BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022700
Article Type:	Research
Date Submitted by the Author:	09-Mar-2018
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Keywords:	Central retinal vein occlusion, macular edema, anti-VEGF, corticosteroid, network meta-analysis

Comparison of the efficacy and safety of different drug therapies for macular edema secondary to central retinal vein occlusion: a systematic review and network meta-analysis

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ABSTRACT

Objectives: To evaluate the efficacy and safety of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids for the treatment of macular edema (ME) secondary to central retinal vein occlusion (CRVO).

Design: Systematic review and network meta-analysis.

Participants: Patients from previously reported randomized controlled trials (RCTs) comparing anti-VEGF agents and corticosteroids for the treatment of ME secondary to CRVO.

Methods: Literature searches were conducted using PubMed, Medline, Embase, Cochrane Library, and *clinicaltrials.gov* until March 2017. Therapeutic effects were estimated using the proportions of patients gaining/losing ⩾15 letters, best-corrected visual acuity (BCVA), and central retinal thickness (CRT). Treatment safety was estimated using the proportions of adverse events, namely increased intraocular pressure (IOP), cataracts, vitreous hemorrhage (VH), and retinal tear. The software ADDIS (version 1.16.8) was used for analysis.

Results: Eleven RCTs comprising 2060 patients were identified. Regarding patients gaining ⩾15 letters, aflibercept and ranibizumab were found to be significantly more effective than sham/placebo at 6 months. Regarding patients losing ⩾15 letters at 6 months, ranibizumab showed significant clinical improvement compared to dexamethasone. Aflibercept, bevacizumab, or ranibizumab showed greater improvements in BCVA than sham/placebo at 6 months. Intravitreal ranibizumab injection demonstrated greater CRT reduction than both sham and dexamethasone did. Dexamethasone had a higher risk of increased IOP than aflibercept and ranibizumab. Ranibizumab demonstrated a greater risk of cataracts than dexamethasone. Aflibercept and ranibizumab demonstrated low incidence of VH and retinal tear, respectively, and were considered superior to other drugs. Aflibercept had a slight advantage over ranibizumab as assessed by benefit-risk analysis.

Conclusions: Anti-VEGF agents have advantages in the treatment of ME secondary to CRVO. Aflibercept and ranibizumab showed marked BCVA improvement and CRT reduction. Aflibercept may have a slight advantage over ranibizumab. The results of this study can serve as a reference for clinicians to provide patient-tailored treatment.

Review registration

PROSPERO CRD42017064076

Strengths and limitations of this study

- This meta-analysis included the most recent reports.
- Strict inclusion and exclusion criteria were used to perform a comprehensive comparison of aflibercept, ranibizumab, bevacizumab, pegaptanib, dexamethasone, and triamcinolone treatments.
- Our data contained some biases that might have influenced our results.
- Detailed data at long-term follow-up time points are required to improve the accuracy and robustness of our findings.
- The details of AEs were not always reported in each study.

Keywords: Central retinal vein occlusion (CRVO), macular edema, anti-VEGF, corticosteroid, network meta-analysis

INTRODUCTION

Central retinal vein occlusion (CRVO), a common retinal vascular disorder, is characterized by dilated and tortuous retinal veins with hemorrhages in all four quadrants of the retina.[1,2] CRVO can reduce vision severely,[3,4] and its prevalence is estimated at 0.80 per 1000 persons, indicating that approximately 2.5 million adults are affected by CRVO globally.[1] CRVO is caused by a combination of risk factors, including advanced age, atherosclerosis, hypertension, diabetes mellitus, thrombophilia, hyperlipidemia, glaucoma, and other vessel wall changes or hemodynamic abnormalities.[5,6] Macular edema (ME) is the most common complication in CRVO that can lead to impaired central vision,[7] and ME secondary to CRVO is the second most common retinal vascular disease after diabetic retinopathy.[1,8,9]

The serious consequences of CRVO and its increasing prevalence make effective and widely applicable treatments necessary. Preventing ME and improving visual acuity (VA) are the two most important goals of treatment of ME secondary to CRVO. During the past several decades, various therapeutic approaches have been advocated for CRVO. The Central Vein Occlusion Study (CVOS) demonstrated that macular grid photocoagulation could decrease ME in patients with CRVO; however, it failed to improve VA when compared with that in the observation group.[10,11] Although intravitreal corticosteroid agents (e.g., triamcinolone acetonide injections and dexamethasone implants), which have anti-inflammatory, antiangiogenic, and anti-edematous properties,[12] demonstrate some adverse events (AEs), they have been used to treat ME and improve VA in CRVO patients. Intravitreal triamcinolone has recently been shown to have a beneficial effect on ME secondary to CRVO and a preventive effect on neovascularization.[13-15] Kuppermann *et al*. also reported that dexamethasone implants might be a potential treatment option for persistent ME.[16]

Vascular endothelial growth factor (VEGF) is a homodimeric protein that can stimulate vascular endothelial cell growth and induce vascular permeability.[17] It plays a crucial role in the pathophysiology process of ME,[18] and its levels were elevated in the ocular fluids of patients with CRVO.[19] Therefore, several anti-VEGF agents, including aflibercept, ranibizumab, bevacizumab, and pegaptanib, have been widely used for treating ME secondary to CRVO, because they significantly improve visual and anatomic outcomes in CRVO patients.[20-23]

Currently, intravitreal corticosteroid agents and intravitreal anti-VEGF agents are the common clinical therapies for ME secondary to CRVO. Nevertheless, these different drug treatment strategies

have not been comprehensively compared, and there are no head-to-head trials or clear guidance to determine the best treatment strategy for CRVO patients. Therefore, a systematic review of randomized controlled trials (RCTs) is needed to indirectly compare the efficacies of anti-VEGF agents and intravitreal corticosteroids agents for treating ME secondary to CRVO.

A previous network meta-analysis of RCTs that examined CRVO treatments had mainly focused on the efficacy outcomes at 6 months and failed to include pegaptanib.[24] In addition, it only considered the functional outcomes (e.g., letters gained and VA improvement) as therapeutic effects without consideration of anatomical outcomes and AEs. Therefore, the current systematic review and network meta-analysis was performed to overcome the shortcomings of the previous study and to include data from the latest RCTs. In the present study, we aimed to indirectly compare the clinical efficacy and safety of aflibercept, ranibizumab, bevacizumab, pegaptanib, dexamethasone, and triamcinolone for the treatment of ME secondary to CRVO. The clinical efficacy outcomes include best-corrected visual acuity (BCVA) improvement, central retinal thickness (CRT) reduction, and the proportion of ⩾15 letters gained or lost. The safety outcomes include the proportion of common AEs, such as increased intraocular pressure (IOP), cataracts, neovascular glaucoma, and vitreous hemorrhage (VH). We hope that our findings will aid ophthalmologists in choosing the best treatment options for their patients.

METHODS

This systematic review was performed according to the PRISMA Statement, and the review was conducted and reported according to the PRISMA NMA Checklist of items (Appendix 1).[25-26] We developed a systematic review protocol and registered it with PROSPERO (CRD42017064076). (Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064076).

Patient and Public Involvement

We used secondary data from peer-reviewed published articles, so no patients or public were not involved in this network meta-analysis.

Literature search

Literature searches were performed using five databases (Embase, Medline, Pubmed Central,

Cochrane Library, and *ClinicalTrials.gov*) to identify relevant articles published until the end of March 2017. The following terms were searched in each database: central retinal vein occlusion (CRVO), anti-VEGF agents, corticosteroids, and randomized controlled trials (RCTs). The full search strategies are described in supplementary Appendix 2. In addition, supplementary searches were performed to search for other relevant studies in the World Health Organization (WHO) International Clinical Trials Registry Platform, Google Scholar, and other websites of professional associations. Language or study design restrictions were not used. When titles or abstracts or both fit our search terms, abstracts were reviewed to exclude irrelevant studies (e.g., case reports, reviews, or experimental treatments). We then carefully read all the remaining articles to determine if they contained data that were applicable to our study.

Article inclusion/exclusion criteria

In this network meta-analysis, studies were selected based on the following inclusion criteria: 1) The study was an RCT. 2) Ranibizumab, bevacizumab, aflibercept, pegaptanib dexamethasone, or triamcinolone was used. 3) Subjects were adults (≥ 18 years) of either sex with ME secondary to CRVO. 4) Studies had to report at least one of the following outcomes: proportions of patients gaining/losing ≥ 15 letters (3 lines) from baseline to 6 or 12 months, the mean change in BCVA from baseline to 6 or 12 months, the mean change in CRT from baseline to 6 or 12 months, or the proportions of patients with AEs at 6 or 12 months. Studies that met any of the following criteria were excluded from our meta-analysis: 1) review article; 2) duplicate publication; 3) sufficient information not published (e.g., full text not accessible, full text did not contain raw data, or inconsistent or erroneous data provided), and 4) subjects with CRVO did not have ME prior to treatment.

Risk of bias assessment

The included studies were examined independently for biases by two authors using *Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions*.[27] The following study characteristics were assessed for biases: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting

(reporting bias), and other factors that contribute to biases (e.g., extreme baseline imbalance, study design, and trial stopped early because of data-dependent developments). The status of each of the above items was listed as "yes" to indicate a low risk, "no" to indicate a high risk, or "unclear" to indicate an unknown risk of bias.

Data extraction

The following information on study characteristics and clinical treatments were collected from all included studies:

1) Basic information

   Name of first author, year of publication, design of trial, location of study, setting, follow-up time, clinical trial registration

2) Participants and criteria

   Baseline characteristics (age, gender, baseline VA, baseline CRT, duration of ME, etc.), inclusion criteria, exclusion criteria

3) Interventions

   Different treatment groups and number of patients included

4) Outcomes

   Primary outcomes, other outcomes, outcome assessment

Some data that were not reported in articles were published online at *ClinicalTrials.gov* or other meta-analyses.

Evaluation indicator

The indicators of treatment efficacy included the proportions of patients gaining/losing $\geqslant$ 15 letters from baseline to 6 or 12 months and the mean changes in BCVA and CRT. The safety indicators included the proportions of patients with various AEs.

Statistical analyses

Our analysis classified anti-VEGF agents and corticosteroids used in monotherapy as separate treatment nodes irrespective of their doses: aflibercept, ranibizumab, bevacizumab, pegaptanib, dexamethasone, triamcinolone, and placebo or sham (i.e., conventional therapy/usual care).

Network meta-analysis allows the integration of data from both direct and indirect evidence, and it can be used to estimate comparisons between pairs of treatments that have not been compared in individual studies.[28,29] The network meta-analysis was performed within a Bayesian framework by using the Markov Chain Monte Carlo (MCMC) method.[30] The measures of treatment effects were relative risk (RR) for dichotomous outcomes and the weighted mean difference (WMD) for continuous outcomes. Bayesian statistical inference provides probability distributions for treatment effect parameters, with 95% credible intervals (95% CrI), which can be interpreted as a 95% probability that the parameter takes a value within the specified range.[31,32] If 1.0 was not included in the 95% CrI, the results were considered statistically significant. A consistency model could be used if the clinical features of the studies, such as patients, interventions, control, measurement, and research results on design index, were similar; however, this method could not exclude the existence of inconsistencies. Consistency analysis could be performed in the presence of similarity and homogeneity, and on this basis, it is possible to rank the effect of different treatment strategies. When performing this network meta-analysis, we relied on the assumptions of transitivity and consistency.[33] The consistency of results was qualitatively examined if sufficient evidence was available. If both direct and indirect evidences existed, node-splitting and pairwise meta-analyses were used to evaluate the inconsistency of direct comparisons in indirect evidences in the network meta-analysis.[34] $P < 0.05$ indicates significant heterogeneity.

The data of the included studies were analyzed using the STATA 14® (StataCorp LP, College Station, TX)[35] and the Aggregate Data Drug Information System (ADDIS v1.16.8, Drugis, Groningen, NL).[36] The risk of bias graph was drawn using Review Manager 5.3.5 software. During data analysis, four parallel chains were used and 50,000 samples were obtained after a 20,000-sample burn-in in each chain.[37] Convergence was assessed using the Brooks-Gelman-Rubin method. This method compares within-chain and between-chain variance to calculate the Potential Scale Reduction Factor (PSRF). A PSRF close to one indicates that approximate convergence has been reached.[38]

RESULTS

Literature search results

The PRISMA flowchart of the selection process of studies included in this network meta-analysis is

illustrated in Figure 1. In total, 1032 articles were initially identified in our literature searches. Of these, 556 articles were potentially relevant and screened after duplicates had been removed. A title and abstract review eliminated an additional 508 articles. Full-text examinations excluded seven additional articles[39-45] (7 studies) owing to various reasons presented in Table 1. Finally, 41 articles[23, 46-85] (11 studies) were included in this systematic review and network meta-analysis. The specific literature of both included and excluded studies is shown in Appendix 3.

