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Comparison of anti-vascular endothelial growth factor treatment for myopia choroidal neovascularization: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives To evaluate the efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF), especially to compare the efficacy of different anti-VEGF retreatment regimens in patients with myopia choroidal neovascularization (CNV).

Data sources PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov were searched from inception to 31 July 2022.

Study selection Randomized controlled trials (RCTs) comparing anti-VEGF with sham, photodynamic therapy (PDT) or PDT combination therapy for patients with myopia CNV were reviewed and selected.

Data extraction and synthesis Two reviewers independently conducted data extraction and quality assessment. We used a random-effects model for all analyses. Primary outcomes included best-corrected visual acuity (BCVA) and central foveal thickness. Secondary outcomes included number of patients who gained more than 3 lines in BCVA, number of anti-VEGF injections and ocular adverse events (AEs).

Results Seven RCTs involving 1007 patients were included. Compared with sham and PDT treatment, anti-VEGF therapy achieved better BCVA gain of -0.28 logMAR (95% CI:-0.36 to -0.20, $P < 0.00001$) and -0.14 logMAR (95% CI:-0.17 to -0.10, $P < 0.00001$), respectively, and no definitive increased risk of ocular AEs were observed in anti-VEGF therapy group. There were no significant differences in the efficacy and safety of anti-VEGF monotherapy compared with PDT combination therapy. The comparison of different anti-VEGF retreatment regimens showed that disease activity criteria resulted in similar visual improvement and required fewer anti-VEGF injections compared to visual acuity stabilization criteria (WMD=0.83, 95% CI: 0.42 to 1.25, $P < 0.0001$).

Conclusions Anti-VEGF therapy is effective and well-tolerated for myopia CNV patients. Anti-VEGF retreatment regimen guided by disease activity criteria can achieve comparable efficacy and potentially reduce anti-VEGF injections.

PROSPERO registration number CRD42021292806.

Key Words anti-VEGF; myopia choroidal neovascularization; retreatment regimen; meta-analysis.

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Strengths and limitations of this study

- The major strength of this study was designed to compare different anti-VEGF retreatment regimens and found disease activity criteria may be a more recommended retreatment regimen.
- This meta-analysis described a review protocol that was formally registered on PROSPERO and provided the latest RCTs of anti-VEGF for myopic CNV.
- The number of included studies was relatively small, and some RCTs had small sample size. Further more large and high quality research were needed.
- The heterogeneity in some parameters partly due to inconsistent follow-up times of included RCTs, may affect the overall reliability of the results.

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INTRODUCTION

Pathologic myopia is characterized by excessive elongation of the eyeball leading to various degenerative changes in the retina and visual deterioration [1]. Among the complications of pathologic myopia, choroidal neovascularization (CNV) and mechanical rupture of Bruch membrane are the most serious degenerative changes [2]. Pathologic myopia is the second cause of CNV after neovascular age-related macular degeneration (nAMD), approximately 5.2% to 11.3% of pathological myopia patients developing to myopic CNV [3 4]. Myopic CNV has a higher prevalence in Asian population and most of patients present at 50 years of age or younger rather than old age [5]. Without treatment, the majority of myopic CNV patients will develop a poor visual outcome. A 10 years follow-up study showed that over 95% of myopic CNV patients' visual acuity (VA) reduced to 0.1 or even worse after 5 and 10 years of onset [6].

Before the use of anti-VEGF therapy in myopic CNV, treatment strategies mainly include laser photocoagulation, verteporfin photodynamic therapy (PDT) and submacular surgery [7]. But the clinical application of these approaches are limited by complications such as myopic CNV recurrence, scarring, atrophy, and choroidal ischemia [8-10]. PDT has been the most widely used treatment for myopic CNV since the Verteporfin in Photodynamic Therapy (VIP) study showed that patient treated with PDT had a better visual outcome compared to placebo over 12 months [11]. However, the 2-year follow up of the VIP trial reported PDT treatment had no statistically significant benefit with a high percentage of reoccurrence of intraretinal fluid [12]. Another study showed the development of chorioretinal atrophy was seen in 83% of PDT treated patient at 5 years [13]. Since anti-vascular endothelial growth factor (anti-VEGF) therapy become available, PDT has fallen out of favour and only considered if anti-VEGF therapy is contraindicated.

VEGF is a proangiogenic cytokine that stimulates the development of CNV and the abnormal increase of intraocular VEGF [14]. Anti-VEGF can bind VEGF receptor to inactivate endogenous VEGF and inhibit the migration and proliferation of vascular

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endothelial cell, thereby inhibiting neovascularization [15]. The earliest report of intraocular injection of anti-VEGF drugs for myopic CNV was in 2006 and become more and more widely used in recently years [16 17]. Although previous studies have shown that anti-VEGF therapy resulted in better visual, comparative studies mainly consist of non-RCTs and a small number of RCTs, which limits the strength to support clinical application [18 19]. Furthermore, despite clinical approval of anti-VEGF therapy for myopia CNV, the optimal retreatment regimen has not been unified [20].

In recent years, new RCTs about anti-VEGF therapy for myopia CNV have been published and long-term data on efficacy and safety have been accumulated. Most importantly, two large RCTs have been completed to compare the therapeutic effects of different anti-VEGF retreatment regimens [21 22]. Our objective was to update the latest clinical evidence and to explore a preferred anti-VEGF retreatment regimen for myopic CNV.

METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [23].

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data sources and search strategy

The databases of PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov were searched from inception to 31 July 2022. The meta-analysis protocol was approved and registered in PROSPERO website with a registration number of CRD42021292806. A range of MESH words and free terms regarding CNV, anti-VEGF, ranibizumab (Lucentis), bevacizumab (Avastin), aflibercept (Eylea), conbercept (Lumitin), RCT were used in all combinations possible to search for relevant articles. The search strategy is provided in the online supplementary

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appendix 1. No language restriction was applied. We also manually searched the reference lists of included studies to identify other potentially eligible articles.

Eligibility criteria

We included the following published studies if they met the criteria: (1) patients with active myopia CNV (with spherical equivalent ≥ -6.0 dioptres and an axial length ≥ 25.0 mm); (2) studies were RCTs that directly compared intravitreal anti-VEGF drugs with sham or PDT or PDT combination therapy, and comparison of different anti-VEGF retreatment regimen also included; (3) studies reported one or more of interest outcomes. Exclusion criteria were employed as follows: (1) patients were previously treated with several drugs; (2) comparative studies between different anti-VEGF drugs, noncomparative studies, animal studies or case reports; (3) unfinished studies or unavailable data.

Data extraction and quality assessment

Titles and abstracts were independently scanned by two reviewers using the above selection criteria. Disagreements were discussed and if necessary, resolved by a third reviewer. Data were extracted in a prespecified data extraction form. The following data were extracted from the articles included: general data (title, first author, study design, inclusion and exclusion criteria), basic characteristics (age, sex, sample size), intervention groups, follow-up time, primary outcomes (BCVA and central foveal thickness (CFT)) and secondary outcomes (the number of patients who gained more than 3 lines in BCVA, the number of anti-VEGF injection and the number of serious or nonserious ocular adverse events (AEs)). Quality for RCTs was assessed using the Cochrane risk of bias tool [24].

Data synthesis and statistical analysis

The meta-analysis was conducted using Review Manager 5.3 supplied by Cochrane Collaboration (Oxford, United Kingdom). The weighted mean difference (WMDs) with 95% confidence interval (CIs) were measured for continuous data, while the risk ratios (RRs) with 95% CIs were measured for dichotomous data. Visual outcome was measured using the Early Treatment Retinopathy study (ETDRS) chart, the data were

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converted to logarithmic visual acuity (logMAR) for analyses [25 26]. Heterogeneity between studies was assessed using the I^2 test. $I^2 > 50\%$ was defined as the presence of substantial heterogeneity [27]. Due to the possibility of heterogeneity being present between studies, a more conservative version of the random-effects model was applied. A value of $p<0.05$ was chosen as the significance level for outcome measures.

RESULTS

Literature search

In total, 3376 relevant articles were identified initially. After removed 841 duplicates, we screened the remaining 2535 articles and 2497 articles were excluded based on the titles and abstracts. The remaining 38 articles were retrieved for full-text review, and 7 eligible RCTs [21 22 28-32] were included for meta-analysis (figure 1). Among the 7 included RCTs, 1 RCT compared anti-VEGF with sham treatment, 4 RCTs compared anti-VEGF with PDT, and 2 RCTs compared anti-VEGF monotherapy with PDT combination therapy. Besides, 2 RCTs compared different anti-VEGF retreatment regimens guided by VA stabilization criteria or disease activity criteria, respectively.

Study characteristics

The basic characteristics of included 7 RCTs are shown in table 1. The study included a total of 1007 participants. The followed-up duration was 12 to 24 months. The mean age ranged from 44.6 to 62.4 years and females accounted for 52.5% to 76.5%. The anti-VEGF treatments used in the included studies were intravitreal bevacizumab (IVB 1.25mg), ranibizumab (IVR 0.5mg) and aflibercept (IVA 2.0mg). The PDT monotherapy received standard fluence PDT (50 J/cm^2) and the PDT combination therapy received reduced fluence PDT (25 J/cm^2) in combination with intravitreal anti-VEGF.

For different anti-VEGF retreatment regimens, patients retreatment guided by VA stabilization criteria received anti-VEGF on day 1 and month 1, and thereafter monthly injections were performed when there was a loss of VA (change in BCVA

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and investigator judgment). Patients retreatment guided by disease activity criteria received anti-VEGF on day 1, and thereafter monthly injections were performed when observed disease activity (intraretinal or subretinal fluid assessed by optical coherence tomography, or active leakage assessed by fluorescein angiography).

Table 1 Characteristics of the included seven studies

Study/ Year	Study Design	NCT Trial No.	Patients	Sample Size (Patient)	Mean Age (Year)	Sex (M/F)	Intervention Groups	Follow-up (Months)
MYRROR 2014[28]	RCT	01249664	Subfoveal or juxtafoveal CNV secondary to high myopia	121	58.2±13.3	29/92	IVA (2.0 mg); Sham (no Drug)	12
Parodi 2010[29]	RCT	None	Juxtafoveal CNV secondary to pathologic myopia	37	49.45	13/24	IVB (1.25 mg); SF PDT (50 J/cm^2)	24
Moreno 2013[30]	RCT	00967850	Subfoveal and/or juxtafoveal CNV secondary to pathologic myopia	42	None	None	IVB (1.25 mg); SF PDT (50 J/cm^2)	24
RADIANCE 2014[21]	RCT	01217944	Subfoveal or juxtafoveal or extrafoveal CNV secondary to pathologic myopia	276	55.56±13.96	68/209	IVR (0.5 mg): guided by VA stabilization; IVR (0.5 mg): guided by disease activity; SF PDT (50 J/cm^2)	12
BRILLIANCE 2019[22]	RCT	01922102	Subfoveal or juxtafoveal or extrafoveal CNV secondary to pathologic myopia	457	51.2±12.7	146/311	IVR (0.5 mg): guided by VA stabilization; IVR (0.5 mg): guided by disease activity; SF PDT (50 J/cm^2)	12
Saviano 2013[31]	RCT	None	Subfoveal or juxtafoveal CNV secondary to pathologic myopia	34	62.4	8/26	IVB (1.25 mg); IVB (1.25 mg) + RF PDT*	12
Rinaldi 2016[32]	RCT	01968486	Subfoveal or juxtafoveal CNV secondary to pathologic myopia	40	44.6±4.48	19/21	IVR (0.5 mg); IVR (0.5 mg) + RF PDT (25 J/cm^2)	12

RCT, randomized controlled trial; NCT, national clinical trial; CNV, choroidal neovascularization; PDT, photodynamic therapy; anti-VEGF, anti-vascular endothelial growth factor; M/F, male/female; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVA, intravitreal aflibercept; VA, visual acuity; SF PDT, standard fluence photodynamic therapy; RF PDT, reduced fluence photodynamic therapy.

Risk of bias assessment

Risk of bias assessment for included RCTs is shown in the online supplementary appendix 2. Two RCTs [21 22] were considered to be at low risk of bias for all domains. Most unclear risk of bias was assigned in domains of selection bias or detection bias [28]

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[29 31]. Two RCTs [30 31] were considered to be high risk of bias for performance bias and attrition bias, respectively.

Anti-VEGF versus sham treatment

MYRROR study [28] compared aflibercept with sham treatment and results were presented at the end of 6-month, as the sham treatment group could receive aflibercept when needed. The results showed that patients in anti-VEGF treatment achieved significant better BCVA (WMD=-0.28 logMA; 95% CI -0.36 to -0.20, p<0.00001; figure 2) and CFT reduction (WMD=-66.80; 95% CI -114.87 to -18.73, p=0.006; figure 3) than sham treatment group. The number of patients who gained more than 3 lines in BCVA was significantly higher in the anti-VEGF treatment than in the sham treatment group (RR= 4.02, 95% CI 1.33 to 12.15, p=0.01; figure 4). The incidence of serious (p=0.55; table 2) and non-serious ocular AEs (p=0.13; table 2) were similar in anti-VEGF and sham treatment group. There were 3 serious ocular AEs (only 1 macular hole in study eye) in anti-VEGF and no event occurred in sham treatment group. The most common non-serious ocular AEs in anti-VEGF treated patients were mild conjunctival hemorrhage, punctate keratitis, eye pain and dry eye, but did not lead to the interruption of treatment.

