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# A Network Meta-Analysis of Retreatment Rates following Bevacizumab, Ranibizumab, Aflibercept, and Laser for Retinopathy of Prematurity

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***Topic:*** To compare bevacizumab, ranibizumab, aflibercept, and laser treatment as primary therapies for retinopathy of prematurity (ROP) in terms of retreatment rate.

***Clinical relevance:*** Anti-VEGF agents are increasingly used as primary treatment for ROP and may provide superior outcomes compared with laser in posterior disease. Head-to-head comparisons between different anti-VEGFs are lacking.

***Methods:*** We searched CENTRAL, Embase, MEDLINE, and CINAHL databases for randomized controlled trials and nonrandomized comparative studies that had been reported as of March 2022. We included studies that used bevacizumab, ranibizumab, aflibercept or laser for ROP with comparable cohorts and treatment criteria. Studies were evaluated by the Grading of Recommendations, Assessment, Development and Evaluation framework, and those with biased case selection, nonrandomized case-control, or lack of control group were excluded. Frequentist meta-analyses of proportions determined the absolute primary retreatment rate of each modality and Bayesian network meta-analyses compared pairs of treatments in type 1 and Zone I ROP.

***Results:*** In all, 30 studies (4686 eyes) were included in the network meta-analyses. For type 1 ROP, single-treatment success rates (i.e., likelihood of needing no further treatment) were 89.3% (95% confidence interval [CI]: 83.8%−93.8%; n = 1552) for laser, 87.0% (95% CI: 78.6%−93.8%; n = 2081) for bevacizumab, 80.7% (95% CI: 62.0%−94.4%; n = 326) for aflibercept, and 74.0% (95% CI: 62.7%−84.1%; n = 727) for ranibizumab. Bayesian network meta-analysis indicates that laser treatment is associated with a significant 62% (95% credible interval [CrI]: 16%−83%) reduction in retreatment risk compared with ranibizumab, while no significant difference was found among other pairwise comparisons. The mean ± standard error of the mean times to secondary treatment following primary aflibercept (12.96 ± 0.47 weeks) and bevacizumab (11.36 ± 0.54 weeks) therapy were significantly longer than that for primary ranibizumab (9.29 ± 0.43weeks) therapy ($P = 7 \times 10^{-7}$ and $P = 9 \times 10^{-3}$, respectively). For Zone I ROP, single-treatment success rates were 91.2% (95% CI: 83.6−96.9; n = 231) for bevacizumab, 78.3% (95% CI: 61.4−91.9; n = 100) for ranibizumab, and 65.9% (95% CI: 41.4−87.2; n = 158) for laser treatment. In this case, Bayesian network meta-analysis suggests that primary bevacizumab is associated with a significant 67% (95% CrI:10%−90%) reduction in retreatment risk compared with laser treatment.

***Conclusions:*** Laser was associated with a lower rate of retreatment than ranibizumab in type 1 ROP (Zones I and II combined), while bevacizumab was associated with a lower rate of retreatment than laser in Zone I ROP. Aflibercept and bevacizumab demonstrate longer duration of action than ranibizumab for ROP. *Ophthalmology 2022;■:1−13 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

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Retinopathy of prematurity (ROP) is a retinal vascular disorder affecting preterm infants. Globally, it is a leading cause of potentially preventable blindness in children due to aberrant neovascularization in areas of avascular retina leading to retinal detachment.[1] In developed countries, ROP now occurs mostly in infants with extremely low birth weight (BW) and low gestational age (GA).[2]

The decision to treat ROP is based on the clinical appearance of retinal vasculature, defined by location (zone), severity (stage), and the presence of plus disease indicative of venous dilation and arterial tortuosity.[3] Over the past decades, treatment methods for ROP have evolved from cryotherapy through to ablative laser therapy targeting the peripheral avascular retina. However, ROP



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could sometimes progress despite treatment, and side effects of ablative therapy include reduced field of vision[3] and myopia,[4] although there is debate as to how much of the latter may be related to severity of disease itself. Furthermore, practical limitations of laser therapy include the requirement for general anesthesia or sedation, which can be associated with significant morbidity in this vulnerable group of infants, as well as its operator-dependence such that retreatment is sometimes needed for laser-skipped areas.[5]

More recently, the roles of vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1-alpha (HIF1α) have been established in the pathogenesis of ROP.[4] This, combined with results of the BEAT-ROP trial[6] in 2011 supporting the use of 0.625 mg of intravitreal bevacizumab (Avastin) for posterior ROP (aggressive posterior ROP and Zone I disease), has led to increased utilization of anti-VEGF agents as a primary treatment for ROP. Furthermore, anti-VEGF treatment is associated with lower likelihood of visual field defects and high myopia compared with laser treatment.[7]

Bevacizumab is an antiangiogenic humanized monoclonal antibody (149 kDa) that blocks VEGF-A. Ranibizumab (Lucentis) is a monoclonal antibody fragment (Fab; 48 kDa) derived from the same parent antibody as bevacizumab. The intraocular half-life of bevacizumab in nonvitrectomized human eyes has been estimated at 9.8 days, compared with 7.2 days for ranibizumab.[8] The RAINBOW trial showed that 0.2 mg of intravitreal ranibizumab was as effective as, and possibly superior to, laser treatment for type 1 ROP.[9,10] Aflibercept (Eylea) is a 115-kDa fusion protein combining binding domains from human VEGF receptor 1, human VEGF receptor 2, and the Fc region of a human immunoglobulin G1. Aflibercept binds to multiple isoforms of VEGF-A, VEGF-B, and placental growth factor, thus "trapping" these circulating VEGFs for degradation. It is under investigation as monotherapy for ROP against laser in several randomized controlled trials (RCTs).[11,12]

While anti-VEGFs have less effect on eye growth compared with laser treatment, they can be associated with late ROP reactivation, which requires retreatment (often with laser photocoagulation under general anesthesia).[13] Hence, frequent and long-term monitoring of anti-VEGF–treated eyes is required. Systemic dissemination of anti-VEGF drugs after intraocular administration has been shown,[14–17] but there is no definitive evidence of developmental adverse effects.[18,19]

To date, most studies and systematic reviews have focused on comparing intravitreal anti-VEGF against laser treatment while head-to-head comparisons between different anti-VEGF agents are lacking, particularly in terms of high-quality RCTs. Moreover, many existing studies investigate efficacy (in terms of anatomical and visual outcomes) as the primary outcome. While efficacy is of prime importance, when multiple therapeutic modalities are available that offer similar high efficacies, the treatment choice may be determined by differences in retreatment rates. This factor has very significant clinical implications on the long-term monitoring regime and potential requirement for general anesthesia (e.g., for secondary laser treatment) in neonates with complex comorbidities. Herein, we performed a network meta-analysis (NMA) to fully utilize the available clinical data to explore relative differences in retreatment rates following primary ROP therapy with bevacizumab, ranibizumab, aflibercept, or laser. Objective retreatment criteria were used, including retreatment for ROP reactivation, persistence, or progression.

An NMA is a statistical technique that can directly and indirectly compare treatments, even when pairs of treatments have not been compared head-to-head in the same study.[20] This uses a network of intervention arms constructed from direct comparisons between different treatment modalities to estimate indirect comparisons.[21] The NMA summarizes RCTs and nonrandomized comparative studies of several different treatments by providing point estimates for their association with a given end point and estimating how well the entire network of intervetions fits together (consistency).[20] NMAs have been used successfully in other fields of medicine to overcome the challenges of complex multiarm RCTs and the impractically large sample sizes required for comparing multiple alternative treatments for the same condition.[22] This NMA compares the effectiveness of the 3 main anti-VEGF agents currently available alongside laser for ROP as measured by the risk of disease reactivation needing retreatment. The results are expected to inform clinical decision making and guideline development.

## Methods

### Literature Search and Inclusion Criteria

We performed a systematic review of publications on the use of anti-VEGF drugs for the treatment of ROP. A synthesis of data inclusion was created in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched with the terms "ROP" OR "retinopathy" AND the anti-VEGF agents (bevacizumab, ranibizumab, aflibercept) in the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Embase, and MEDLINE via PubMed from the date of database inception to 18 March 2022, with no language restrictions. The electronic database searches were supplemented with manual searches for published and ongoing RCTs in international trial registers. For example, we searched ClinicalTrials.gov using the term "retinopathy of prematurity" and the names of the 3 anti-VEGF agents.