Table 1 Excluded studies and exclusion reason

Studies (Author, year)	Exclusion reason
Larsen, 2016	No control group
Spaide, 2009	No control group
Wang, 2011	Compared IVB to combination of IVB and triamcinolone
Ramezani, 2006	Follow-up time less than 6 months
Kreutzer, 2015	Compared IVR to isovolemic hemodilution
Ding, 2011	A randomized but open-label trial
Gado, 2014	Missing data

IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab.

Characteristics and outcomes of included studies

Eleven studies comprising 2060 patients with ME secondary to CRVO were included in this meta-analysis. A network graph was constructed to show the network of eligible comparisons for the network meta-analysis (Figure 2). Briefly, the follow-up duration was at least 6 months and the patients' ages and gender distributions did not vary significantly among different drug treatment groups. The median sample size was 174 individuals (range 29–437). The characteristics of the 11 included studies are presented in Appendix 4. The detailed study results are presented in Appendix 5.

Methodological quality of included studies

The biases of the 11 included studies were assessed using the Cochrane Collaboration's tool as listed in Appendix 6. Each risk of bias item is expressed as a percentage across all included studies in Figure 3. In terms of methodological quality, three trials (27.3%) had a high risk of bias.

Efficacy of interventions on the proportions of patients with gaining/losing ⩾ 15 letters at 6 or 12 months

The improvement of VA was the most important functional measure of treatment efficacy. The proportions of patients gaining ⩾ 15 letters were considered the primary outcome in many included studies. Table 2 shows the RR and 95% CrI in the proportions of patients gaining and losing ⩾ 15 letters from baseline for all possible comparisons at 6 months using the consistency model.

Table 2 Network meta-analysis results in ≥15 letters gained (lower part) and lost (upper part) at 6 months

Treatment

with statistically significant effect **Relative risk (95% CrI) in proportions of losing ≥15 letters**

Aflibercept	1.67 (0.01, 321.97)	8.34 (0.14, 746.87)	1.61 (0.01, 289.03)	0.30 (0.00, 30.02)	8.48 (0.49, 176.53)	3.42 (0.03，534.31)
1.06 (0.07,13.87)	Bevacizumab	5.08 (0.03, 1194.75)	0.99 (0.00, 367.38)	0.18 (0.00, 51.64)	5.15 (0.07, 385.18)	2.05 (0.01, 626.99)
5.67 (0.73, 13.87)	5.12 (0.38, 76.39)	Dexamethasone	0.19 (0.00, 33.43)	0.04 (0.00, 0.99)	1.01 (0.03, 23.86)	0.40 (0.00, 64.91)
4.44 (0.34, 58.62)	4.10 (0.20, 88.77)	0.81 (0.06, 11.76)	Pegaptanib	0.19 (0.00,43.40)	5.21 (0.09, 386.38)	2.11 (0.01, 672.55)
1.17 (0.14, 10.25)	1.04 (0.08, 16.70)	0.20 (0.04, 1.07)	0.25 (0.02, 4.08)	Ranibizumab	28.43 (0.95,921.74)	11.32 (0.06, 2413.4)
6.97 (1.73, 29.70)	6.23 (0.76, 59.04)	1.22 (0.24, 5.85)	1.54 (0.18, 13.37)	6.04 (1.15, 29.10)	Sham/Placebo	0.41 (0.01, 20.59)
1.04 (0.06, 13.91)	0.94 (0.04, 21.87)	0.18 (0.01, 2.67)	0.24 (0.01, 4.65)	0.88 (0.05, 13.74)	0.15 (0.01, 1.31)	Triamcinolone

Relative risk (95% CrI) in proportions of gaining ≥15 letters

In terms of the proportions of patients gaining ⩾ 15 letters, aflibercept (RR: 6.97, 95% CrI: 1.73–29.70), bevacizumab (RR: 6.23, 95% CrI: 0.76–59.04), dexamethasone (RR: 1.22, 95% CrI: 0.24–5.85), pegaptanib (RR: 1.54, 95% CrI: 0.18–13.37), ranibizumab (RR: 6.04, 95% CrI: 1.15–29.10), and triamcinolone (RR: 6.97, 95% CrI: 1.73–29.70) had a higher probability of being more effective than sham/placebo treatment at 6 months. Among them, aflibercept and ranibizumab were significantly superior to the sham/placebo group. Ranibizumab was significantly superior to dexamethasone (p = 0.04, 95% CrI: 0.00–0.09) in terms of the proportions of patients losing ⩾ 15 letters. Table 3 and Figure 4 show the rank probabilities of these drugs for the treatment of CRVO according to the proportions of patients gaining ⩾ 15 letters at 6 months, while Table 4 and Figure 5 show the rank probabilities of the proportions of patients losing ⩾ 15 letters at 6 months.

Table 3 Ranking based on simulations about gaining ≥15 letters at 6 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Aflibercept	0.22	0.31	0.27	0.15	0.03	0.01	0.00
Bevacizumab	0.27	0.22	0.20	0.20	0.07	0.03	0.02
Dexamethasone	0.00	0.01	0.02	0.06	0.29	0.36	0.25
Pegaptanib	0.02	0.03	0.05	0.12	0.35	0.18	0.24
Ranibizumab	0.17	0.25	0.29	0.24	0.04	0.01	0.00
Sham/Placebo	0.00	0.00	0.00	0.02	0.14	0.39	0.46
Triamcinolone	0.32	0.18	0.17	0.21	0.07	0.03	0.02

Table 4 Ranking based on simulations about losing ≥15 letters at 6 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Aflibercept	0.02	0.04	0.08	0.18	0.27	0.29	0.13
Bevacizumab	0.10	0.09	0.13	0.18	0.19	0.18	0.14
Dexamethasone	0.37	0.24	0.18	0.12	0.06	0.03	0.00
Pegaptanib	0.09	0.08	0.13	0.18	0.20	0.18	0.13
Ranibizumab	0.00	0.01	0.03	0.06	0.12	0.23	0.53
Sham/Placebo	0.27	0.40	0.23	0.08	0.01	0.00	0.00
Triamcinolone	0.16	0.13	0.23	0.20	0.14	0.09	0.06

Because some specific data were not extracted or reported, the outcomes of the proportions of patients gaining/losing ⩾ 15 letters at 12 months did not involve all drugs. Table 5 shows the RR and 95% CrI in proportions of patients gaining and losing ⩾ 15 letters from baseline for all possible comparisons at 12 months using the consistency model.

Table 5 Network meta-analysis results in ≥15 letters gained (lower part) and lost (upper part) at 12 months

■ **Treatment**

■ **with statistically significant effect** **Relative risk (95% CrI) in proportions of losing ≥15 letters**

Aflibercept	3.45 (0.10, 91.91)	-	-	0.64 (0.04, 10.37)	3.35 (0.44, 24.39)	1.48 (0.09, 21.82)
0.93 (0.13, 7.06)	Bevacizumab	-	-	0.18 (0.01, 5.93)	0.99 (0.07, 16.67)	0.43 (0.02, 12.71)
2.22 (0.34, 13.46)	2.34 (0.23, 23.20)	Dexamethasone	-	-	-	-
-	-	-	Pegaptanib	-	-	-
1.45 (0.21, 9.28)	1.56 (0.15, 15.34)	0.65 (0.07, 5.76)	-	Ranibizumab	5.32 (0.68,50.28)	2.41 (0.14, 41.26)

3.08	(0.99,	3.26	(0.56,	1.40	(0.32,	-	2.08	(0.45,	Sham/Placebo	0.45	(0.07,
8.85)		17.47)		6.14)			10.09)			2.68)	
0.59	(0.07,	0.63	(0.05,	0.27	(0.03,	-	0.40	(0.04,	0.19	(0.03,	Triamcinolone
4.52)		7.43)		2.60)			4.22)		1.10)		

Relative risk (95% CrI) in proportions of gaining ≥15 letters

In terms of the proportions of patients gaining ⩾ 15 letters at 12 months, aflibercept (RR: 3.08, 95% CrI: 0.99–8.85), bevacizumab (RR: 3.26, 95% CrI: 0.56–17.47), dexamethasone (RR: 1.40, 95% CrI: 0.32–6.14), ranibizumab (RR: 2.08, 95% CrI: 0.45–10.09), and triamcinolone (RR: 5.21, 95% CrI: 0.91–31.67) had a higher probability of being more effective than sham/placebo treatment at 12 months; however, the differences were not significantly different. Table 6 and Figure 6 show the rank probabilities of these drugs for the treatment of CRVO according to the proportions of patients gaining ⩾ 15 letters at 12 months, while Table 7 and Figure 7 show the rank probabilities of the proportions of patients losing ⩾ 15 letters at 12 months.

Table 6 Ranking based on simulations about gaining ≥15 letters at 12 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Aflibercept	0.12	0.33	0.34	0.15	0.04	0.01
Bevacizumab	0.24	0.29	0.20	0.15	0.07	0.05
Dexamethasone	0.02	0.05	0.10	0.20	0.39	0.23
Ranibizumab	0.06	0.13	0.22	0.35	0.15	0.08
Sham/Placebo	0.00	0.00	0.01	0.07	0.31	0.61
Triamcinolone	0.55	0.20	0.12	0.08	0.03	0.02

Table 7 Ranking based on simulations about losing ≥15 letters at 12 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Aflibercept	0.05	0.10	0.22	0.35	0.27
Bevacizumab	0.47	0.18	0.15	0.11	0.08
Ranibizumab	0.03	0.05	0.13	0.28	0.52
Sham/Placebo	0.37	0.50	0.12	0.01	0.00
Triamcinolone	0.09	0.17	0.38	0.24	0.12

Efficacy of interventions on the mean changes in BCVA from baseline at 6 months

Table 8 shows the mean changes and 95% CrI of BCVA improvement for all possible comparisons by the network meta-analysis using the consistency model. Patients treated with aflibercept (RR:

17.88, 95% CrI: 7.59–29.11), bevacizumab (RR: 19.32, 95% CrI: 5.17–33.11), and ranibizumab (RR: 13.78, 95% CrI: 1.58–24.91) showed greater improvements in BCVA than those treated with sham/placebo group at 6 months, and the differences were significant. Triamcinolone (RR: 7.48, 95% CrI: -6.05–20.78) was also superior to sham injection, but the difference was not significant. Overall, patients treated with anti-VEGF agents (aflibercept, ranibizumab, or bevacizumab) had a higher probability of improvement in BCVA than those treated with corticosteroid agents (triamcinolone or dexamethasone).

Table 8 Network meta-analysis results in BCVA changes (lower part) and CRT changes (upper part) at 6 months

■ **Treatment**

■ **with statistically significant effect** **Weighted mean difference (95% CrI) in CRT change, mm**

Aflibercept		-		-		-		-		-	
-1.42	(-18.40, 17.85)	Bevacizumab		-		-		-		-	
21.60	(-0.36, 44.17)	22.89	(-1.36, 46.69)	Dexamethasone		205.30	(-64.62, 470.88)	46.08	(-345.04, 447.19)	-	
4.04	(-11.09, 21.23)	5.51	(-12.60, 24.12)	-17.42	(-32.78, -1.28)	Ranibizumab		-156.80	(-452.68, 144.63)	-	
17.88	(7.59, 29.11)	19.32	(5.17, 33.11)	-3.72	(-23.60, 15.43)	13.78	(1.58, 24.91)	Sham/Placebo		-	
10.37	(-6.22, 28.27)	11.94	(-1.35, 24.40)	-11.08	(-34.93, 12.35)	6.42	(-11.52, 23.89)	-7.48	(-20.78, 6.05)	Triamcinolone	

Weighted mean difference (95% CrI) in BCVA changes, letters

Table 9 and Figure 8 show the rank probability of these drugs for the treatment of CRVO according to the BCVA improvement at 6 months.

Table 9 Ranking based on simulations about BCVA changes from baseline at 6 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Aflibercept	0.34	0.45	0.16	0.04	0.01	0.00
Bevacizumab	0.54	0.28	0.14	0.02	0.01	0.00
Dexamethasone	0.01	0.01	0.02	0.07	0.19	0.70
Ranibizumab	0.10	0.21	0.53	0.14	0.02	0.00
Sham/Placebo	0.00	0.00	0.01	0.06	0.68	0.25
Triamcinolone	0.01	0.05	0.14	0.66	0.10	0.04

Efficacy of interventions on mean changes in CRT from baseline at 6 months

The CRT represents anatomic changes in the fovea after treatment. As certain studies did not report CRT changes after treatment, the evaluation of CRT only involved ranibizumab, dexamethasone, and sham injections. Intravitreal ranibizumab injections showed greater reduction in CRT than both sham injection (RR: -156.80, 95% CrI: -452.68–144.63) and dexamethasone (RR: -205.30, 95% CrI: -470.88–64.62). Table 10 and Figure 9 show the rank probability of these three drugs for the treatment of CRVO according to CRT reductions at 6 months.

