Retreatment and recurrence rates following Bevacizumab, Ranibizumab, Aflibercept and Laser for Retinopathy of Prematurity: A Systematic Review and Meta-analysis

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Abstract

Introduction

Retinopathy of prematurity is a vaso-proliferative retinal disorder that affects preterm newborns. For decades, the use of cryotherapy and laser has been the standard of care for retinopathy of prematurity. Recently, the use of anti-VEGF agents for ROP has been widely used. This systematic review measures retreatment rates following certain anti-VEGF agents and laser for ROP.

Methods

We searched Medline, Scopus, ClinicalTrial.gov, and Cochrane library databases for all RCTs that used bevacizumab, ranibizumab, aflibercept and laser for ROP. Studies were assessed for risk of bias by the CASP criteria. Review Manager (RevMan) (2014) Version 5.3 was utilized to carry out the meta-analysis for our study.

Results

Analysis revealed that laser treatment is associated with a lower risk of retreatment than anti- VEGF medications. Similarly, in the subgroup analysis of the anti-VEGF medications used, groups using Aflibercept and Ranibizumab reported higher retreatment rates. In contrast, studies using Bevacizumab reported lower retreatment rates than laser therapy. Furthermore, there was a significant difference in the recurrence rate of patients using anti-VEGF and laser therapy. Patients that underwent laser therapy had lower recurrence rates than the anti-VEGF groups in most trials. In the subgroup analysis, both Ranibizumab and Aflibercept reported higher recurrence rates, which favored laser treatment. However, the two trials that included Bevacizumab reported lower recurrence with Bevacizumab than with laser.

Discussion

Our results suggest that laser treatment for ROP is associated with a lower risk of retreatment and recurrence than Ranibizumab and Aflibercept, which was consistent with similar systematic reviews. On the other hand, this study found that Bevacizumab was superior to laser therapy with lower retreatment and recurrence rates.

Conclusion

This study showed that laser was superior to both ranibizumab and aflibercept as it had a lower risk of disease reactivation requiring retreatment. However, when reviewing studies that examined bevacizumab compared to laser. Bevacizumab showed a lower retreatment rate.

INTRODUCTION

Retinopathy of prematurity (ROP), formerly known as retrolental fibroplasia, is a vaso- proliferative retinal disorder that exclusively affects preterm newborns. as vascularization of the retina normally starts

during the 12th week of gestation and is not fully completed until 36–40 gestational weeks, preterm infants commonly present with incomplete retinal vascularization at birth, which could resolve spontaneously or complicate to more serious conditions in some cases if left untreated [1,2].

ROP is known to manifest in two phases, with the first extending from birth to 30-34 weeks of age. The first phase is marked by a decrease in the vascularization rate of the retina, primarily due to high oxygen exposure from the outside environment. The relative hyperoxia of the extrauterine environment (70% oxygen saturated uterine blood compared to 100% saturated room air), as well as supplemental oxygen usually delivered to premature infants, are expected to be the main contributors to this process [3].

However, after 30-34 weeks of age, the second phase would start manifesting due to the increase in the retina's metabolic needs paired with decreased vascularity and perfusion, driving the growth of new vessels between the vascularized and avascular zones of the retina as an adaptive mechanism [4]. However, this hypoxia-induced retinal neovascularization is pathological and would lead to a fibrous scar, which could eventually extend and separate the retina from the retina pigment epithelium causing retinal detachment and blindness [3]. This phase exhibits abnormally elevated levels of vascular endothelial growth factor (VEGF), the main contributor to vasculogenesis and angiogenesis, which prompted the recent use of intravitreal injections of anti-VEGF treatments as a therapeutic intervention for ROP [5].

For the past decades, cryotherapy and laser photocoagulation have been used as the principal stay interventions for ROP [4]. However, both ablation methods were found to be destructive and could leave patients with high myopia, visual field loss, and retinal destruction in some cases [4,6]. Moreover, numerous studies concluded that the use of anti-VEGF treatments for ROP patients leads to better refractive outcomes, fewer complications, and lower recurrence rates [7,8,9].