Predefined eligibility criteria for evidence inclusion were as follows: (i) RCTs or nonrandomized studies; (ii) studies of premature infants with type 1 ROP as defined by the Early Treatment of ROP (ETROP) study[23]; and (iii) studies comparing the anti-VEGF agents with laser or another anti-VEGF agent as monotherapy for type 1 ROP. We defined retreatment as any eye that received secondary treatment due to (i) reactivation of ROP in keeping with criteria presented in the International Classification of Retinopathy of Prematurity, third edition,[24] (i.e., disease regression followed by reappearance of pre-plus or plus disease, extraretinal new vessels, or fibrovascular ridge); (ii) persistent ROP (any stage) or failure to regress; or (iii) progression of ROP severity despite treatment. We included 2 eyes (of 1 infant) for laser retreatment of abnormal vascular hyperpermeability following bevacizumab monotherapy, which we interpreted as a case of ROP

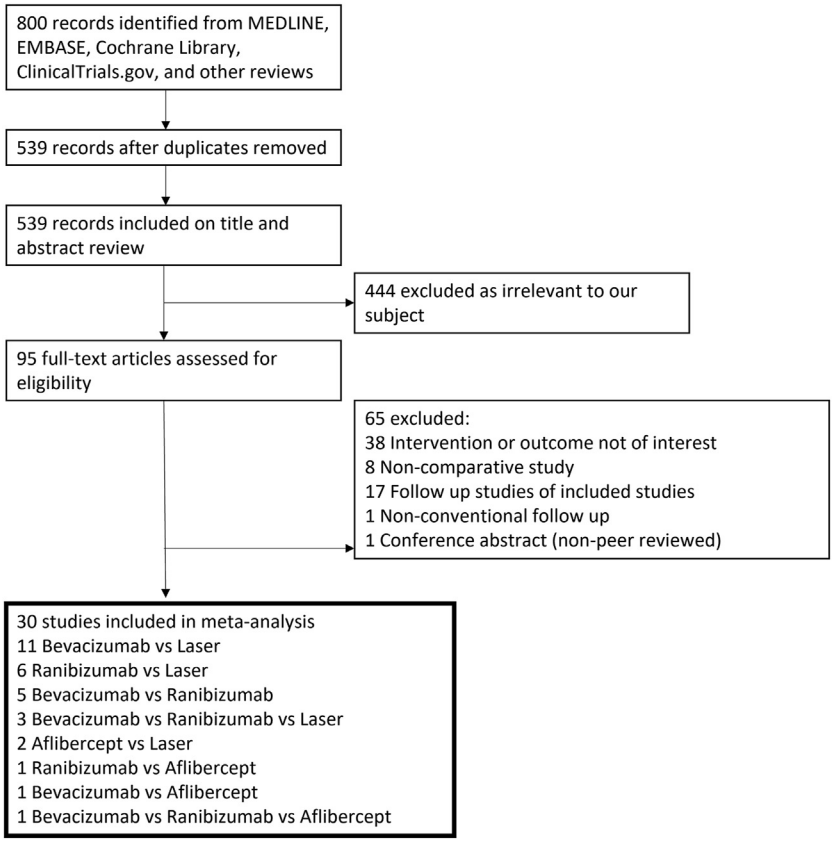


**Figure 1.** Flowchart of database search and study selection.

reactivation.[25] We did not include eyes retreated solely for laser-skipped areas or persistent avascular retina, as these represent subjective treatment choices that remain controversial and do not fulfill criteria for ROP reactivation presented in the International Classification of Retinopathy of Prematurity, third edition. Other reasons for exclusion were (i) studies with unreported outcomes, (ii) studies that did not report ROP retreatment rates, and (iii) subgroups of patients who received planned combined treatment with anti-VEGF and laser. As only a small number of RCTs of anti-VEGF therapy for ROP were available, likely because of the complexity and ethical challenges surrounding the implementation of interventional RCTs in premature infants, we also included nonrandomized retrospective cohort studies in our meta-analyses. To ensure transitivity, all studies were assessed to ensure the study populations were similar in terms of mean GA, BW, and length of follow-up (minimum 6 months) for capturing any ROP retreatment. For anti-VEGF treatment studies, we pooled data from cohorts treated with each drug (i.e., 0.625 mg in 0.025 ml of bevacizumab, 0.20−0.30 mg in 0.02−0.03 ml of ranibizumab, 0.4−1.0 mg in 0.01−0.025 ml of aflibercept), and we made the assumption that the small dose variations for ranibizumab and aflibercept do not have significant impact on reactivation rates. We included results from the FIREFLEYE RCT (aflibercept vs. laser) by extracting data reported on ClinicalTrials.gov that have not been formally published via peer review. The data reported results as number of infants rather than eyes; thus, we assumed that infants were treated bilaterally. The fact that the proportions do not give exact patient numbers may suggest that some eyes or patients were excluded from the analysis. These factors may have some effect on the accuracy of the results but are unlikely to affect the overall conclusions.

## Data Extraction

For each included study, we extracted the population characteristics (GA, BW, and postmenstrual age [PMA] at treatment); treatment modalities; primary outcome (number of eyes requiring retreatment for ROP within 6 months of primary therapy); and time (number of weeks) between initial and secondary treatment. In studies containing planned combination-treatment groups (e.g., a study comparing bevacizumab monotherapy, laser monotherapy, and combined bevacizumab+laser therapy), we extracted the outcome data for the bevacizumab and laser monotherapy arms only. For studies involving the same patient populations, duplication of data was avoided by including only the most complete data set.

We first compared retreatment rates of intravitreal anti-VEGFs and laser treatment for all ROP that reached the treatment threshold (i.e., type 1 ROP). Given the current pattern of clinical practice, there is a likelihood of bias toward selecting anti-VEGF over laser for posterior ROP (e.g., Zone I or posterior Zone II disease) in nonrandomized studies. In addition, given that Zone I ROP disease typically has worse outcomes, we separately compared the retreatment rates following primary treatment of Zone I ROP with anti-VEGFs or laser. Since the study aim was focused on ROP retreatment rates, comparisons of other adverse outcomes such as reduced visual acuity and myopia are beyond the scope of this systematic review and NMA.