Table 10 Ranking based on simulations about CRT changes from baseline at 6 months

Drug	Rank 1	Rank 2	Rank 3
Dexamethasone	0.61	0.34	0.05
Ranibizumab	0.01	0.16	0.83
Sham/Placebo	0.37	0.51	0.12

Adverse events

Many AEs were reported after drug treatment in the 11 studies, which comprised 2060 patients (Table 11). The most common ocular AE reported in more than two studies that could be compared by network meta-analysis were increased IOP, cataracts, VH, and retinal tear. Figure 10 shows the rank probability of the drugs for the treatment of CRVO according to the four aforementioned AEs.

Table 11 Main adverse events after drug treatment reported according to the included studies

Drugs / Adverse events	Aflibercept	Ranibizumab	Bevacizumab	Dexamethasone	Triamcinolone	Sham/ Placebo
IOP increased	10/104	7/124		78/252	8/125	6/235
Cataract				13/263		7/176
Neovscular glaucoma	0/114	0/129			3/25	7/223
Conjunctival hemorrhage	9/104	16/125		13/119		3/68
Vitreous hemorrhage	0/114	9/144				13/217
Eye irritation	3/104					7/68
Eye pain	12/104	15/124		15/119		3/68
Retinal hemorrhage	0/114					2/74
Retinal tear	0/114	0/15				2/88
Iris neovascularization	0/114	0/124		9/119		2/74
Endophthalmitis	1/114					0/74
Retinal ischemia	1/104	1/124		6/119		3/68
Iris rubeosis			0/30			5/30

Consistency analysis of network model

Based on direct versus indirect evidence, we compared the effect estimate twice using node-splitting,

considering that direct and indirect evidences existed together. The first was the comparison of ranibizumab, dexamethasone, and sham/placebo, while the second was bevacizumab, triamcinolone, and sham/placebo. Table 12 shows the comparisons of the estimated quantiles for the direct and indirect evidence, as well as the combined evidence. No inconsistencies were observed (P>0.05). These data suggest that our model is relatively robust.

Table 12 Node-splitting meta-analysis of two comparison

Name	Direct Effect	Indirect Effect	Overall	P-Value
≥15 letters gained (6 months)				
IVR, Sham	-1.50 (-3.92, 0.83)	-2.35 (-5.58, 1.10)	-1.80 (-3.37, -0.14)	0.50
IVR, DEX	-1.87 (-4.13, 0.43)	-1.05 (-4.42, 2.25)	-1.61 (-3.18, 0.07)	0.50
DEX, Sham	-0.46 (-2.73, 1.88)	0.33 (-2.88, 3.63)	-0.20 (-1.77, 1.42)	0.49
≥15 letters lost (6 months)				
IVR, Sham	2.70 (-1.55, 7.04)	4.63 (-1.35, 11.10)	3.35 (-0.05, 6.83)	0.51
IVR, DEX	4.23 (-0.34, 9.40)	2.20 (-3.79, 8.57)	3.35 (0.01, 7.02)	0.51
DEX, Sham	0.48 (-3.75, 4.78)	-1.52 (-8.23, 4.84)	0.01 (-3.42, 3.17)	0.52
BCVA changes (6 months)				
IVB, Sham	-16.48 (-37.18, 3.97)	-23.22 (-50.85, 5.12)	-19.78 (-31.99, -5.60)	0.54
IVB, Tria	-13.57 (-31.94, 5.21)	-6.61 (-34.12, 20.15)	-12.13 (-23.87, 1.28)	0.57
Tria, Sham	-9.49(-29.15, 9.89)	-2.71 (-31.65, 25.52)	-7.36 (-19.70, 4.64)	0.58

BCVA, mean change in best corrected visual acuity; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; DEX, Dexamethasone; Tria, triamcinolone

Benefit-risk analysis between anti-VEGF agents and dexamethasone

For the purpose of the proposed methods, benefit-risk analysis is defined as the quantitative synthesis of drug efficacy (or effectiveness) and AE profile.[86] Based on the existing data from the included studies, benefit-risk analysis could be performed if efficacy outcomes and safety outcomes were both reported at the same time. When considering gaining $\geqslant$ 15 letters at 6 months as a benefit index and increased IOP as a risk index, aflibercept and ranibizumab were superior to dexamethasone in the treatment of ME secondary to CRVO (Figure 11). When considering gaining $\geqslant$ 15 letters at 6 months as a benefit index and cataracts as a risk index, ranibizumab exhibited a greater benefit of

visual improvement as well as a higher risk of cataracts than dexamethasone (Figure 12).

Benefit-risk analysis of aflibercept versus ranibizumab

Aflibercept and ranibizumab are the two most widely used anti-VEGF agents in the treatment of CRVO worldwide. However, there are few head-to-head RCTs comparing the efficacy and safety of aflibercept and ranibizumab directly. Gaining $\geqslant$ 15 letters at 6 months was considered a benefit index were considered a risk index; increased IOP, vitreous hemorrhage, and retinal tear were considered risk indices separately. Thus, aflibercept exhibited slightly better visual improvement and a lower risk of the latter three adverse events than ranibizumab (Figure 13). Moreover, Figure 14 shows the rank acceptability of aflibercept and ranibizumab by the benefit-risk analysis.

DISCUSSION

Intravitreal corticosteroids (triamcinolone or dexamethasone) are a potential therapeutic option for CRVO patients despite their limitations.[12] However, a broader understanding has led to the discovery that eyes with retinal vein occlusion [including branch retinal vein occlusion (BRVO) and CRVO] also have increased vitreal levels of VEGF,[19,87] a special protein that plays an important role in the pathogenesis of ME.[88] Therefore, inhibiting VEGF and/or reducing its levels seem to be rational strategies for treating CRVO. Notably, multiple clinical trials have shown a significant reduction in plasma VEGF levels in CRVO patients after intravitreal injection of anti-VEGF agents. Therefore, comparisons of the efficacy and safety of intravitreal anti-VEGF injection and intravitreal corticosteroids are needed in patients with ME secondary to CRVO.

Network meta-analysis can exploit all available direct evidence and use statistical methods to obtain indirect evidence to form a coherent knowledge base, which provides information to compare the treatment efficacy and safety between pairs of drugs that may never have been evaluated in individual head-to-head trials. The network meta-analysis methodology itself has been validated and matured over recent years, and its utility and added value have been demonstrated.[89-91]

In terms of the proportions of patients gaining $\geqslant$ 15 letters at 6 months, our results showed that only aflibercept and ranibizumab had a significantly better efficacy than the sham/placebo group. Between the four main anti-VEGF agents and the two corticosteroids, our results showed no evidence of differences in effectiveness at both 6 and 12 months. According to the rank probability of

the existing data, aflibercept, bevacizumab, and triamcinolone are the best three drugs, with no statistical significance, in gaining ⩾ 15 letters at 6 and 12 months. However, bevacizumab and triamcinolone were used off-label and lacked safety data. Therefore, aflibercept would be considered the first choice to improve VA in the treatment of ME secondary to CRVO. Aflibercept targets a wider range of cytokines and may have a stronger binding affinity,[92] which could explain the greater efficacy in visual improvement, than ranibizumab, bevacizumab, and pegaptanib. Unlike corticosteroids, anti-VEGF could decrease the vitreal levels of VEGF. Aflibercept and ranibizumab exhibited significantly better efficacy at 6 months but not at 12 months, indicating that the effects of aflibercept and ranibizumab were less obvious than the effects of the sham/placebo group as the follow-up time progressed.

In terms of the proportion of patients that lost ⩾ 15 letters at 6 or 12 months, the pooled result showed that only ranibizumab was superior to dexamethasone, with a significant difference at 6 months. Although no significant difference was found among the other drug treatment groups, anti-VEGF agents showed a tendency toward better efficacy in visual improvement than corticosteroids did. Among the anti-VEGF agents, ranibizumab had the lowest risk of patients losing ⩾15 letters.

Apart from the ⩾ 15 letters gained or lost, BCVA changes from baseline could reflect visual recovery. At 6 months, aflibercept, bevacizumab, and ranibizumab showed a greater improvement in BCVA than the sham/placebo group, with a statistically significant difference. The results support the efficacy of anti-VEGF agents for VA improvement to some extent, which is consistent with the aforementioned results of ⩾ 15 letters gained or lost. In the case of visual improvement, anti-VEGF agents, especially ranibizumab and aflibercept, were better than corticosteroids.

CRT, an anatomical index reflecting macular, was also considered as an important outcome to estimate the efficacy of these drugs. Only three RCTs reported a CRT reduction. According to the outcomes reported, ranibizumab afforded more reduction in CRT at 6 months than dexamethasone, and bevacizumab afforded more reduction than triamcinolone. As for intravitreal anti-VEGF injections, the resolution of exudative fluid and retinal edema is important for the favorable treatment of BCVA.[93]

A low incidence of AEs should also be considered besides the better efficacy of different drug treatments. In this network meta-analysis, increased IOP, cataracts, VH, and retinal tear are the four

most frequently reported AEs from the included studies. More reported data can lead to more accurate analyses. As shown in Figure 10, dexamethasone has a higher risk of increased IOP compared to that of aflibercept and ranibizumab. In contrast, ranibizumab was associated with a higher probability of cataracts than dexamethasone. Cataracts are associated with injection frequency, and dexamethasone needs fewer injections than anti-VEGF agents. Gu *et al*. reported that the advantages of dexamethasone are fewer number of injections and long-term efficacy, while the advantages of ranibizumab include lower incidence of increased IOP,[94] which is similar to the results of our pooled data. A head-to-head trial called COMRADE-B demonstrated that elevated IOP occurred more frequently with dexamethasone than with ranibizumab treatment, similar to BRVO.[95] In addition, aflibercept showed lower incidence of VH and ranibizumab showed lower incidence of retinal tear. AEs mainly arise from the disease process itself or as a result of the side effects during the course of treatment. Intravitreal anti-VEGF or corticosteroid injections and traumatic procedures sometimes cause AEs such as endophthalmitis. Safety is as important as efficacy after treatment, and both must be considered comprehensively in the selection of drugs for CRVO.

When comparing ranibizumab, dexamethasone, and sham/placebo, as well as bevacizumab, triamcinolone, and sham/placebo, node-splitting and pairwise meta-analysis could be used to estimate the efficacy based on direct versus indirect evidence. If direct and indirect evidence existed together, the consistencies could be tested. Since no inconsistencies were observed in this network meta-analysis, we performed sensitivity analysis of the comparison of random and fixed effects models, which was more accurate.[34] The unchanged outcome suggests that our model was robust according to known data, and therefore, the results of this network meta-analysis would be useful in clinical practice.

As mentioned above, both dexamethasone and ranibizumab have their own advantages and disadvantages.[94] Broadly speaking, each drug has benefits and risks; therefore, estimating benefits and risks consistently is necessary. Although anti-VEGF agents can avoid the increased IOP caused by dexamethasone, the high risk of developing cataracts after anti-VEGF treatment, especially ranibizumab, cannot be ignored.

Aflibercept and ranibizumab are the two, on-label maximum dosage drugs recently approved in Europe and America. According to the data of benefit-risk analysis between the two drugs from the

included studies, aflibercept had a slight advantage over ranibizumab. However, this does not mean that aflibercept is effective for all patients. Patients need to choose medications according to their actual situation. During our clinical practice, some patients were not responsive to anti-VEGF agents, but instead responded to dexamethasone.

Considering that intravitreal anti-VEGF agents are expensive, intravitreal corticosteroids should be considered to reduce the overall treatment cost. However, care should be taken when using these treatments because elevated IOP is seen more frequently with corticosteroid therapy than with anti-VEGF therapy, as demonstrated by our network meta-analysis. Regardless of the treatment administered, all patients with CRVO should be closely monitored for IOP changes and VA.

This is the second network meta-analysis providing an indirect comparison of drugs to treat ME secondary to CRVO, and our study possesses several strengths when compared to previous systematic reviews.[24] First, our meta-analysis included the most recent reports, analyzing studies published as late as May 1, 2017. Second, we performed a comprehensive comparison of aflibercept, ranibizumab, bevacizumab, pegaptanib, dexamethasone, and triamcinolone treatment using strict inclusion and exclusion criteria. Third, the 12-month follow-up time point was also considered in addition to 6 months, because the outcome at 12 months could better show the duration of efficacy after treatment.

