.40 (0.095 to 1.6)	0.031 (0.00016 to 1.8)	1.7 (0.17 to 21)	4.2 (0.44 to 200)
Ranibizumab 0.3 mg	1.2 (0.42 to 3.6)	1.9 (0.39 to 12)	0.89 (0.24 to 3.7)	0.73 (0.18 to 2.7)	0.23 (0.0029 to 6.7)	2.1 (0.17 to 27)	N/A
Ranibizumab 0.5 mg	1.4 (0.77 to 2.8)	1.0 (0.29 to 4.6)	1.6 (0.70 to 3.6)	1.4 (0.63 to 3.2)	2.7 (0.33 to 39)	0.78 (0.16 to 3.6)	6.0 (1.8 to 71)

Intervention	24 Month Outcomes						
	Consecutive IOP increases ≥ 5 compared to baseline	IOP increases ≥ 10 compared to baseline	Consecutive IOP measurements ≥ 21	IOP measurements ≥ 25	IOP measurements ≥ 30	Initiation of IOP lowering drops	Increases in IOP as per the clinicians' discretion
	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Aflibercept	1.1 (0.77 to 1.7)	1.3 (0.45 to 3.1)	1.2 (0.65 to 2.5)	1.1 (0.45 to 2.6)	1.0 (0.21 to 4.1)	1.2 (0.62 to 2.7)	2.7 (0.63 to 20)
Bevacizumab	1.3 (0.75 to 2.1)	0.82 (0.26 to 2.6)	0.99 (0.35 to 3.0)	1.1 (0.36 to 3.1)	0.92 (0.20 to 4.0)	1.1 (0.46 to 2.6)	1.4 (0.13 to 25)
Ranibizumab 0.3 mg	1.2 (0.79 to 2.0)	1.3 (0.49 to 3.6)	1.2 (0.43 to 3.6)	1.6 (0.63 to 4.1)	0.87 (0.21 to 3.3)	1.4 (0.72 to 3.2)	4.0 (0.89 to 26)
Ranibizumab 0.5 mg	1.5 (1.1 to 2.2)	1.2 (0.58 to 3.0)	1.5 (0.76 to 2.8)	1.6 (0.75 to 3.4)	0.92 (0.30 to 2.8)	1.1 (0.60 to 2.0)	4.1 (1.3 to 24)

Legend

	High/Moderate Certainty of Evidence	Low/Very Low Certainty of Evidence
Among the best	No more harmful than control	May be no more harmful than control
Intermediate	More harmful than control, but no worse than any alternatives	May be more harmful than control, but no worse than any alternatives
Among the worst	More harmful than control and some alternatives	May be more harmful than control and some alternatives

Figure 2. Tables showing network meta-analysis results sorted based on Grading of Recommendations Assessments, Development, and Evaluations certainty of evidence and effect estimate for the comparisons between antivascular endothelial growth factor agents and control interventions at 12 and 24 months. CrI = credible interval; IOP = intraocular pressure; OR = odds ratio.

measurements of 25 mmHg or more, and IOP measurements of 30 mmHg or more. For these outcomes, the only comparisons with significant effects were ranibizumab 0.5 mg, which showed higher rates than bevacizumab of IOP measurements of 30 mmHg or more at 12 months, and ranibizumab 0.5 mg, which showed higher rates than control interventions for the rate of consecutive IOP increases of 5 mmHg or more at 24 months. A low certainty of evidence was found for both comparisons. All other comparisons at 12 and 24 months for these 5 outcomes did not show a statistically significant effect. This result was found when pooling all studies, examining the different disease types, and excluding studies with a high risk of bias; however, the certainty of evidence for these comparisons was downgraded because of the imprecision in the estimates.

