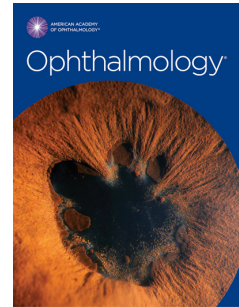


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A Network Meta-Analysis of Retreatment Rates following Bevacizumab, Ranibizumab, Aflibercept and Laser for Retinopathy of Prematurity

Emer T Chang¹, Amandeep S Josan^{1,2}, Ravi Purohit¹, Chetan K Patel^{1,3}, Kanmin Xue^{1,2,*}

¹Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

²Nuffield Laboratory of Ophthalmology, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

³Ophthalmology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

*Correspondence: Kanmin Xue, Nuffield Department of Clinical Neurosciences, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK

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This article contains additional online-only material (<http://www.aaojournal.org>). The following should appear online-only: Supplementary Tables S1- S4, Supplementary Figure S1- S5.

R code available at <https://github.com/amanasj/ROP-meta-analysis>

ABSTRACT

Topic: To compare bevacizumab, ranibizumab, aflibercept and laser 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 for randomised controlled trials and non-randomised comparative studies as of March 2022. We included studies that used bevacizumab, ranibizumab, aflibercept and laser for ROP with comparable cohorts and treatment criteria. Studies were evaluated by the GRADE framework and those with biased case selection, non-randomised case-control, or lack of control group were excluded. Frequentist meta-analyses of proportions were performed to determine the absolute primary retreatment rate of each modality followed by Bayesian network meta-analyses to compare pairs of treatments in Type 1 and Zone I ROP.

Results: 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% CI: 83.8-93.8; n=1552) for laser, 87.0% (78.6-93.8; n=2081) for bevacizumab, 80.7% (62.0-94.4; n=326) for aflibercept, and 74.0% (62.7-84.1; n=727) for ranibizumab. Bayesian network meta-analysis indicates that laser is associated with a significant 62% (95% CrI: 16-83) reduction in retreatment risk compared with ranibizumab, while no significant differences were found between other pair-wise comparisons. The mean time to secondary treatment following primary aflibercept (12.96 weeks \pm 0.47 SEM) and bevacizumab (11.36 \pm 0.54) were significantly longer than primary ranibizumab (9.29 \pm 0.43) therapy (p=7E-07 and p=9E-03 respectively). For Zone I ROP, single treatment success rates were 91.2% (83.6-96.9; n=231) for bevacizumab, 78.3% (61.4-91.9; n=100) for ranibizumab, and 65.9% (41.4-87.2; n=158) for laser. In this case, Bayesian network meta-

analysis suggests that primary bevacizumab is associated with a significant 67% (10-90) reduction in retreatment risk compared with laser. No moderating effects were found to arise from gestational age, birth weight, or post-menstrual age at treatment when considering each modality in isolation using a frequentist approach.

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 lower rate of retreatment than laser in Zone I ROP. Aflibercept and bevacizumab demonstrate longer duration of action than ranibizumab for ROP.

INTRODUCTION

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 neovascularisation in areas of avascular retina leading to retinal detachment.¹ In developed countries ROP now occurs mostly in extreme low birthweight and low gestation infants.²

The decision to treat ROP is based on clinical appearance of retinal vasculature, defined by location (Zone), severity (Stage), and 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 could sometimes progress despite treatment and side effects of ablative therapy include reduced field of vision³ and myopia⁴, although there is debate as to how much of the latter may be related to severity of disease itself. Furthermore, real-world limitations of laser therapy include the requirement for general anaesthesia 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 (HIF1 α) have been established in the pathogenesis of ROP.⁴ This, combined with results of

the BEAT-ROP trial⁶ in 2011 supporting use of 0.625mg intravitreal bevacizumab (Avastin) for posterior ROP (aggressive posterior ROP and Zone I disease), has led to increased utilization of anti-VEGF agents as primary treatment for ROP. Furthermore, anti-VEGF treatment is associated with lower likelihood of visual field defects and high myopia compared with laser.⁷

Bevacizumab is an anti-angiogenic humanised monoclonal antibody (149 kDa) that blocks VEGF-A. Ranibizumab (Lucentis) is a monoclonal antibody fragment (Fab, 48kDa) derived from the same parent antibody as bevacizumab. The intraocular half-life of bevacizumab in non-vitrectomised human eyes has been estimated at 9.8 days compared with 7.2 days for ranibizumab.⁸ The RAINBOW trial showed that 0.2mg of intravitreal ranibizumab was as effective as, and possibly superior to, laser 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 IgG1. 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 RCTs.^{11,12}

Whilst anti-VEGFs have less effect on eye growth compared with laser, they can be associated with late ROP reactivation which requires retreatment (often with laser photocoagulation under general anaesthesia)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 while head-to-head comparisons between different anti-VEGF agents are lacking, particularly in terms of high quality RCTs. Moreover, many existing studies have 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. The latter has very significant clinical implications on the long-term monitoring regime and potential requirement for general anaesthesia