Nonetheless, evidence that clearly examines the retreatment rates and recurrence of anti- VEGF and laser therapies in treating ROP remains relatively limited and scattered. Thus, in this paper, we reviewed eligible randomized controlled trials that compared the effectiveness of anti-VEGF agents alongside laser for ROP as measured by the risk of disease reactivation needing retreatment.

METHODS

Registration:

This study was registered on PROSPERO under the registration ID CRD42022328304.

Eligibility criteria:

All randomized clinical trials that evaluated the use of anti-VEGF for retinopathy of prematurity were considered eligible for inclusion in this systematic review.

Study identification:

We searched Medline, Scopus, ClinicalTrial.gov, and Cochrane library databases for all related articles using the MeSH terms (or keywords when applicable) “Anti-vascular endothelial growth factor” OR “anti-VEGF” AND “retinopathy of prematurity” OR “ROP”. Two authors separately screened the articles through titles and abstracts and discrepancies were resolved by consensus and a third independent reviewer. To confirm eligibility, two reviewers then separately screened the full text of the screened articles, and discrepancies were resolved by consensus and a third reviewer.

Data extraction:

Two independent reviewers extracted information related to studies’ characteristics. For each included study, we extracted the population characteristics (GA, BW); treatment modalities, number of eyes requiring retreatment for ROP, and time between initial and secondary treatment. For studies involving the same patient populations, duplication of data was avoided by including the most complete data set. Since the study aim was focused on ROP retreatment rates, comparisons of adverse outcomes such as myopia and reduced visual acuity are beyond the scope of this systematic review and meta-analysis.

Data analysis:

We utilized Review Manager (RevMan) (2014) Version 5.3 to carry out the meta-analysis for our study. We delineated a confidence level of 95%, and a P-value less than or equal to 0.05 was considered statistically significant. The results of the meta-analysis were represented using forest plots and risk ratios [RR] for each of the evaluated variables. Evaluation of study quality:

Critical Appraisal Skills Programme (CASP) criteria for randomized controlled trials [10] was utilized to assess the studies included in this systematic review. The study design, research methodology, and study results were the three main domains addressed in the criteria.

RESULTS

***Literature search**:*

A total of (195) studies were screened by two authors through their titles and abstracts using the specified inclusion and exclusion criteria to examine their eligibility. Of the screened articles, 189 studies were excluded (including duplicates), and 6 potential studies were left. Upon assessing the 6 papers by two reviewers with discrepancies being resolved by consensus and a third reviewer, one more study was excluded since the agent pegaptanib, known as Macugen, is discontinued and is no longer available. Eventually, 5 studies were eligible for inclusion in this systematic review (Figure 1). Of the 5 included studies, two trials compared ranibizumab to laser therapy, two trials compared bevacizumab to laser therapy, and one compared aflibercept to laser (table 1). In total, these studies comprise 1064 eyes of 610 infants (352 eyes receiving ranibizumab, 152 eyes receiving bevacizumab, 146 receiving aflibercept, and 414 receiving laser).

Table1. characteristics of all studies included in the analysis

Table 1. Characteristics of All Studies Included in the 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		
	Bevacizu-mab	Ranibiz-umab	Aflibercе-pt	Laser				IVB	IVR	IVA	Laser	IVB	IVR	IVA	Laser	IVB	IVR	IVA
Stahl et al. [15]	N/A	IVR (0.2mg and 0.1mg)	N/A	Laser	RCT	225	450	0	0.2mg 148 0.1mg 154	0	148	N/A	24 in 0.2 24 in 0.1	N/A	1	N/A	**0.2:** 55 days (range 29–111) **0.1:** 57 days (30–128)	N/A
Karkhaneh et al. [18]	IVB (0.625mg/ 0.025ml)	N/A	N/A	Laser	RCT	79	158	86	0	0	72	9	N/A	N/A	1	5 ±1.66 weeks	N/A	N/A
Zhang et al. [19]	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	12.62 weeks ± 7.93	N/A
Helen A et al. [?]	IVB (0.625mg/ 0.025ml)	N/A	N/A	Laser	RCT	143	286	66	0	0	68	6	N/A	N/A	32	8.6 ± 19.2 for zone I 14.4 ± 0.8 for zone II	N/A	N/A
Stahl et al. [21]	N/A	N/A	IVA (0.4mg)	Laser	RCT	113	218	0	0	146	76	N/A	N/A	26	5	N/A	N/A	3.7 weeks