Table 1. Characteristics of All Studies Included in the Type 1 ROP Analysis

| Study | Treatment Type | | | | Study Design | No. of Patients | Total No. of Eyes | No. of Eyes Receiving Initial Treatment | | | | No. of Eyes Requiring Retreatment | | | | Mean Time between Initial and 2nd Treatment, Weeks (unless otherwise stated) | | | Reason for Retreatment (Number of Eyes) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Bevacizumab* | *Ranibizumab* | *Aflibercept* | *Laser* | | | | *IVB* | *IVR* | *IVA* | *Laser* | *IVB* | *IVR* | *IVA* | *Laser* | *IVB* | *IVR* | *IVA* | |
| Murakami et al. 2021[36] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 26 | 52 | 24 | 0 | 0 | 28 | 4 | n/a | n/a | 0 | 9 | n/a | n/a | + (4) |
| Zayek et al. 2021[37] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 146 | 292 | 122 | 0 | 0 | 170 | 20 | n/a | n/a | 4 | median:8 | n/a | n/a | + (12) |
| Mori et al. 2020[25] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 66 | 132 | 26 | 0 | 0 | 106 | 12 | n/a | n/a | 8 | n/a | n/a | n/a | NV (2), + (18) |
| Demir et al. 2019[38] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 65 | 121 | 57 | 0 | 0 | 64 | 9 | n/a | n/a | 17 | n/a | n/a | n/a | NV (26) |
| Chen et al. 2018a[39] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 25 | 49 | 29 | 0 | 0 | 20 | 28 | n/a | n/a | 2 | 19 | n/a | n/a | Per (30) |
| Mueller et al. 2017[40] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 54 | 108 | 74 | 0 | 0 | 34 | 10 | n/a | n/a | 0 | median:12.7 | n/a | n/a | Per (10) |
| Nicoară et al. 2016[41] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 23 | 46 | 34 | 0 | 0 | 12 | 3 | n/a | n/a | 2 | n/a | n/a | n/a | Per (5) |
| Hwang et al. 2015[42] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 28 | 54 | 22 | 0 | 0 | 32 | 3 | n/a | n/a | 1 | 9 | n/a | n/a | NV (1), + (2), Pro (1) |
| Kong et al. 2015[43] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 42 | 80 | 43 | 0 | 0 | 37 | 3 | n/a | n/a | 4 | 8.86 | n/a | n/a | + (3), Pro (4) |
| Isaac et al. 2015[44] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | r | 25 | 45 | 23 | 0 | 0 | 22 | 0 | n/a | n/a | 1 | n/a | n/a | n/a | Per (1) |
| Mintz-Hittner 2011[6] | IVB (0.625 mg/0.025 ml) | n/a | n/a | Laser | RCT | 143 | 286 | 140 | 0 | 0 | 146 | 6 | n/a | n/a | 32 | 16 | n/a | n/a | NV (38) |
| Fleck et al. 2022[10] | n/a | IVR (0.2 mg) | n/a | Laser | | 142 | 284 | 0 | 146 | 0 | 138 | n/a | 40 | n/a | 34 | n/a | median:7.64 | n/a | + (25), Per (48) |
| Chmielarz-Czarnocińska et al. 2021[45] | n/a | IVR (0.25 mg/0.025 ml) | n/a | Laser | r | 176 | 346 | 0 | 120 | 0 | 226 | n/a | 80 | n/a | 46 | n/a | n/a | n/a | + or Per (126) |
| Lyu et al. 2019[46] | n/a | IVR (0.25 mg/0.025 ml) | n/a | Laser | r | 14 | 27 | 0 | 17 | 0 | 10 | n/a | 2 | n/a | 3 | n/a | n/a | n/a | Per (3), Pro (2) |
| Leng et al. 2018[47] | n/a | IVR (0.25 mg) | n/a | Laser | r | 61 | 122 | 0 | 24 | 0 | 98 | n/a | 10 | n/a | 42 | n/a | n/a | n/a | U (52) |
| Zhang et al. 2017[48] | n/a | IVR (0.3 mg/0.03 ml) | n/a | Laser | RCT | 50 | 100 | 0 | 50 | 0 | 50 | n/a | 26 | n/a | 2 | n/a | 12.62 | n/a | + (28) |
| Chan et al. 2016[49] | n/a | IVR (0.25 mg/0.025 ml) | n/a | Laser | r | 9 | 18 | 0 | 8 | 0 | 10 | n/a | 6 | n/a | 2 | n/a | 7.43 | n/a | Per (5), U (3) |
| FIREFLEYE 2022[12] | n/a | n/a | IVA 0.4 mg (0.01 ml) | Laser | RCT | 113 | 226 | 0 | 0 | 150 | 76 | n/a | n/a | 11 | 7 | n/a | n/a | n/a | U (18) |
| Ekinci et al. 2020[50] | n/a | n/a | IVA 1 mg/0.025 ml | Laser | r | 27 | 51 | 0 | 0 | 24 | 27 | n/a | n/a | 6 | 2 | n/a | n/a | 18.2 | + (6), Per (2) |
| Ling et al. 2020[51] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | n/a | Laser | r | 176 | 340 | 231 | 48 | 0 | 61 | 23 | 10 | n/a | 11 | 8.8 | 8.3 | n/a | + (44) |
| Kabataş et al. 2017[52] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | n/a | Laser | r | 54 | 108 | 24 | 12 | 0 | 72 | 2 | 2 | n/a | 10 | 17 | 13.7 | n/a | + (4), Per (10) |
| Gunay et al. 2016[53] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | n/a | Laser | r | 134 | 264 | 107 | 44 | 0 | 113 | 6 | 6 | n/a | 0 | 14 | 8.75 | n/a | Both Pro and + (12) |
| Chen et al. 2018b[54] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | n/a | n/a | r | 36 | 66 | 40 | 26 | 0 | 0 | 4 | 0 | n/a | n/a | n/a | n/a | n/a | Per (4) |
| Kang et al. 2018[55] | IVB (0.625 mg/0.025 ml) | IVR (0.2 mg/0.02 ml) | n/a | n/a | r | 83 | 153 | 101 | 52 | 0 | 0 | 8 | 7 | n/a | n/a | n/a | n/a | n/a | U (15) |

Table 1. (Continued.)

| Study | Treatment Type | | | | Study Design | No. of Patients | Total No. of Eyes | No. of Eyes Receiving Initial Treatment | | | | No. of Eyes Requiring Retreatment | | | | Mean Time between Initial and 2nd Treatment, Weeks (unless otherwise stated) | | | Reason for Retreatment (Number of Eyes) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Bevacizumab* | *Ranibizumab* | *Aflibercept* | *Laser* | | | | *IVB* | *IVR* | *IVA* | *Laser* | *IVB* | *IVR* | *IVA* | *Laser* | *IVB* | *IVR* | *IVA* | |
| Kimyon et al. 2018[56] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | n/a | n/a | r | 37 | 68 | 40 | 28 | 0 | 0 | 4 | 2 | n/a | n/a | n/a | n/a | n/a | n/a + (6) |
| Erol et al. 2015[57] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | n/a | n/a | r | 20 | 36 | 21 | 15 | 0 | 0 | 2 | 4 | n/a | n/a | 14 | 8 | n/a | n/a + (6) |
| Wong et al. 2015[58] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | n/a | n/a | r | 6 | 10 | 4 | 6 | 0 | 0 | 0 | 3 | n/a | n/a | n/a | 7.43 | n/a | n/a + (3) |
| Sukgen et al. 2019[59] | n/a | IVR (0.25 mg/0.025 ml) | IVA 1 mg/0.025 ml | n/a | r | 63 | 126 | 0 | 54 | 72 | 0 | n/a | 12 | 6 | n/a | n/a | 8.2 | 14.2 | + (18) |
| Riazi-esfahani et al. 2021[60] | IVB (0.625 mg/0.025 ml) | n/a | IVA 1 mg/0.025 ml | n/a | r | 453 | 889 | 865 | 0 | 24 | 0 | 34 | n/a | 14 | n/a | 6.71 | n/a | 14.86 | + (48) |
| Süren et al. 2022[61] | IVB (0.625 mg/0.025 ml) | IVR (0.25 mg/0.025 ml) | IVA 1 mg/0.025 ml | n/a | r | 111 | 187 | 54 | 77 | 56 | 0 | 8 | 19 | 8 | n/a | 13 | 8 | 12 | U (35) |

+ = reappearance of pre-plus or plus disease; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; n/a = not applicable; NV = extraretinal new vessels (including abnormal fluorescein leakage); Per = persistent retinopathy of prematurity (any stage) or failure to regress; Pro = progression in severity of retinopathy of prematurity; r = retrospective nonrandomized study; RCT = randomized controlled trial; ROP = Retinopathy of prematurity; U = undefined, retreatment occurred because of reactivation that was not further defined.

## Data Analysis

**Frequentist Meta-Analyses of Proportions.** All statistical analysis was performed in R (version 4.0.5).[26] We used a conventional frequentist meta-analysis of proportions (R-package: metafor, version 3.0.2[27]) to calculate dichotomous outcome measures (number of eyes requiring retreatment). A Freeman−Tukey double arcsine transformed proportion was used to calculate effect sizes and associated sampling variances to generate a summary proportional effect size with 95% confidence intervals (CIs) and $I^2$ statistic to assess heterogeneity. The choice of transformation is dependent of the type of data. In cases such as that encountered in this data set, a Freeman−Tukey double arcsine transformation is effective at normalizing for situations where extreme values for incidence rates exist, and it is also effective at stabilizing the variances.[28] Questions do emerge on the method of back-transformation, with potentially misleading results arising from choosing a harmonic mean in cases where the sample size is very large. We note that for our data set, sample sizes are well within the upper limits where issues of back-transformational errors are likely to occur.[29] A random-effects model was used for these meta-analyses. To visualize the statistical power of each study contained in the analysis, we created a sunset power-enhanced funnel plot with metaviz,[30] using the lower bound of the overall summary effect size derived from the frequentist analysis.

**Bayesian NMAs.** Transitivity is a key underlying assumption of NMA—the model assumes that retrospective studies are of high quality (i.e., they do not compare 2 treatments with unequal methodology or significant biases) such that comparisons between studies can be made. We assessed the clinical variables that may act as effect modifiers across treatment comparisons, including GA at birth, BW, and PMA at treatment. These patient characteristics were found to be comparable across all treatment groups.