(e.g. for secondary laser) in neonates with complex co-morbidities. Herein, we performed a network meta-analysis (NMA) to fully utilise 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 The NMA summarises RCTs and non-randomised comparative studies of several different treatments by providing point estimates for their association with a given endpoint and estimate how well the entire network fits together (inconsistency).²⁰ Network meta-analyses have been used successfully in other fields of medicine to overcome the challenges of complex multi-arm RCTs and impractically large sample sizes required for comparing multiple alternative treatments for the same condition.²¹ This is the first NMA to compare the effectiveness of the three 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 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 Cochrane Central Register of Controlled Trials, CINAHL, Embase, PubMed via Medline from the date of their 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 three anti-VEGF agents.

Predefined eligibility criteria for evidence inclusion were as follows: (i) randomised controlled trials (RCTs) or non-randomised studies; (ii) studies of premature infants with Type 1 ROP as defined by the Early Treatment of ROP (ETROP) study²²; (iii) studies compared the anti-VEGF agents with laser or another anti-VEGF agent as monotherapy for Type 1 ROP. We defined retreatment as any eyes that received secondary treatment due to (i) reactivation of ROP in keeping with ICROP3 criteria²³ (i.e. disease regression followed by reappearance of pre-plus or plus disease, extraretinal new vessels and/or fibrovascular ridge); (ii) persistent ROP (any stage) or failure to regress; or (iii) progression of ROP severity despite treatment. Two eyes (of one infant) were included for laser retreatment of abnormal vascular hyper-permeability following bevacizumab monotherapy, which we interpreted as a case of ROP reactivation.²⁴ We did not include eyes retreated solely for laser skipped areas or persistent avascular retina as these represent subjective treatment choices which remain controversial and do not fulfil ICROP3 criteria for ROP reactivation. Other reasons for exclusion were (i) studies with unreported outcomes, (ii) studies that did not report ROP retreatment rates, and (iii) sub-groups 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 non-randomised 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 gestational age, birth weight, 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, 0.4-1.0mg in 0.01-0.025ml of aflibercept), and 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 versus laser) by extracting data reported on

ClinicalTrials.gov which 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 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 impact on the overall conclusions.

Data extraction

For each included study, we extracted the population characteristics (gestational age (GA), birth weight (BW) and post-menstrual 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 likelihood of bias towards selecting anti-VEGF over laser for posterior ROP (e.g. Zone I or posterior Zone II disease) in non-randomised 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.

Data analysis

Frequentist meta-analyses of proportions

All statistical analysis was performed in R (Version 4.0.5).²⁵ We used a conventional frequentist meta-analysis of proportions (R-package: metafor v3.0.2²⁶) to calculate dichotomous outcome measures (number of eyes requiring retreatment). 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 (CI) 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 dataset, a Freeman-Tukey double arcsine transformation is effective at normalising for situations where extreme values for incidence rates exist and is also effective at stabilising the variances.²⁷ Questions do arise 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 dataset sample sizes are well within the upper limits where issues of back transformational errors are likely to occur.²⁸ A random effects model was used for these meta-analyses. We created the sunset power-enhanced funnel plot with metaviz²⁹ to visualise the statistical power of each study contained in the analysis using the lower bound of the overall summary effect size derived from the frequentist analysis.

Bayesian network meta-analyses

Transitivity is a key underlying assumption of network meta-analysis – the model assumes that retrospective studies are of high quality (i.e. did not compare two 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 network meta-analysis and meta-regression using the R-package, gemtc v1.0.1,^{30,31} to compare relative effect sizes of bevacizumab, ranibizumab, aflibercept and laser 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. This model simulates, using Markov Chain Monte Carlo (MCMC) 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, vague priors and ended the simulation only once we ensured model convergence after running four chains. 200,000 iterations were used in total, discarding all but every 10th iteration as commonly performed for thinning purposes. The first 8,000 iterations were disregarded, and the remaining 192,000 iterations used to estimate the parameters.

Convergence of models was ensured by visual inspection of the four Markov chains and after considering the Gelman-Rubin-Brooks plots. Statistical evaluation of 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 consistency of the network meta-analysis. The full R code details of the conventional frequentist meta-analysis of proportions and Bayesian network meta-analysis along with meta-regression models is 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 tool³² to assess risk of bias based on the following domains: randomisation, blinding 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 non-randomised comparative studies, we used the Newcastle-Ottawa scale.³³ 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 non-randomised comparative studies acceptable follow-up was set to

at least six 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 (GRADE) framework was used to assess the quality and certainty of evidence for the primary outcome.³⁴ 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 two independent investigators (EC and RP).

Comparison of time to retreatment following primary anti-VEGF therapy

We collected the mean (+/- standard deviation) time to secondary treatment following primary anti-VEGF therapy from the included studies where data is 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's ANOVA test on these combined summary means and Games-Howell post hoc test to find which treatment pairs were statistically different. Normality using Shapiro-Wilk test on residuals and homogeneity of variances using Levene's test were employed to validate our choice of statistical tests.