Assessment of bias:

The overall pooled evidence for this systematic review and meta-analysis exhibited minimal bias risk. Most of the RCTs included in this paper had a low risk of bias, as indicated in Figure 2. (10) Concerns of bias in certain studies included a lack of or unclear reporting of masking procedures, intention-to-treat analyses, matching of participants' baseline characteristics, and/or precision of the intervention estimate. Since participant blinding was understandably not feasible in the majority of trials due to the intervention nature and infant study population, it was considered as an unlikely source of bias.

Heterogeneity:

All articles included in this systematic review were randomized controlled trials. However, the variation in the types of anti-VEGF medications and doses and the limited number of available trials have played a role in the variability of the included articles. In terms of retreatment, there was high heterogeneity ($p<0.00001$, $I^2=94.1\%$) between studies in addition to a significant total heterogeneity in terms of recurrence ($p<0.00001$, $I^2=95.1\%$).

Retreatment of Anti-VEGF vs Laser Therapy:

All five of the randomized controlled trials included in this review (n= 1064 eyes) reported the rates of retreatment for both patients receiving anti-VEGF injections and laser therapy [11,12,13,14,15]. Our meta-analysis results revealed that laser treatment is associated with a lower risk of retreatment than anti-VEGF injections (RR = 2.11, 95% CI 1.46-3.05, P<0.0001, I2 = 92%). Similarly, in the subgroup analysis of the three anti-VEGF medications, both groups using ranibizumab (RR = 17.23, 95% CI 5.34-55.59, P<0.00001, I2 = 0%) and aflibercept (RR = 2.71, 95% CI 1.08-6.77, P=0.03, I2 = not applicable) reported higher retreatment rates, favoring laser treatment. In contrast, studies investigating bevacizumab

showed higher retreatment rates in patients that received laser therapy than patients that received bevacizumab. (RR = 0.44, 95% CI 0.24-0.79, P=0.006, I2 = 91%), as depicted in Figure 3.

Recurrence of Anti-VEGF vs Laser Therapy

Out of the five RCTs we included in our study, only four trials reported recurrence rates. Overall, there was a significant difference in the recurrence rate between patients using anti-VEGF and laser therapy. Patients that underwent laser therapy had lower recurrence rates than the anti-VEGF groups in most trials. (RR = 2.00, 95% CI: 1.47 to 2.72, p<0.0001, I^2= 93%, Figure 3). In the subgroup analysis, both Ranibizumab (RR = 4.54, 95% CI: 2.81 to 7.33, p=0.09, I^2= 66%, Figure 4) and Aflibercept (RR = 2.78, 95% CI: 1.21 to 6.35, I^2= not applicable, Figure 4) showed higher recurrence rates, which favored laser treatment.

However, the two trials that included Bevacizumab reported lower recurrence with Bevacizumab than with laser. However, the two trials that included Bevacizumab (RR = 0.13, 95% CI: 0.05 to 0.34, I^2= not applicable, Figure 4) reported lower recurrence with Bevacizumab than laser therapy.