Table 2 Meta-analysis results of the number of anti-VEGF injections, serious and non-serious ocular adverse events

Comparison	No. of RCTs (no. of Patients)	Risk ratio (95% CI)	P	I^2 (%)	P for heterogeneity
The number of anti-VEGF injections					
Anti-VEGF vs PDT combination	2(74) [31 32]	1.30 (1.24,1.37)	0.00001	32	0.23
Retreatment criteria：VA stabilization vs disease activity	2(587) [21 22]	0.83 (0.42,1.25)	0.0001	0	0.38
The number of serious ocular adverse events					
Anti-VEGF vs Sham treatment	1(121) [28]	2.46 (0.13,46.36)	0.55	—	—
Anti-VEGF vs PDT	4(525) [21 22 29 30]	0.81(0.11,6.10)	0.84	0	0.62
Retreatment criteria：VA stabilization vs disease activity	2(587) [21 22]	1.06 (0.15,7.45)	0.96	0	0.96
The number of non-serious ocular adverse events					
Anti-VEGF vs Sham treatment	1(121) [28]	0.57 (0.28,1.18)	0.13	—	—

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Anti-VEGF vs PDT	4(525) [21 22 29 30]	1.02(0.77,1.36)	0.88	0	0.90
Anti-VEGF vs PDT combination	2(74) [31 32]	1.57 (0.77,3.22)	0.22	—	—
Retreatment criteria：VA stabilization vs disease activity	2(587) [21 22]	1.04 (0.83,1.31)	0.72	0	0.41

RCT, randomized controlled trial; anti-VEGF, anti-vascular endothelial growth factor; PDT, photodynamic therapy; VA, visual acuity.

Anti-VEGF versus PDT

Four RCTs [21 22 29 30] compared anti-VEGF with PDT treatment. For the RADIANCE and BRILLIANCE study [21 22], results were presented at the end of 3-month, as patients in PDT group could receive ranibizumab when needed. A significant increase of BCVA from baseline was observed in both groups. Compared to PDT, the mean improvement of BCVA (WMD=-0.14 logMAR; 95% CI -0.17 to -0.10, p<0.00001, I^2=68%; figure 2) and reduction of CFT (WMD=-44.32; 95% CI -59.85 to -28.79, p<0.00001, I^2=20%; figure 3) were superior in anti-VEGF group. And the number of patients who gained more than 3 lines in BCVA was more in anti-VEGF group (RR=2.42; 95% CI 1.68 to 3.50, p<0.00001, I^2=0%; figure 4), too. Anti-VEGF group recorded 2 serious ocular AEs (1 retinal detachment and 1 retinoschisis) and PDT group recorded 1 endophthalmitis (p=0.84; table 2).The non-serious ocular AEs showed no significant differences between the two groups (p=0.88; table 2) and most frequently reported were conjunctival hemorrhage and punctate keratitis.

Anti-VEGF monotherapy versus PDT combination therapy

Two small RCTs [31 32] compared anti-VEGF monotherapy with PDT combination therapy. The mean BCVA (WMD=0.07 logMAR; 95% CI -0.00 to 0.14, p=0.06, I^2=61%; figure 2) and CFT (WMD=6.40; 95% CI -20.10 to 32.90, p=0.64; figure 3) were improved both in anti-VEGF monotherapy and PDT combination therapy group, but there were no statistical difference between them. The number of patients who gained more than 3 lines in BCVA (RR=0.92; 95% CI 0.57 to 1.49, p=0.74; figure 3) was similar in both groups, too. Nevertheless, the anti-VEGF injections in PDT combination therapy was statistically fewer than anti-VEGF monotherapy group (WMD=1.30; 95% CI 1.24 to 1.37, p<0.00001, I^2=32%; table 2). No serious ocular

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AE was documented and some mild non-serious ocular AEs were observed in both groups, including ocular hyperemia, myodesopsia, conjunctival hemorrhage and eye pain (p=0.22; table 2).

Anti-VEGF retreatment regimens: VA stabilization criteria versus disease activity criteria

Two RCTs [21 22] compared the therapeutic effect of different anti-VEGF retreatment regimens. No significant difference in mean BCVA (WMD=-0.00 logMAR; 95% CI −0.04 to 0.03, p=0.91, I^2=0%; figure 2) and CFT change (WMD=2.31; 95% CI -11.46 to 16.08, p=0.74, I^2=0%; figure 3). The number of patients who gained more than 3 lines in BCVA got the same results (RR=1.07; 95% CI 0.90 to 1.27, p=0.47, I^2=0%; figure 4). Interestingly, the number of anti-VEGF injections guided by disease activity criteria was significantly fewer than VA stabilization criteria group (WMD=0.83; 95% CI 0.42 to 1.25, p<0.0001, I^2=0%; table 2). Safety profile showed no significant difference in patients between the two anti-VEGF retreatment regimens. There were 2 serious ocular AEs, respective 1 retinal detachment in VA stabilization criteria and 1 retinoschisis in disease activity criteria group (p=0.96; table 2). The most frequently reported non-serious ocular AE was conjunctival hemorrhage (p=0.72; table 2).

DISCUSSION

In this meta-analysis, we evaluated the efficacy and safety of anti-VEGF treatment and compared two different anti-VEGF retreatment regimens. Evidences showed that anti-VEGF was superior to improving VA compared to sham or PDT treatment. Moreover, anti-VEGF monotherapy showed similar visual improvement compared to PDT combination therapy. For different retreatment regimens, anti-VEGF retreatment guided by disease activity criteria could achieve similar visual gain and need fewer anti-VEGF injections compare to VA stabilization criteria. Therefore, this review could provide the latest update on the systematic review of anti-VEGF treatment and provide evidence for optimizing retreatment regimens for myopia CNV.

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Myopic CNV was a progressive disease and VA in the sham treatment group became worse than baseline without treatment [21]. The short-term treatment effect of PDT was remarkable, but the long-term effect was poor and the recurrence rate was high [13 14]. Analysis results indicated that anti-VEGF therapy had a better visual and anatomical improvement than sham or PDT treatment. Moreover, the post hoc analyses of RADIANCE study demonstrated BCVA gain of anti-VEGF therapy was sustained over additional 36 months [33]. There was no significant difference in VA improvement between anti-VEGF monotherapy and PDT combination therapy, but PDT combination therapy needed fewer anti-VEGF injections. However, PDT combination therapy would increase the cost of PDT related treatment, so whether it was more cost-effective treatment needs further evaluation.

For safety estimation, there were no significant differences in the incidence of serious and non-serious ocular AEs between anti-VEGF therapy and other treatments. The most common ocular AEs of anti-VEGF treatment were mild conjunctival hemorrhage and punctate keratitis, which were well tolerated in myopic CNV patients. Although some cases reported that new onset myopic macular retinoschisis (MRS) may be a complication of anti-VEGF intravitreal therapy, only 1 MRS event was reported in MYRROR study, and another study also found there was no association between the new onset of MRS and anti-VEGF therapy [34-36].

Currently, the guidance and consensus statement recommended anti-VEGF therapy for myopic CNV, but did not point out the definite retreatment regimen [20]. Most clinical research refer to retreatment regimen guided by disease activity criteria (intraretinal or subretinal fluid) or VA stabilization criteria (increased BCVA or blurring or metamorphops), or both [37-40]. The use of different retreatment criteria may affect retreatment rates and the number of anti-VEGF injections. Fewer injections can lead to lower risk of AEs, preferable compliance, and lower cost. Simultaneous monthly measurement of VA stabilization and disease activity to guide anti-VEGF retreatment is more accurate, but it also imposes a considerable economic burden on health systems. Therefore, it is crucial to determine an optimal retreatment regimen, especially for myopic CNV patients in developing countries [41].

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Two multicenter RCTs [21 22] compared different anti-VEGF retreatment regimens for myopic CNV. The results found that disease activity criteria had similar visual efficacy and safety compared to VA stabilization criteria, but the number of anti-VEGF injections needed was significantly fewer in disease activity criteria. Analyzing the reasons, the anatomical changes that typically precede the actual VA loss, thereby anti-VEGF retreatment guided by disease activity criteria could control disease progression earlier and more sensitive than VA stabilization criteria [42]. VA stabilization retreatment criteria required more frequent injections of anti-VEGF, which means higher treatment costs and increases the possibility of AEs. Thus, anti-VEGF retreatment guided by disease activity criteria may be a more preferred option for the treatment of myopic CNV.

However, there were some limitations in this meta-analysis. The number of included studies was relatively small, and some RCTs had small sample size. The large degree of heterogeneity in some parameters partly due to inconsistent follow-up times of included RCTs. Besides, the followed-up duration was limited to 12-24 months, which were too short to catch more significant differences in progression of anti-VEGF therapy. Therefore, large, high quality and long-term clinical evidence is needed to support our view in the future.

CONCLUSIONS

The meta-analysis suggests that anti-VEGF is effective and well tolerated for improving VA in patients with myopic CNV comparing with sham, PDT and PDT combination therapy. Compared with VA stabilization criteria, anti-VEGF retreatment guided by disease activity criteria can produce similar therapeutic efficacy and reduce anti-VEGF injections, which may be a more recommended retreatment regimen for myopic CNV patients.

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Contributors LD: reviewed literature, data collection, prepared and revised the manuscript. GL: supervision, data collection and data analysis. ZS: data collection and revised the manuscript. XC: data collection and data analysis. JB: data analysis and critical appraisal. CZ: supervision, critical appraisal and revised the manuscript.

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Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1 Flow diagram of study selection process that was conducted in PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov.

Figure 2 Forest plot of studies examining the mean change in BCVA (logMAR).

Figure 3 Forest plot of studies examining the number of patients who gained more than 3 lines in BCVA.

Figure 4 Forest plot of studies examining the mean change in CFT.

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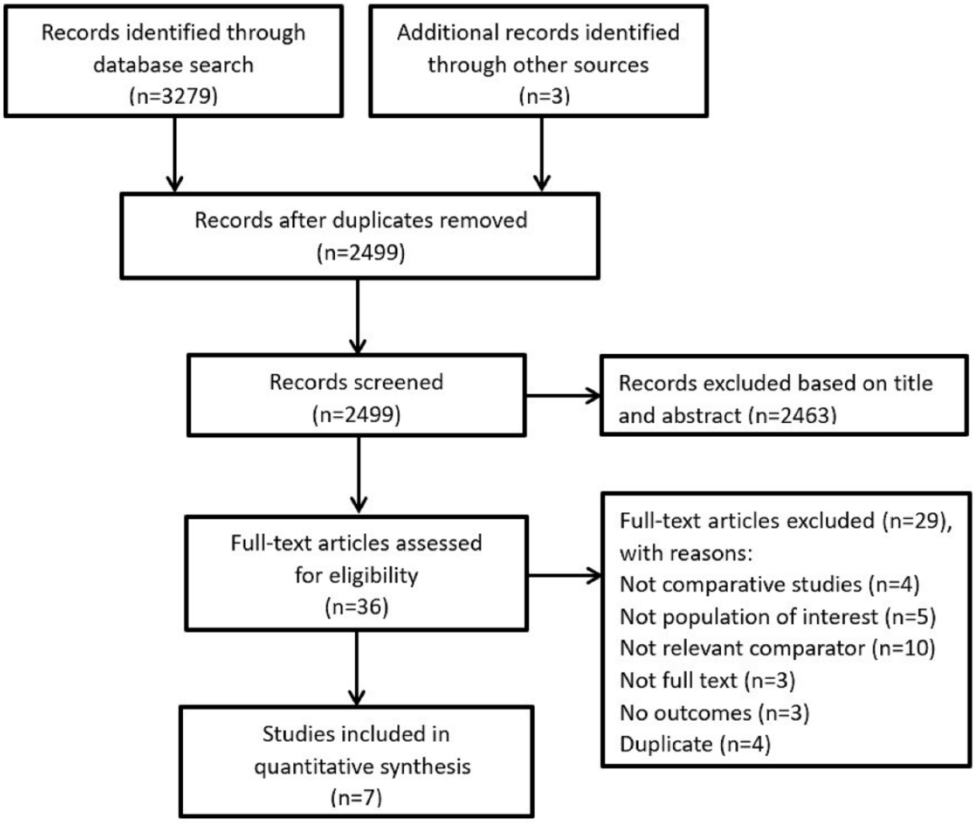

Figure 1 Flow diagram of study selection process that was conducted in PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov.

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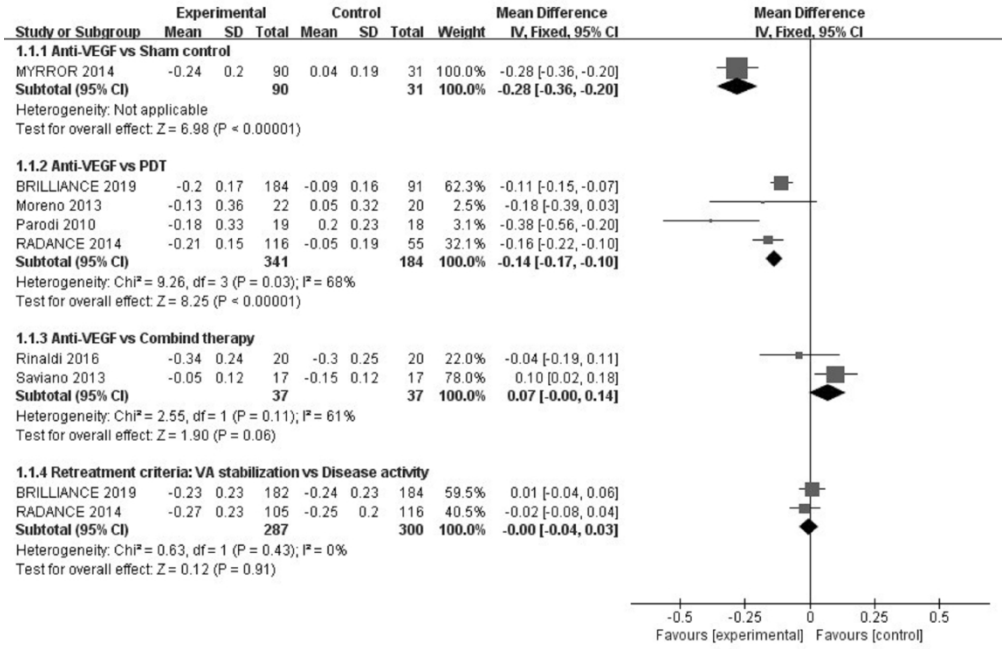

Figure 2 Forest plot of studies examining the mean change in BCVA (logMAR).