RESULTS

Literature search

800 records were retrieved during the initial electronic database search, of which 30 studies were included in the meta-analysis (**Figure 1**).^{6,10,12,24,35-60} 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), non-comparative studies (8), repeated cohort in follow-up studies (17), non-peer

reviewed conference abstracts (1) and non-conventional follow up (1). The 30 included studies consisted of 4 RCTs and 26 retrospective consecutive cohorts (**Table 1**). 11 studies comparing bevacizumab with laser therapy,^{6,24,35–43} 6 studies comparing ranibizumab with laser,^{10,44–48} 5 studies comparing bevacizumab with ranibizumab,^{53–57} 3 studies comparing bevacizumab, ranibizumab and laser,^{50–52} 2 studies comparing aflibercept with laser,^{12,49} 1 study comparing ranibizumab and aflibercept,⁵⁸ 1 study compared bevacizumab and aflibercept and 1 study compared bevacizumab, ranibizumab, aflibercept.⁶⁰ 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 (**Supplementary Table S1** available at <http://www.aaojournal.org>). There were some concerns of bias for RCTs due to lack of reporting/absent: (i) allocation sequence concealment until participants were assigned to interventions; (ii) intention-to-treat analysis; and (iii) pre-specified analysis plan finalised before outcome data collected. Most non-randomised studies had a low risk of bias (**Supplementary Table S2** available at <http://www.aaojournal.org>). Moderate risk of bias in some non-randomised studies were due to: (i) lack of demonstration that patients who had been received any previous treatments before intravitreal injections were excluded; and (ii) no adjusting relative risk for confounders (i.e. age). Hence the overall quality of evidence for retreatment rate due to ROP reactivation, persistence and/or progression is moderate.

Heterogeneity

There was significant ($p < 0.05$) heterogeneity in the studies reporting 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 seen between studies are beyond those attributable to chance/random sampling. Hence, we assume that there is a distribution of true effect sizes for each treatment. This distribution is simulated in the Bayesian network meta-analysis.

Small study publication bias

For Type 1 ROP data, visual inspection of funnel plots showed no obvious asymmetry and Egger's 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 are reported rather than pairwise comparisons. It is likely 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.²⁷ The sunset power-enhanced funnel plots show the power of each study contained in Type 1 ROP analysis and Zone I ROP analysis was high ($>92\%$ and $>83\%$, respectively) (**Supplementary Figure S1A and B**, at <http://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 follow up minimum 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% (62.7-84.1), 80.7% (95% CI: 62.0-94.4) and 89.3% (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 ($n=326$).

282

283 **Bayesian network meta-analysis of anti-VEGF and laser treatment for Type 1 ROP**

284 **Figure 2A** and **2B** illustrate the network of eligible comparisons for Type 1 ROP and Zone I ROP,
285 respectively. Most of the data available enable comparisons between laser, bevacizumab and
286 ranibizumab as primary monotherapies for ROP. There is, however, relative paucity of data available
287 for aflibercept therapy in Zone I ROP to date. These networks were verified by MCMC validation
288 plots and inconsistency analysis which showed no evident of inconsistency. Further validation with
289 Gelman-Rubin-Brooks plots showed that the Potential Scale Reduction Factor (PSRF) is within
290 acceptable limits (<1.05).

291 A Bayesian network meta-analysis was performed to compare the risks of requiring retreatment
292 following primary bevacizumab, aflibercept, ranibizumab or laser for Type 1 ROP (**Figure 3**). This
293 showed that laser is associated with a significant 62% (95% credible intervals, CrI:16-83) reduction
294 in risk of needing retreatment compared to ranibizumab in Type 1 ROP (**Figure 3D**). In contrast, the
295 95% CrI of all other pairwise comparisons crossed $RR=1$, indicating there were no significant
296 differences between them.

297 **Time to retreatment following primary anti-VEGF therapy**

298 20 out of 30 included studies reported time to retreatment data (**Supplementary Table S4**). The
299 combined weighted mean time to retreatment for bevacizumab, ranibizumab and aflibercept are
300 plotted in **Supplementary Figure S5**. Combined mean time to secondary treatment following
301 primary anti-VEGF injections were 9.29 weeks (SEM=0.43, SD=4.47) for ranibizumab, 11.36 weeks
302 (SEM=0.55, SD=4.31) for bevacizumab, 12.96 weeks (SEM=0.47, SD=2.24) for aflibercept. Due to
303 unequal variances, we performed Welch's ANOVA test on these combined summary means and
304 found a p-value <0.0001 . A Games-Howell post hoc test demonstrated two statistically significant
305 differences: both aflibercept and bevacizumab were associated with longer time to retreatment than
306 ranibizumab ($p=7E-07$ and $p=9E-03$, respectively) (**Supplementary figure S5**).