For the outcome examining increases in IOP as per the clinicians' discretion, ranibizumab 0.5 mg was found to have higher rates of IOP increases at 12 and 24 months compared with control interventions. The certainties of evidence for these estimates were low and very low, respectively. This was because of the substantial imprecision in estimates resulting from the sparse networks and the trials with a high risk of bias in the 24-month comparison. All other comparisons for this outcome were not significant and similarly were limited by imprecision. The implications of any difference between groups for this specific outcome are of highly uncertain clinical importance given the level of certainty associated with the significant findings, the inherent limitations of this outcome (i.e., no standardization across trials for what constituted an increase in IOP), and the lack of significant effects across the other more precise outcomes.

The outcome examining rates of initiation of IOP-lowering therapy is of particular interest given its clinical relevance. No significant effect was found for this outcome across all comparisons when examining all studies and each subgroup. For each intervention compared with control interventions at 24 months, moderate certainty of evidence in the network effect estimate was found.

In comparisons with no statistically significant effects, it is important to consider which comparisons have a 95% CI precise enough to rule out clinically important differences. Without an established minimally important difference, GRADE suggests using a default threshold of a 25% change in relative risk for identifying potentially clinically relevant results.[68] Consequently, because all the comparisons with no significant effect in this review have 95% CrIs that cross this threshold, the level of imprecision downgraded

the certainty of evidence and precludes definitive conclusions with the available data. Additional evidence is needed to improve the precision of the estimates and to improve the certainty of evidence.

Previous reviews investigating this topic have shown conflicting results. Bracha et al,[8] in their 2017 narrative review, concluded that, although many studies found no sustained effect, the post hoc analyses of the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration trial, the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration trial, and Protocol I provide the best-quality evidence suggesting that patients may experience long-term IOP increases after anti-VEGF injections. We were able to build on these results by performing a quantitative analysis and incorporated the risk of bias involved with post hoc analyses to provide a certainty of evidence for an effect. Zhou et al[33] in their 2016 systematic review and meta-analysis suggested that sustained elevations in IOP occurred as a result of anti-VEGF agents; however, the study was limited by the available literature at the time and included only 5 RCTs of varying durations. Given these limitations, they were unable to separate studies by the definition of IOP increases used. By incorporating the more recent literature, our meta-analysis demonstrated that it is likely that no sustained increases in IOP result from anti-VEGF use. More recently, the American Academy of Ophthalmology published a report in 2019 summarizing the current state of the literature.[9] They concluded that the results were mixed, and, thus, a possibility exists for long-term IOP elevations resulting from anti-VEGF agents. No meta-analysis was performed in this review, and given that many of the referenced studies were retrospective, their results may have been influenced by publication bias. Finally, in 2020, de Vries et al[70] published a systematic review and meta-analysis of observational and interventional studies and concluded that at 12 months, the longest interval they examined, no increase in IOP occurred with anti-VEGF use.

The results of this investigation can aid in informing patients regarding the risks and benefits of anti-VEGF therapy, can assist in providing clarity regarding the need for prophylactic IOP-lowering therapy, and can help guide practice patterns to inform the frequency of IOP monitoring in patients receiving anti-VEGF therapy. Furthermore, it is feasible that future anti-VEGF therapy may have a different IOP safety profile. This NMA provides evidence for the current anti-VEGF agents and can inform future guideline development and decision making.

Our investigation is not without limitations. Given that IOP was not the primary outcome of the included trials, no standardized method of measuring IOP or standardized time at which IOP was measured was found across included trials. The follow-up frequency varied across, and occasionally within, trials; consequently, the rates of IOP increases may be biased by more frequent measurement. The definition of IOP increases also varied across the 26 RCTs, limiting the power of each outcome assessment. Although the current study found no conclusive evidence of IOP increases in patients receiving anti-VEGF therapy, the analysis was limited by imprecision and may not be sensitive enough to identify small proportions of patients who do experience clinically meaningful increases in IOP. These limitations highlight the need for future studies including RCTs with IOP as the primary outcome and large observational studies using electronic medical records or other health databases. We propose that future studies use the recommended thresholds for defining ocular hypertension as defined by the National Institute for Health and Care Excellence of 24 mmHg.[71] We also propose further standardization in IOP measurement protocols to help unify future studies and suggest that future studies include measurements related to glaucomatous disease to facilitate evidence synthesis to inform clinical decision making.