Although the results of this work may be important for clinical treatment, there are certain limitations that need to be considered. First, our data contained some biases, which may have influenced our results. Second, more detailed data at long-term follow-up time points (e.g., 24 months) are required to improve the accuracy and robustness of our findings for clinical applications. Third, the details of AEs were not always reported in each study, and the data available can only indicate the relative safety of every intervention for CRVO. To assess the efficacy of these treatments more accurately, additional high-quality RCTs with comprehensive safety data will be necessary.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab, pegaptanib, dexamethasone, and triamcinolone are needed. Further long-term, prospective studies are needed to examine and compare the safety and efficacy of CRVO-associated ME treatment strategies. Including data from future studies in subsequent meta-analyses will improve conclusion accuracy and robustness and provide better clinical guidance. In addition, as patients can be concerned about the cost of treatment, clinicians may prefer aflibercept because it requires fewer injections.[24]

CONCLUSION

Our analysis confirms that anti-VEGF agents have more advantages than corticosteroids in the treatment of ME secondary to CRVO. A higher proportion of the patients who received intravitreal anti-VEGF injections gained ⩾ 15 letters than those treated with corticosteroids at both 6 and 12 months. Among these anti-VEGF agents, aflibercept and ranibizumab were the best drugs for BCVA improvement and CRT reduction. In terms of adverse events, the results of network meta-analysis showed that 1) dexamethasone was associated with a higher risk of increased IOP than aflibercept and ranibizumab, 2) ranibizumab had a higher probability of cataract formation than dexamethasone, 3) aflibercept exhibited superiority in terms of low incidence of VH, and 4) ranibizumab exhibited superiority in terms of low incidence of retinal tear. Aflibercept was shown to have a slight advantage over ranibizumab by benefit-risk analysis, but with no statistical difference. More high-quality RCTs will be necessary as the results of this study provide only a reference for clinicians. Each patient must be evaluated individually for the appropriate treatment regimen.

ACKNOWLEDGMENTS

The authors thank the researchers whose studies were included in this network meta-analysis and provided useful data to us.

FOOTNOTES

Funding: This study was funded by the National Key Research and Development Program of China (Grant No. 2016YFC0904800) and the National Natural Science Foundation of China (Grant No. 81570851).

Conflicts of interest: None declared.

Author contributions: T. Qian: study conception, study design, data collection, data analysis, manuscript writing, and final manuscript approval; M. Zhao: study design, data collection, and critical manuscript revision; Y. Wan: statistical analysis; M. Li: statistical analysis; X. Xu: study conception, study design, critical manuscript revision, and final manuscript approval.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

Figure 1. Study selection flow diagram

Figure 2. Network graph of all treatment comparisons for all studies
Each node represents one drug. The size of nodes is proportional to the number of randomized participants (sample size). Lines represent direct comparisons within randomized controlled trials, and the width of the lines is proportional to the number of trials comparing each pair of treatments.

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item are presented as percentages across all included studies.

Figure 4. Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to gaining ⩾ 15 letters at 6 months. Afliber, aflibercept; Bevac, bevacizumab; Dexa, dexamethasone; Pegapt, pegaptanib; Ranibi, ranibizumab; Triamci, triamcinolone.

Figure 5. Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to losing ⩾ 15 letters at 6 months. Afliber, aflibercept; Bevac, bevacizumab; Dexa, dexamethasone; Pegapt, pegaptanib; Ranibi, ranibizumab; Triamci, triamcinolone.

Figure 6. Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to gaining ⩾ 15 letters at 12 months. Afliber, aflibercept; Bevac, bevacizumab; Dexa, dexamethasone; Pegapt, pegaptanib; Ranibi, ranibizumab; Triamci, triamcinolone.

Figure 7. Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to losing ⩾ 15 letters at 12 months. Triamcinol, triamcinolone.

Figure 8. Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to best-corrected visual acuity changes from baseline at 6 months. Bevaciz, bevacizumab; Dexame, dexamethasone; Ranibiz, ranibizumab; Triamcin, triamcinolone.

Figure 9. Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to central retinal thickness reduction from baseline at 6 months.

Figure 10. Rank probabilities of four adverse events: a) Increased IOP (intraocular pressure), b) Cataracts, c) Vitreous hemorrhage, d) Retinal tear

Figure 11. Benefit-risk analysis of aflibercept and ranibizumab versus dexamethasone considering gaining ⩾ 15 letters and increased IOP (intraocular pressure): a) Aflibercept *vs.* dexamethasone; b) Ranibizumab *vs.* dexamethasone.
Key benefit-risk summary with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Aflibercept/Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

Figure 12. Benefit-risk analysis of ranibizumab versus dexamethasone considering gaining ⩾ 15 letters and cataracts.
Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

Figure 13. Benefit-risk analysis of aflibercept versus ranibizumab considering gaining ⩾ 15 letters at 6 months and the three main adverse events: a) increased IOP (intraocular pressure); b) vitreous hemorrhage; c) retinal tear.
Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Ranibizumab (red) or Aflibercept (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

Figure 14. Rank acceptability of aflibercept versus ranibizumab considering gaining ⩾ 15 letters at 6 months and the three main adverse events: a) increased IOP (intraocular pressure); b) vitreous hemorrhage; c) retinal tear.

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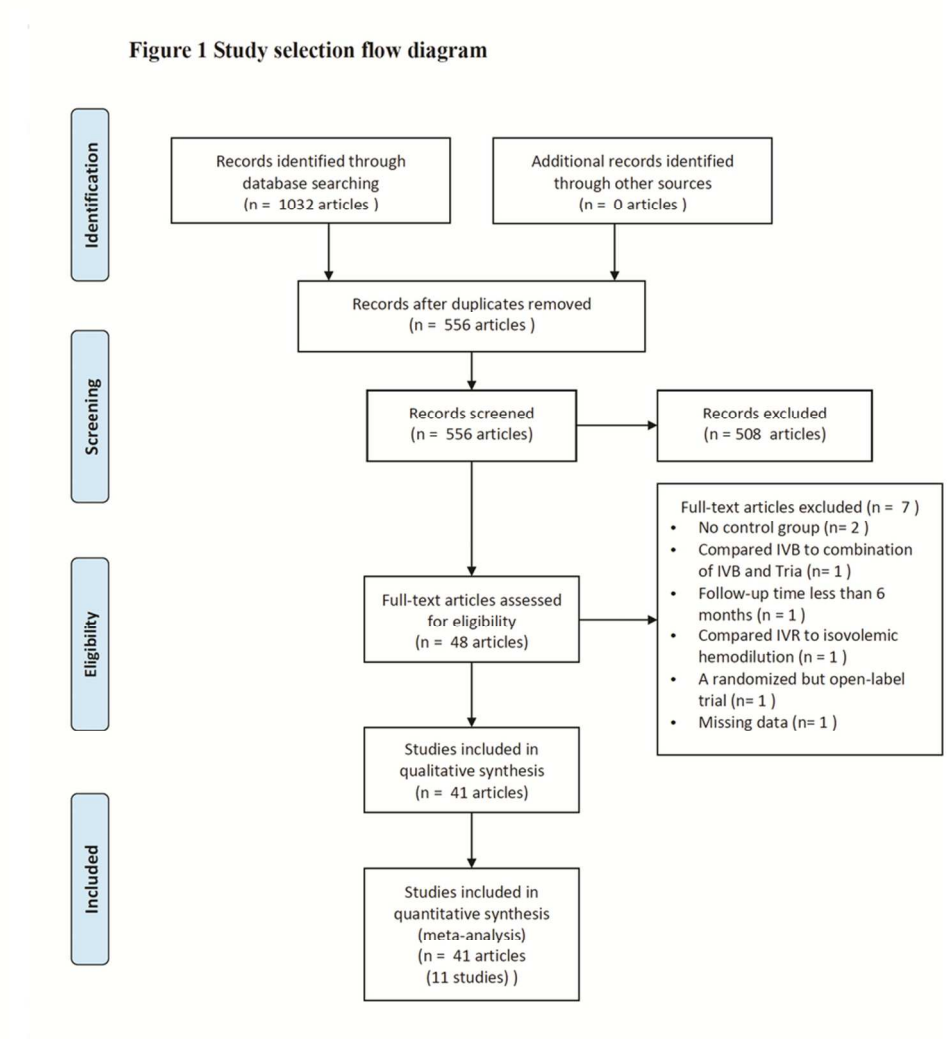

Study selection flow diagram

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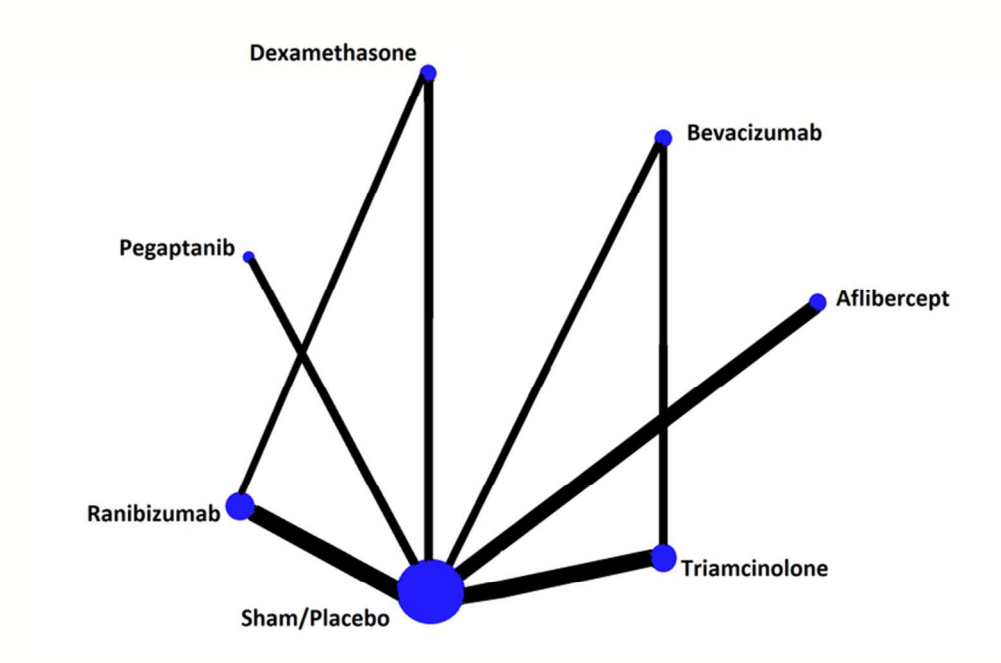
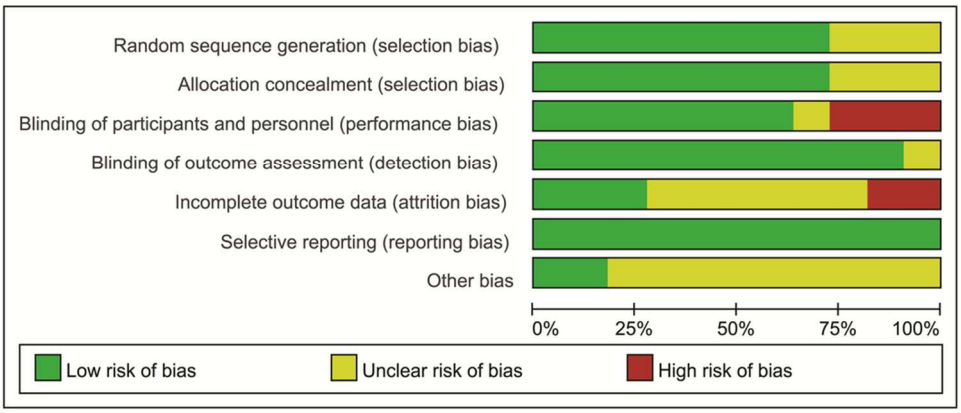


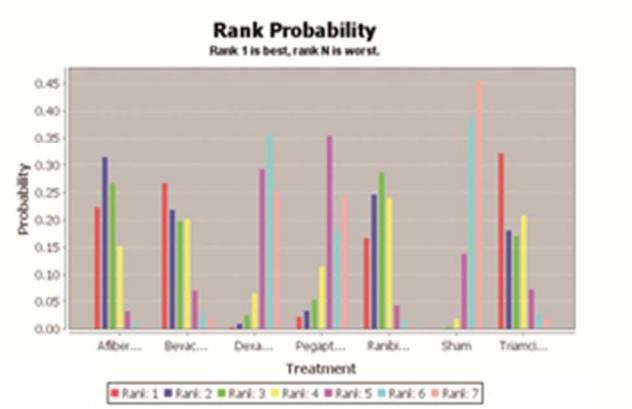
Network graph of all treatment comparisons for all studies
Each node represents one drug. The size of nodes is proportional to the number of randomized participants (sample size). Lines represent direct comparisons within randomized controlled trials, and the width of the lines is proportional to the number of trials comparing each pair of treatments.