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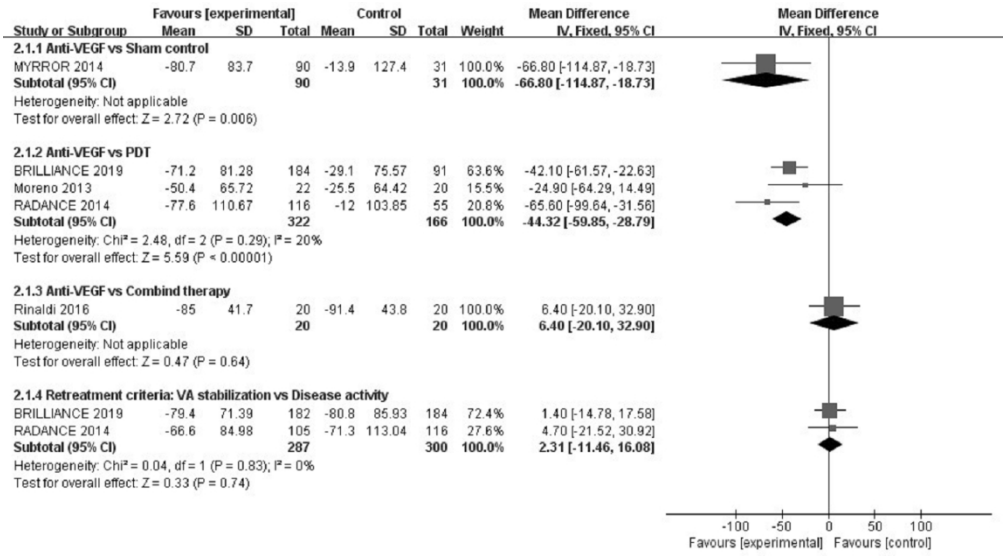

Figure 3 Forest plot of studies examining the number of patients who gained more than 3 lines in BCVA.

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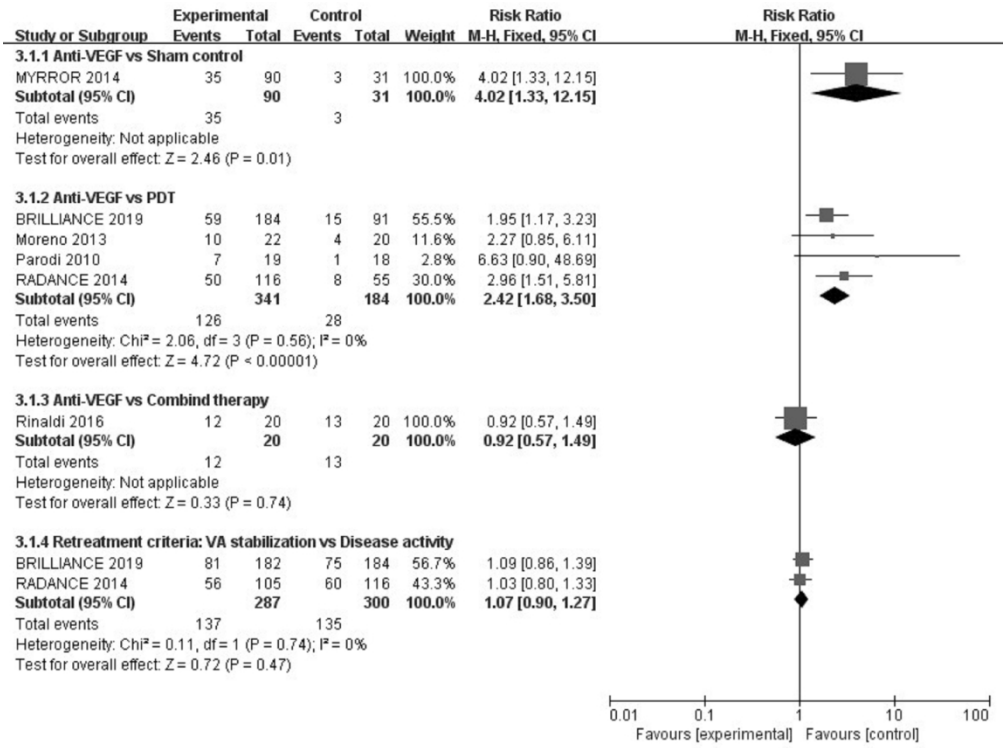

Figure 4 Forest plot of studies examining the mean change in CFT.

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Search strategy

1. PubMed search strategy

Date: From inception to 31 July 2022

Search strategy:

#1 AntiVEGF [All Fields]

#2 Anti-VEGF [All Fields]

#3 "Vascular Endothelial Growth Factors"[Mesh Terms]

#4 "Vascular Endothelial Growth Factors"[All Fields]

#5 VEGFs [All Fields]

#6 ranibizumab [MeSH Terms]

#7 ranibizumab [All Fields]

#8 rhumab [All Fields]

#9 bevacizumab [MeSH Terms]

#10 bevacizumab [All Fields]

#11 Avastin [All Fields]

#12 altuzan [All Fields]

#13 vasi [All Fields]

#14 aflibercept [All Fields]

#15 aflibercept[Supplementary Concept]

#16 eylea [All Fields]

#17 "VEGF Trap" [All Fields]

#18 Zaltrap [All Fields]

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#19 "AVE 0005" [All Fields]

#20 conbercept [All Fields]

#21 KH902 [All Fields]

#22 "KH902 fusion protein"[Supplementary Concept]

#23 Brolucizumab [Supplementary Concept]

#24 Brolucizumab [All Fields]

#25 Beovu [All Fields]

#26 RTH258 [All Fields]

#27 ESBA1008 [All Fields]

#28 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27

#29 "Choroidal Neovascularization" [MeSH Terms]

#30 "CNV" [All Fields]

#31 mCNV [All Fields]

#32 Choroid AND Neovascularization * [All Fields]

#33 Choroidal AND Neovascularization *[All Fields]

#34 #29 OR #30 OR #31 OR #32 OR #33

#35 Controlled Clinical Trial [Publication Type]

#36 Randomized Controlled Trial [Publication Type]

#37 "Controlled Clinical Trial" [All Fields]

#38 "Randomized Controlled Trial" [All Fields]

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#39 "Randomized Controlled Trial" [All Fields]

#40 RCT [All Fields]

#41 random*[All Fields]

#42 trial [All Fields]

#43 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42

#44 #28 AND #34 AND #43

Items: 920

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2. EMBASE search strategy

Date: From inception to 31 July 2022

Search strategy:

#1 AntiVEGF [All Fields]

#2 Anti-VEGF [All Fields]

#3 'vasculotropin inhibitor'/exp

#4 vasculotropin [All Fields]

#5 'Vascular Endothelial Growth Factors' [All Fields]

#6 VEGFs [All Fields]

#7 'ranibizumab'/exp

#8 ranibizumab [All Fields]

#9 lucenti [All Fields]

#10 rhumab [All Fields]

#11 'bevacizumab'/exp

#12 bevacizumab [All Fields]

#13 Avastin [All Fields]

#14 altuzan [All Fields]

#15 vasi [All Fields]

#16 aflibercept [All Fields]

#17 'aflibercept'/exp

#18 eylea [All Fields]

#19 'VEGF Trap' [All Fields]

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#20 Zaltrap [All Fields]

#21 'AVE 0005' [All Fields]

#22 'conbercept'/exp

#23 KH902 [All Fields]

#24 'Brolucizumab'/exp

#25 Brolucizumab [All Fields]

#26 Beovu [All Fields]

#27 RTH258 [All Fields]

#28 ESBA1008 [All Fields]

#29 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28

#30 'Choroidal Neovascularization'/exp

#31 CNV [All Fields]

#32 mCNV [All Fields]

#33 (Choroid AND Neovascularization*) [All Fields]

#34 (Choroidal AND Neovascularization*) [All Fields]

#35 #30 OR #31 OR #32 OR #33 OR #34

#36 'controlled clinical trial'/exp

#37 'randomized controlled trial'/exp

#38 "Controlled Clinical Trial" [All Fields]

#39 "Randomized Controlled Trial" [All Fields]

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#40 RCT [All Fields]

#41 random* [All Fields]

#42 trial [All Fields]

#43 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42

#44 #29 AND #35 AND #43

Items: 1754

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3. The Cochrane Library search strategy

Date: From inception to 31 July 2022

Search strategy:

Search term: [Title Abstract Keyword]

#1 AntiVEGF

#2 Anti-VEGF

#3 "Vascular Endothelial Growth Factors"

#4 VEGFs

#5 ranibizumab

#6 lucenti

#7 rhumab

#8 bevacizumab

#9 Avastin

#10 altuzan

#11 vasi

#12 aflibercept

#13 eylea

#14 "VEGF Trap"

#15 Zaltrap

#16 "AVE 0005"

#17 conbercept

#18 KH902

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#19 Beovu

#20 Brolucizumab

#21 RTH258

#22 ESBA1008

#23 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#24 "Choroidal Neovascularization"

#25 CNV

#26 mCNV

#27 (Choroid AND Neovascularization*)

#28 (Choroidal AND Neovascularization*)

#29 #24 OR #25 OR #26 OR #27 OR #28

#30 "Controlled Clinical Trial"

#31 "Randomized Controlled Trial"

#32 RCT

#33 random*

#34 trial

#35 #30 OR #31 OR #32 OR #33 OR #34

#36 #23 AND #29 AND #35

Items: 654

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4. Clinicaltrial.gov search strategy

Date: From inception to 31 July 2022

Condition or disease: Choroidal Neovascularization

Other terms: AntiVEGF OR Anti-VEGF OR "Vascular Endothelial Growth Factors" OR VEGFs OR ranibizumab OR lucenti OR rhumab OR bevacizumab OR Avastin OR altuzan OR vasi OR aflibercept OR eylea OR "VEGF Trap" OR Zaltrap OR "AVE 0005" OR conbercept OR KH902 OR Brolucizumab OR Beovu OR RTH258 OR ESBA1008

Study type: Interventional Studies (Clinical Trials)

Study Results: Studies With Results

Status: Recruitment: Completed

Items: 44

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Risk of bias assessment for included studies using Cochrane Collaboration's Tool.

1. Risk of bias assessment for MYRROR (2014)[1]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "MYRROR was an international, phase III, multicenter, randomized, double-masked, sham-controlled study. Eligible patients were randomized in a 3:1 ratio to receive intravitreal aflibercept or sham control (stratified by country). " The trial was described as randomised, but the method of sequence generation was not specified, we assessed as " Unclear risk " .
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	Low risk	Quote: "MYRROR was an

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and personnel (performance bias) All outcomes		international, phase III, multicenter, randomized, double-masked, sham-controlled study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "MYRROR was an international, phase III, multicenter, randomized, double-masked, sham-controlled study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In total, 122 patients were randomized, of whom 91 received intravitreal aflibercept 2.0 mg and 31 received sham; 122 patients were included in the safety set. In the full analysis set, 121 patients were included (90 patients received intravitreal aflibercept 2.0 mg and 31 received sham). " Quote: "According to participant flow data on ClinicalTrials.gov, 5 participants were withdrawn from

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		the study and 1 participant did not complete visits to week 48 due to adverse events, both in the aflibercept group. However, only 1 participant failed to fulfil requirements of full analysis set after randomisation. "
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

1. Ikuno Y, Ohno-Matsui K, Wong TY, et al. Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularization: The MYRROR Study. Ophthalmology 2015; 122:1220-7.

2. Risk of bias assessment for Parodi et al (2010)[2]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " Each patient was randomly allocated to 1 of the 3 treatment groups through a computer-generated number. "
Allocation concealment	Unclear risk	Not reported

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(selection bias)		
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "At each scheduled examination, a complete ophthalmological assessment was carried out by an investigator who had had no previous contact with the subject and was unaware of the treatment previously administered. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty-four patients affected by juxtafoveal CNV in pathologic myopia were recruited; 4 patients were excluded because they could not attend the scheduled examinations; 3 patients were not recruited because they were affected by media opacity. "
Selective reporting	Low risk	All prespecified outcomes were

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(reporting bias)		reported.
Other bias	Low risk	No other bias identified.

2. Parodi MB, Iacono P, Papayannis A, et al. Laser photocoagulation, photodynamic therapy, and intravitreal bevacizumab for the treatment of juxtafoveal choroidal neovascularization secondary to pathologic myopia. Arch Ophthalmol 2010; 128:437-42.

3. Risk of bias assessment for Moreno et al (2013)[3,4]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was done by the promotor and was provided by the IOBA." Quote: "We performed a multicenter prospective study on 55 highly myopic eyes from 55 patients with CNV who were randomized to PDT (Group 1) or intravitreal bevacizumab (IVB) (Group 2)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation was done by the promotor and was provided by the IOBA."

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Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was doubled masked: (the follow-up physician and the optometrist) and the patient were masked."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was doubled masked: (the follow-up physician and the optometrist) and the patient were masked."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Twenty-four eyes in group 1 (86%) and 25 eyes in group 2 (92.6%) completed 1 year of follow-up and 20 eyes in group 1 (71.4%) and 22 eyes in group 2 (78.6%) completed 2 years of follow-up." The loss to follow-up was > 20% at 2 years and no reason was reported.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

3. Ruiz-Moreno JM, López-Gálvez MI, Montero Moreno JA, et al. Intravitreal bevacizumab in

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myopic neovascular membranes: 24-month results. Ophthalmology 2013; 120:1510-1.e1.

4. Zhu Y, Zhang T, Xu G, et al. Anti-vascular endothelial growth factor for choroidal neovascularisation in people with pathological myopia. Cochrane Database Syst Rev 2016; 12:CD011160.

4. Risk of bias assessment for RADIANCE (2014)[5]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization list was produced by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio."
Allocation concealment (selection bias)	Low risk	Quote: "At enrollment, patients received the lowest available randomization number that then assigned them in a 2:2:1 ratio to 1 of the 3 treatment groups."
Blinding of participants and personnel	Low risk	Quote: "Due to the different appearances and routes of

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(performance bias) All outcomes		administration between the 2 treatments, all patients received either sham injection or PDT sham in conjunction with the study treatment. The PDT sham consisted of intravenous injection of 5% dextrose solution followed by light application of PDT. " Quote: "The treating investigator was unmasked and administered the randomized study medication per the protocol; however, they were not involved in any other aspects of the study and could not communicate details of the treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To ensure masking, 2 investigators were involved at each study center. All study assessments were made by the evaluating investigator, VA assessor, or other site personnel

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		who were masked to the treatment assignment. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "6(5.7%) patients discontinued from the study: 1(0.9%) unsatisfactory therapeutic effect; 1(0.9%) subject withdrew consent; 3(2.8%) lost to follow-up; 1(0.9%) protocol deviation. 4(3.4%) patients discontinued from the study: 2(1.7%) subject withdrew consent; 1(0.9%) lost to follow-up; 1(0.9%) protocol deviation. "
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

5. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology 2014; 121:682-92.e2.