In conclusion, to summarize, we systematically reviewed all eligible RCTs comparing anti-VEGF agents with each other or with a control intervention for the management of neovascular AMD, RVOs, and DME. We examined the 7 most frequently reported IOP outcomes before injection at both 12 and 24 months and used GRADE NMA guidelines to provide a certainty of evidence for each outcome. Our results suggest that no clear effect on IOP exists among anti-VEGF agents and between anti-VEGF agents and control interventions; however, the level of imprecision precludes definitive conclusions with the currently available data. Additional evidence is needed to improve the precision of the estimates and the certainty of evidence.

Acknowledgments

The authors thank the Diabetic Retinopathy Clinical Research Network for sharing their data with the authors. The source of this data is the Diabetic Retinopathy Clinical Research Network, but the analyses, content, and conclusions presented herein are solely the responsibility of the authors and have not been reviewed or approved by the Diabetic Retinopathy Clinical Research Network.

Footnotes and Disclosures

Originally received: August 9, 2021.
Final revision: November 9, 2021.
Accepted: November 29, 2021.
Available online: December 4, 2021. Manuscript no. D-21-01589.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): K.K.: Consultant − Lyceum Health

P.K.: Consultant − Novartis, Bayer, Biogen, Regeneron, Kanghong, Allergan, RegenxBio

S.J.G.: Consultant − Allergan, Apellis, Bausch & Lomb, Boehringer Ingelheim, Johnson and Johnson, Kanaph; Financial support − American Academy of Ophthalmology, Apellis, Boehringer Ingelheim, NGM Bio, Regeneron

D.S.: Consultant − Amgen, Bayer, Genentech, Novartis, Optovue; Financial support − Amgen, Genentech, Heidelberg, Optovue, Regeneron, Topcon

S.S.: Financial support − Novartis, Bayer, Allergan, Roche, Boehringer, Ingelheim, Optos Plc, Novartis, Bayer; Lecturer − Novartis, Bayer, Optos Plc; Advisory board − Novartis, Bayer, Allergan, Roche, Boehringer, Ingelheim, Optos Plz, Oxurion, Ophthea, Apellis, Oculis, Heidelberg Engineering

C.C.W.: Consultant − Acuela, Adverum Biotechnologies, Inc., Aerpio, Alimera Sciences, Allegro Ophthalmics, LLC, Allergan, Apellis Pharmaceuticals, Bayer AG, Chengdu Kanghong Pharmaceuticals Group Co., Ltd., Clearside Biomedical, DORC (Dutch Ophthalmic Research Center), EyePoint Pharmaceuticals, Gentech/Roche, GyroscopeTx, IVERIC Bio, Kodiak Sciences, Inc., Novartis AG, ONL Therapeutics, Oxurion NV, PolyPhotonix, Recens Medical, Regeron Pharmaceuticals, Inc., REGENXBIO, Inc., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited; Financial support − Adverum Biotechnologies, Inc., Aerie Pharmaceuticals, Inc., Aerpio, Alimera Sciences, Allergan, Apellis Pharmaceuticals, Chengdu Kanghong Pharmaceutical Group Co., Ltd., Clearside Biomedical, Gemini Therapeutics, Genentech/Roche, Graybug Vision, Inc., GyroscopeTx, Ionis Pharmaceuticals, IVERIC Bio, Kodiak Sciences, Inc., Neurotech LLC, Novartis AG, Opthea, Outlook Therapeutics, Inc., Recens Medical, Regeneron Pharmaceuticals, Inc., REGENXBIO, Inc., Samsung Pharm Co., Ltd., Santen Pharmaceutical Co., Ltd., Xbrane Biopharma AB

S.J.B.: Consultant − Adverum, Alimera, Apellis, Allergan, Eyepoint, Kala, Genentech, Novartis, Oxurion, Roche, Zeiss