69x47mm (300 x 300 DPI)



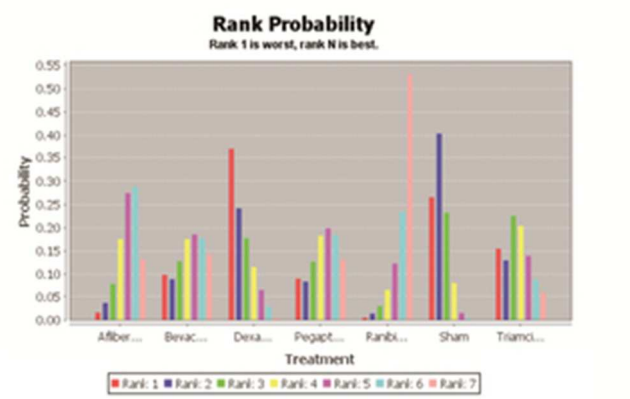
Risk of bias graph: review authors' judgments about each risk of bias item are presented as percentages across all included studies

93x42mm (300 x 300 DPI)



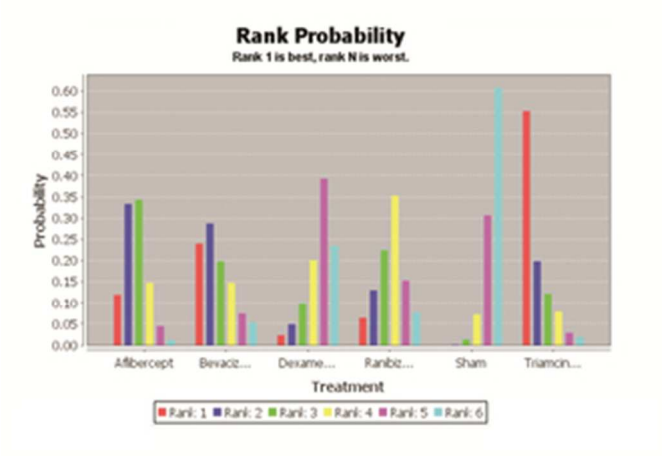
Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to gaining ≥ 15 letters at 6 months. Afliber, aflibercept; Bevac, bevacizumab; Dexa, dexamethasone; Pegapt, pegaptanib; Ranibi, ranibizumab; Triamci, triamcinolone

27x18mm (300 x 300 DPI)



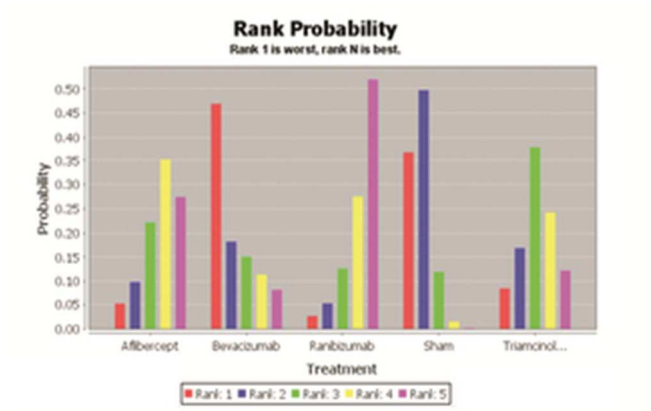
Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to losing ≥ 15 letters at 6 months. Afliber, aflibercept; Bevac, bevacizumab; Dexa, dexamethasone; Pegapt, pegaptanib; Ranibi, ranibizumab; Triamci, triamcinolone

27x18mm (300 x 300 DPI)



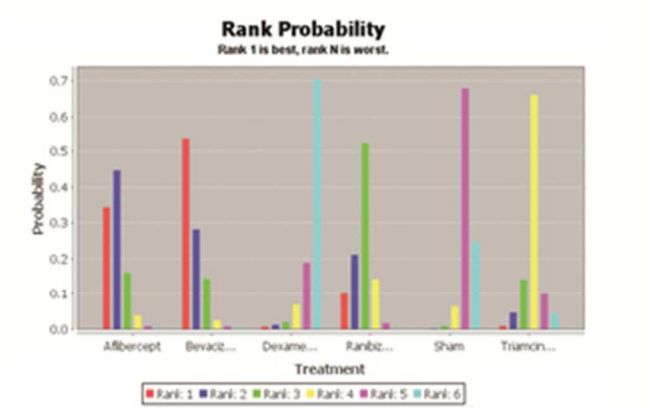
Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to gaining ≥ 15 letters at 12 months. Afliber, aflibercept; Bevac, bevacizumab; Dexa, dexamethasone; Pegapt, pegaptanib; Ranibi, ranibizumab; Triamci, triamcinolone

27x19mm (300 x 300 DPI)



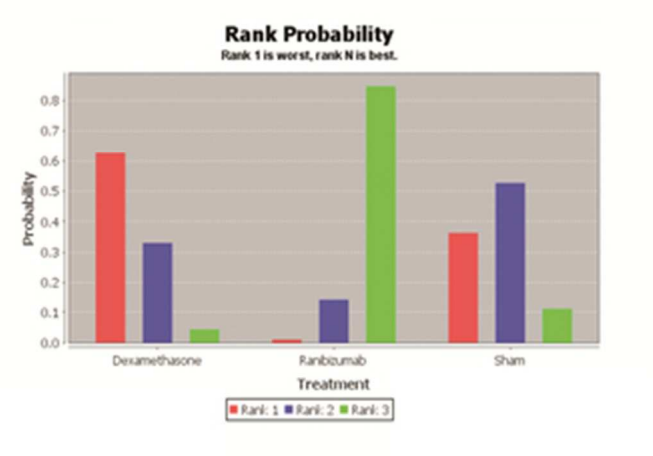
Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to losing ≥ 15 letters at 12 months. Triamcinol, triamcinolone

27x18mm (300 x 300 DPI)



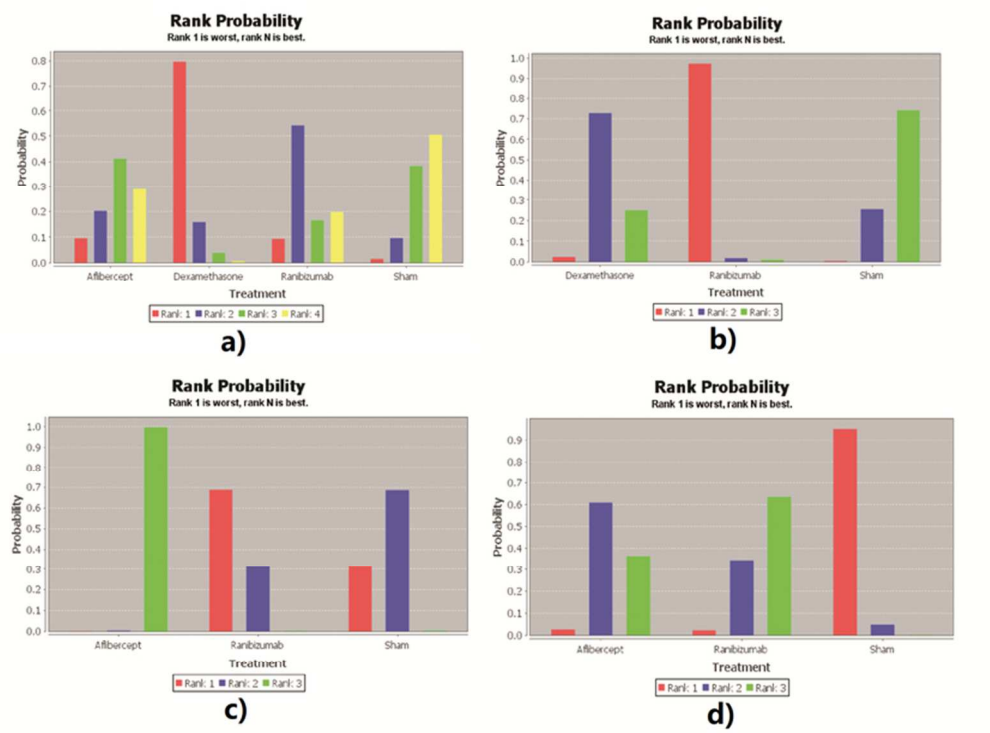
Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to best-corrected visual acuity changes from baseline at 6 months. Bevaciz, bevacizumab; Dexame, dexamethasone; Ranibiz, ranibizumab; Triamcin, triamcinolone.

27x18mm (300 x 300 DPI)



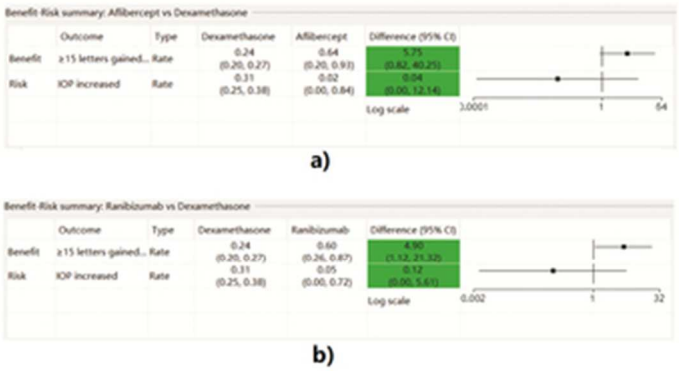
Rank probabilities of different drugs in the treatment of macular edema secondary to central retinal vein occlusion with respect to central retinal thickness reduction from baseline at 6 months.

28x19mm (300 x 300 DPI)



Rank probabilities of four adverse events: a) Increased IOP (intraocular pressure), b) Cataracts, c) Vitreous hemorrhage, d) Retinal tear

70x53mm (300 x 300 DPI)

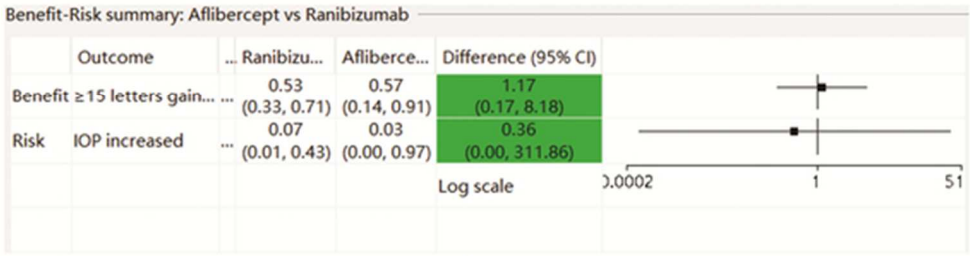


Benefit-risk analysis of aflibercept and ranibizumab versus dexamethasone considering gaining ≥ 15 letters and increased IOP (intraocular pressure): a) Aflibercept vs. dexamethasone; b) Ranibizumab vs. dexamethasone.
Key benefit-risk summary with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Aflibercept/Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

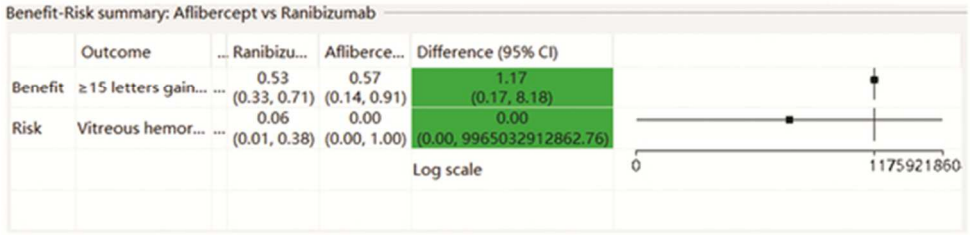
29x16mm (300 x 300 DPI)

Benefit-risk analysis of ranibizumab versus dexamethasone considering gaining ≥ 15 letters and cataracts. Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

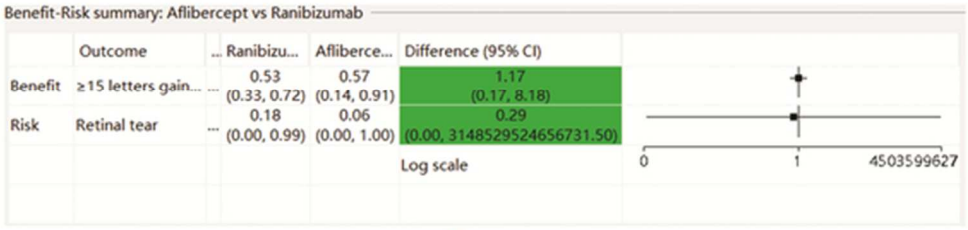
13x3mm (300 x 300 DPI)



a)



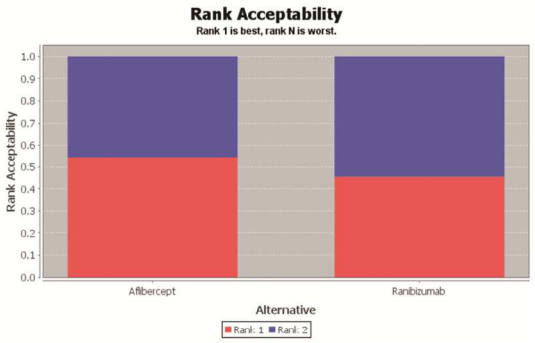
b)



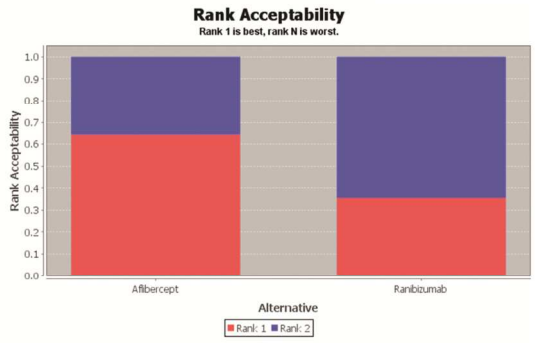
c)

Benefit-risk analysis of aflibercept versus ranibizumab considering gaining ≥ 15 letters at 6 months and the three main adverse events: a) increased IOP (intraocular pressure); b) vitreous hemorrhage; c) retinal tear. Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Ranibizumab (red) or Aflibercept (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

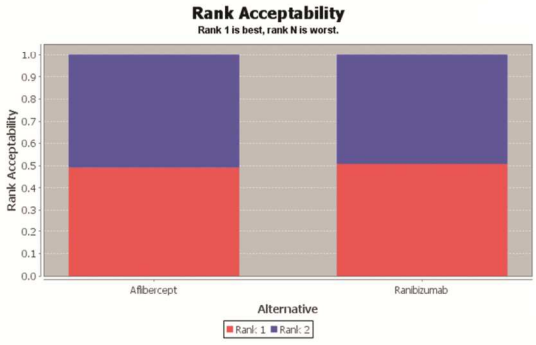
49x47mm (300 x 300 DPI)



a)



b)



c)

Rank acceptability of aflibercept versus ranibizumab considering gaining ≥ 15 letters at 6 months and the three main adverse events: a) increased IOP (intraocular pressure); b) vitreous hemorrhage; c) retinal tear.