We performed a Bayesian NMA and meta-regression using the R-package gemtc (version 1.0.1)[31,32] to compare relative effect sizes of bevacizumab, ranibizumab, aflibercept, and laser treatment in terms of retreatment risk and estimated summary risk ratios. A network within a Bayesian hierarchical model was constructed to directly and indirectly compare the various treatment modalities and ensure the most comprehensive comparisons of relative effects for any given pairwise comparison of anti-VEGF or laser treatment. This model simulates, using the Markov chain Monte Carlo method, distributions of treatment comparisons and then infers, by indirect means via a network, any missing treatment arms. For the Bayesian implementation, we used a binomial likelihood for dichotomous outcomes and vague priors, and we ended the simulation only once we ensured model convergence after running 4 chains. We used 200 000 iterations were used in total, discarding all but every 10th iteration, as is commonly performed for thinning purposes. The first 8000 iterations were disregarded, and the remaining 192 000 iterations were used to estimate the parameters.

Convergence of models was ensured by visual inspection of the 4 Markov chains and after considering the Gelman−Rubin−Brooks plots. Statistical evaluation of the inconsistency of the network was assessed using the node split method. *P* values ($P > 0.05$) showed no inconsistencies between direct, indirect, and network analysis results, thus supporting the consistency of the NMA. The full R code details of the conventional frequentist meta-analysis of proportions and Bayesian NMA along with meta-regression models are provided as R markdown files on GitHub: https://github.com/amanasj/ROP-meta-analysis.

**Quality Assessment.** For RCTs, we used the Cochrane Risk of Bias 2 tool[33] to assess risk of bias based on the following domains: randomization, masking of participants and assessors, management of missing outcome, attrition, and reporting bias. Studies were

graded as "low risk," "some concerns," or "high-risk." Conflicts of interest and industry sponsorship were also considered. For nonrandomized comparative studies, we used the Newcastle−Ottawa scale.[34] The quality of these studies was assessed based on (i) how the participants represented the patient population of interest, (ii) selection of comparative group participants, (iii) outcome assessment, and (iv) the length and adequacy of follow-up when applicable. For both RCTs and nonrandomized comparative studies, acceptable follow-up was set to at least 6 months after initial treatment and a loss to follow-up of less than 10% was deemed acceptable.

The Grading of Recommendations, Assessment, Development and Evaluation framework was used to assess the quality and certainty of evidence for the primary outcome.[35] This incorporated the risk of bias assessments with evaluation of the following domains: directness of evidence, consistency, precision of results, publication bias risk, and magnitude of effect. The data accuracy was validated by 2 independent investigators (E.C. and R.P.).

**Comparison of Time to Retreatment following Primary Anti-VEGF Therapy.** We collected the mean ± standard deviation (SD) time to secondary treatment following primary anti-VEGF therapy from the included studies where data are available. If a study stated only time to reactivation, we assumed this to be an approximation of the time to retreatment. We excluded studies with no reported SDs or those that reported medians. For each anti-VEGF agent, we calculated the summary mean by combining each reported study mean with weighting for the study sample size. SDs were also combined using sample size weightings. We then performed a Welch analysis of variance test on these combined summary means and a Games−Howell post hoc test to find which treatment pairs were statistically different. Normality using a Shapiro−Wilk test on residuals and homogeneity of variances using a Levene test were employed to validate our choice of statistical tests.

# Results

## Literature Search

During the initial electronic database search, 800 records were retrieved, of which 30 studies were included in the meta-analysis (Fig 1).[6,10,12,25,36−61] The reasons for exclusion of studies were duplicated studies (261), outcome measures not relevant to this study (444), intervention or outcome not of interest (38), noncomparative studies (8), repeated cohort in follow-up studies (17), non−peer reviewed conference abstracts (1), and nonconventional follow-up (1). The 30 included studies consisted of 4 RCTs and 26 retrospective consecutive cohorts (Table 1). Of these, 11 studies compared bevacizumab and laser therapy[6,25,36−44]; 6 studies compared ranibizumab and laser[10,45−49]; 5 studies compared bevacizumab and ranibizumab[54−58]; 3 studies compared bevacizumab, ranibizumab, and laser[51−53]; 2 studies compared aflibercept and laser[12,50]; 1 study compared ranibizumab and aflibercept[59]; 1 study compared bevacizumab and aflibercept[60]; and 1 study compared bevacizumab, ranibizumab, and aflibercept.[61] In total, these comprise 4686 eyes of 2408 infants that received primary treatment for ROP with bevacizumab (2081 eyes), ranibizumab (727 eyes), aflibercept (326 eyes), or laser (1552 eyes).

## Assessment of Bias

The majority of included RCTs had a low risk of bias (Table S1, available at www.aaojournal.org). There were some concerns of bias for RCTs due to lack of reporting in the following categories: (i) allocation sequence concealment until participants were assigned to interventions; (ii) intention-to-treat analysis; or (iii) prespecified analysis plan finalized before outcome data were collected. Most nonrandomized studies had a low risk of bias (Table S2, available at www.aaojournal.org). Moderate risk of bias in some nonrandomized studies were due to (i) lack of demonstration that patients who had received any previous treatments before intravitreal injections were excluded; and (ii) no adjusting relative risk for confounders (e.g., age). Hence, the overall quality of evidence for retreatment rate due to ROP reactivation, persistence, or progression is moderate.

## Heterogeneity

There was significant ($P < 0.05$) heterogeneity in the studies reporting on bevacizumab, ranibizumab, and laser. This implies that there is no common single true effect size for each treatment modality across different studies and that the differences found between studies are beyond those attributable to chance or random sampling. Hence, we assume that there is a distribution of true effect sizes for each treatment. This distribution is simulated in the Bayesian NMA.

## Small-Study Publication Bias

For type 1 ROP data, visual inspection of funnel plots showed no obvious asymmetry, and Egger regression confirmed no significant asymmetry ($P > 0.05$), so there is no evidence of small-study bias.

It has been noted that measures of heterogeneity and publication bias may not be entirely relevant for meta-analysis of proportions where incidence rates rather than pairwise comparisons are reported. It is likely that these measures play a more significant role in pairwise analysis where heterogeneity can be reliably assessed and where publication bias is a quantifiable metric. However, we report these measures for completeness until a more rigorous analysis of their benefits is provided in the literature.[28] The sunset power-enhanced funnel plots show that the power of each study contained in type 1 ROP analysis and Zone I ROP analysis was high (> 92% and > 83%, respectively) (Fig S1A, B, available at www.aaojournal.org).

## Efficacies of Anti-VEGF Agents and Laser Treatment for Type 1 ROP

**Frequentist Meta-Analysis of Proportions.** For type 1 ROP, based on a minimum follow-up period of 24 weeks (mean 83.1 weeks, SD 53.3 weeks), all treatment modalities demonstrate high efficacy with a predicted 87.0% (95% CI: 78.6%−93.8%) of eyes requiring no retreatment following primary bevacizumab injection. The predicted single-treatment success rates (i.e. likelihood of requiring no retreatment) for ranibizumab, aflibercept, and laser were 74.0% (95% CI: 62.7%−84.1%), 80.7% (95% CI: 62.0%−94.4%), and 89.3% (95% CI: 83.8%−93.8%), respectively. These effect sizes were all significant ($P < 0.05$), despite the aflibercept treatment group having a relatively small sample size (n = 326).