307

308

309 **Assessment of gestational age, birth weight and post-menstrual age at treatment as potential**
310 **moderators for treatment outcome in Type 1 ROP**

311 **Frequentist meta-regression of proportions:** a meta-regression was performed on each individual
312 treatment modality to assess if the ROP retreatment rates were moderated or varied consistently
313 across the range of gestational ages, birth weights, and post-menstrual ages at primary treatment
314 within the studies. No association was found between retreatment rates and GA, BW or PMA at
315 treatment when considering individual treatments within a frequentist framework.

316

317 **Bayesian meta-regression:** The only treatment pair comparison to demonstrate statistically
318 significant moderating effect was between laser and ranibizumab. At low PMA (up to 35.6 weeks)
319 treatment with laser is associated with a statistically significant reduction in risk of requiring
320 retreatment than ranibizumab (**Supplementary Figure S2** available at <http://www.aaojournal.org>).
321 Between 25.8 to 26.7 weeks GA, laser is associated with a statistically significant reduction in risk of
322 requiring retreatment when compared to ranibizumab (**Supplementary Figure S3** available at
323 <http://www.aaojournal.org>). Between birth weights of 846 to 932 g, laser is associated with
324 significant reduction in risk of requiring retreatment when compared to ranibizumab
325 (**Supplementary Figure S4** available at <http://www.aaojournal.org>). All other treatment
326 comparisons yielded no statistically significant differences across the range of gestational ages, birth
327 weights or post-menstrual age at treatment.

328

329 **Efficacies of anti-VEGF agents and laser treatment for Zone I ROP**

330 To avoid potential treatment selection bias in posterior disease whereby anti-VEGF therapy might
331 be preferred to laser for posterior disease, we conducted a separate analysis on eyes with Zone I
332 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 non-randomised studies
(**Supplementary Table S3** available at <http://www.aaajournal.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. There was no data available for aflibercept.

Bayesian network meta-analysis 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 (**Figure 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 that undergo ROP screening.⁶¹ Significant variations exist between infants with ROP in terms of co-morbidities 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 network meta-analysis to help overcome these practical challenges by combining the clinical data from 30 studies involving 4686 eyes. This study focused on the rate of retreatment for ROP reactivation, persistence or progression as the outcome measure, since it is clinically highly relevant and 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 three common anti-VEGF agents and laser for all Type 1 ROP, and then separately performed 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 onto a Bayesian network meta-analysis approach to investigate relative risks of one treatment against another.

Our results suggest that laser treatment of Type 1 ROP is associated with lower risk of retreatment than ranibizumab (62% reduction in risk of retreatment) (GRADE assessment: low to medium certainty of evidence). This is consistent with recent systematic reviews showing that laser is associated with lower likelihood of ROP reactivation and additional treatment but may be confounded by treatment selection bias for posterior disease.^{13,62} In addition, it should be noted that the treatment burden on the infant undergoing repeat intravitreal injections of ranibizumab under local anaesthesia (e.g. for disease reactivation) is not clinically equivalent to retreatment with laser under sedation or general anaesthesia (e.g. for failure to regress due to skipped areas), but these important qualitative differences are not easily borne out through meta-analyses. Whilst there was no statistically significant difference amongst the three anti-VEGF agents themselves, a cursory view of rankings (which do not consider credible intervals) 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 intraocular half-lives of the drugs.⁸ Previous studies have hypothesised that ranibizumab may be associated with a higher reactivation rate than bevacizumab due to shorter half-life.^{47,63–65} By the same logic, aflibercept might be expected to provide lower risk of reactivation due to its longer intraocular half-life than the other two 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 (**Supplementary Figure S1A** available at <http://www.aaojournal.org>).

It should also be noted that while ranking of anti-VEGF agents by retreatment rates may be appealing in order to minimise the probability of needing secondary laser under general anaesthesia in vulnerable infants, it needs to be balanced against differences in systemic half-lives between the drugs. The 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, they generally occurred earlier following intravitreal ranibizumab (mean \pm SD: 9.29 ± 4.47 weeks) than with bevacizumab (11.36 ± 4.31 weeks) and aflibercept (12.96 ± 2.24 weeks). The smaller standard deviation 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 optimise clinical monitoring intervals for each treatment modality, and plan secondary procedures such as examination under anaesthesia 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 tentatively suggests that ranibizumab may also be associated with lower retreatment rate, but the results did not reach statistical significance (with credible interval crossing the RR=1 equivalence value). The sunset power-enhanced plot (**Supplementary Figure S1B** available at <http://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 two anti-VEGF agents, bevacizumab may be associated with marginally lower retreatment rate than ranibizumab for Zone I ROP, although the threshold for statistical significance for this pairwise comparison was not reached (**Figure 4A**). Consistent with our findings, the BEAT-ROP study 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 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 non-vitrectomised human eye in comparison to 9.82 days for bevacizumab could have fewer side effects.^{9,69–72} Therefore the greater retreatment rate seen 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 that had been treated with laser and those that received bevacizumab.³⁵ Further studies comparing the long-term developmental outcomes following different anti-VEGF treatments for ROP are needed.