81x163mm (300 x 300 DPI)

Appendix 1. PRISMA NMA Checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	P4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P4-5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	P5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	P5-P6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P5-P6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P7

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P6
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	P6-P7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P6-P7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	P7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • Handling of multi-arm trials; • Selection of variance structure; • Selection of prior distributions in Bayesian analyses; and • Assessment of model fit.	P7-P8
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	P8-P9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P6-P7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • Alternative formulations of the treatment network; and • Use of alternative prior distributions for Bayesian analyses (if applicable).	P7-P8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P8
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Table1-3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P9, Table3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise	P9-P12

		comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	P11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	Figure11-14, P11-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	P16-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	P18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	P20

PICOS = population, intervention, comparators, outcomes, study design.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix 2. Search strategies

We searched the Embase, Medline, EMBASE, Cochrane Library and *clinicaltrials.gov* by the end of March 2017. We provided below the search strategies of the five database.

Embase search strategy

1. exp Central retinal vein occlusion/
2. exp Central vein occlusion/
3. exp Retinal vein occlusion/
4. exp Retinal vein/
5. ((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).tw.
6. (CRVO or CVO or RVO or VO).tw.
7. or/1-6
8. exp retina macula edema/
9. exp cystoid/
10. (macula$ adj3 oedema).tw.
11. (macula$ adj3 edema).tw.
12. (CME or CMO).tw.
13. or/8-12
14. exp Anti-Vascular Endothelial Growth Factors/
15. exp Vascular Endothelial Growth Factors/

16. exp anti-VEGF Agents/
17. exp Endothelial Growth Factors/
18. exp Angiogenesis Inducing Agents/
19. exp Angiogenesis Inhibitors/
20. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or vastin or aflibercept$ or Eylea or VEGF-Trap).tw.
21. (anti adj2 VEGF$).tw.
22. (endothelial adj2 growth adj2 factor$).tw.
23. or/14-22
24. exp corticosteroids/
25. exp Glucocorticoid/
26. exp Steroids/
27. (dexamethasone$ or Ozurdex or triamcinolone$).tw.
28. or/24-27
29. exp randomized controlled trial/
30. exp controlled clinical trial/
31. exp randomized/
32. exp randomized/
33. or/29-32
34. exp Sham/
35. or/23, 28, 33, 34
36. 7 and 13 and 35

CENTRAL search strategy

#1 MeSH descriptor Central Retinal Vein Occlusion

#2 MeSH descriptor Central Vein Occlusion

#3 MeSH descriptor Retinal Vein Occlusion

#4 MeSH descriptor Retinal Vein

#5 retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)

#6 CRVO or CVO or RVO or RV

#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

#8 MeSH descriptor Macular Edema

#9 MeSH descriptor Edema Oedema

#10 macula* near/3 oedema

#11 macula* near/3 edema

#12 CME or CMO

#13 (#8 OR #9 OR #10 OR #11 OR #12)

#14 MeSH descriptor Anti-Vascular Endothelial Growth Factors

#15 MeSH descriptor Vascular Endothelial Growth Factors

#16 MeSH descriptor anti-VEGF Agents

#17 MeSH descriptor Endothelial Growth Factors

#18 MeSH descriptor Angiogenesis Inducing Agents

#19 MeSH descriptor Angiogenesis Inhibitors

#20 macugen* or pegaptanib* or lucentis* or rhufab* or ranibizumab* or bevacizumab* or vastin or aflibercept* or Eylea or VEGF-Trap

#21 anti near/2 VEGF*

#22 endothelial near/2 growth near/2 factor*

#23 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)

#24 MeSH descriptor corticosteroids

#25 MeSH descriptor Glucocorticoid

#26 MeSH descriptor Steroids

#27 dexamethasone* or Ozurdex or triamcinolone*

#28 (#24 OR #25 OR #26 OR #27)

#29 MeSH descriptor randomized controlled trial

#30 MeSH descriptor controlled clinical trial

#31 MeSH descriptor randomized

#32 MeSH descriptor randomised

#33 (#29 OR #30 OR #31 OR #32)

#34 Sham injection

#35 (#23 OR #28 OR #33 OR #34)

#36 (#7 AND #13 AND #35)

MEDLINE search strategy

1. exp Central retinal vein occlusion/

2. exp Central vein occlusion/
3. exp Retinal vein occlusion/
4. exp Retinal vein/
5. ((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).tw.
6. (CRVO or CVO or RVO or VO).tw.
7. or/1-6
8. exp retina macula edema/
9. exp cystoid/
10. (macula$ adj3 oedema).tw.
11. (macula$ adj3 edema).tw.
12. (CME or CMO).tw.
13. or/8-12
14. exp Anti-Vascular Endothelial Growth Factors/
15. exp Vascular Endothelial Growth Factors/
16. exp anti-VEGF Agents/
17. exp Endothelial Growth Factors/
18. exp Angiogenesis Inducing Agents/
19. exp Angiogenesis Inhibitors/
20. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or vastin or aflibercept$ or Eylea or VEGF-Trap).tw.
21. (anti adj2 VEGF$).tw.

22. (endothelial adj2 growth adj2 factor$).tw.
23. or/14-22
24. exp corticosteroids/
25. exp Glucocorticoid/
26. exp Steroids/
27. (dexamethasone$ or Ozurdex or triamcinolone$).tw.
28. or/24-27
29. randomized controlled trial.pt
30. controlled clinical trial.pt
31. randomized.ab,ti
32. randomized/ab.ti
33. or/29-32
34. exp Sham/
35. or/23, 28, 33, 34
36. 7 and 13 and 35

Cochrane Library search strategy

#1 MeSH descriptor: [Central Retinal Vein Occlusion] explode all trees

#2 MeSH descriptor: [Central Vein Occlusion] explode all trees

#3 MeSH descriptor: [Retinal Vein Occlusion] explode all trees

#4 MeSH descriptor: [Retinal Vein] explode all trees

#5 (retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or

steno* or block* or embolism*))

#6 MeSH descriptor: [CRVO or CVO or RVO or RV] explode all trees

#7 {or #1-#6}

#8 MeSH descriptor: [Macular Edema] explode all trees

#9 MeSH descriptor: [Edema Oedema] explode all trees

#10 (macula* near/3 oedema)

#11 (macula* near/3 edema)

#12 (CME or CMO)

#13 {or #8-#12}

#14 MeSH descriptor: [Anti-Vascular Endothelial Growth Factors] explode all trees

#15 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees

#16 MeSH descriptor: [anti-VEGF Agents] explode all trees

#17 MeSH descriptor: [Endothelial Growth Factors] explode all trees

#18 MeSH descriptor: [Angiogenesis Inducing Agents] explode all trees

#19 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees

#20 macugen*

#21 pegaptanib*

#22 lucentis*

#23 rhufab*

#24 ranibizumab*

#25 bevacizumab*

#26 vastin

#27 aflibercept*

#28 Eylea

#29 VEGF-Trap

#30 (anti near/2 VEGF*)

#31 (endothelial) near/2 (factor*)

#32 {or #14-#31}

#33 MeSH descriptor: [corticosteroids] explode all trees

#34 MeSH descriptor: [Glucocorticoid] explode all trees

#35 MeSH descriptor: [Steroids] explode all trees

#36 (dexamethasone* or Ozurdex or triamcinolone*)

#37 {or #33-#36}

#38 MeSH descriptor: [randomized controlled trial] explode all trees

#39 MeSH descriptor: [controlled clinical trial] explode all trees

#40 MeSH descriptor: [randomized] explode all trees

#41 MeSH descriptor: [randomised] explode all trees

#42 {or #38-#41}

#43 MeSH descriptor: [Sham] explode all trees

#44 #32 or #37 or #42 or #43

#45 #7 AND #13 AND #44

ClinicalTrials.gov search strategy

(Angiogenesis or Vascular Endothelial Growth Factors or Anti-VEGF or pegaptanib or lucentis or rhufab or ranibizumab or bevacizumab or vastin or aflibercept or Eylea or VEGF-Trap) OR (Steroids or dexamethasone or Ozurdex or triamcinolone) AND (Macula Oedema or Macula Edema) AND (Central retinal vein occlusion or Retinal vein occlusion)

Appendix 3 Specific literatures of included and excluded studies

Included studies

GENEVA, 2010

- Haller J A, Bandello F, Belfort R, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion[J]. Ophthalmology, 2010, 117(6): 1134-1146. e3.
- Haller J A, Bandello F, Belfort R, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: twelve-month study results[J]. Ophthalmology, 2011, 118(12): 2453-2460.
- Yeh W S, Haller J A, Lanzetta P, et al. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant[J]. Ophthalmology, 2012, 119(6): 1190-1198.

ROVO, 2013

- Aggermann T, Brunner S, Krebs I, et al. A prospective, randomised, multicenter trial for surgical treatment of central retinal vein occlusion: results of the Radial Optic Neurotomy for Central Vein Occlusion (ROVO) study group[J]. Graefe's Archive for Clinical and Experimental Ophthalmology, 2013, 251(4): 1065-1072.

SCORE, 2009

- Myers D, Blodi B, Ip M, et al. Reading center evaluation of OCT images from patients enrolled in the standard care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study[J]. Investigative Ophthalmology & Visual Science, 2006, 47(13): 5194-5194.
- Bhavsar A R, Ip M S, Glassman A R. The risk of endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE clinical trials[J]. American journal of ophthalmology, 2007, 144(3): 454-456.
- Oden N L, VanVeldhuisen P C, Scott I U, et al. Temporal variability of OCT in retinal vein occlusion participants in the SCORE study[J]. Investigative Ophthalmology & Visual Science, 2007, 48(13): 107-107.
- Ip M, Oden N, VanVeldhuisen P, et al. The standard care vs. corticosteroid for retinal vein occlusion study: design and baseline characteristics[J]. Am Acad Ophthalmol, 2008, 260.
- Scott I U, VanVeldhuisen P C, Oden N L, et al. SCORE Study report 1: baseline associations between central retinal thickness and visual acuity in patients with retinal vein occlusion[J]. Ophthalmology, 2009, 116(3): 504-512.
- Scott I U, Blodi B A, Ip M S, et al. SCORE Study Report 2: interobserver

agreement between investigator and reading center classification of retinal vein occlusion type[J]. Ophthalmology, 2009, 116(4): 756-761.

- Ip M S, Oden N L, Scott I U, et al. SCORE Study report 3: study design and baseline characteristics[J]. Ophthalmology, 2009, 116(9): 1770-1777. e1.
- Domalpally A, Blodi B A, Scott I U, et al. The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study system for evaluation of optical coherence tomograms: SCORE study report 4[J]. Archives of ophthalmology, 2009, 127(11): 1461-1467.
- Ip M S, Scott I U, VanVeldhuisen P C, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5[J]. Archives of ophthalmology, 2009, 127(9): 1101.
- Scott I U, Ip M S, VanVeldhuisen P C, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6[J]. Archives of ophthalmology, 2009, 127(9): 1115.
- Scott I U, Oden N L, VanVeldhuisen P C, et al. SCORE Study Report 7: incidence of intravitreal silicone oil droplets associated with staked-on vs luer cone syringe design[J]. American journal of ophthalmology, 2009, 148(5): 725-732. e7.
- Blodi B A, Domalpally A, Scott I U, et al. Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study system for evaluation of stereoscopic color fundus photographs and fluorescein angiograms: SCORE Study Report 9[J]. Archives of ophthalmology, 2010, 128(9): 1140-1145.
- Scott I U, VanVeldhuisen P C, Oden N L, et al. Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus COrticosteroid for REtinal Vein Occlusion Study report 10[J]. Ophthalmology, 2011, 118(2): 345-352.
- Chan C K, Ip M S, VanVeldhuisen P C, et al. SCORE Study report# 11: incidences of neovascular events in eyes with retinal vein occlusion[J]. Ophthalmology, 2011, 118(7): 1364-1372.
- Weinberg D V, Wahle A E, Ip M S, et al. Score Study report 12: development of venous collaterals in the Score Study[J]. Retina, 2013, 33(2): 287-295.
- Domalpally A, Peng Q, Danis R, et al. Association of outer retinal layer morphology with visual acuity in patients with retinal vein occlusion: SCORE Study Report 13[J]. Eye, 2012, 26(7): 919-924.
- Scott I U, VanVeldhuisen P C, Oden N L, et al. Baseline characteristics and response to treatment of participants with hemiretinal compared with branch retinal or central retinal vein occlusion in the Standard Care vs COrticosteroid for REtinal Vein Occlusion (SCORE) study: SCORE Study report 14[J]. Archives of Ophthalmology, 2012, 130(12): 1517-1524.