### *Bayesian NMA of Anti-VEGF and Laser Treatment for Type 1 ROP*

Figure 2A, B illustrates the network of eligible comparisons for type 1 ROP and Zone I ROP, respectively. Most of the data available enable comparisons between laser, bevacizumab, and ranibizumab as primary monotherapies for ROP. However, there is a relative paucity of data available for aflibercept therapy in Zone I ROP to date. These networks were verified by Markov chain Monte Carlo validation plots and inconsistency analysis, which showed no evidence of inconsistency. Further validation

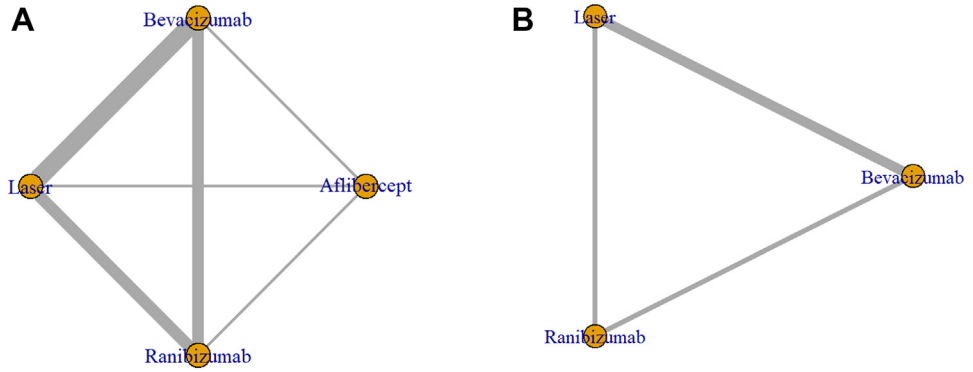


**Figure 2.** Network meta-analysis of eligible comparisons for single-treatment success rates following anti-vascular endothelial growth factor (VEGF) (bevacizumab, ranibizumab, aflibercept) or laser therapy for **A,** type 1 retinopathy of prematurity and **B,** Zone I retinopathy of prematurity. Widths of lines are proportional to the number of studies comparing pairs of treatment modalities.

with Gelman–Rubin–Brooks plots showed that the potential scale reduction factor is within acceptable limits (< 1.05).

A Bayesian NMA was performed to compare the risks of requiring retreatment following primary bevacizumab, aflibercept, ranibizumab or laser for type 1 ROP (Figure 3). This showed that laser treatment is associated with a significant 62% (95% credible interval [CrI]:16%–83%) reduction in risk of needing retreatment compared with ranibizumab in type 1 ROP (Figure 3D). In contrast, the 95% CrI of all other pairwise comparisons crossed Risk Ratio (RR) = 1, indicating there were no significant differences between them.

## Time to Retreatment following Primary Anti-VEGF Therapy

Of 30 included studies, 20 reported time to retreatment data (Table S3, available at www.aaojournal.org). The combined weighted mean time to retreatment for bevacizumab, ranibizumab and

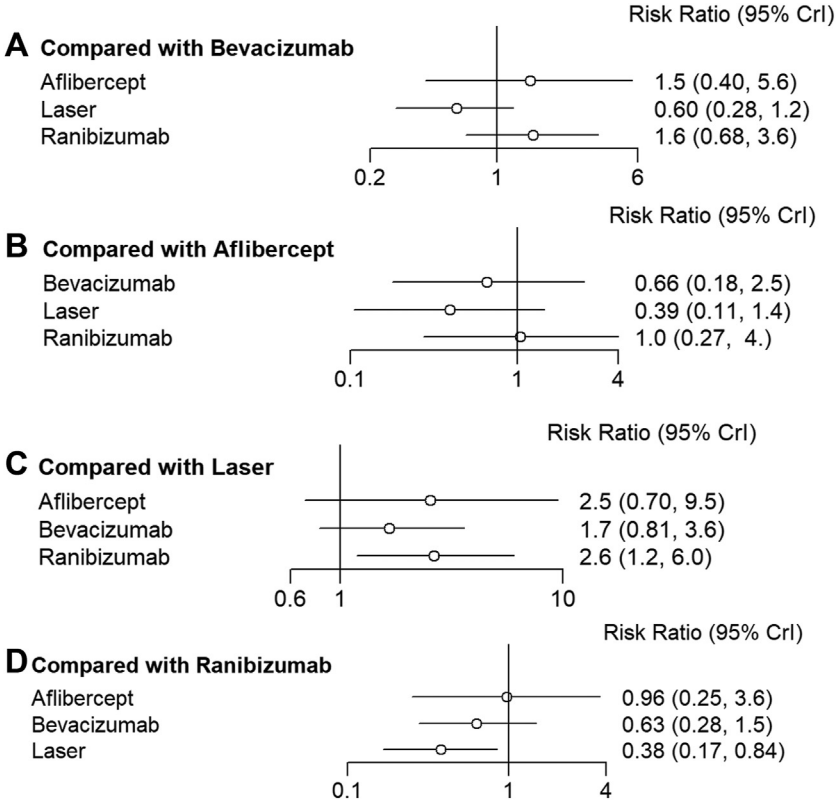


**Figure 3.** Forest plots of network meta-analysis of risk of retreatment following primary therapy with anti-vascular endothelial growth factor (VEGF) agents or laser in type 1 retinopathy of prematurity. In each panel, 3 treatment modalities (treatment 1, shown in regular font) were compared against a reference treatment modality (treatment 2, shown in bold) which may be **A,** bevacizumab; **B,** aflibercept; **C,** laser; or **D,** ranibizumab. Risk ratio < 1 means that the risk of requiring retreatment is lower with treatment 1 than with treatment 2. 95% CrI = 95% credible interval.

aflibercept are plotted in Fig S2 (available at www.aaojournal.org). Combined mean times to secondary treatment following primary anti-VEGF injections were 9.29 weeks (standard error of the mean [SEM] = 0.43 weeks, SD = 4.47 weeks) for ranibizumab, 11.36 weeks (SEM = 0.55 weeks, SD = 4.31 weeks) for bevacizumab, 12.96 weeks (SEM = 0.47 weeks, SD = 2.24 weeks) for aflibercept. Because of unequal variances, we performed a Welch analysis of variance test on these combined summary means and found a $P$ value $< 0.0001$. A Games–Howell post hoc test demonstrated 2 statistically significant differences: both aflibercept and bevacizumab were associated with longer time to retreatment than ranibizumab ($P = 7 \times 10^{-7}$ and $P = 9 \times 10^{-3}$, respectively) (Fig S2, available at www.aaojournal.org).

### Assessment of GA, BW, and PMA at Treatment as Potential Moderators for Treatment Outcome in Type 1 ROP

**Frequentist Meta-Regression of Proportions.** A meta-regression was performed on each individual treatment modality to assess whether the ROP retreatment rates were moderated or varied consistently across the range of GAs, BWs, and PMAs at primary treatment within the studies. No association was found between retreatment rates and GA, BW, or PMA at treatment when considering individual treatments within a frequentist framework.

**Bayesian Meta-Regression.** The only treatment pair comparison to demonstrate a statistically significant moderating effect was between laser and ranibizumab treatments. At low PMA ($\leq$ 35.6 weeks), treatment with laser is associated with a statistically significant reduction in risk of requiring retreatment compared with ranibizumab (Fig S3, available at www.aaojournal.org). Between 25.8 and 26.7 weeks GA, laser treatment is associated with a statistically significant reduction in risk of requiring retreatment when compared with ranibizumab treatment (Fig S4, available at www.aaojournal.org). Between BWs of 846 and 932 g, laser treatment is associated with significant reduction in risk of requiring retreatment compared with ranibizumab treatment (Fig S5, available at www.aaojournal.org). All other treatment comparisons yielded no statistically significant difference across the range of GAs, BWs, or PMA at time of treatment.

### Efficacies of Anti-VEGF Agents and Laser Treatment for Zone I ROP

To avoid potential treatment-selection bias in posterior disease, whereby anti-VEGF therapy might be preferred to laser for posterior disease, we conducted a separate analysis on eyes with Zone I ROP treated with anti-VEGF agents or laser. Out of the 30 studies, only 10 studies included data on eyes with Zone I ROP, consisting of 2 RCTs and 8 retrospective nonrandomized studies (Table S4, available at www.aaojournal.org).

**Frequentist Meta-Analysis of Proportions.** Based on the included studies, all treatment modalities demonstrated high predicted single-treatment success rates: 91.2% (95% CI: 83.6%–96.9%) for bevacizumab, 78.3% (95% CI: 61.4%–91.9%) for ranibizumab, and 65.9% (95% CI: 41.4%–87.2%) for laser treatment. There were no data available for aflibercept.

**Bayesian NMA of Anti-VEGF and Laser Treatment for Zone I ROP.** The only treatment comparison that reached statistical significance was that for bevacizumab versus laser, where bevacizumab was associated with a 67% (95% CrI: 10%–90%) reduction in risk of retreatment compared with laser (Fig 4). The large credible intervals associated with all other pairwise comparisons suggest that retreatment rates of other combinations are not significantly different, i.e., effectiveness of other treatment pairs cannot be dissociated to statistical significance.