T.S.: Scientific advisory panel − Bayer Healthcare, Novartis Pharma AG; Financial support − Bayer Healthcare, Novartis Pharma AG, Roche, Genentech, Apellis, Allergan, Chengdu Kanghong Biotechnology

M.B.: Financial support − Pendopharm, Bioventus, Acumed

V.C.: Advisory board member − Novartis, Bayer, Roche; Financial support − Novartis, Bayer, Allergan

HUMAN SUBJECTS: No human subjects were included in this study. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis NMA guidelines. This study was exempt from ethics approval as all syntheses were performed utilizing previous clinical trial data for which informed consent and ethics approval had been obtained. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

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Obtained funding: N/A; Study was performed as part of the authors' regular employment duties. No additional funding was provided.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CI** = confidence interval; **CrI** = credible interval; **DME** = diabetic macular edema; **GRADE** = Grading of Recommendations Assessments, Development, and Evaluations; **IOP** = intraocular pressure; **NMA** = network meta-analysis; **OR** = odds ratio; **RCT** = randomized controlled trial; **RVO** = retinal vein occlusion; **VEGF** = vascular endothelial growth factor.

Keywords:
Anti-VEGF therapy, Diabetic macular edema, Neovascular age-related macular degeneration, Ocular hypertension, Retinal vein occlusion.

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References

1. Jiang Y, Mieler WF. Update on the use of anti-VEGF intravitreal therapies for retinal vein occlusions. *Asia-Pacific J Ophthalmol*. 2017;6(6):546−553.
2. Hooper P, Boucher MC, Cruess A, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy—executive summary. *Can J Ophthalmol*. 2012;47(2):91−101.
3. Dunbar Hoskins Jr H. MC for QEC. Retina summary benchmarks—2018—American Academy of Ophthalmology. Available at: https://www.aao.org/summary-benchmark-detail/retina-summary-benchmarks-2018; 2017. Accessed 31.08.19.
4. Nikkhah H, Karimi S, Ahmadieh H, et al. Intravitreal injection of anti-vascular endothelial growth factor agents for ocular vascular diseases: clinical practice guideline. *J Ophthalmic Vis Res*. 2018;13(2):158−169.
5. Virgili G, Parravano M, Evans JR, et al. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database Syst Rev*. 2018;2018(10):CD007419.
6. Solomon SD, Lindsley K, Vedula SS, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2019;2019(3):CD005139.