DISCUSSION

Summary of the results

This study focused on the risk of disease reactivation requiring treatment for patients with retinopathy of prematurity. 5 eligible randomized clinical trials were reviewed. Of the 5 RCTs, 2 investigated ranibizumab, 2 investigated bevacizumab, and 1 investigated aflibercept. A total of 1064 eyes with ROP who were treated with anti-VEGF agents were included. 352 eyes received ranibizumab, 152 received bevacizumab, 146 received aflibercept, and a total of 414 received laser. In terms of retreatment rate, 74 out of 352 in two studies that used ranibizumab required retreatment, and 15 out of 152 who were on bevacizumab required retreatment. And finally, 26 out of 146 who were on aflibercept required retreatment (risk ratios can be found in Figure 2)

Our results suggest that laser treatment for ROP is associated with a lower risk of retreatment than ranibizumab and aflibercept. This finding is consistent with a recent systematic review by Emer Chang (16). On the other hand, this study found that bevacizumab was associated with a reduction in rate of retreatment and recurrence when compared to laser. Similar to our findings, the BEAT- ROP trial was the first major RCT to establish bevacizumab as superior to laser for ROP in Zone I or posterior Zone II in terms of a lower rate of reactivation requiring retreatment. (17)

Limitations

First of all, the reliability of this data is impacted by the limited number of studies included in this review. This is due to the lack of randomized controlled trials that assess the retreatment and recurrence rates of anti-VEGF agents for retinopathy of prematurity. Additionally, there was high heterogeneity between

the studies which may have an impact when comparing studies. Even though the doses used in all RCTs were not identical, we focused on selecting studies using similar doses of anti-VEGF for a fair comparison. Another discrepancy was found in one of the 5 RCTs that did not clearly report the mean time between initial treatment and retreatment which affected the ability to draw accurate conclusions regarding this significant time for each agent

Future direction

In the future, studies should more closely examine how anti-VEGF affect the long-term progression of the disease, focusing on the benefit and side effects that may emerge in the years following the therapy. Most of the studies included in this review did not focus on the long-term effects of anti-VEGF or on the natural history of the disease. Thus, research into the long-term outcomes of anti-VEGF therapy is urgently needed. It is also beneficial to focus on the prevention of recurrence in high-risk patients during the initial therapy to avoid future complications.

Additionally, it is important to obtain more evidence regarding the severity of retinopathy of prematurity, such as the zone and stage, in treated patients in order to understand how refractive error develops. Unfortunately, very limited data on the incidence of refractive errors in patients prevented us from including such data in this review.

CONCLUSION

We present a systematic review and meta-analysis comparing bevacizumab, ranibizumab and aflibercept to laser therapy for the treatment of ROP, focusing mainly on the risk of disease reactivation manifested by the need for a retreatment. This study showed that laser was superior to both ranibizumab and aflibercept as it had a lower risk of disease reactivation requiring retreatment. However, when reviewing studies that examined bevacizumab compared to laser. Bevacizumab showed a lower retreatment and recurrence rate.

Abbreviations

ROP: retinopathy of prematurity

Anti-VEGF: anti-vascular endothelial growth factor

RCT: randomized clinical trial

CASP: Critical Appraisal Skills Programme

IVR: intravitreal ranibizumab

IVT-AFL: intravitreal aflibercept

Declarations

Ethics approval and consent to participate:

NA

Consent for publication:

NA

Availability of data and materials:

The data that support the findings of this study are available in the manuscript, should the journal require any additional data, it will be provided by the corresponding author.

Competing interests:

The authors declare that they have no conflict of interest

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Authors' contribution:

First and corresponding author: Arwa Alghamdi. The following authors (Aletani, Alasmari, Ezzi, Alharbi, Omer) contributed equally. Dr. Talaat reviewed the manuscript, therefore; he is the 7th author

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All contributors are co-authors that participated in the making of the manuscript.