5. Risk of bias assessment for BRILLIANCE (2019)[6]

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 2:2:1 to one of three treatment arms using an interactive response technology system (see Figure, Supplemental Digital Content 3, http://links.lww.com/IAE/A901, which shows treatment schedule and study design)."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible patients were randomized 2:2:1 to one of three treatment arms using an interactive response technology system (see Figure, Supplemental Digital Content 3, http://links.lww.com/IAE/A901, which shows treatment schedule and study design). "
Blinding of participants and personnel (performance bias) All	Low risk	Quote: "BRILLIANCE was a 12-month, Phase III, randomized, double-masked, multicenter,

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outcomes		active-controlled clinical trial." Quote: "For masking purpose, sham ranibizumab or sham vPDT was applied." Quote: "All patients were masked to the study treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In addition, to fulfill the masking, there were at least two investigators involved into the study: masked (assessing) investigator performing all assessments and capturing data; and an unmasked (treating) investigator administering the randomized study treatment when needed according to the protocol."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "9(4.9%) patients discontinued from the study in group 1: 1(0.5%) adverse event; 7(3.8%) subject withdrew consent; 1(0.5%) lost to follow-up." Quote: "9(4.9%) patients

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		discontinued from the study in group 2: 2(1.1%) adverse event; 3(1.6%) subject withdrew consent; 2(1.1%) administrative problems; 2(1.1%) physician's decision." Quote: "8(8.8%) patients discontinued from the study in group 3: 7(7.7%) subject withdrew consent; 1(1.1%) physician's decision."
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

6. Chen Y, Sharma T, Li X, et al. Ranibizumab versus verteporfin photodynamic therapy in Asian patients with myopic choroidal neovascularization: BRILLIANCE, a 12-month, randomized, double-masked study. Retina 2019; 39:1985-1994.

6. Risk of bias assessment for Saviano et al (2013)[7]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Thirty-four patients were included in the study and then randomized into two different

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		treatment groups." The trial was described as randomised, but the method of sequence generation was not specified, we assessed as " Unclear risk " .
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

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7. Saviano S, Piermarocchi R, Leon PE, et al. Combined therapy with bevacizumab and photodynamic therapy for myopic choroidal neovascularization: A one-year follow-up controlled study. Int J Ophthalmol 2014; 7:335-9.

7. Risk of bias assessment for Rinaldi et al (2016)[8]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using computer-generated random numbers: each number corresponded to a type of treatment."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed using computer-generated random numbers: each number corresponded to a type of treatment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was a prospective, comparative, interventional, randomized, openlabel clinical trial."

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Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study was a prospective, comparative, interventional, randomized, openlabel clinical trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the follow-up at 48 weeks."
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

8. Rinaldi M, Semeraro F, Chiosi F, et al. Reduced-fluence verteporfin photodynamic therapy plus ranibizumab for choroidal neovascularization in pathologic myopia. Graefes Arch Clin Exp Ophthalmol 2017; 255:529-539.

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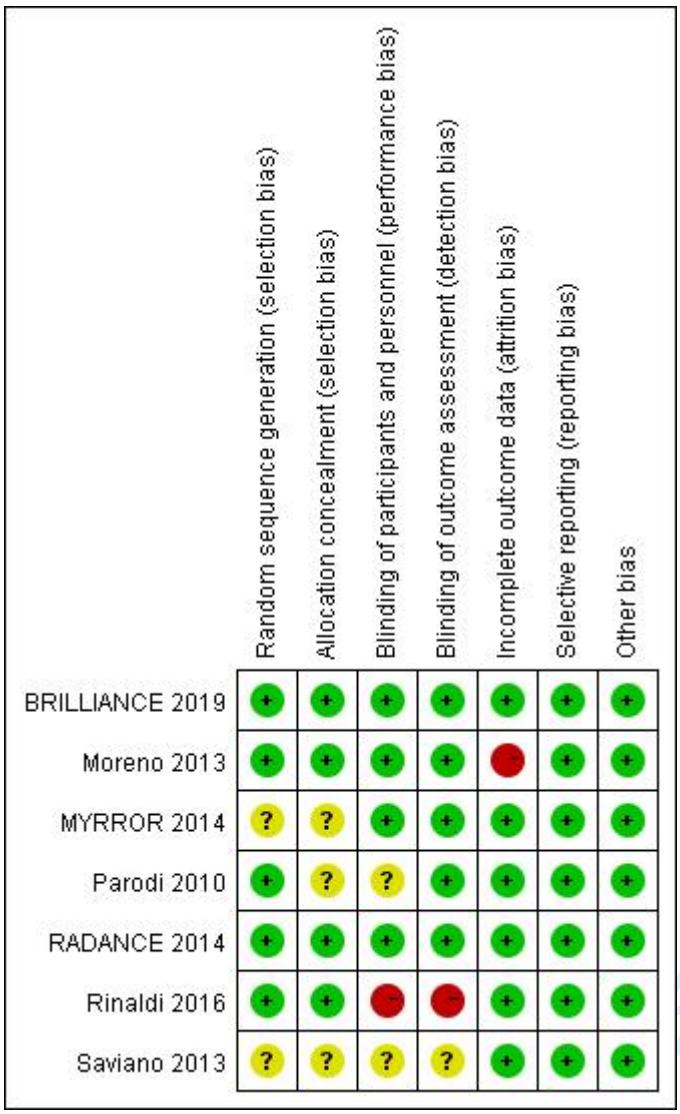
2. Risk of bias summary for included RCTs.



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Reporting checklist for systematic review (with or without a meta-analysis).

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Title	#1	Identify the report as a systematic review	1
Abstract			
Abstract	#2	Report an abstract addressing each item in the PRISMA 2020 for Abstracts checklist	2
Introduction			
Background/rationale	#3	Describe the rationale for the review in the context of existing knowledge	4,5
Objectives	#4	Provide an explicit statement of the objective(s) or question(s) the review addresses	5
Methods			

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Eligibility criteria	#5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	5,6
Information sources	#6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	5
Search strategy	#7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	5
Selection process	#8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process	6
Data collection process	#9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process	6
Data items	#10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (for example, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect	6
Study risk of bias assessment	#11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process	6
Effect measures	#12	Specify for each outcome the effect measure(s) (such as risk ratio, mean difference) used in the synthesis or presentation of results	6
Synthesis methods	#13a	Describe the processes used to decide which studies	6

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		were eligible for each synthesis (such as tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	
Synthesis methods	#13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions	6
Synthesis methods	#13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	6
Synthesis methods	#13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	6
Synthesis methods	#13e	Describe any methods used to explore possible causes of heterogeneity among study results (such as subgroup analysis, meta-regression)	6
Synthesis methods	#13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results	6
Reporting bias assessment	#14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	6
Certainty assessment	#15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	6
Data items	#10b	List and define all other variables for which data were sought (such as participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	6
Results			
Study selection	#16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (http://www.prisma-statement.org/PRISMAStatement/FlowDiagram)	7

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Study selection	#16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	7
Study characteristics	#17	Cite each included study and present its characteristics	7
Risk of bias in studies	#18	Present assessments of risk of bias for each included study	8
Results of individual studies	#19	For all outcomes, present for each study (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (such as confidence/credible interval), ideally using structured tables or plots	8-11
Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	8-11
Results of syntheses	#20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (such as confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	8-11
Results of syntheses	#20c	Present results of all investigations of possible causes of heterogeneity among study results	8-11
Results of syntheses	#20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results	supplement 2
Risk of reporting biases in syntheses	#21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	supplement 1
Certainty of evidence	#22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	8-11
Discussion			
Results in context	#23a	Provide a general interpretation of the results in the context of other evidence	11,12
Limitations of	#23b	Discuss any limitations of the evidence included in the	13

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included studies		review	
Limitations of the review methods	#23c	Discuss any limitations of the review processes used	n/a
Implications	#23d	Discuss implications of the results for practice, policy, and future research	13
Other information			
Registration and protocol	#24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	5
Registration and protocol	#24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	5
Registration and protocol	#24c	Describe and explain any amendments to information provided at registration or in the protocol	n/a
Support	#25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	14
Competing interests	#26	Declare any competing interests of review authors	14
Availability of data, code, and other materials	#27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	14

Notes:

- 20d: supplement 2
- 21: supplement 1 The PRISMA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 30. August 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Comparison of anti-vascular endothelial growth factor treatment for myopia choroidal neovascularization: a systematic review and meta-analysis of randomized controlled trials

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Primary Subject Heading:	Ophthalmology
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Comparison of anti-vascular endothelial growth factor treatment for myopia choroidal neovascularization: a systematic review and meta-analysis of randomized controlled trials

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[1]

Running title：Anti-VEGF treatment for myopia CNV

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ABSTRACT

Objectives To evaluate the efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) therapy for myopia choroidal neovascularization (CNV), and to compare the efficacy of two different anti-VEGF retreatment criteria.

Data sources PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov were searched from inception to 31 July 2022.

Study selection Randomized controlled trials (RCTs) comparing anti-VEGF with sham, photodynamic therapy (PDT) or PDT combination therapy in patients with myopia CNV were reviewed and selected. RCTs comparing visual acuity stabilization or disease activity as anti-VEGF retreatment criteria were also included in the study.

Data extraction and synthesis Two reviewers independently conducted data extraction and quality assessment. We used a random-effects model for all analyses. Primary outcomes included best-corrected visual acuity (BCVA) and central foveal thickness. Secondary outcomes included number of patients who gained more than 3 lines in BCVA, number of anti-VEGF injections and ocular adverse event (AE).

Results Seven RCTs involving 1007 patients were included. Compared to sham and PDT therapy, anti-VEGF therapy achieved better BCVA gains of -0.28 logMAR (95% CI -0.36 to -0.20, $P < 0.00001$) and -0.14 logMAR (95% CI -0.17 to -0.10, $P < 0.00001$), respectively. Both ranibizumab and bevacizumab improved patients' vision better than PDT therapy and no definitive increased risk of ocular AE was observed. Analysis of two small RCTs showed that PDT combination therapy had similar visual improvement and needed fewer anti-VEGF injections compared to anti-VEGF monotherapy (WMD=1.30; 95% CI 1.24 to 1.37, p<0.00001). Anti-VEGF retreatment guided by disease activity criteria resulted in comparable visual improvement and reduced anti-VEGF injections compared with retreatment guided by visual acuity stabilization (WMD=0.83; 95% CI 0.42 to 1.25, $P < 0.0001$).

Conclusions Anti-VEGF therapy is effective and well-tolerated for myopia CNV patients. Anti-VEGF retreatment guided by disease activity criteria can achieve comparable efficacy and potentially reduce anti-VEGF injections.

PROSPERO registration number CRD42021292806.

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Key Words anti-VEGF; myopia choroidal neovascularization; retreatment regimen; meta-analysis.

Strengths and limitations of this study

- This meta-analysis included all available data from the most recent RCTs and comprehensively compared anti-VEGF with different treatment strategies for myopic CNV.
- Our review included multicenter RCTs comparing the efficacy and number of injections of disease activity and visual acuity stabilization as anti-VEGF retreatment criteria to recommend superior anti-VEGF retreatment criteria.
- The number of included RCTs was relatively small, and some RCTs had small sample sizes, requiring larger relevant studies.
- The inconsistent follow-up time points may account for the heterogeneity of some parameters, which limits the generalizability of the study results.

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INTRODUCTION

Pathologic myopia is characterized by excessive elongation of the eyeball, leading to various degenerative changes in the retina and visual deterioration [1]. Among the complications of pathologic myopia, choroidal neovascularization (CNV) and mechanical rupture of Bruch membrane are the most serious degenerative changes [2]. Pathologic myopia is the second cause of CNV after neovascular age-related macular degeneration (nAMD), with approximately 5.2% to 11.3% of pathological myopia patients developing to myopic CNV [3 4]. Myopic CNV has a higher prevalence in Asian population, with most patients developing the disease at age 50 or younger, rather than in old age [5]. Without treatment, the majority of myopic CNV patients will develop a poor visual outcome. A 10-year follow-up study showed that over 95% of myopic CNV patients had reduced visual acuity (VA) to 0.1 or worse at 5 and 10 years after onset [6].

Before the use of anti-VEGF therapy in myopic CNV, treatment strategies mainly included laser photocoagulation, verteporfin photodynamic therapy (PDT), and submacular surgery [7-10]. However, the clinical application of these approaches is limited by complications such as myopic CNV recurrence, scarring, atrophy, and choroidal ischemia [7 11 12]. PDT has been the most widely used treatment for myopic CNV since the Verteporfin in Photodynamic Therapy (VIP) study showed that patients treated with PDT had better visual outcomes over 12 months compared to placebo [8]. However, the 2-year follow up of the VIP trial reported no statistically significant benefit from PDT treatment and a high recurrence rate of intraretinal fluid after treatment [9]. Another study showed that 83% of PDT treated patients developed choroidal atrophy after 5 years [13]. Since anti-vascular endothelial growth factor (anti-VEGF) therapy become available, PDT has fallen out of favor and only considered when anti-VEGF therapy is contraindicated.

VEGF, a proangiogenic cytokine that stimulates the development of CNV, is abnormally increased in the eyes of myopic CNV patients [14]. Anti-VEGF binds to VEGF receptor to inactivate endogenous VEGF and inhibit the migration and

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proliferation of vascular endothelial cell, thereby inhibiting neovascularization [15]. The earliest report of intraocular injection of anti-VEGF drugs for myopic CNV was in 2006 and has been increasingly used in recent years [16 17]. Although previous studies have shown that anti-VEGF therapy leads to better vision, comparative studies mainly consist of non-RCTs and a small number of RCTs, which limits the strength to support clinical application [18 19]. Furthermore, despite clinical approval of anti-VEGF therapy for myopia CNV, the optimal retreatment criteria have not been unified [20].