7. Shalchi Z, Mahroo O, Bunce C, Mitry D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database Syst Rev*. 2020;2020(7):CD009510.
8. Bracha P, Moore NA, Ciulla TA, et al. The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: a review. *Surv Ophthalmol*. 2018;63(3):281−295.
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(4):611−622.
10. Carnota-Méndez P, Méndez-Vázquez C, Otero-Villar J, Saavedra-Pazos JA. Effect of prophylactic medication and influence of vitreous reflux in pressure rise after intravitreal injections of anti-VEGF drugs. *Eur J Ophthalmol*. 2014;24(5):771−777.
11. Katayama BYNY, Bonini-Filho MA, Messias AMV, et al. Comparison of acetazolamide, brimonidine, and anterior chamber paracentesis for ocular hypertension control after initial intravitreal bevacizumab injection. *J Glaucoma*. 2014;23(7):461−463.
12. Gregori NZ, Weiss MJ, Goldhardt R, et al. Ocular decompression with cotton swabs lowers intraocular pressure elevation after intravitreal injection. *J Glaucoma*. 2014;23(8):508−512.
13. Al-Abdullah AA, Nowilaty SR, Asghar N, et al. Intraocular pressure trends after intravitreal injections of anti-vascular endothelial growth factor agents for diabetic macular edema. *Retina*. 2015;35(3):440−448.
14. 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(10):1435−1440.
15. Choi DY, Ortube MC, McCannel CA, et al. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. *Retina*. 2011;31(6):1028−1035.
16. 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(5):1102−1108.
17. Wehrli SJ, Tawse K, Levin MH, et al. A lack of delayed intraocular pressure elevation in patients treated with intravitreal injection of bevacizumab and ranibizumab. *Retina*. 2012;32(7):1295−1301.
18. Kim D, Nam WH, Kim HK, Yi K. Does intravitreal injections of bevacizumab for age-related macular degeneration affect long-term intraocular pressure? *J Glaucoma*. 2014;23(7):446−448.
19. 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(6):1266−1271.e1.
20. 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(2):1023−1034.
21. Sniegowski M. Sustained intraocular pressure elevation after intravitreal injection of bevacizumab and ranibizumab associated with trabeculitis. *Open Ophthalmol J*. 2010;4(1):28−29.
22. Dedania VS, Bakri SJ. Sustained elevation of intraocular pressure after intravitreal anti-VEGF agents. *Retina*. 2015;35(5):841−858.
23. Ricca AM, Morshedi RG, Wirostko BM. High intraocular pressure following anti-vascular endothelial growth factor therapy: proposed pathophysiology due to altered nitric oxide metabolism. *J Ocul Pharmacol Ther*. 2015;31(1):2−10.
24. Wen JC, Reina-Torres E, Sherwood JM, et al. Intravitreal anti-VEGF injections reduce aqueous outflow facility in patients with neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2017;58(3):1893−1898.
25. O'Bryhim BE, Lin JB, Piggott KD, et al. Anterior chamber angles after intravitreal injections for macular degeneration. *Ophthalmol Retina*. 2020;4(7):750.
26. Theoulakis PE, Lepidas J, Petropoulos IK, et al. Effect of brimonidine/timolol fixed combination on preventing the short-term intraocular pressure increase after intravitreal injection of ranibizumab. *Klin Monbl Augenheilkd*. 2010;227(4):280−284.
27. Trivedi D, Denniston AK, Murray PI. Safety profile of anterior chamber paracentesis performed at the slit lamp. *Clin Exp Ophthalmol*. 2011;39(8):725−728.
28. Schmickl CN, Owens RL, Orr JE, et al. Side effects of acetazolamide: a systematic review and meta-analysis assessing overall risk and dose dependence. *BMJ Open Respir Res*. 2020;7(1):e000557.
29. Zimmerman TJ, Baumann JD, Hetherington J. Side effects of timolol. *Surv Ophthalmol*. 1983;28(suppl):243−249.
30. Avery RL, Bakri SJ, Blumenkranz MS, et al. Intravitreal injection technique and monitoring: updated guidelines of an expert panel. *Retina*. 2014;34:S1−S18.
31. Gohdes DM, Balamurugan A, Larsen BA, Maylahn C. Age-related eye diseases: an emerging challenge for public health professionals. *Prev Chronic Dis*. 2005;2(3):A17.
32. Zhao YX, Chen XW. Diabetes and risk of glaucoma: systematic review and a meta-analysis of prospective cohort studies. *Int J Ophthalmol*. 2017;10(9):1430−1435.
33. Zhou Y, Zhou M, Xia S, et al. Sustained elevation of intraocular pressure associated with intravitreal administration of anti-vascular endothelial growth factor: a systematic review and meta-analysis. *Sci Rep*. 2016;6(1):1−9.
34. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med*. 2017;12(1):103−111.
35. Roever L, Biondi-Zoccai G. Network meta-analysis to synthesize evidence for decision making in cardiovascular research. *Arq Bras Cardiol*. 2016;106(4):333−337.
36. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163−171.
37. Li T, Puhan MA, Vedula SS, et al. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Med*. 2011;9:79.
38. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162:777−784.
39. Lattanzio R, Cicinelli MV, Bandello F. Intravitreal steroids in diabetic macular edema. *Dev Ophthalmol*. 2017;60:78−90.
40. Sarao V, Veritti D, Boscia F, Lanzetta P. Intravitreal steroids for the treatment of retinal diseases. *ScientificWorldJournal*. 2014;2014:989501.

41. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(7829):d5928.
42. Brooks S, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *J Comput Graph Stat*. 1998;7:434–445.
43. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods*. 2016;7(1):80–93.
44. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*. 2014;349:g5630.
45. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol*. 2018;93:36–44.
46. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*. 2019;321(19):1880–1894.
47. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR Study. *Ophthalmology*. 2006;116(1):57–65.e5.
48. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013;382(9900):1258–1267.
49. Boyer DS, Nguyen QD, Brown DM, et al. Outcomes with as-needed ranibizumab after initial monthly therapy: long-term outcomes of the phase III RIDE and RISE trials. *Ophthalmology*. 2015;122(12):2504–2513.e1.
50. Gillies MC, Hunyor AP, Arnold JJ, et al. Effect of ranibizumab and aflibercept on best-corrected visual acuity in treat-and-extend for neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol*. 2019;137(4):372–379.
51. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology*. 2015;122(10):2044–2052.
52. Hykin P, Prevost AT, Vasconcelos JC, et al. Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: a randomized clinical trial. *JAMA Ophthalmol*. 2019;137(11):1256–1264.
53. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE Study. *Ophthalmology*. 2011;118(4):615–625.
54. Ishibashi T, Li X, Koh A, et al. The REVEAL study: ranibizumab monotherapy or combined with laser versus laser monotherapy in Asian patients with diabetic macular edema. *Ophthalmology*. 2015;122(7):1402–1415.
55. ClinicalTrials.gov. Efficacy of ranibizumab Prn treatment compared to aflibercept bimonthly intravitreal injections on retinal thickness stability in patients with wet AMD—study results. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01958918?term=NCT01958918&draw=2&rank=1&view=results. Accessed 25.01.21.
56. Li X, Dai H, Li X, et al. Efficacy and safety of ranibizumab 0.5 mg in Chinese patients with visual impairment due to diabetic macular edema: results from the 12-month REFINE study. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(3):529–541.
57. Tadayoni R, Waldstein SM, Boscia F, et al. Sustained benefits of ranibizumab with or without laser in branch retinal vein occlusion: 24-month results of the BRIGHTER Study. *Ophthalmology*. 2017;124:1778–1787.
58. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064–1077.e35.
59. Martin DF, Ying G, Grunwald JE, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897–1908.
60. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145(2):239–248.e5.
61. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology*. 2011;118(5):831–839.
62. Scott IU, VanVeldhuisen PC, Ip MS, et al. Comparison of monthly vs treat-and-extend regimens for individuals with macular edema who respond well to anti-vascular endothelial growth factor medications: secondary outcomes from the SCORE2 randomized clinical trial. *JAMA Ophthalmol*. 2018;136:337–345.
63. Wei W, Weisberger A, Zhu L, et al. Efficacy and safety of ranibizumab in Asian patients with branch retinal vein occlusion: results from the randomized BLOSSOM study. *Ophthalmol Retina*. 2020;4(1):57–66.
64. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193–1203.
65. Berger A, Sheidow T, Cruess AF, et al. Efficacy/safety of ranibizumab monotherapy or with laser versus laser monotherapy in DME. *Can J Ophthalmol*. 2015;50(3):209–216.
66. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study). 12-Month data: report 2. *Ophthalmology*. 2010;117(6):1078–1086.e2.
67. 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(9):1802–1810.
68. Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Available at: https://gdt.gradepro.org/app/handbook/handbook.html; 2013. Accessed 03.08.21.
69. Brignardello-Petersen R, Izcovich A, Rochwerg B, et al. GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. *BMJ*. 2020;371:m3907.
70. de Vries VA, Bassil FL, Ramdas WD. The effects of intravitreal injections on intraocular pressure and retinal nerve fiber layer: a systematic review and meta-analysis. *Sci Rep*. 2020;10(1):1–10.
71. National Institute for Health and Care Excellence. Glaucoma: diagnosis and management. NICE Guidance [NG81]. 1 November 2017. Available at: https://www.nice.org.uk/guidance/ng81/resources. Accessed 24.05.21.