The present network meta-analysis has a number of limitations. There was high heterogeneity among studies. This is an expected feature when incorporating non-randomised studies into a meta-analysis of proportions. We sought to minimise this by using a random effects model for the meta-analysis and 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 towards using smaller doses than those commonly cited in the literature with the rationale to minimise systemic side-effects.⁷³ Data from non-randomised cohort studies were combined with RCTs for the purpose of the network meta-analysis. Whilst 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 ensured to carry out in this study.⁷⁴ Only higher quality, consecutive non-randomised data with comparable methods and treatment criteria were included. A further limitation of this study arises due to the paucity of data on aflibercept for ROP. We extracted recently released data from the FIREFLEYE RCT (aflibercept versus laser) from *ClinicalTrials.gov* on the assumption that infants were treated bilaterally, therefore the results should be taken with caution. Whilst this is a limitation, small inaccuracies within this dataset are unlikely to significantly impact on overall conclusions of the meta-analyses. Any discussion on 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 three 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 the first 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). Pair-wise comparisons between other anti-VEGF agents did not yield statistically significant differences in terms of 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 than laser (67% reduced risk). We note that another RCT, BUTTERFLEYE¹¹, comparing aflibercept versus laser 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.

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671 **FIGURE LEGENDS**672 **Table 1. Characteristics of all studies included in the Type 1 ROP analysis.**

673

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

675

676 **Figure 2. Network meta-analysis of eligible comparisons for single treatment success rates**
677 **following anti-VEGF (bevacizumab, ranibizumab, aflibercept) or laser therapy for (A) Type 1**
678 **ROP and (B) Zone I ROP.** Width of lines are proportional to the number of studies comparing pairs
679 of treatment modalities.

680

681 **Figure 3. Forest plots of network meta-analysis of risk of retreatment following primary**
682 **therapy with anti-VEGF agents or laser in Type 1 ROP.** In each panel, three treatment modalities
683 (Treatment 1, shown in regular font) were compared against a reference treatment modality
684 (Treatment 2, shown in bold) which may be bevacizumab (A), aflibercept (B), laser (C), or
685 ranibizumab (D). Risk Ratio <1: risk of requiring retreatment is lower with Treatment 1 than
686 Treatment 2. 95% CrI: 95% credible intervals.

687

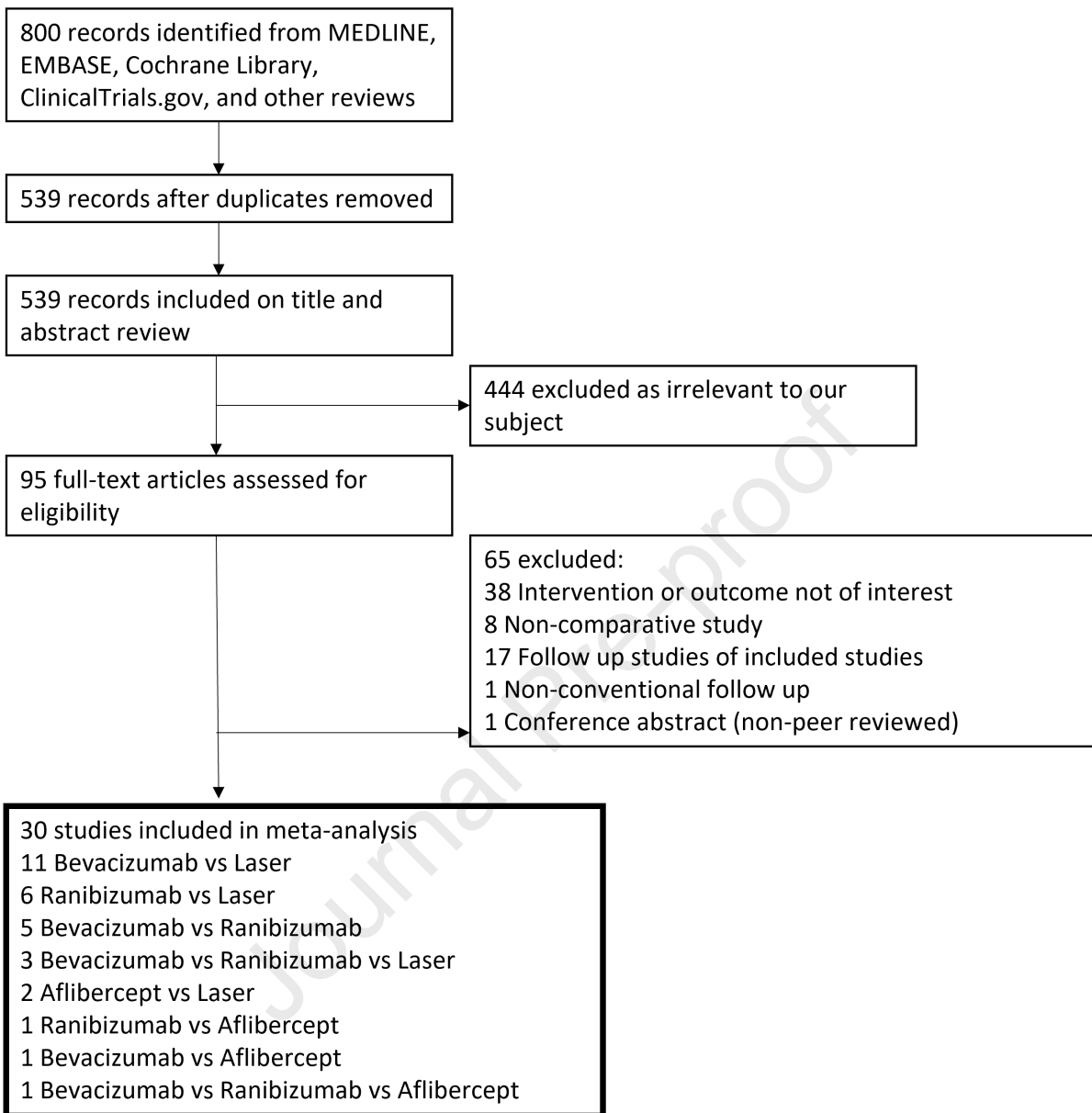
688 **Figure 4. Forest plots of network meta-analysis of risk of retreatment following primary**
689 **therapy with anti-VEGF agents or laser in Zone I ROP.** In each panel, two treatment modalities
690 (Treatment 1, shown in regular font) were compared against a reference treatment modality
691 (Treatment 2, shown in bold) which may be bevacizumab (A), laser (B), or ranibizumab (C). Risk
692 Ratio <1: risk of requiring retreatment is lower with Treatment 1 than Treatment 2. 95% CrI: 95%
693 credible intervals.