In recent years, new RCTs about anti-VEGF therapy for myopia CNV have been published and long-term data on efficacy and safety have been accumulated. Most importantly, two large RCTs have been completed to compare the therapeutic effects of different anti-VEGF retreatment criteria [21 22]. Our aim was to update the latest clinical evidence and to explore preferred anti-VEGF retreatment criteria for myopic CNV.

METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [23].

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data sources and search strategy

The databases of PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov were searched from inception to 31 July 2022. The meta-analysis protocol was approved and registered in PROSPERO website with a registration number of CRD42021292806. A range of MESH words and free terms regarding CNV, anti-VEGF, ranibizumab (Lucentis), bevacizumab (Avastin), aflibercept (Eylea), conbercept (Lumitin), RCT were used in all possible combinations to search for relevant articles. The search strategy is provided in the online supplementary material

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1. No language restriction was applied. We also manually searched the reference lists of included studies to identify other potentially eligible articles.

Eligibility criteria

We included the following published studies if they met the criteria: (1) patients with active myopia CNV (with spherical equivalent ≥ -6.0 dioptres and an axial length ≥ 25.0 mm); (2) studies were RCTs that directly compared intravitreal anti-VEGF drugs with sham or PDT or PDT combination therapy for the treatment of patients with myopia CNV; (3) RCTs comparing VA stabilization or disease activity as anti-VEGF retreatment criteria were included, with VA stabilization criteria was defined as no change in best-corrected visual acuity (BCVA) as compared with the two preceding monthly visits and disease activity criteria was defined as vision impairment attributable to intraretinal or subretinal fluid or active leakage secondary to myopia CNV； (4) studies reported one or more of interest outcomes. Exclusion criteria were employed as follows: (1) patients were previously treated with several drugs; (2) comparative studies between different anti-VEGF drugs, noncomparative studies, animal studies or case reports; (3) unfinished studies or unavailable data.

Data extraction and quality assessment

Titles and abstracts were scanned independently by two reviewers using the selection criteria described above. Disagreements were discussed and if necessary, resolved by a third reviewer. Data were extracted in a prespecified data extraction form. The following data were extracted from the included articles: general data (title, first author, study design, inclusion and exclusion criteria), basic characteristics (age, sex, sample size), intervention groups, follow-up time, primary outcomes (BCVA and central foveal thickness (CFT)) and secondary outcomes (number of patients who gained more than 3 lines in BCVA, number of anti-VEGF injections, and number of serious or nonserious ocular adverse events (AEs)). The quality of the RCTs was assessed using the Cochrane risk of bias tool [24].

Data synthesis and statistical analysis

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The meta-analysis was conducted using Review Manager 5.3 supplied by Cochrane Collaboration (Oxford, United Kingdom). The weighted mean difference (WMDs) with 95% confidence interval (CIs) were measured for continuous data, while the risk ratios (RRs) with 95% CIs were measured for dichotomous data. Visual outcomes were measured using the Early Treatment Retinopathy study (ETDRS) chart and the data were converted to logarithmic visual acuity (logMAR) for analyses [25 26]. Heterogeneity between studies was assessed using the I^2 test. $I^2 > 50\%$ was defined as the presence of substantial heterogeneity [27]. Due to the possibility of heterogeneity being present between studies, a more conservative version of the random-effects model was applied. A value of $p<0.05$ was chosen as the significance level for outcome measures.

RESULTS

Literature search

A total of 3376 relevant articles were initially identified. After removing 841 duplicates, we screened the remaining 2535 articles and excluded 2497 articles based on the titles and abstracts. The remaining 38 articles were retrieved for full-text review, and seven eligible RCTs [21 22 28-32] were included in the meta-analysis (figure 1). Among the seven RCTs included, one RCT compared anti-VEGF with sham treatment, four RCTs compared anti-VEGF with PDT, and two RCTs compared anti-VEGF monotherapy with PDT combination therapy. Besides, two RCTs compared different anti-VEGF retreatment criteria guided by VA stabilization criteria or disease activity criteria, respectively.

Study characteristics

The basic characteristics of seven RCTs included are shown in table 1. The study included a total of 1007 participants. The followed-up duration was 12 to 24 months. The mean age ranged from 44.6 to 62.4 years, with 52.5% to 76.5% of female. The anti-VEGF treatments used in the included studies were intravitreal bevacizumab (IVB 1.25mg), ranibizumab (IVR 0.5mg) and aflibercept (IVA 2.0mg). The PDT

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monotherapy received standard fluence PDT (50 J/cm^2), and the PDT combination therapy received reduced fluence PDT (25 J/cm^2) in combination with intravitreal anti-VEGF.

For different anti-VEGF retreatment criteria, patient retreatment guided by VA stabilization criteria received anti-VEGF on day 1 and month 1, followed by monthly injections when there was a loss of BCVA. Patient retreatment guided by disease activity criteria received anti-VEGF on day 1, followed by monthly injections when disease activity was observed.

Table 1 Characteristics of the included seven studies

Study/ Year	Study Design	NCT Trial No.	Patients	Sample Size (Patient)	Mean Age (Year)	Sex (M/F)	Intervention Groups	Follow-up (Months)
MYRROR 2014[28]	RCT	01249664	Subfoveal or juxtafoveal CNV secondary to high myopia	121	58.2±13.3	29/92	IVA (2.0 mg); Sham (no Drug)	12
Parodi 2010[29]	RCT	None	Juxtafoveal CNV secondary to pathologic myopia	37	49.45	13/24	IVB (1.25 mg); SF PDT (50 J/cm^2)	24
Moreno 2013[30]	RCT	00967850	Subfoveal and/or juxtafoveal CNV secondary to pathologic myopia	42	None	None	IVB (1.25 mg); SF PDT (50 J/cm^2)	24
RADIANCE 2014[21]	RCT	01217944	Subfoveal or juxtafoveal or extrafoveal CNV secondary to pathologic myopia	276	55.56±13.96	68/209	IVR (0.5 mg): guided by VA stabilization; IVR (0.5 mg): guided by disease activity; SF PDT (50 J/cm^2)	12
BRILLIANCE 2019[22]	RCT	01922102	Subfoveal or juxtafoveal or extrafoveal CNV secondary to pathologic myopia	457	51.2±12.7	146/311	IVR (0.5 mg): guided by VA stabilization; IVR (0.5 mg): guided by disease activity; SF PDT (50 J/cm^2)	12
Saviano 2013[31]	RCT	None	Subfoveal or juxtafoveal CNV secondary to pathologic myopia	34	62.4	8/26	IVB (1.25 mg); IVB (1.25 mg) + RF PDT*	12
Rinaldi 2016[32]	RCT	01968486	Subfoveal or juxtafoveal CNV secondary to pathologic myopia	40	44.6±4.48	19/21	IVR (0.5 mg); IVR (0.5 mg) + RF PDT (25 J/cm^2)	12

RCT, randomized controlled trial; NCT, national clinical trial; CNV, choroidal neovascularization; PDT, photodynamic therapy; anti-VEGF, anti-vascular endothelial growth factor; M/F, male/female; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVA, intravitreal aflibercept; VA, visual acuity; SF PDT, standard fluence photodynamic therapy; RF PDT, reduced fluence photodynamic therapy.

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Risk of bias assessment

Risk of bias assessment for included RCTs is shown in the online supplementary material 2. Two RCTs [21] [22] were considered to be at low risk of bias for all domains. Most unclear risk of bias was assigned in domains of selection bias or detection bias [28] [29] [31]. Two RCTs [30] [31] were considered to be at high risk of bias for performance bias and attrition bias, respectively.

Anti-VEGF therapy versus sham

MYRROR study [28] compared aflibercept with sham treatment, and results were presented at the end of 6-month because sham group could receive aflibercept when needed. The results showed that compared with the sham group, patients in anti-VEGF treatment achieved significant better BCVA (WMD=-0.28 logMA; 95% CI -0.36 to -0.20, p<0.00001; figure 2) and CFT reduction (WMD=-66.80 μm; 95% CI -114.87 to -18.73, p=0.006; figure 3. The number of patients who gained more than 3 lines in BCVA was significantly higher in the anti-VEGF treatment than in the sham treatment group (RR= 4.02, 95% CI 1.33 to 12.15, p=0.01; supplemental figure). BCVA was significantly improved in patients treated with anti-VEGF compared with the sham group (-0.24 ± 0.20 logMA vs 0.04 ± 0.19 logMA), and a greater proportion of patients achieved more than 3 lines in BCVA (38.89% vs 9.68%). In addition, anti-VEGF-treated patients had a substantially larger mean decrease in CFT than sham patients (-80.7 ± 83.7 μm vs -13.9 ± 127.4 μm).

The incidence of serious (p=0.55; table 2) and non-serious ocular AEs (p=0.13; table 2) were similar in anti-VEGF and sham treatment groups. There were 3 serious ocular AEs (only 1 macular hole in study eye) in anti-VEGF group and no event occurred in sham treatment group. The most common non-serious ocular AEs in anti-VEGF treated patients were mild conjunctival hemorrhage, punctate keratitis, eye pain and dry eye, but did not lead to the interruption of treatment.

Table 2 Meta-analysis results of the number of anti-VEGF injections, serious and non-serious ocular adverse events

Comparison	No. of RCTs	Risk ratio	P	I^2 (%)	P for

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	(no. of Patients)	(95% CI)			heterogeneity
The number of anti-VEGF injections					
Anti-VEGF monotherapy vs PDT combination therapy	2(74) [31 32]	1.30 (1.24,1.37)	0.00001	32	0.23
Anti-VEGF retreatment criteria: VA stabilization vs Disease activity	2(587) [21 22]	0.83 (0.42,1.25)	0.0001	0	0.38
The number of serious ocular adverse events					
Anti-VEGF therapy vs Sham	1(121) [28]	2.46 (0.13,46.36)	0.55	—	—
Anti-VEGF therapy vs PDT	4(525) [21 22 29 30]	0.81(0.11,6.10)	0.84	0	0.62
Anti-VEGF retreatment criteria: VA stabilization vs Disease activity	2(587) [21 22]	1.06 (0.15,7.45)	0.96	0	0.96
The number of non-serious ocular adverse events					
Anti-VEGF therapy vs Sham	1(121) [28]	0.57 (0.28,1.18)	0.13	—	—
Anti-VEGF therapy vs PDT	4(525) [21 22 29 30]	1.02(0.77,1.36)	0.88	0	0.90
Anti-VEGF monotherapy vs PDT combination therapy	2(74) [31 32]	1.57 (0.77,3.22)	0.22	—	—
Anti-VEGF retreatment criteria: VA stabilization vs Disease activity	2(587) [21 22]	1.04 (0.83,1.31)	0.72	0	0.41

RCT, randomized controlled trial; anti-VEGF, anti-vascular endothelial growth factor; PDT, photodynamic therapy; VA, visual acuity.

Anti-VEGF therapy versus PDT

Four RCTs [21 22 29 30] compared anti-VEGF with PDT treatment, with two studies comparing ranibizumab [21 22] and the other two comparing bevacizumab [29 30] with PDT treatment. For the RADIANCE and BRILLIANCE study [21 22], results were presented at the end of 3-month because patients in PDT group could receive ranibizumab when needed. A significant increase of BCVA from baseline was observed in both groups. Compared to PDT, the mean improvement of BCVA (WMD=-0.14 logMAR; 95% CI -0.17 to -0.10, p<0.00001, I^2=68%; figure 2) and reduction of CFT (WMD=-44.32 μm; 95% CI -59.85 to -28.79, p<0.00001, I^2=20%; figure 3) were superior in anti-VEGF group. And the number of patients who gained more than 3 lines in BCVA was higher in anti-VEGF group (RR=2.42; 95% CI 1.68 to 3.50, p<0.00001, I^2=0%; supplemental figure), too. More clinically meaningful VA improvements were obtained with either ranibizumab or bevacizumab treatment. Compared to PDT,

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patients treated with ranibizumab had a better mean BCVA of -0.13 logMAR and a greater reduction in CFT of 47.89 µm; bevacizumab-treated patients had a better mean BCVA of -0.29 logMAR and a greater reduction in CFT of 24.90 µm (supplementary material 3, figure 1 and 2).

Anti-VEGF group recorded 2 serious ocular AEs (1 retinal detachment and 1 retinoschisis) and PDT group recorded 1 endophthalmitis (p=0.84; table 2). This endophthalmitis occurred in a patient in the PDT group who received PDT on the first day followed by an injection of anti-VEGF. Therefore, endophthalmitis was considered to be related to anti-VEGF injection. The non-serious ocular AEs showed no evidence of a difference between the two groups (p=0.88; table 2), conjunctival hemorrhage and punctate keratitis were most commonly reported.

Anti-VEGF monotherapy versus PDT combination therapy

Two small RCTs [31] [32] compared anti-VEGF monotherapy with PDT combination therapy. There was no evidence of differences in mean BCVA (WMD=0.07 logMAR; 95% CI -0.00 to 0.14, p=0.06, I^2=61%; figure 2) and CFT (WMD=6.40 µm; 95% CI -20.10 to 32.90, p=0.64; figure 3) between the two groups. The number of patients who gained more than 3 lines in BCVA (RR=0.92; 95% CI 0.57 to 1.49, p=0.74; figure 3) was similar in both groups, too. Patients in both the anti-VEGF monotherapy group and the PDT combination therapy group obtained significant visual function and anatomic improvements. Nevertheless, the anti-VEGF injections in PDT combination therapy was statistically fewer than anti-VEGF monotherapy group (WMD=1.30; 95% CI 1.24 to 1.37, p<0.00001, I^2=32%; table 2). No serious ocular AEs were documented, but some mild non-serious ocular AEs were observed in both groups, including ocular hyperemia, myodesopsia, conjunctival hemorrhage and eye pain (p=0.22; table 2).