## Discussion

Treatment-requiring (type 1) ROP affects only a small proportion (around 4%) of premature infants who undergo ROP screening.[62] Significant variations exist between infants with ROP in terms of comorbidities and risk factors for disease progression. These factors make large-scale comparative studies of multiple ROP treatment modalities very challenging, as evidenced by the paucity of high-quality RCTs to date. In this study, we demonstrate the power of NMA to help overcome these practical challenges by combining the clinical data from 30 studies involving a total of 4686 eyes. This study focused on the rate of retreatment for ROP reactivation, persistence, or progression as the outcome measure, since this rate is clinically highly relevant and it is possible to apply objective inclusion criteria across all studies. Our criteria for retreatment excluded eyes that received secondary treatment solely for laser-skipped area or persistent avascular retina in the absence of ROP reactivation. Given the current pattern of clinical practice where anti-VEGF injection may be preferred to laser for posterior (Zone I or posterior Zone II) ROP, we first compared the retreatment rates of the 3 common anti-VEGF agents and laser treatment for all type 1 ROP, and then we separately performed a similar analysis for Zone I ROP only. Moreover, we performed the traditional frequentist meta-analysis of proportions to explore retreatment rates for each treatment modality individually before proceeding to a Bayesian NMA approach to investigate relative risks of one treatment against another.

Our results suggest that laser treatment of type 1 ROP is associated with a lower risk of retreatment than ranibizumab (62% reduction in risk of retreatment) (Grading of Recommendations, Assessment, Development and Evaluation assessment: low to medium certainty of evidence). This finding is consistent with recent systematic reviews showing that laser treatment is associated with a lower likelihood of ROP reactivation and additional treatment but may be confounded by treatment-selection bias for posterior disease.[13,63] In addition, it should be noted that the treatment burden on the infant undergoing repeat intravitreal injections of ranibizumab under local anesthesia (e.g., for disease reactivation) is not clinically equivalent to retreatment with laser under sedation or general anesthesia (e.g., for failure to regress because of skipped areas), but these important qualitative differences are not easily borne out through meta-analyses. While there was no statistically significant difference among the 3 anti-VEGF agents themselves, a cursory view of rankings (which do not consider CrIs) revealed bevacizumab ranked first, followed by aflibercept second and ranibizumab last, in terms of retreatment rates. To some extent, this ranking may reflect differences in the intraocular half-lives of the drugs.[8] Previous studies have hypothesized that

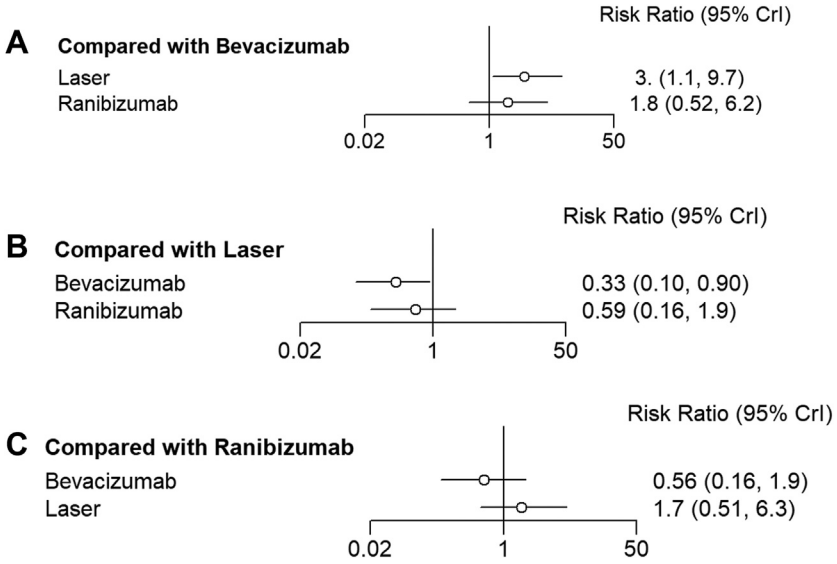


**Figure 4.** Forest plots of network meta-analysis of risk of retreatment following primary therapy with anti-vascular endothelial growth factor (VEGF) agents or laser in Zone I retinopathy of prematurity. In each panel, 2 treatment modalities (treatment 1, shown in regular font) were compared against a reference treatment modality (treatment 2, shown in bold type) which may be **A,** bevacizumab; **B,** laser; or **C,** ranibizumab. Risk ratio < 1 means that the risk of requiring retreatment is lower with treatment 1 than with treatment 2. 95% CrI = 95% credible interval.

ranibizumab may be associated with a higher reactivation rate than bevacizumab because of its shorter half-life.[48,57,64,65] By the same logic, aflibercept might be expected to provide a lower risk of reactivation because of its longer intraocular half-life than the other 2 anti-VEGF agents and ability to bind both VEGF-A and -B.[66,67] However, our results did not demonstrate this to be the case, despite adequate power as judged by sunset power-enhanced funnel plots (Fig S1A, available at www.aaojournal.org).

It should also be noted that while a ranking of anti-VEGF agents by retreatment rates may be appealing in order to minimize the probability of needing a secondary laser procedure under general anesthesia in vulnerable infants, it needs to be balanced against differences in systemic half-lives among the drugs. The mean ± SD serum half-lives after intravitreal administration of aflibercept, bevacizumab, and ranibizumab are 11.4 ± 4.8 days, 18.7 ± 5.8 days, and 5.8 ± 1.8 days, respectively.[8]

In terms of timing of any ROP retreatment, retreatments generally occurred earlier following intravitreal ranibizumab (mean ± SD: 9.29 ± 4.47 weeks) than after bevacizumab (11.36 ± 4.31weeks) or aflibercept (12.96 ± 2.24weeks). The smaller SD for aflibercept may indicate that the timing of any ROP reactivation is more "predictable" than those associated with ranibizumab or bevacizumab, but further validation is required. These findings could help to optimize clinical monitoring intervals for each treatment modality and to plan secondary procedures such as examination under anesthesia and secondary laser treatment.

In contrast to type 1 ROP, we found that primary bevacizumab was associated with a 67% reduction in rate of retreatment than laser in Zone I ROP. Comparison of ranibizumab against laser treatment tentatively suggests that ranibizumab may also be associated with a lower retreatment rate, but the results did not reach statistical significance (with credible interval crossing the relative risk = 1 equivalence value). The sunset power-enhanced plot (Fig S1B, available at www.aaojournal.org) showed there was very high power across all studies reflecting a very high summary effect size for all treatment options, which minimizes the possibility of type 2 errors. Therefore, results that show no statistical differences are likely due to no differences rather than insufficient data. Among the 2 anti-VEGF agents, bevacizumab may be associated with a marginally lower retreatment rate than ranibizumab for Zone I ROP, although the threshold for statistical significance for this pairwise comparison was not reached (Fig 4A). Consistent with our findings, the BEAT-ROP trial was the first major RCT to establish bevacizumab as superior to laser for the treatment of ROP in Zone I or posterior Zone II in terms of lower rate of reactivation requiring retreatment.[6] The proposed mechanistic rationale is that intravitreal anti-VEGF provides a more rapid reduction in VEGF drive than laser treatment in aggressive or rapidly progressing posterior ROP.[68] While bevacizumab is still widely used around the world as off-label treatment for ROP, ranibizumab is currently the only approved pharmacological therapy for ROP based on the RAINBOW study.[8]

While potential systemic developmental side effects of intraocular anti-VEGF therapies are beyond the scope of this analysis, they may be a relevant consideration that influences treatment choice. It may be speculated that ranibizumab, with a shorter half-life of 7.19 days in nonvitrectomized human eye in comparison with 9.82 days

for bevacizumab, could have fewer side effects.[9,69–72] Therefore, the greater retreatment rate found in ranibizumab-treated eyes may be offset by the possibility of fewer systemic effects. Whether intravitreal anti-VEGFs can cause significant developmental impact is disputed. A recent study demonstrated no significant difference in developmental delay between 5-year-olds who had been treated with laser and those who received bevacizumab.[36] Further studies comparing the long-term developmental outcomes following different anti-VEGF treatments for ROP are needed.