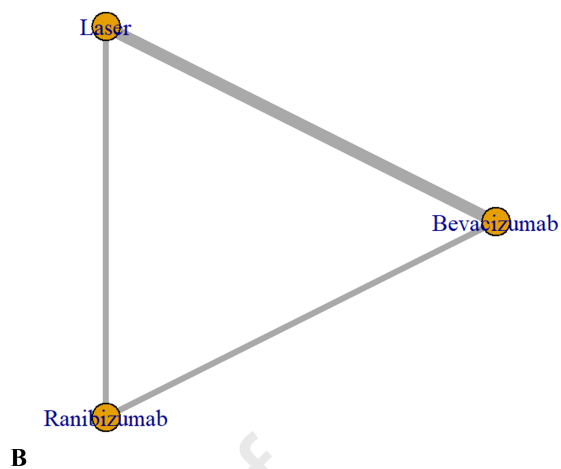
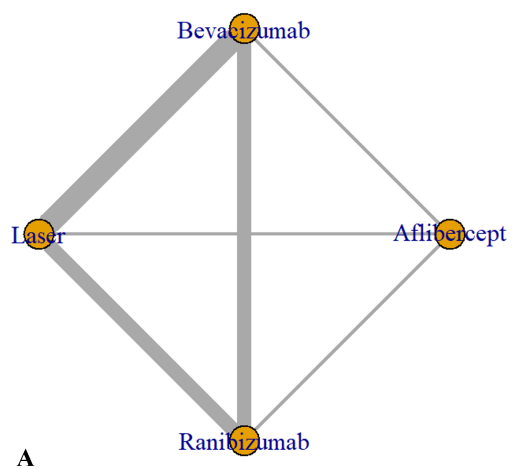
Study	Treatment type				Study design	Number of patients	Total number of eyes	Number of eyes receiving initial treatment				Number of eyes requiring re-treatment				Mean time between initial and 2nd treatment (weeks)				Reasons for re-treatment
	Bevacizumab	Ranibizumab	Aflibercept	Laser				IVB	IVR	IVA	Laser	IVB	IVR	IVA	Laser	IVB	IVR	IVA	Laser	
Murakami 2021	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	n/a	+ (4)
Zayek 2021	IVB (0.625mg/0.025mL)	n/a	n/a	laser	r	146	292	122	0	0	170	20	n/a	n/a	4	8	n/a	n/a	n/a	+ (12)
Mori 2020	IVB (0.625mg/0.025mL)	n/a	n/a	laser	r	66	132	26	0	0	106	12	n/a	n/a	8	n/a	n/a	n/a	n/a	NV(2), +(18)
Demir 2019	IVB(0.625 mg/0.025ml)	n/a	n/a	laser	r	65	121	57	0	0	64	9	n/a	n/a	17	2.9	n/a	n/a	n/a	NV (26)
Chen 2018a	IVB(0.625mg/0.025mL)	n/a	n/a	laser	r	25	49	29	0	0	20	28	n/a	n/a	2	19	n/a	n/a	n/a	1 Per (30)
Mueller 2017	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	12.7	n/a	n/a	n/a	Per(10)
Nicoara 2016	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	n/a	Per (5)
Hwang 2015	IVB (0.625mg/0.025ml)	n/a	n/a	laser	r	28	54	22	0	0	32	3	n/a	n/a	1	9	n/a	n/a	n/a	2.6 NV(1), +(2), Pro (1)
Kong 2015	IVB (0.625mg/0.025mL)	n/a	n/a	laser	r	42	80	43	0	0	37	3	n/a	n/a	4	8.86	n/a	n/a	n/a	6.93 + (3), Pro (4)
Isaac 2015	IVB (0.625mg/0.025mL)	n/a	n/a	laser	r	25	45	23	0	0	22	0	n/a	n/a	1	n/a	n/a	n/a	n/a	2 Per (1)
Mintz Hittner 2011	IVB(0.625mg/0.025mL)	n/a	n/a	laser	RCT	143	286	140	0	0	146	6	n/a	n/a	32	n/a	n/a	n/a	n/a	NV (38)
Fleck 2022	n/a	IVR (0.2 mg)	n/a	laser		142	284	0	146	0	138	n/a	40	n/a	34	n/a	6.9	n/a	n/a	2.3 + (25), Per(48)
Chmielarz -Czarnocińska 2021	n/a	IVR (0.25 mg/0.025 m)	n/a	laser	r	176	346	0	120	0	226	n/a	80	n/a	46	n/a	n/a	n/a	n/a	+ or Per (126)
Lyu 2019	n/a	IVR (0.25mg/0.025mL)	n/a	laser	r	14	27	0	17	0	10	n/a	2	n/a	3	n/a	n/a	n/a	n/a	Per(3), Pro(2)
Leng 2018	n/a	IVR (0.25mg)	n/a	laser	r	61	122	0	24	0	98	n/a	10	n/a	42	n/a	n/a	n/a	n/a	U(52)
Zhang 2017	n/a	IVR (0.3mg/0.03mL)	n/a	laser	RCT	50	100	0	50	0	50	n/a	26	n/a	2	n/a	8.27	n/a	n/a	+ (28)
Chan 2016	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	7.43	n/a	n/a	n/a	Per (5), U (3)
FIREFLEYE 2022	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	n/a	U(18)
Ekinci 2020	n/a	n/a	IVA 1mg/0.025mL	laser	r	27	51	0	0	24	27	n/a	n/a	6	2	n/a	n/a	14	1	+(6),Per(2)
Ling 2020	IVB(0.625mg/0.025mL)	IVR(0.25mg/0.025mL)	n/a	laser	r	176	340	231	48	0	61	23	10	n/a	11	8.8	8.3	n/a	3.6	+(44)
Kabatas 2017	IVB(0.625mg/0.025mL)	IVR(0.25mg/0.025mL)	n/a	laser	r	54	108	24	12	0	72	2	2	n/a	10	17	13.7	n/a	1.43	+(4), Per (10)
Gunay 2016	IVB (0.625mg/0.025mL)	IVR (0.25/0.025mL)	n/a	laser	r	134	264	107	44	0	113	6	6	n/a	0	14	8.75	n/a	n/a	both Pro and + (12)
Chen 2018b	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	2.5	n/a	n/a	n/a	Per (4)
Kang 2018	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	n/a	U (15)
Kimyon 2018	IVB (0.625 mg/0.025 mL)	IVR (0.25mg/0.025mL)	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 2015	IVB (0.625 mg/0.025 mL)	IVR(0.25mg/0.025mL)	n/a	n/a	r	20	36	21	15	0	0	2	4	n/a	n/a	14.7	6.7	n/a	n/a	+(6)
Wong 2015	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	5.9	n/a	n/a	+(3)
Sukgen 2019	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	7.34	16.46	n/a	+(18)
Riazi-esfahani 2021	IVB(0.625mg/0.025mL)	n/a	IVA 1mg/0.025mL	n/a	r	453	889	865	0	24	0	34	n/a	14	n/a	6.7143	n/a	14.86	n/a	+(48)
Suren 2022	IVB(0.625mg/0.025mL)	IVR(0.25mg/0.025mL)	IVA 1 mg/0.025 mL	n/a	r	111	187	54	77	56	0	8	19	8	n/a	13	8	12	n/a	U (35)