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Figures

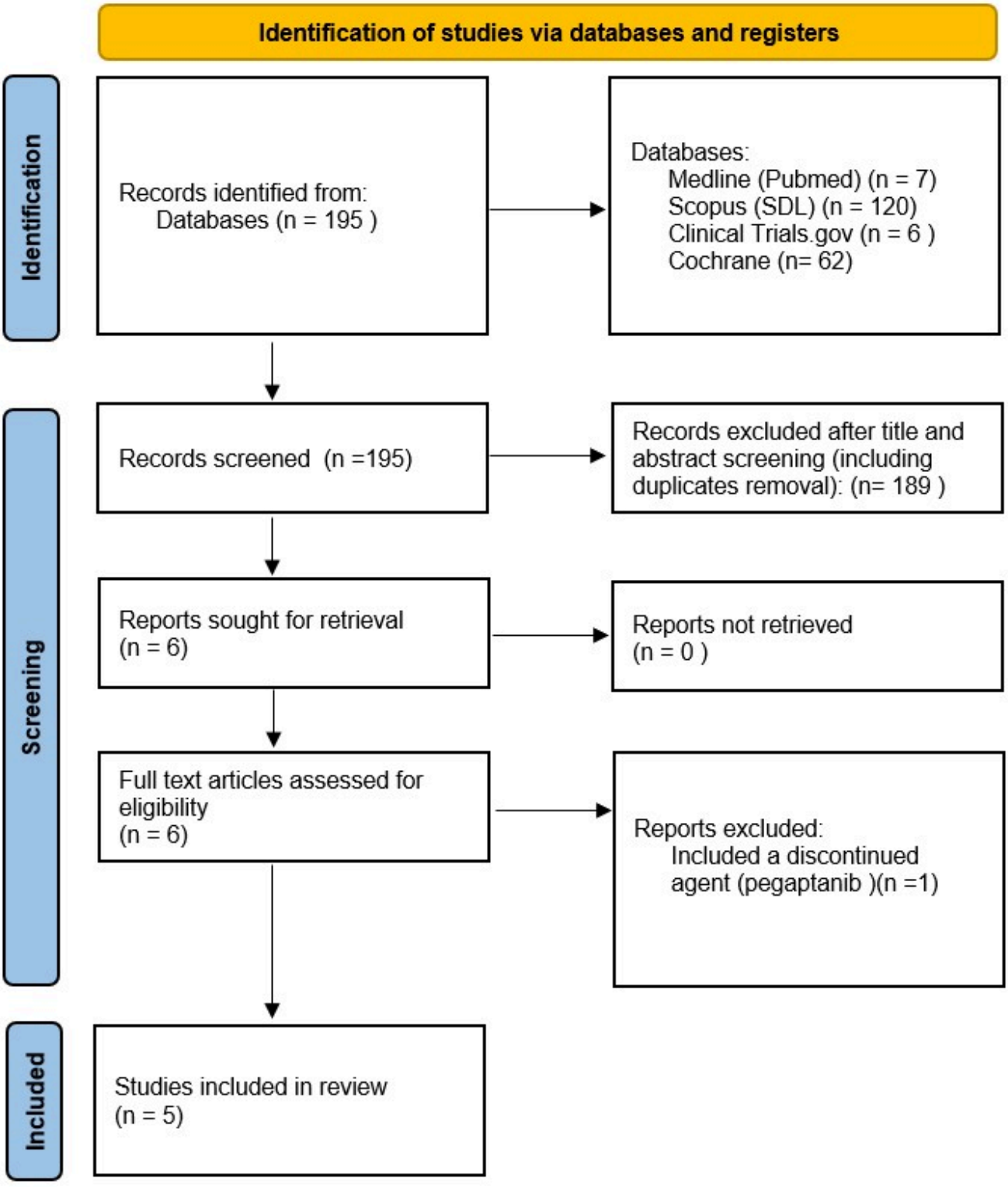

Figure 1

PRISMA flow diagram

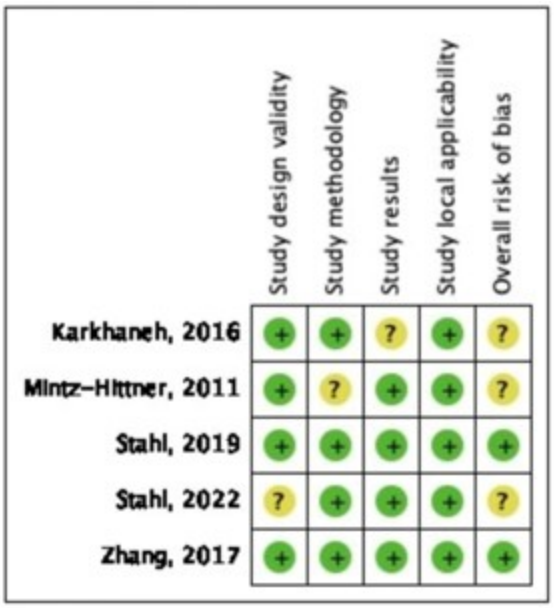