This NMA has a number of limitations. There was high heterogeneity among studies. This is an expected feature when incorporating nonrandomized studies into a meta-analysis of proportions. We sought to minimize this by using a random-effects model for the meta-analysis, and we explored the effects of GA, BW, and PMA at treatment as potential moderators. A thorough search for potential sources of heterogeneity was also conducted. Overall, we believe, based on the criteria outlined in "Methods," transitivity was preserved among the included studies, despite high statistical heterogeneity. A high level of heterogeneity may also impact the summary effect size used in the calculation of the power of individual studies. We ensured that the doses of anti-VEGF drugs were similar for the purpose of fair comparisons. However, there has been a recent shift toward using smaller doses than those commonly cited in the literature, with the rationale to minimize systemic side effects.[73] Data from nonrandomized cohort studies were combined with RCTs for the purpose of the NMA. While this approach could introduce bias, several recent studies have found it acceptable on the basis of thoughtful inclusion and open assessment of bias, as we made sure to carry out in this study.[74] Only higher quality, consecutive, nonrandomized data with comparable methods and treatment criteria were included. A further limitation of this study arose because of the paucity of data on aflibercept for ROP. We extracted recently released data from the FIREFLEYE RCT (aflibercept vs. laser) from ClinicalTrials.gov on the assumption that infants were treated bilaterally; therefore, the results should be taken with caution. While this is a limitation, small inaccuracies within this data set are unlikely to significantly impact the overall conclusions of the meta-analyses. Any discussion of the ranking of different anti-VEGF agents should be viewed with caution, as there were considerable overlaps between the credible intervals for primary success rates of the 3 anti-VEGF agents. Therefore, we primarily presented the data in informative comparative forest plots and relative-effect tables rather than rank-probability plots.[75]

## Conclusions

We present a network meta-analysis comparing primary bevacizumab, ranibizumab, aflibercept, and laser treatment for type 1 and Zone I ROP. The results indicate that laser is associated with significantly reduced risk of requiring retreatment in type 1 ROP compared with ranibizumab (62% reduced risk). Pairwise comparisons between other anti-VEGF agents did not yield statistically significant differences in terms of mean retreatment rate, but aflibercept (12.96 weeks) and bevacizumab (11.36 weeks) were associated with significantly longer time to secondary treatment than ranibizumab (9.29 weeks). For Zone I ROP, bevacizumab is associated with significantly reduced risk of requiring retreatment compared with laser treatment (67% reduced risk). We note that another RCT, BUTTERFLEYE,[11] comparing aflibercept versus laser treatment is yet to submit results, which would further expand the data set. Comparison of outcomes with different doses of each anti-VEGF agent could further refine clinical management. Other emerging anti-VEGF agents, such as brolucizumab and conbercept,[76] may also contribute to the diversity of therapeutic options available for treating ROP in the future.

## Footnotes and Disclosures

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No animal subjects were used in this study.

Author Contributions:

Conception and design: Chang, Josan, Purohit, Patel, Xue

Data collection: Chang, Purohit

Analysis and interpretation: Chang, Josan, Purohit, Patel, Xue

Obtained funding: Xue

Overall responsibility: Xue

Abbreviations and Acronyms:
**BW** = birth weight; **CI** = confidence interval; **CrI** = credible interval; **GA** = gestational age; **NMA** = network meta-analysis; **PMA** = postmenstrual age; **RCT** = randomized controlled trial; **ROP** = retinopathy of prematurity; **SD** = standard deviation; **SEM** = standard error of the mean; **VEGF** = vascular endothelial growth factor.

Keywords:
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## References

1. National Eye Institute, National Institutes of Health. Retinopathy of prematurity. https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinopathy-prematurity. Accessed September 17, 2021.
2. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev*. 2008;84:77−82.
3. Good WV, Flynn JT, Flach AJ, et al. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc*. 2004;102:233−250.
4. Hartnett ME. Pathophysiology and mechanisms of severe retinopathy of prematurity. *Ophthalmology*. 2015;122:200−210.
5. Jiang JB, Strauss R, Luo XQ, et al. Anaesthesia modalities during laser photocoagulation for retinopathy of prematurity: a retrospective, longitudinal study. *BMJ Open*. 2017;7:e013344.
6. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med*. 2011;364:603−615.
7. Pertl L, Steinwender G, Mayer C, et al. A systematic review and meta-analysis on the safety of vascular endothelial growth factor (VEGF) inhibitors for the treatment of retinopathy of prematurity. *PLoS One*. 2015;10:e0129383.
8. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmarcokinetics and pharmacodynamics of intravitreal aflibercept, bevacizumab, and ranibizumab. *Retina*. 2017;37:1847−1858.
9. Stahl A, Lepore D, Fielder A, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet*. 2019;394:1551−1559.
10. Fleck BW, Reynolds JD, Zhu Q, et al. Time course of retinopathy of prematurity regression and reactivation after treatment with ranibizumab or laser in the RAINBOW trial. *Ophthalmol Retina*. 2022;6:628−637.
11. Regeneron Pharmaceuticals. Study to assess the efficacy, safety, and tolerability of intravitreal aflibercept compared to laser photocoagulation in patients with retinopathy of prematurity (BUTTERFLEYE). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04101721. Accessed September 10, 2021.
12. Bayer, Regeneron Pharmaceuticals. Aflibercept for retinopathy of prematurity—intravitreal injection versus laser therapy (FIRFLEYE). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04004208. Accessed March 22, 2022.
13. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. *Cochrane Database Syst Rev*. 2018;1:CD009734.
14. Sato T, Wada K, Arahori H, et al. Serum concentrations of bevacizumab (Avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. *Am J Ophthalmol*. 2012;153:327−333.e1.
15. Hong YR, Kim YH, Kim SY, et al. Plasma concentrations of vascular endothelial growth factor in retinopathy of prematurity after intravitreal bevacizumab injection. *Retina*. 2015;35:1772−1777.
16. Hoerster R, Muether P, Dahlke C, et al. Serum concentrations of vascular endothelial growth factor in an infant treated with ranibizumab for retinopathy of prematurity. *Acta Ophthalmol (Copenh)*. 2013;91:e74−e75.
17. Wu WC, Lien R, Liao PJ, et al. Serum levels of vascular endothelial growth factor and related factors after intravitreous bevacizumab injection for retinopathy of prematurity. *JAMA Ophthalmol*. 2015;133:391−397.
18. Bazvand F, Riazi-Esfahani H, Mirshahi A, et al. Ocular complications following intravitreal bevacizumab injection for retinopathy of prematurity and assessment of risk factors. *Int J Retina Vitreous*. 2021;7:1−8.
19. Quinn GE, Darlow BA. Concerns for development after bevacizumab treatment of ROP. *Pediatrics*. 2016;137:e20160057.
20. Rouse B, Chaimani A, Li T. Network meta-analysis: An introduction for clinicians. *Intern Emerg Med*. 2017;12:103−111.
21. Chaimani A, Caldwell DM, Li T, et al. Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al (eds). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). *Cochrane*; 2022. http://www.training.cochrane.org/handbook.
22. Furukawa TA, Salanti G, Atkinson LZ, et al. Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. *BMJ Open*. 2016;6:e010919.
23. Early Treatment For Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003;121:1684−1694.
24. Chiang MF, Quinn GE, Fielder AR, et al. International Classification of Retinopathy of Prematurity, Third Edition. *Ophthalmology*. 2021;128:e51−e68.
25. Mori Y, Arima M, Ueda E, et al. Risk factors for myopia at 1-year corrected age following laser photocoagulation for retinopathy of prematurity. *Eye*. 2020;35:2820−2825.
26. R Core Team. R: A Language and Environment for Statistical Computing. 2021 https://www.R-project.org/. Accessed March 31, 2022.
27. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36:1−48.
28. Barker TH, Migliavaca CB, Stein C, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. *BMC Med Res Methodol*. 2021;21:189.
29. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods*. 2019;10:476−483.
30. Kossmeier M, Tran US, Voracek M. Power-enhanced funnel plots for meta-analysis: the sunset funnel plot. *Zeitschrift für Psychologie*. 2020;228:43−49.