Anti-VEGF retreatment criteria: VA stabilization versus disease activity

Two RCTs [21] [22] compared the therapeutic effect of different anti-VEGF retreatment criteria. No evidence of a difference in mean BCVA (WMD=-0.00 logMAR; 95% CI

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−0.04 to 0.03, p=0.91, I^2=0%; figure 2) and CFT change (WMD=2.31 μm; 95% CI -11.46 to 16.08, p=0.74, I^2=0%; figure 3) between the two groups. Similar results were obtained for the number of patients who gained more than 3 lines in BCVA (RR=1.07; 95% CI 0.90 to 1.27, p=0.47, I^2=0%; supplemental figure). Interestingly, the number of anti-VEGF injections guided by disease activity criteria was significantly fewer than in VA stabilization criteria group (WMD=0.83; 95% CI 0.42 to 1.25, p<0.0001, I^2=0%; table 2). The mean change in BCVA (-0.24 ± 0.23 logMA vs -0.24 ± 0.22 logMA) and patients who gained more than 3 lines in BCVA (47.74% vs 45.00%) from baseline was similar in both anti-VEGF retreatment groups. For anatomical changes, clinically relevant decrease in CFT (-74.72 ± 76.74 μm vs -77.13 ± 97.24 μm) from baseline was observed in both groups.

Safety profile showed no evidence of a difference in patients between the two anti-VEGF retreatment criteria. There were 2 serious ocular AEs, respective 1 retinal detachment in VA stabilization criteria and 1 retinoschisis in disease activity criteria group. The most commonly reported non-serious ocular AE was conjunctival hemorrhage (p=0.72; table 2).

DISCUSSION

In this meta-analysis, we evaluated the efficacy and safety of anti-VEGF treatment and compared two different anti-VEGF retreatment criteria. Evidences showed that anti-VEGF was superior to improving VA compared to sham or PDT treatment. PDT combination therapy showed similar visual improvement and needed fewer anti-VEGF injections compared to anti-VEGF monotherapy. For different retreatment criteria, anti-VEGF retreatment guided by disease activity criteria could achieve similar visual gain and need fewer anti-VEGF injections compare to VA stabilization criteria. Therefore, this review can provide the latest update on the systematic review of anti-VEGF treatment and provide evidence for optimizing retreatment criteria for myopia CNV.

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Myopic CNV was a progressive disease and VA in the sham treatment group became worse than at baseline without treatment [21]. The short-term treatment effect of PDT was remarkable, but the long-term effect was poor and the recurrence rate was high [9 13]. Analysis results indicated that anti-VEGF therapy had a better visual and anatomical improvement than sham or PDT treatment. The analysis showed that both ranibizumab or bevacizumab improved patients' visual acuity better compared to PDT treatment. Moreover, the post hoc analyses of RADIANCE study demonstrated BCVA gain of anti-VEGF therapy was sustained over additional 36 months [33].

When comparing anti-VEGF monotherapy, PDT combination therapy showed similar visual improvement with fewer anti-VEGF injections. The reduction in the number of anti-VEGF injections may be beneficial for patients who are unwilling or unable to participate in monthly monitoring visits. Patients may also benefit from a reduced risk of complications related to surgery as well as the low-cost benefits of anti-VEGF. Thus, combined PDT with anti-VEGF therapy may be an alternative for the treatment of myopia CNV patients. However, larger comparative studies with longer follow-up are needed to adequately compare the efficacy and cost-effectiveness of anti-VEGF monotherapy with PDT combination therapy.

For safety estimation, there was no evidence of a difference in the incidence of serious and non-serious ocular AEs between anti-VEGF therapy and other treatments. The most common ocular AEs of anti-VEGF treatment were mild conjunctival hemorrhage and punctate keratitis, which were well tolerated in myopic CNV patients. Although some cases reported that new onset myopic macular retinoschisis (MRS) may be a complication of anti-VEGF intravitreal therapy, only 1 MRS event was reported in MYRROR study, and another study also found there was no association between the new onset of MRS and anti-VEGF therapy [34-36].

Currently, the guidance and consensus statement recommended anti-VEGF therapy for myopic CNV, but do not point out the definite criteria for retreatment [12 20]. Most clinical research refer to retreatment criteria guided by disease activity criteria (intraretinal or subretinal fluid or active leakage) or VA stabilization criteria (BCVA change), or both [37-40]. The use of different retreatment criteria may affect retreatment

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rates and the number of anti-VEGF injections. Fewer anti-VEGF injections can lead to lower risk of AEs, preferable compliance, and lower cost. Simultaneous monthly measurement of VA stabilization and disease activity to guide anti-VEGF retreatment are more accurate, but it also imposes a considerable economic burden on health systems. Therefore, it is crucial to determine optimal retreatment criteria, especially for myopic CNV patients in developing countries [41].

Two multicenter RCTs [21 22] compared different anti-VEGF retreatment criteria for myopic CNV. The results found that disease activity criteria had similar visual efficacy and safety compared to VA stabilization criteria, but the disease activity criteria required significantly fewer anti-VEGF injections. Analyzing the reasons, the anatomical changes that typically precede the actual VA loss, thereby anti-VEGF retreatment guided by disease activity criteria could control disease progression earlier and more sensitive than VA stabilization criteria [42 43]. VA stabilization retreatment criteria required more frequent injections of anti-VEGF, which means higher treatment costs and increases the possibility of AEs. Thus, anti-VEGF retreatment guided by disease activity criteria may be a more preferred option for the treatment of myopic CNV.

However, there were some limitations in this meta-analysis. The number of included studies was relatively small, and some RCTs had small sample size. There was substantial heterogeneity in some parameters, partly due to inconsistent follow-up times of included RCTs. Besides, the followed-up duration was limited to 12-24 months, which were too short to catch more significant differences in progression of anti-VEGF therapy. Therefore, large, high quality and long-term clinical evidence is needed to support our view in the future.

CONCLUSIONS

The meta-analysis suggests that anti-VEGF is effective and well tolerated for improving VA in patients with myopic CNV comparing with sham and PDT therapy. Compared with VA stabilization criteria, anti-VEGF retreatment guided by disease

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activity criteria can produce similar therapeutic efficacy and reduce anti-VEGF injections, which may be a more recommended retreatment criterion for myopic CNV patients. Moreover, considering the limitations of the relatively small number and size of studies, it remains uncertain whether the combination of PDT with anti-VEGF therapy can be a good alternative to anti-VEGF monotherapy.

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Contributors LD: reviewed literature, data collection, prepared and revised the manuscript. GL: supervision, data collection and data analysis. ZS: data collection and revised the manuscript. XC: data collection and data analysis. JB: data analysis and critical appraisal. CZ: supervision, critical appraisal and revised the manuscript.

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Figure legends

Figure 1 Flow diagram of study selection process that was conducted in PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov.

Figure 2 Forest plot of studies examining the mean change in BCVA (logMAR).

Figure 3 Forest plot of studies examining the mean change in CFT.

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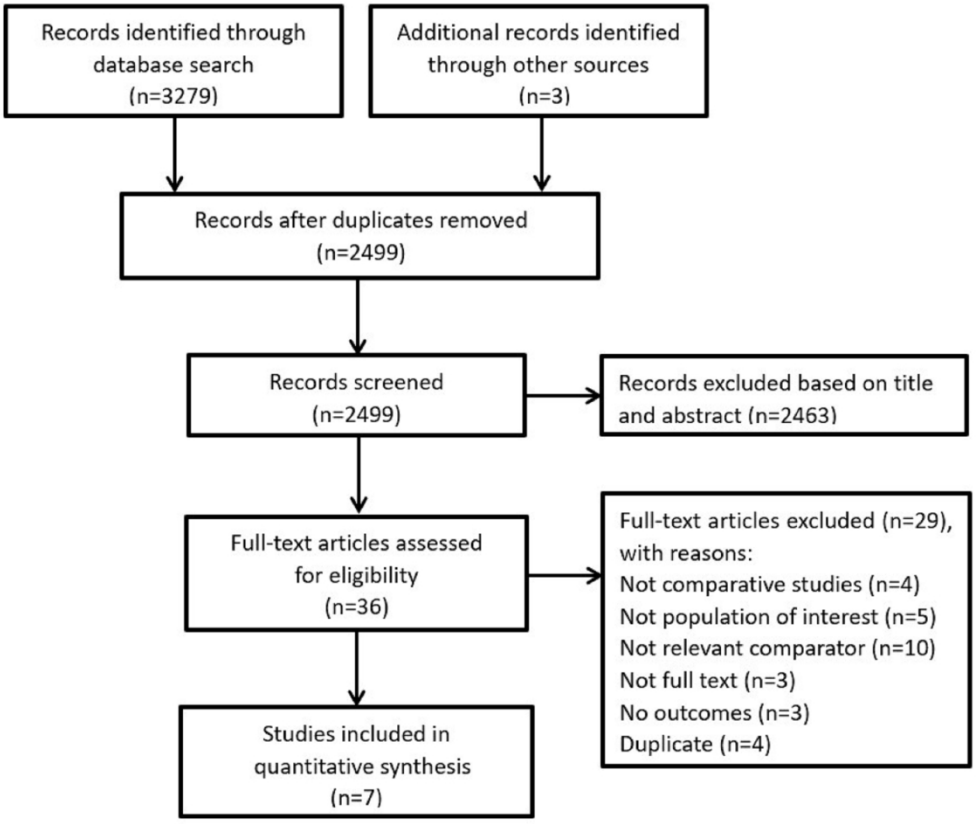

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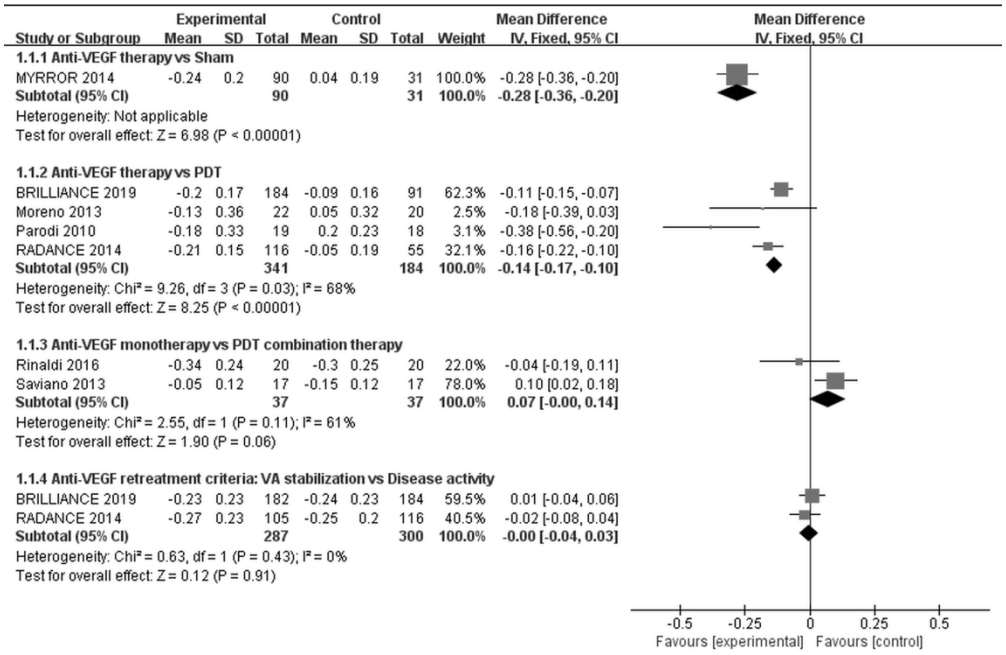

Figure 2 Forest plot of studies examining the mean change in BCVA (logMAR).

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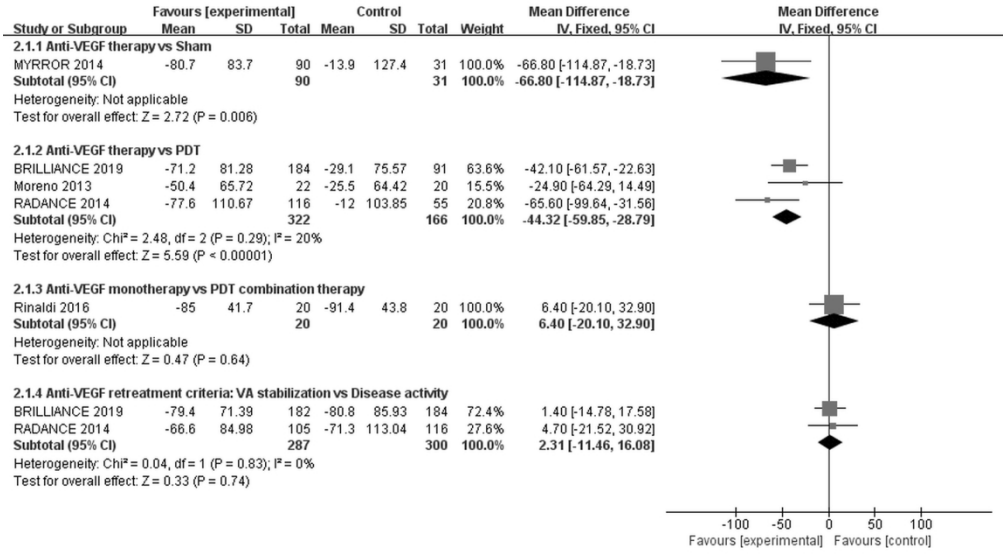

Figure 3 Forest plot of studies examining the mean change in CFT.