CRUISE, 2010

- Brown D M, Campochiaro P A, Singh R P, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study[J]. Ophthalmology, 2010, 117(6): 1124-1133. e1.
- Campochiaro P A, Brown D M, Awh C C, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study[J]. Ophthalmology, 2011, 118(10): 2041-2049.
- Heier J S, Campochiaro P A, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial[J]. Ophthalmology, 2012, 119(4): 802-809.

ROCC, 2010

- Kinge B, Stordahl P B, Forsaa V, et al. Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study[J]. American journal of ophthalmology, 2010, 150(3): 310-314.

COPERNICUS, 2012

- Boyer D, Heier J, Brown D M, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study[J]. Ophthalmology, 2012, 119(5): 1024-1032.
- Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study[J]. American journal of ophthalmology, 2013, 155(3): 429-437. e7.

GALILEO, 2013

- Gillies M. Intravitreal Vegf Trap-eye In Central Retinal Vein Occlusion: Results Of The Phase 3 Copernicus And Galileo Studies[J]. Clinical & Experimental Ophthalmology, 2012, 40: 44.
- Holz F G, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study[J]. British Journal of Ophthalmology, 2013; 97(3):278-284.

Epstein, 2012

- Epstein D, Algvere P, von Wendt G, et al. Long-term benefit from bevacizumab for macular edema in central retinal vein occlusion: 12-month results of a prospective study[J]. Acta Ophthalmologica, 2012, 90: 48.
- Epstein D L J, Algvere P V, von Wendt G, et al. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study[J]. Ophthalmology, 2012, 119(6): 1184-1189.

- Epstein D L, Algvere P V, von Wendt G, et al. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study[J]. Ophthalmology, 2012, 119(12): 2587-2591.

Wroblewski, 2009

- Wells III J A. Pegabtanib sodium for treatment of macular edema secondary to Central Retinal Vein Occlusion (CRVO)[J]. Investigative Ophthalmology & Visual Science, 2006, 47(13): 4279-4279.
- Wells J A. Safety and efficacy of pegaptanib sodium in treating macular edema secondary to Central Retinal Vein Occlusion[J]. Am Acad Ophthalmol, 2006.
- Ciulla T A. Treatment of macular edema following central retinal vein occlusion with pegaptanib sodium (macugen): a one-year study[J]. Am Acad Ophthalmol, 2007.
- Csaky K G. Pegaptanib (Macugen) for Macular edema in Central Retinal Vein Occlusion: early OCT results and effect of therapy reinitiation[J]. American Academy of Ophthamology, 2007.
- Wells III J A, Wroblewski J J, Macugen in CRVO Study Group. Pegaptanib sodium for the treatment of macular edema following Central Retinal Vein Occlusion (CRVO): functional outcomes[J]. Investigative Ophthalmology & Visual Science, 2007, 48(13): 1544-1544.
- Patel S S, Macugen in CRVO Study Group. Pegaptanib sodium for the treatment of macular edema following Central Retinal Vein Occlusion (CRVO): anatomical outcomes[J]. Investigative Ophthalmology & Visual Science, 2007, 48(13): 311
- Wroblewski J J, Wells J A, Adamis A P, et al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion[J]. Archives of ophthalmology, 2009, 127(4): 374-380.

Ramezani, 2014

- Ramezani A, Esfandiari H, Entezari M, et al. Three intravitreal bevacizumab versus two intravitreal triamcinolone injections in recent onset central retinal vein occlusion[J]. Acta ophthalmologica, 2014, 92(7).

COMRADE-C, 2016

- Hoerauf H, Feltgen N, Weiss C, et al. Clinical efficacy and safety of ranibizumab versus dexamethasone for central retinal vein occlusion (COMRADE C): a European label study[J]. American journal of ophthalmology, 2016, 169: 258-267.

Excluded studies

Exclusion reason 1: No control group (n= 1)

- Larsen M, Waldstein S M, Boscia F, et al. Individualized ranibizumab regimen driven by stabilization criteria for central retinal vein occlusion: twelve-month results of the CRYSTAL study[J]. Ophthalmology, 2016, 123(5): 1101-1111.
- Spaide R F, Chang L K, Klancnik J M, et al. Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion[J]. American journal of ophthalmology, 2009, 147(2): 298-306.

Exclusion reason 2: Compared IVB to combination of IVB and Tria (n= 1)

- Wang H Y, Li X, Wang Y S, et al. Intravitreal injection of bevacizumab alone or with triamcinolone acetonide for treatment of macular edema caused by central retinal vein occlusion[J]. International journal of ophthalmology, 2011, 4(1): 89.

Exclusion reason 3: Follow-up time less than 6 months (n = 1)

- Ramezani A, Entezari M, Moradian S, et al. Intravitreal triamcinolone for acute central retinal vein occlusion; a randomized clinical trial[J]. Graefe's Archive for Clinical and Experimental Ophthalmology, 2006, 244(12): 1601-1606.

Exclusion reason 4: Compared IVR to isovolemic hemodilution (n = 1)

- Kreutzer T C, Wolf A, Dirisamer M, et al. Intravitreal ranibizumab versus isovolemic hemodilution in the treatment of macular edema secondary to central retinal vein occlusion: twelve-month results of a prospective, randomized, multicenter trial[J]. Ophthalmologica, 2015, 233(1): 8-17.

Exclusion reason 5: A randomized but open-label trial (n= 1)

- Ding X, Li J, Hu X, et al. Prospective study of intravitreal triamcinolone acetonide versus bevacizumab for macular edema secondary to central retinal vein occlusion[J]. Retina, 2011, 31(5): 838-845.

Exclusion reason 6: Missing data (n= 1)

- Gado A S, Macky T A. Dexamethasone intravitreous implant versus bevacizumab for central retinal vein occlusion-related macular oedema: a prospective randomized comparison[J]. Clinical & experimental ophthalmology, 2014, 42(7): 650-655.

Appendix 4 Characteristics of included studies

GENEVA, 2010 [46-48] **Group1: DEX 0.7mg; Group2: DEX 0.35mg; Group3: Sham**	
Basic information	**Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Location:** international **Setting:** multicentre (167 centres in 24 countries) **Follow-up:** primary end point for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months **Clinical trial registration:** NCT00168324 and NCT00168298 at *clinicaltrials.gov*
Participants and criteria	**Baseline characteristics:** ➢ Age: mean 62.7 to 65.2 years ➢ Gender: male 50.8 to 56.3% (CRVO and BRVO together) ➢ Baseline VA (ETDRS letters): DEX 0.7mg:52.4±10.6; Sham: 53.3±10.8 ➢ Baseline CRT (μm): DEX 0.7mg: 647.6; Sham: 619.8 ➢ Duration of macular edema: mean 4.8 to 4.9 months;<90 days: 14.3 to 15.4%; >90 to <180 days: 54.4 to 57.4%, >180 days: 27.1 to 31.3% **Inclusion criteria:** ➢ ⩾18years; ➢ VA reduction due to macular edema due to CRVO according to the investigator's opinion, is unlikely to be adversely affected if not treated for 6 months; ➢ duration of macular edema 6 weeks to 9 months in patients with CRVO; ➢ BCVA 34 to 68 ETDRS letters (20/200 and 20/50 Snellen equivalent) in the study eye and >34 letters in the non-study eye; ➢ CRT⩾300 μm (OCT) in the study eye. **Exclusion criteria:** ➢ clinically significant epiretinal membrane; ➢ use of periocular corticosteroid within 6 months or topical nonsteroidal anti-inflammatory drug or corticosteroid within 1 month; ➢ intraocular surgery or laser within 30 days of study or anticipated; ➢ history of intravitreal use of corticosteroid or any other drug; ➢ glaucoma or current ocular hypertension requiring more than 1 medication to control IOP in the study eye, or a history of steroid-induced IOP increase in either eye ➢ active retinal or optic disc neovascularization, active or history of choroidal neovascularization; ➢ history of herpetic infection or pars plana vitrectomy; ➢ rubeosis iridis, any active infection aphakia or anterior-chamber intraocular lens; ➢ any ocular condition that would prevent a 15-letter VA improvement; ➢ preretinal or vitreous haemorrhage, lens opacity, media opacity that would preclude clinical or photographic evaluation; ➢ active ocular infection; ➢ diabetic retinopathy in the either eye; ➢ uncontrolled systemic disease; ➢ current or anticipated use of systemic steroids or anticoagulants

Interventions	**DEX 0.7mg (n=136):** sustained delivery, biodegradable dexamethasone intravitreal implant (Ozurdex), 0.7mg dexamethasone implant inserted into the vitreous cavity through the pars plana using a customised, single-use **DEX 0.35mg (n=154):** DEX 0.35 mg implant inserted following the same method **Sham (n=147):** a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Regimen for all groups:** At baseline (day 0), study eyes were randomized to either a sham procedure or treatment with the dexamethasone intravitreal implant 0.7 mg or 0.35 mg using a 1:1:1 allocation ratio. Before inserting the implant, the study eye was anaesthetised with topical and subconjunctival anaesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection; patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure **Extension:** patients completing 180 days were eligible to enter a 6 month open label extension where they received DEX 0.7 mg implant
Outcomes	**Primary outcomes:** gain of≥15 ETDRS letters; for the open-label extension: safety **Other outcomes:** proportion of eyes achieving at least a 10 and 15 letters improvement from baseline; the proportion of eye losing≥15 letters; BCVA, CRT and safety; subgroup analysis according to RVO diagnosis (BRVO and CRVO) and duration of macular edema at baseline **Outcome assessment:** evaluation at 1, 7, 30, 60, 90 and 180 days after study treatment for both parts of the study
ROVO, 2013 [49] **Group1:Tria 4mg; Group2:RON; Group3: Pla**	
Basic information	**Design:** RCT, placebo-controlled **Location:** Austria **Setting:** multicentre (7 centres in 7 countries) **Follow-up:** primary end point 12 months **Clinical trial registration:** NCT00532142 at *clinicaltrials.gov*
Participants and criteria	**Baseline characteristics:** ➢ Age: Not reported ➢ Gender: 64% male ➢ Baseline VA (ETDRS letters): 1.07 logMAR (interquartile range 0.78 to 1.7) (~46.5 letters) ➢ Baseline CRT (μm): 569 to 657 ➢ Duration of macular edema: not reported **Inclusion criteria:** ➢ history of CRVO not longer than 12 months; ➢ VA of ≥0.3 logMAR (≤85 letters) (for perfused CRVO: VA >1 logMAR (>50 letters) or no VA improvement over 4 weeks) **Exclusion criteria:** ➢ dense cataract (grade 3 and 4-precluding judgement of the fundus); ➢ severe ophthalmologic conditions (severe retinopathy, presence of advanced opticatrophy, uncontrolled glaucoma);

	➢ pregnancy; ➢ VA <0.3 logMAR (higher than 0.5 Snellen); ➢ allergy against fluoresceine or indocyanine green, and any handicap which could prevent patients from attending follow-up visits.
Interventions	**Tria 4mg (n=25):** single intravitreal injection of 4 mg triamcinolone acetonide **RON (n=38):** radial optical neurotomy under general anaesthesia (detailed procedure described) **Pla (n=20):** eyes prepared as for triamcinolone injection but sham injection performed (empty syringe without needle pressed against the eye)
Outcomes	**Primary outcome:** ⩾15 ETDRS letters gained; **Other outcomes:** BCVA, CRT, safety **Outcome assessment:** 12 months
SCORE, 2009 [50-66] **Group1:Tria 4mg; Group2: Tria 1mg; Group3:Obs**	
Basic information	**Design:** RCT **Location:** USA **Setting:** multicentre **Follow-up:** primary end point 12 months, follow-up planned up to 36 months **Clinical trial registration:** NCT00105207 at *clinicaltrials.gov*
Participants and criteria	**Baseline characteristics:** ➢ Age: 68.0±12.4 years (overall) Tria 4mg: 67.5±12.0 years; Tria 1mg: 67.4±12.4 years; Obs: 69.2±12.8 years ➢ Gender: 55% male (overall) Tria 4mg: 53.3% male; Tria 1mg: 56.0% male; Obs: 54.5% male ➢ Baseline VA (ETDRS letters): 51.2±14.1 (overall) Tria 4mg: 51.0±14.4; Tria 1mg: 50.6±14.9; Obs: 52.1±13.1 ➢ Baseline CRT (μm): 659±229 (overall) Tria 4mg: 641±248; Tria 1mg: 643±226; Obs: 695±208 ➢ Duration of macular edema: 4.3±3.7 months **Inclusion criteria:** ➢ ETDRS visual acuity letter score of⩾73 (approximate Snellen equivalent of 20/40 or worse) and⩽19 (approximate Snellen equivalent of 20/400 or better). Note: the original lower limit of visual acuity was expanded from > 34 letters to > 24 letters 5 months after accrual began and then from > 24 letters to > 19 letters 12 months after accrual began; ➢ Center-involved macular edema caused by CRVO or BRVO present on clinical examination; ➢ Mean CRT of OCT fast macular scans⩾250 μm ➢ Media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs **Exclusion criteria:** ➢ Presence of macular edema due to a cause other than CRVO ➢ Presence of an ocular condition such that visual acuity would not improve from resolution of the edema (e.g., foveal atrophy)