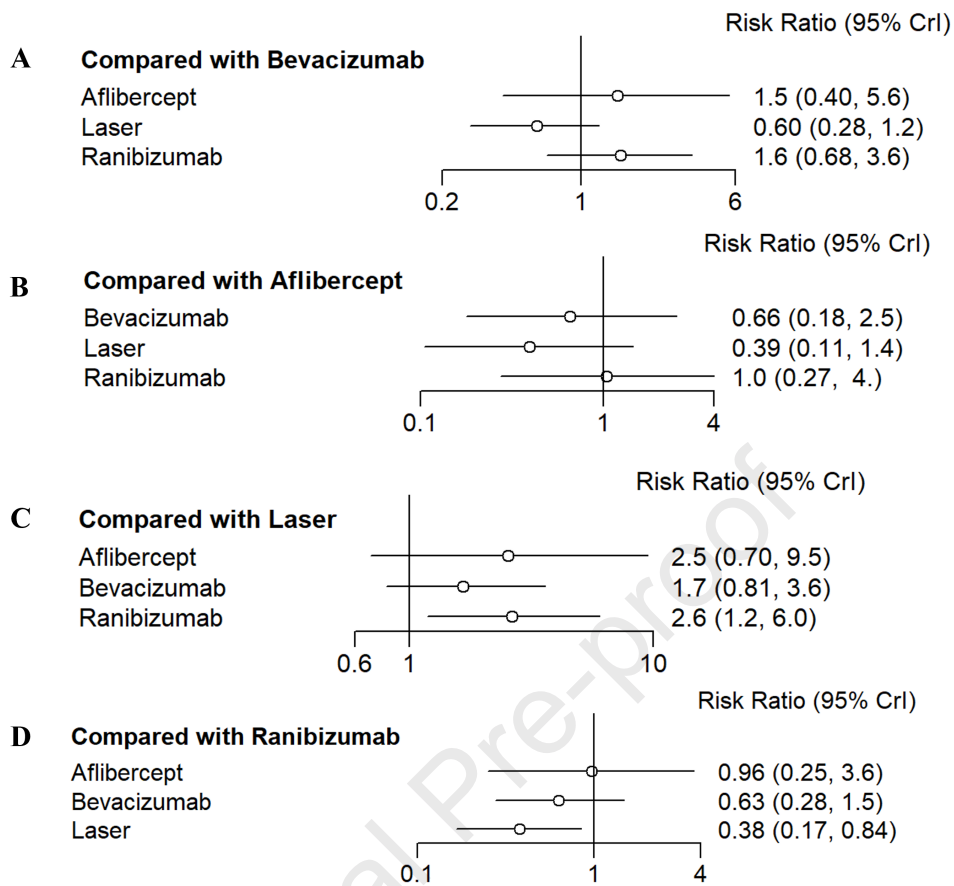
RCT, randomised controlled trial; r, retrospective non-randomised studies; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVA, intravitreal aflibercept;