31. van Valkenhoef G, Kuiper J. gemtc: Network Meta-Analysis Using Bayesian Methods, version 1.0−1, from CRAN. https://rdrr.io/cran/gemtc/. Accessed September 17, 2021.
32. van Valkenhoef G, Kuiper J. Package "gemtc": Network Meta-Analysis Using Bayesian Methods. May 15, 2021. https://cran.r-project.org/web/packages/gemtc/gemtc.pdf
33. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
34. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 17, 2021.
35. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PLoS One*. 2014;9:e99682.
36. Murakami T, Sugiura Y, Okamoto F, et al. Comparison of 5-year safety and efficacy of laser photocoagulation and intravitreal bevacizumab injection in retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol*. 2021;259:2849−2855.
37. Zayek M, Parker K, Rydzewska M, et al. Bevacizumab for retinopathy of prematurity: 2-year neurodevelopmental follow-up. *Am J Perinatol*. 2021;38:1158−1166.
38. Demir ST, Güven D, Karapapak M, et al. Evaluation of treatment models in the treatment of retinopathy of prematurity. *Sisli Etfal Hastan Tip Bul*. 2019;53:290−295.
39. Chen TA, Schachar IH, Moshfeghi DM. Outcomes of intravitreal bevacizumab and diode laser photocoagulation for treatment-warranted retinopathy of prematurity. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49:126−131.
40. Mueller B, Salchow DJ, Waffenschmidt E, et al. Treatment of type I ROP with intravitreal bevacizumab or laser photocoagulation according to retinal zone. *Br J Ophthalmol*. 2017;101:365−370.
41. Nicoară SD, Ştefănuţ AC, Nascutzy C, et al. Regression rates following the treatment of aggressive posterior retinopathy of prematurity with bevacizumab versus laser: 8-year retrospective analysis. *Med Sci Monit*. 2016;22:1192−1209.
42. Hwang CK, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: a 5-year retrospective analysis. *Ophthalmology*. 2015;122:1008−1015.
43. Kong L, Dinh KL, Schechet SA, et al. Comparison of ocular and developmental outcomes in laser and bevacizumab-treated infants with retinopathy of prematurity. *Ophthalmol Res*. 2015;3:13−22.
44. Isaac M, Mireskandari K, Tehrani N. Treatment of type 1 retinopathy of prematurity with bevacizumab versus laser. *JAAPOS*. 2015;19:140−144.
45. Chmielarz-Czarnocińska A, Pawlak M, Szpecht D, et al. Management of retinopathy of prematurity (ROP) in a Polish cohort of infants. *Sci Rep*. 2021;11:4522.
46. Lyu J, Zhang Q, Chen C, et al. Ranibizumab injection and laser photocoagulation to treat type 1 retinopathy of prematurity after 40 weeks post menstrual age: a retrospective case series study. *BMC Ophthalmol*. 2019;19:60.
47. Leng Y, Huang W, Ren G, et al. The treatment and risk factors of retinopathy of prematurity in neonatal intensive care units. *BMC Ophthalmol*. 2018;18:301.
48. Zhang G, Yang M, Zeng J, et al. Comparison of intravitreal injection of ranibizumab versus laser therapy for zone II treatment-requiring retinopathy of prematurity. *Retina*. 2017;37:710−717.
49. Chan JJT, Lam CPS, Kwok MKM, et al. Risk of recurrence of retinopathy of prematurity after initial intravitreal ranibizumab therapy. *Sci Rep*. 2016;6:27082.
50. Ekinci DY, Çelik K. Comparison of the efficacy between intravitreal aflibercept and laser photocoagulation in the treatment of retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus*. 2020;57:54−60.
51. Ling KP, Liao PJ, Wang NK, et al. Rates and risk factors for recurrence of retinopathy of prematurity after laser or intravitreal anti-vascular endothelial growth factor monotherapy. *Retina*. 2020;40:1793−1803.
52. Kabataş EU, Kurtul BE, Altıaylık Özer P, Kabataş N. Comparison of intravitreal bevacizumab, intravitreal ranibizumab and laser photocoagulation for treatment of type 1 retinopathy of prematurity in Turkish preterm children. *Curr Eye Res*. 2017;42:1054−1058.
53. Gunay M, Sukgen EA, Celik G, Koçluk Y. Comparison of bevacizumab, ranibizumab, and laser photocoagulation in the treatment of retinopathy of prematurity in Turkey. *Curr Eye Res*. 2017;42:462−469.
54. Chen YC, Chen SN, Yang BCL, et al. Refractive and biometric outcomes in patients with retinopathy of prematurity treated with intravitreal injection of ranibizumab as compared with bevacizumab: a clinical study of correction at three years of age. *J Ophthalmol*. 2018;2018:4565216.
55. Kang HG, Choi EY, Byeon SH, et al. Anti-vascular endothelial growth factor treatment of retinopathy of prematurity: efficacy, safety, and anatomical outcomes. *Korean J Ophthalmol*. 2018;32:451−458.
56. Kimyon S, Mete A. Comparison of bevacizumab and ranibizumab in the treatment of type 1 retinopathy of prematurity affecting zone 1. *Ophthalmologica*. 2018;240:99−105.
57. Erol MK, Coban DT, Sari ES, et al. Comparison of intravitreal ranibizumab and bevacizumab treatment for retinopathy of prematurity. *Arq Bras Oftalmol*. 2015;78:340−343.
58. Wong RK, Hubschman S, Tsui I. Reactivation of retinopathy of prematurity after ranibizumab treatment. *Retina*. 2015;35:675−680.
59. Sukgen EA, Koçluk Y. Comparison of clinical outcomes of intravitreal ranibizumab and aflibercept treatment for retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol*. 2019;257:49−55.
60. Riazi-esfahani H, Mahmoudi A, Sanatkar M, et al. Comparison of aflibercept and bevacizumab in the treatment of type 1 retinopathy of prematurity. *Int J Retina Vitreous*. 2021;7:60.
61. Süren E, Özkaya D, Çetinkaya E, et al. Comparison of bevacizumab, ranibizumab and aflibercept in retinopathy of prematurity treatment. *Int Ophthalmol*. 2022;42:1905−1913.
62. Adams GGW, Bunce C, Xing W, et al. Treatment trends for retinopathy of prematurity in the UK: active surveillance study of infants at risk. *BMJ Open*. 2017;7:13366.
63. Popovic MM, Nichani P, Muni RH, et al. Intravitreal anti-vascular endothelial growth factor injection versus laser photocoagulation for retinopathy of prematurity: a meta-analysis of 3,701 eyes. *Surv Ophthalmol*. 2021;66:572−584.
64. Alyamaç Sukgen E, Çömez A, Koçluk Y, Cevher S. The process of retinal vascularization after anti-VEGF treatment in retinopathy of prematurity: a comparison study between ranibizumab and bevacizumab. *Ophthalmologica*. 2016;236:139−147.
65. Lin C-J, Chen S-N, Hwang J-F. Intravitreal ranibizumab as salvage therapy in an extremely low-birth-weight infant with rush type retinopathy of prematurity. *Oman J Ophthalmol*. 2012;5:184−186.
66. Stewart MW, Rosenfeld PJ, Penha FM, et al. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with

intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina*. 2012;32:434–457.

67. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*. 2012;15:171–185.
68. VanderVeen DK, Melia M, Yang MB, Hutchinson AK, Wilson LB, Lambert SR. Anti-vascular endothelial growth factor therapy for primary treatment of type 1 retinopathy of prematurity: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2017;124:619–633.
69. Krohne TU, Eter N, Holz FG, Meyer CH. Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans. *Am J Ophthalmol*. 2008;146:508–512.
70. Krohne TU, Liu Z, Holz FG, Meyer CH. Intraocular pharmacokinetics of ranibizumab following a single intravitreal injection in humans. *Am J Ophthalmol*. 2012;154:682–686.e2.
71. Stahl A, Krohne TU, Eter N, et al. Comparing alternative ranibizumab dosages for safety and efficacy in retinopathy of prematurity: a randomized clinical trial. *JAMA Pediatr*. 2018;172:278–286.
72. Kong L, Bhatt AR, Demny AB, et al. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2015;56:956–961.
73. Wallace DK, Kraker RT, Freedman SF, et al. Assessment of lower doses of intravitreous bevacizumab for retinopathy of prematurity: a phase 1 dosing study. *JAMA Ophthalmol*. 2017;135:654–656.
74. Cameron C, Fireman B, Hutton B, et al. Network meta-analysis incorporating randomized controlled trials and non-randomized comparative cohort studies for assessing the safety and effectiveness of medical treatments: challenges and opportunities. *Syst Rev*. 2015;4:147.
75. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Syst Rev*. 2017;6:79.
76. Wu Z, Zhao J, Lam W, et al. Comparison of clinical outcomes of conbercept versus ranibizumab treatment for retinopathy of prematurity: a multicentral prospective randomised controlled trial. *Br J Ophthalmol*. 2021;0:975–979.