169x93mm (300 x 300 DPI)

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Search strategy

1. PubMed search strategy

Date: From inception to 31 July 2022

Search strategy:

#1 AntiVEGF [All Fields]

#2 Anti-VEGF [All Fields]

#3 "Vascular Endothelial Growth Factors"[Mesh Terms]

#4 "Vascular Endothelial Growth Factors"[All Fields]

#5 VEGFs [All Fields]

#6 ranibizumab [MeSH Terms]

#7 ranibizumab [All Fields]

#8 rhumab [All Fields]

#9 bevacizumab [MeSH Terms]

#10 bevacizumab [All Fields]

#11 Avastin [All Fields]

#12 altuzan [All Fields]

#13 vasi [All Fields]

#14 aflibercept [All Fields]

#15 aflibercept[Supplementary Concept]

#16 eylea [All Fields]

#17 "VEGF Trap" [All Fields]

#18 Zaltrap [All Fields]

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#19 "AVE 0005" [All Fields]

#20 conbercept [All Fields]

#21 KH902 [All Fields]

#22 "KH902 fusion protein"[Supplementary Concept]

#23 Brolucizumab [Supplementary Concept]

#24 Brolucizumab [All Fields]

#25 Beovu [All Fields]

#26 RTH258 [All Fields]

#27 ESBA1008 [All Fields]

#28 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27

#29 "Choroidal Neovascularization" [MeSH Terms]

#30 "CNV" [All Fields]

#31 mCNV [All Fields]

#32 Choroid AND Neovascularization * [All Fields]

#33 Choroidal AND Neovascularization *[All Fields]

#34 #29 OR #30 OR #31 OR #32 OR #33

#35 Controlled Clinical Trial [Publication Type]

#36 Randomized Controlled Trial [Publication Type]

#37 "Controlled Clinical Trial" [All Fields]

#38 "Randomized Controlled Trial" [All Fields]

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#39 "Randomized Controlled Trial" [All Fields]

#40 RCT [All Fields]

#41 random*[All Fields]

#42 trial [All Fields]

#43 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42

#44 #28 AND #34 AND #43

Items: 920

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2. EMBASE search strategy

Date: From inception to 31 July 2022

Search strategy:

#1 AntiVEGF [All Fields]

#2 Anti-VEGF [All Fields]

#3 'vasculotropin inhibitor'/exp

#4 vasculotropin [All Fields]

#5 'Vascular Endothelial Growth Factors' [All Fields]

#6 VEGFs [All Fields]

#7 'ranibizumab'/exp

#8 ranibizumab [All Fields]

#9 lucenti [All Fields]

#10 rhumab [All Fields]

#11 'bevacizumab'/exp

#12 bevacizumab [All Fields]

#13 Avastin [All Fields]

#14 altuzan [All Fields]

#15 vasi [All Fields]

#16 aflibercept [All Fields]

#17 'aflibercept'/exp

#18 eylea [All Fields]

#19 'VEGF Trap' [All Fields]

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#20 Zaltrap [All Fields]

#21 'AVE 0005' [All Fields]

#22 'conbercept'/exp

#23 KH902 [All Fields]

#24 'Brolucizumab'/exp

#25 Brolucizumab [All Fields]

#26 Beovu [All Fields]

#27 RTH258 [All Fields]

#28 ESBA1008 [All Fields]

#29 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28

#30 'Choroidal Neovascularization'/exp

#31 CNV [All Fields]

#32 mCNV [All Fields]

#33 (Choroid AND Neovascularization*) [All Fields]

#34 (Choroidal AND Neovascularization*) [All Fields]

#35 #30 OR #31 OR #32 OR #33 OR #34

#36 'controlled clinical trial'/exp

#37 'randomized controlled trial'/exp

#38 "Controlled Clinical Trial" [All Fields]

#39 "Randomized Controlled Trial" [All Fields]

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#40 RCT [All Fields]

#41 random* [All Fields]

#42 trial [All Fields]

#43 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42

#44 #29 AND #35 AND #43

Items: 1754

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3. The Cochrane Library search strategy

Date: From inception to 31 July 2022

Search strategy:

Search term: [Title Abstract Keyword]

#1 AntiVEGF

#2 Anti-VEGF

#3 "Vascular Endothelial Growth Factors"

#4 VEGFs

#5 ranibizumab

#6 lucenti

#7 rhumab

#8 bevacizumab

#9 Avastin

#10 altuzan

#11 vasi

#12 aflibercept

#13 eylea

#14 "VEGF Trap"

#15 Zaltrap

#16 "AVE 0005"

#17 conbercept

#18 KH902

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#19 Beovu

#20 Brolucizumab

#21 RTH258

#22 ESBA1008

#23 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#24 "Choroidal Neovascularization"

#25 CNV

#26 mCNV

#27 (Choroid AND Neovascularization*)

#28 (Choroidal AND Neovascularization*)

#29 #24 OR #25 OR #26 OR #27 OR #28

#30 "Controlled Clinical Trial"

#31 "Randomized Controlled Trial"

#32 RCT

#33 random*

#34 trial

#35 #30 OR #31 OR #32 OR #33 OR #34

#36 #23 AND #29 AND #35

Items: 654

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4. Clinicaltrial.gov search strategy

Date: From inception to 31 July 2022

Condition or disease: Choroidal Neovascularization

Other terms: AntiVEGF OR Anti-VEGF OR "Vascular Endothelial Growth Factors" OR VEGFs OR ranibizumab OR lucenti OR rhumab OR bevacizumab OR Avastin OR altuzan OR vasi OR aflibercept OR eylea OR "VEGF Trap" OR Zaltrap OR "AVE 0005" OR conbercept OR KH902 OR Brolucizumab OR Beovu OR RTH258 OR ESBA1008

Study type: Interventional Studies (Clinical Trials)

Study Results: Studies With Results

Status: Recruitment: Completed

Items: 44

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Risk of bias assessment for included studies using Cochrane Collaboration's Tool.

1. Risk of bias assessment for MYRROR (2014)[1]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "MYRROR was an international, phase III, multicenter, randomized, double-masked, sham-controlled study. Eligible patients were randomized in a 3:1 ratio to receive intravitreal aflibercept or sham control (stratified by country). " The trial was described as randomised, but the method of sequence generation was not specified, we assessed as " Unclear risk " .
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	Low risk	Quote: "MYRROR was an

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and personnel (performance bias) All outcomes		international, phase III, multicenter, randomized, double-masked, sham-controlled study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "MYRROR was an international, phase III, multicenter, randomized, double-masked, sham-controlled study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In total, 122 patients were randomized, of whom 91 received intravitreal aflibercept 2.0 mg and 31 received sham; 122 patients were included in the safety set. In the full analysis set, 121 patients were included (90 patients received intravitreal aflibercept 2.0 mg and 31 received sham). " Quote: "According to participant flow data on ClinicalTrials.gov, 5 participants were withdrawn from

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		the study and 1 participant did not complete visits to week 48 due to adverse events, both in the aflibercept group. However, only 1 participant failed to fulfil requirements of full analysis set after randomisation. "
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

1. Ikuno Y, Ohno-Matsui K, Wong TY, et al. Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularization: The MYRROR Study. Ophthalmology 2015; 122:1220-7.

2. Risk of bias assessment for Parodi et al (2010)[2]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " Each patient was randomly allocated to 1 of the 3 treatment groups through a computer-generated number. "
Allocation concealment	Unclear risk	Not reported

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(selection bias)		
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "At each scheduled examination, a complete ophthalmological assessment was carried out by an investigator who had had no previous contact with the subject and was unaware of the treatment previously administered. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty-four patients affected by juxtafoveal CNV in pathologic myopia were recruited; 4 patients were excluded because they could not attend the scheduled examinations; 3 patients were not recruited because they were affected by media opacity. "
Selective reporting	Low risk	All prespecified outcomes were

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(reporting bias)		reported.
Other bias	Low risk	No other bias identified.

2. Parodi MB, Iacono P, Papayannis A, et al. Laser photocoagulation, photodynamic therapy, and intravitreal bevacizumab for the treatment of juxtafoveal choroidal neovascularization secondary to pathologic myopia. Arch Ophthalmol 2010; 128:437-42.

3. Risk of bias assessment for Moreno et al (2013)[3,4]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was done by the promotor and was provided by the IOBA." Quote: "We performed a multicenter prospective study on 55 highly myopic eyes from 55 patients with CNV who were randomized to PDT (Group 1) or intravitreal bevacizumab (IVB) (Group 2)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation was done by the promotor and was provided by the IOBA."

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Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was doubled masked: (the follow-up physician and the optometrist) and the patient were masked."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was doubled masked: (the follow-up physician and the optometrist) and the patient were masked."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Twenty-four eyes in group 1 (86%) and 25 eyes in group 2 (92.6%) completed 1 year of follow-up and 20 eyes in group 1 (71.4%) and 22 eyes in group 2 (78.6%) completed 2 years of follow-up." The loss to follow-up was > 20% at 2 years and no reason was reported.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

3. Ruiz-Moreno JM, López-Gálvez MI, Montero Moreno JA, et al. Intravitreal bevacizumab in

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myopic neovascular membranes: 24-month results. Ophthalmology 2013; 120:1510-1.e1.

4. Zhu Y, Zhang T, Xu G, et al. Anti-vascular endothelial growth factor for choroidal neovascularisation in people with pathological myopia. Cochrane Database Syst Rev 2016; 12:CD011160.

4. Risk of bias assessment for RADIANCE (2014)[5]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization list was produced by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio."
Allocation concealment (selection bias)	Low risk	Quote: "At enrollment, patients received the lowest available randomization number that then assigned them in a 2:2:1 ratio to 1 of the 3 treatment groups."
Blinding of participants and personnel	Low risk	Quote: "Due to the different appearances and routes of

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(performance bias) All outcomes		administration between the 2 treatments, all patients received either sham injection or PDT sham in conjunction with the study treatment. The PDT sham consisted of intravenous injection of 5% dextrose solution followed by light application of PDT. " Quote: "The treating investigator was unmasked and administered the randomized study medication per the protocol; however, they were not involved in any other aspects of the study and could not communicate details of the treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To ensure masking, 2 investigators were involved at each study center. All study assessments were made by the evaluating investigator, VA assessor, or other site personnel

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		who were masked to the treatment assignment. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "6(5.7%) patients discontinued from the study: 1(0.9%) unsatisfactory therapeutic effect; 1(0.9%) subject withdrew consent; 3(2.8%) lost to follow-up; 1(0.9%) protocol deviation. 4(3.4%) patients discontinued from the study: 2(1.7%) subject withdrew consent; 1(0.9%) lost to follow-up; 1(0.9%) protocol deviation. "
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

5. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology 2014; 121:682-92.e2.

5. Risk of bias assessment for BRILLIANCE (2019)[6]

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 2:2:1 to one of three treatment arms using an interactive response technology system (see Figure, Supplemental Digital Content 3, http://links.lww.com/IAE/A901, which shows treatment schedule and study design)."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible patients were randomized 2:2:1 to one of three treatment arms using an interactive response technology system (see Figure, Supplemental Digital Content 3, http://links.lww.com/IAE/A901, which shows treatment schedule and study design). "
Blinding of participants and personnel (performance bias) All	Low risk	Quote: "BRILLIANCE was a 12-month, Phase III, randomized, double-masked, multicenter,

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outcomes		active-controlled clinical trial." Quote: "For masking purpose, sham ranibizumab or sham vPDT was applied." Quote: "All patients were masked to the study treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In addition, to fulfill the masking, there were at least two investigators involved into the study: masked (assessing) investigator performing all assessments and capturing data; and an unmasked (treating) investigator administering the randomized study treatment when needed according to the protocol."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "9(4.9%) patients discontinued from the study in group 1: 1(0.5%) adverse event; 7(3.8%) subject withdrew consent; 1(0.5%) lost to follow-up." Quote: "9(4.9%) patients

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		discontinued from the study in group 2: 2(1.1%) adverse event; 3(1.6%) subject withdrew consent; 2(1.1%) administrative problems; 2(1.1%) physician's decision." Quote: "8(8.8%) patients discontinued from the study in group 3: 7(7.7%) subject withdrew consent; 1(1.1%) physician's decision."
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

6. Chen Y, Sharma T, Li X, et al. Ranibizumab versus verteporfin photodynamic therapy in Asian patients with myopic choroidal neovascularization: BRILLIANCE, a 12-month, randomized, double-masked study. Retina 2019; 39:1985-1994.

6. Risk of bias assessment for Saviano et al (2013)[7]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Thirty-four patients were included in the study and then randomized into two different

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		treatment groups." The trial was described as randomised, but the method of sequence generation was not specified, we assessed as " Unclear risk " .
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

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7. Saviano S, Piermarocchi R, Leon PE, et al. Combined therapy with bevacizumab and photodynamic therapy for myopic choroidal neovascularization: A one-year follow-up controlled study. Int J Ophthalmol 2014; 7:335-9.

7. Risk of bias assessment for Rinaldi et al (2016)[8]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using computer-generated random numbers: each number corresponded to a type of treatment."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed using computer-generated random numbers: each number corresponded to a type of treatment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was a prospective, comparative, interventional, randomized, openlabel clinical trial."

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Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study was a prospective, comparative, interventional, randomized, openlabel clinical trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the follow-up at 48 weeks."
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other bias identified.

8. Rinaldi M, Semeraro F, Chiosi F, et al. Reduced-fluence verteporfin photodynamic therapy plus ranibizumab for choroidal neovascularization in pathologic myopia. Graefes Arch Clin Exp Ophthalmol 2017; 255:529-539.

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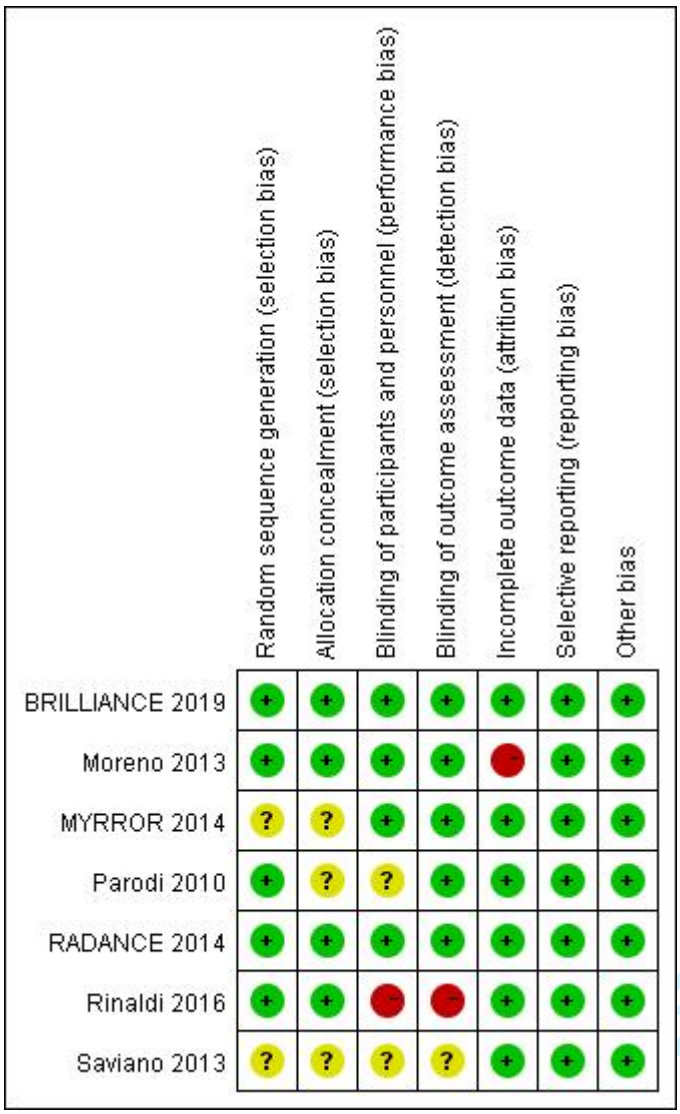
2. Risk of bias summary for included RCTs.