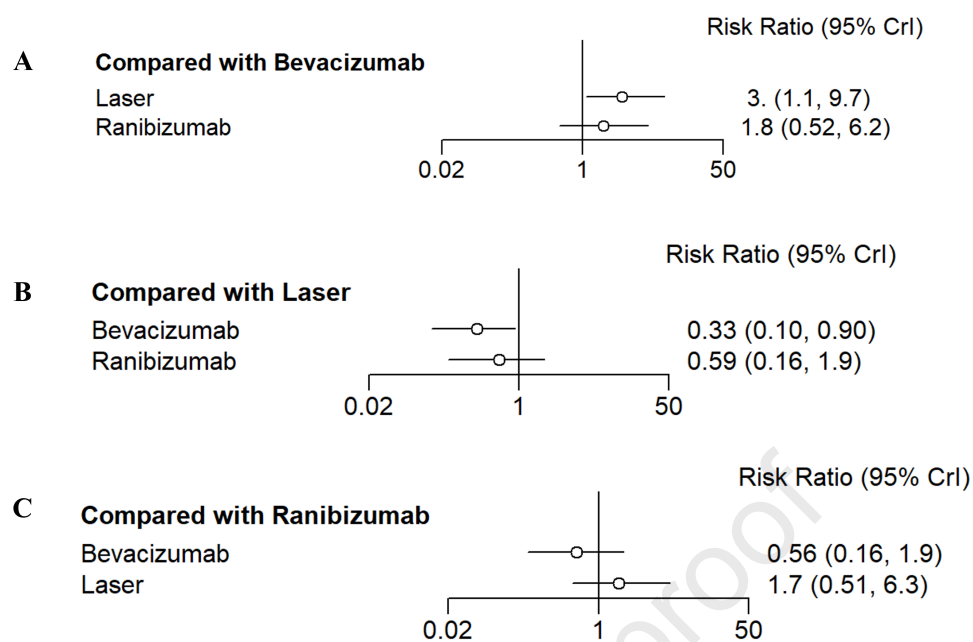
+, reappearance of preplus or plus disease; Per, persistent ROP (any stage) or failure to regress; Pro, progression in ROP severity;

NV, extraretinal new vessels (including abnormal fluorescein leakage); U, undefined/re-treatment occurred due to reactivation which was not further defined; n/a, not applicable.









Precis: The treatment modality associated with the lowest rate of retreatment is laser in Type 1 ROP but bevacizumab in Zone 1 ROP. Aflibercept shows the longest duration of action and narrower timing of retreatment.