Figure 2

Risk of bias summary

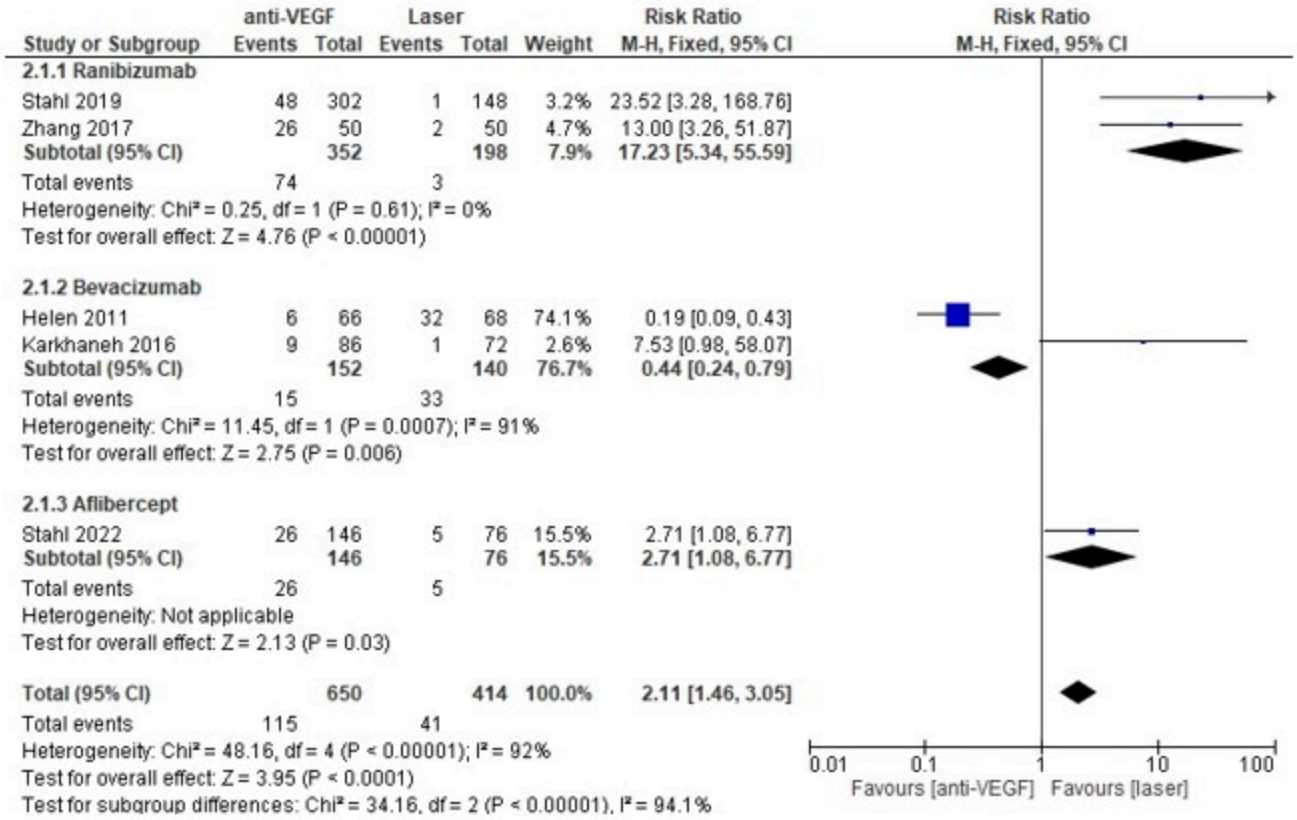

Figure 3

Forest plot for recorded retreatment

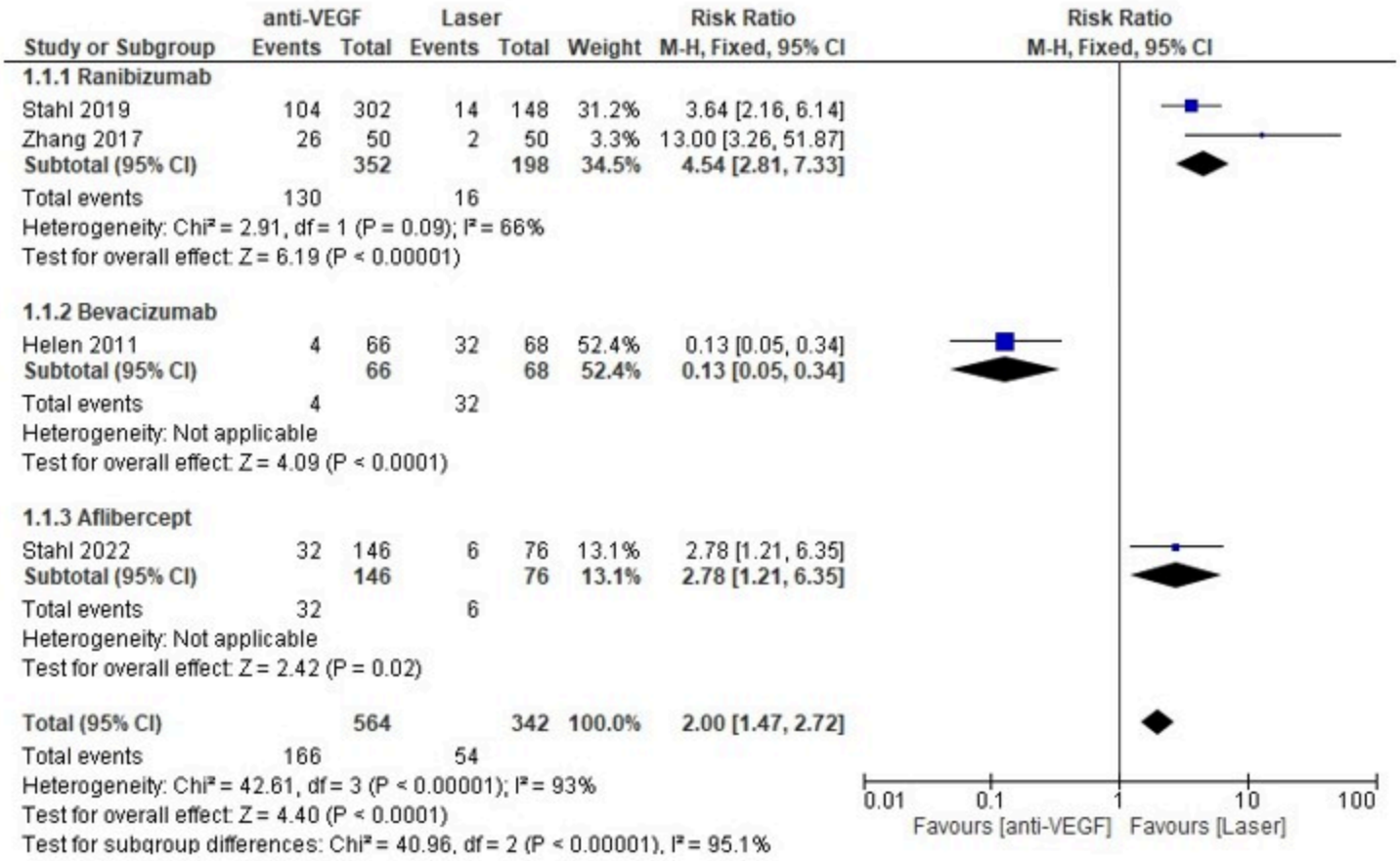

Figure 4

forest plot for recorded recurrence

Supplementary Files

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- GraphicalAbstract.jpg