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Meta-analysis results of different anti-VEGF versus PDT treatment for myopia CNV.

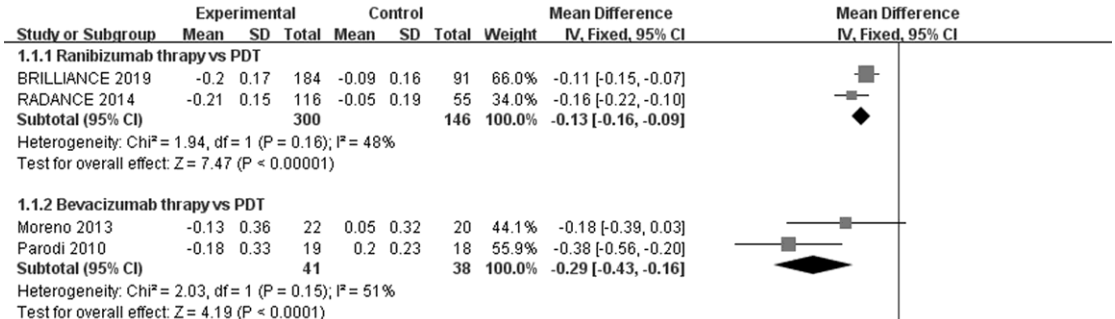

Figure 1 Forest plot of studies examining the mean change in BCVA (logMAR).

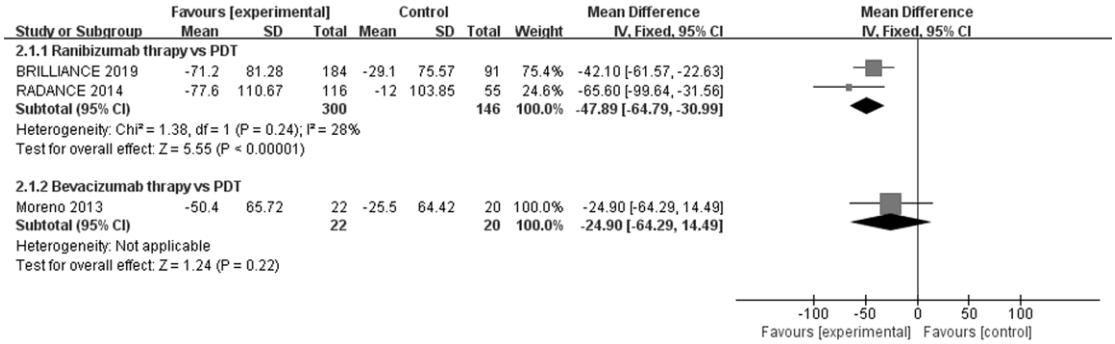

Figure 2 Forest plot of studies examining the mean change in CFT.

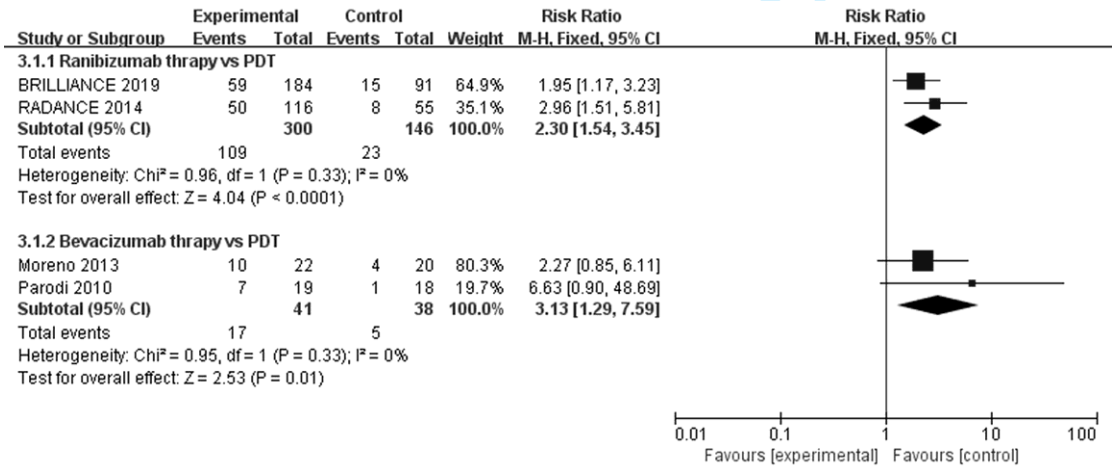

Figure 3 Forest plot of studies examining the number of patients who gained more than 3 lines in BCVA.

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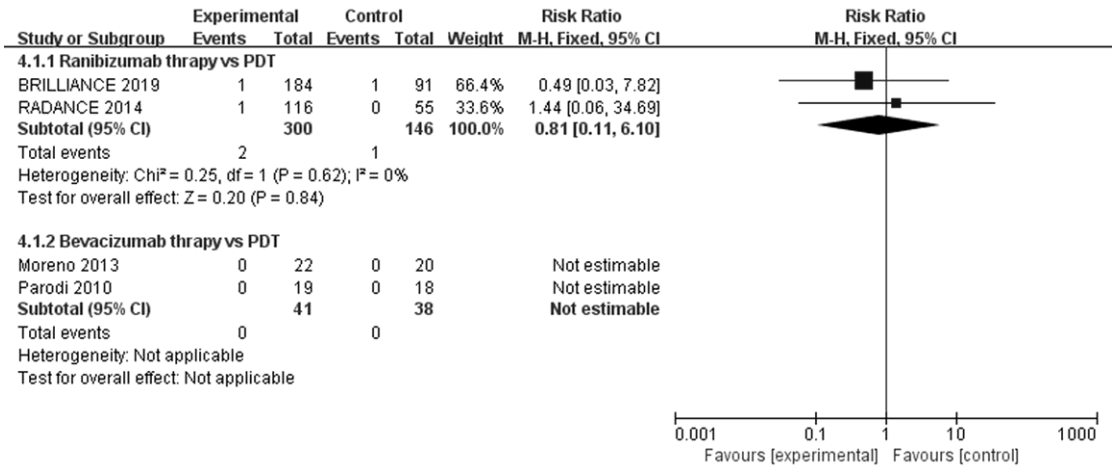

Figure 4 Forest plot of studies examining the serious ocular adverse events.

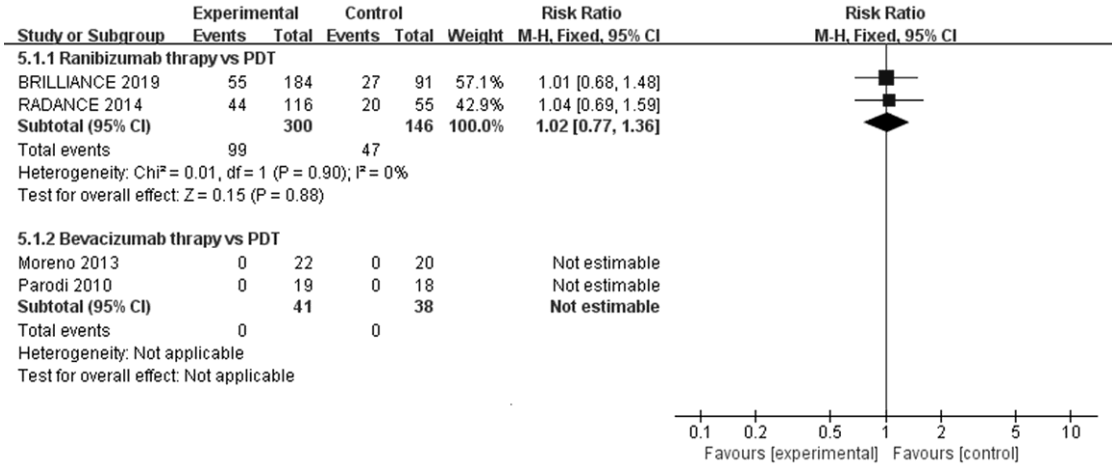

Figure 5 Forest plot of studies examining the non-serious ocular adverse events.

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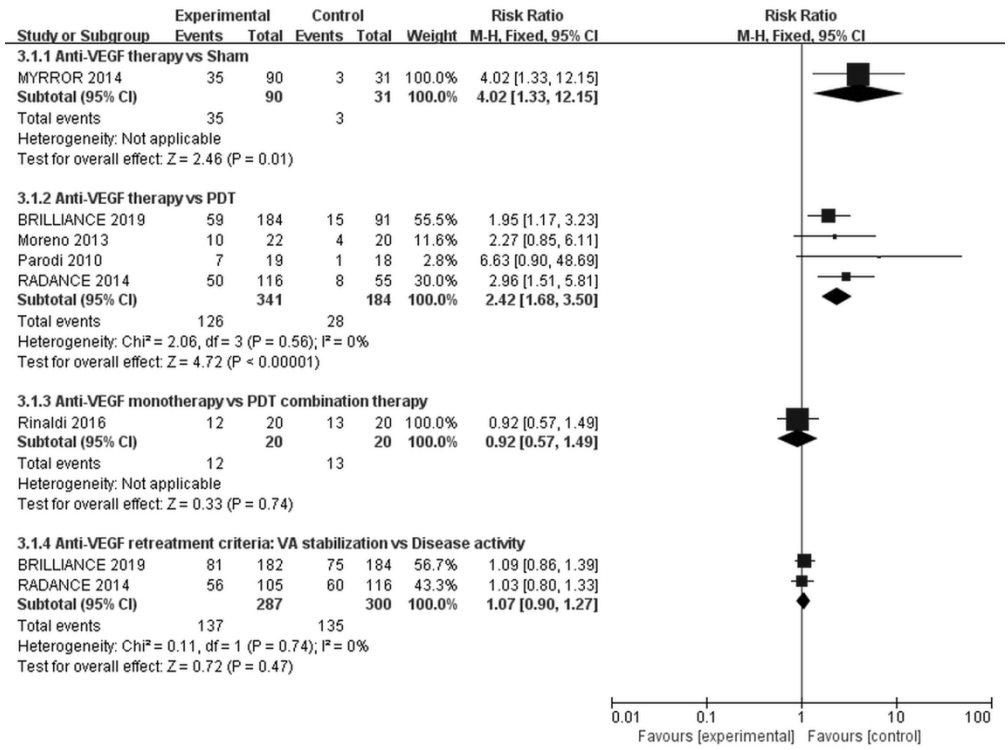

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Reporting checklist for systematic review (with or without a meta-analysis).

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews

		Reporting Item	Page Number
Title			
Title	#1	Identify the report as a systematic review	1
Abstract			
Abstract	#2	Report an abstract addressing each item in the PRISMA 2020 for Abstracts checklist	2
Introduction			
Background/rationale	#3	Describe the rationale for the review in the context of existing knowledge	4,5
Objectives	#4	Provide an explicit statement of the objective(s) or question(s) the review addresses	5
Methods			

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Eligibility criteria	#5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	5,6
Information sources	#6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	5
Search strategy	#7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	5
Selection process	#8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process	6
Data collection process	#9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process	6
Data items	#10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (for example, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect	6
Study risk of bias assessment	#11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process	6
Effect measures	#12	Specify for each outcome the effect measure(s) (such as risk ratio, mean difference) used in the synthesis or presentation of results	6
Synthesis methods	#13a	Describe the processes used to decide which studies	6

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		were eligible for each synthesis (such as tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	
Synthesis methods	#13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions	6
Synthesis methods	#13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	6
Synthesis methods	#13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	6
Synthesis methods	#13e	Describe any methods used to explore possible causes of heterogeneity among study results (such as subgroup analysis, meta-regression)	6
Synthesis methods	#13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results	6
Reporting bias assessment	#14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	6
Certainty assessment	#15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	6
Data items	#10b	List and define all other variables for which data were sought (such as participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	6
Results			
Study selection	#16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (http://www.prisma-statement.org/PRISMAStatement/FlowDiagram)	7

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Study selection	#16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	7
Study characteristics	#17	Cite each included study and present its characteristics	7
Risk of bias in studies	#18	Present assessments of risk of bias for each included study	8
Results of individual studies	#19	For all outcomes, present for each study (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (such as confidence/credible interval), ideally using structured tables or plots	8-11
Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	8-11
Results of syntheses	#20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (such as confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	8-11
Results of syntheses	#20c	Present results of all investigations of possible causes of heterogeneity among study results	8-11
Results of syntheses	#20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results	supplement 2
Risk of reporting biases in syntheses	#21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	supplement 1
Certainty of evidence	#22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	8-11
Discussion			
Results in context	#23a	Provide a general interpretation of the results in the context of other evidence	11,12
Limitations of	#23b	Discuss any limitations of the evidence included in the	13

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included studies		review	
Limitations of the review methods	#23c	Discuss any limitations of the review processes used	n/a
Implications	#23d	Discuss implications of the results for practice, policy, and future research	13
Other information			
Registration and protocol	#24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	5
Registration and protocol	#24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	5
Registration and protocol	#24c	Describe and explain any amendments to information provided at registration or in the protocol	n/a
Support	#25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	14
Competing interests	#26	Declare any competing interests of review authors	14
Availability of data, code, and other materials	#27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	14

Notes:

- 20d: supplement 2
- 21: supplement 1 The PRISMA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 30. August 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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