	➢ Substantial cataract estimated to have reduced visual acuity by⩾3 lines ➢ Prior treatment with intravitreal corticosteroids at any time or peribulbar steroid injection within 6 months before randomization ➢ History of focal/grid macular photocoagulation within 15 weeks (3.5mo) *or* panretinal photocoagulation within 4 mo before randomization *or* anticipated need for PRP within the 4 mo after randomization ➢ Prior pars plana vitrectomy ➢ Major ocular surgery (including cataract extraction) within prior 6 mo or anticipated within the next 6 mo after randomization ➢ Yttrium Aluminum Garnet capsulotomy performed within 2 mo before randomization ➢ IOP ⩾25 mmHg, open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma), steroid-induced IOP elevation that required IOP-lowering treatment or pseudoexfoliation ➢ Aphakia
Interventions	**Tria 4mg (n=91):** 4mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone (average number of injections 2.0 at 12 months) **Tria 1mg (n=92):** 1mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone (average number of injections 2.0 at 12 months) **Obs (n=88):** observation, receive standard care
Outcomes	**Primary outcome:** ⩾15 ETDRS letters gained; **Other outcomes:** BCVA, CRT, safety **Outcome assessment:** follow-up visits every 4 months for 36 months
CRUISE, 2010 [67-69] **Group1: IVR 0.3mg; Group2: IVR 0.5mg; Group3: Sham**	
Basic information	**Design:** double-blind, randomised, sham injection-controlled RCT phase 3 trial **Location:** USA **Setting:** multicenter (95 centres) **Follow-up:** primary end point 6 months, follow-up up to 12 months, with subsequent 6-month open-label PRN treatment with ranibizumab 0.3 mg in the initial 0.3 mg group, 0.5 mg in the initial 0.5 mg group, and 0.5 mg in the initial sham group **Clinical trial registration:** NCT00485836 at *clinicaltrials.gov* **Loss to follow-up:** 2.3% in 0.3 mg group, 8.5% in 0.5 mg group, 11.5% in sham group
Participants and criteria	**Baseline characteristics:** ➢ Age (years): IVR 0.3mg: 69.7±11.6; IVR 0.5mg: 67.6±12.4; Sham: 65.4±13.1 ➢ Gender: IVR 0.3mg: 53.8% male; IVR 0.5mg: 61.5% male; Sham: 55.4% male ➢ Baseline VA (ETDRS letters): IVR 0.3mg: 47.4±14.8; IVR 0.5mg: 48.1±14.6; Sham: 49.2±14.7 ➢ Baseline CRT (μm): IVR 0.3mg: 679.9±242.4; IVR 0.5mg: 688.7±253.1; Sham: 687.0±237.6 ➢ Mean time from diagnosis of CRVO: 3.3 months (median 2 months for each treatment group), with a duration of⩽3 months in 69% of patients. **Inclusion criteria:** ➢ ⩾18 years of age with foveal center-involved macular edema secondary to CRVO diagnosed within 12 months before study initiation

	➢ BCVA 20/40–20/320 Snellen equivalent using the ETDRS charts ➢ CRT⩾250 μm with OCT **Exclusion criteria:** ➢ Prior episode of RVO ➢ Brisk afferent pupillary defect (i.e., obvious and unequivocal) >10-letter improvement in BCVA between screening and day 0 ➢ History of radial optic neurotomy or sheathotomy ➢ Intraocular corticosteroid use in study eye within 3 months before day 0 ➢ History or presence of wet or dry AMD ➢ Panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before day 0 or anticipated within 4 months after day 0 ➢ Laser photocoagulation for macular edema within 4 months before day 0 (for patients who had previously received grid laser photocoagulation, the area of leakage at day 0 must have extended into the fovea (i.e., prior laser treatment was inadequate), and there could be no evidence of laser damage to the fovea ➢ Evidence on examination of any diabetic retinopathy CVA or MI within 3 months before day 0 ➢ Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0 **Exclusion criteria for HORIZON open-label extension trial (months 13 to 24):** ➢ Intraocular surgery within 1 month of study entry ➢ Use of intravitreal bevacizumab in either eye ➢ Concurrent use of any systemic anti-VEGF therapy ➢ Use of any non-FDA approved treatments for RVO in the study eye ➢ Macular edema in the study eye due to causes other than RVO*
Interventions	**IVR 0.3mg (n=132):** intravitreal injections of 0.3 mg ranibizumab monthly for 6 months then PRN (open-label) for 6 months **IVR 0.5mg (n=130):** intravitreal injections of 0.5 mg ranibizumab monthly for 6 months then PRN (open-label) for 6 months **Sham (n=130):** sham procedure (empty syringe without needle pressed to the injection site) monthly for 6 months then PRN 0.5 mg ranibizumab (open-label) for 6 months **Extension:** a 6-month observation period (month 6 to month 12), during which all patients could receive monthly intraocular ranibizumab if they met prespecified functional and anatomic criteria (i.e., Snellen equivalent study eye BCVA ⩽20/40 according to ETDRS chart or mean central subfield thickness ⩾250 μm according to OCT **HORIZON extension trial:** 304 CRUISE patients continued in the HORIZON trial in months 13 to 24, ranibizumab 0.5 mg injection was given if mean central subfield thickness was > 250 μm or if there was evidence of persisting/recurrent macular edema deemed to be affecting the BCVA
Outcomes	**Primary outcome:** BCVA changes from baseline **Other outcomes:** 1) Percentage of patients who gained/lost 15 letters or more from baseline BCVA; 2) Percentage of patients with CRT < 250 μm; 3) Mean changes from baseline CRT over time to month 6; 4) Mean change in NEI VFQ-25 scores; 5) Safety **Outcome assessment:** monthly visits up to 12 months; 3-monthly evaluation up to 24

	months (HORIZON)
ROCC, 2010 [70] **Group1: IVR 0.5mg; Group2: Sham (placebo)**	
Basic information	**Design:** Prospective, randomized, double-masked, placebo-controlled trial RCT **Location:** Norway **Setting:** multicentre, 4 sites in Norway **Follow-up:** 6 months **Clinical trial registration:** NCT00567697 at *clinicaltrials.gov* **Loss to follow-up:** 2 (12.5%) in control group, 1 (6.3%) in IVR 0.5mg group
Participants and criteria	**Baseline characteristics:** ➢ Age (years): 72 (52-88) ➢ Gender: 55.2% male (overall) ➢ Baseline VA (ETDRS letters): Overall: 43±22 letters; IVR 0.5mg (n=15): 45±23; Sham (n=14): 41±22 ➢ Baseline CRT (μm): Overall: 625±159; IVR 0.5mg: 661±161; Sham: 587±154 ➢ Mean duration of CRVO: 78 days (10-163 days) **Inclusion criteria:** ➢ duration≤6 months, ➢ age≥50 years ➢ Macular edema secondary to CRVO who were previously untreated for this disease ➢ Symptom duration≤6 months, age≥50 years, and a BCVA score between≤73 and ≥6 letters **Exclusion criteria:** ➢ Any concomitant ocular disease ➢ Prior treatment of macular disease ➢ History of uncontrolled glaucoma, filtration surgery, or corneal transplantation; cataract surgery 3 months prior to baseline ➢ Aphakia ➢ Cataract or diabetic retinopathy in rapid progression ➢ Vitreous hemorrhage ➢ Previous rhegmatogenous retinal detachment ➢ Pregnant ➢ Received other investigational drugs or current treatment for active systemic infection, or had received medication known to be toxic to the eye ➢ Use of an investigational drug ➢ hypersensitivity or allergy to fluorescein
Interventions	**IVR 0.5mg (n=15):** Receive intravitreal injections of ranibizumab 0.5 mg/0.05 mL (Lucentis; Novartis Inc, Basel, Switzerland) each month for the first 3 months For the remainder of the 6-month study, treatment was administered at the discretion of the physician if macular edema with cysts in the central macular area persisted. **Sham (n=14):** sham procedure **Regimen for all groups:** All patients received chloramphenicol antibiotic eye drops (Kloramfenikol; Nycomed Pharma Inc, Asker, Norway) for 3 days pre- and post-treatment. All treatments were administered after subconjunctival anesthesia with 0.1 mL lidocaine

	(Xylocain; AstraZeneca Inc, Oslo, Norway).
Outcomes	**Primary outcomes:** Mean change from baseline in BCVA and CRT **Secondary outcomes:** Number of treatments needed, safety and tolerability, and development of neovascularization **Outcome assessment:** monthly visits up to 6 months
COPERNICUS, 2012 [71-72] **Group1: IAI 2mg; Group2: Sham**	
Basic information	**Design:** double-blind, randomised, sham injection-controlled RCT, phase 3 trial **Location:** International **Setting:** multicentre, 70 sites in United States, Canada, India, Israel, Argentina and Columbia **Follow-up:** primary end point 6 months (2-year follow-up planned) **Clinical trial registration:** NCT00943072 at *clinicaltrials.gov* **Loss to follow-up:** 14 (18.9%) in control group, 5 (4.3%) in aflibercept 2.0 mg group
Participants and criteria	**Baseline characteristics:** ➢ Age (years): IAI 2mg: 65.5±13.6; Sham: 67.5±14.3; Total: 66.3±13.9 ➢ Gender: IAI 2mg: 61% male; Sham: 52% male ➢ Baseline VA (letters): IAI 2mg: 50.7±13.9; Sham: 48.9±14.4; Total: 50.0±14.1 ➢ Baseline CRT (μm): IAI 2mg: 661.7±237.4; Sham: 672.4±245.3; Total: 665.8±239.8 ➢ NEI VFQ-25 score: IAI 2mg: 77.67±15.96; Sham: 77.78±16.25; Total: 77.71±16.03 ➢ Mean duration from diagnosis: 2.4 months **Inclusion criteria:** ➢ Adults at least 18 years of age with centre-involving CRVO-macular edema diagnosed within 9 months of study initiation ➢ Mean CRT≥250 μm with OCT ➢ BCVA of 20/40 to 20/320 (73 to 24 letters) in study eye. **Exclusion criteria:** ➢ History of vitreoretinal surgery in the study eye, including radial optic neurotomy or sheathotomy; ➢ Current bilateral retinal vein occlusion; ➢ Previous panretinal or macular laser photocoagulation; other causes for decreased visual acuity; ➢ Ocular conditions with poorer prognosis in the fellow eye; ➢ History or presence of AMD, diabetic macular edema, or diabetic retinopathy; ➢ Any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; ➢ Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; ➢ Vitreomacular traction or epiretinal membrane that significantly affected central vision; ➢ Ocular inflammation; ➢ Uveitis; ➢ Any intraocular surgery in the preceding 3 months; ➢ Aphakia;

	➢ Uncontrolled glaucoma, hypertension, or diabetes; ➢ Spherical equivalent of a refractive error of more than -8 diopters; ➢ Myopia; ➢ Infectious blepharitis, keratitis, scleritis, or conjunctivitis; ➢ Cerebral vascular accident or myocardial infarction in the preceding 6 months; ➢ Other conditions that may interfere with interpretation of the results or increase the risk of complications. ➢ Other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study. ➢ Cataract surgery was not allowed during the 3 months before randomization.
Interventions	**IAI (n=114):** aflibercept (VEGF Trap-Eye) 2.0 mg every 4 weeks for 24 weeks **Sham (n=73):** sham procedure **Extension:** Between weeks 24 and 52, patients in both groups were evaluated monthly and were reinjected with VEGF Trap-Eye if they met protocol-specified retreatment criteria or received a sham injection if retreatment was not indicated. After the first year of masked dosing, patients continued in a 1-year extension phase with as needed dosing.
Outcomes	**Primary end point:** Proportion of eyes with a gain of 15 ETDRS letters or more in BCVA from baseline to week 24. **Secondary end points:** Changes from baseline to week 24 in BCVA, CRT, proportion of eyes progressing to ocular neovascularization, and National Eye Institute 25-item Visual Function Questionnaire total score. **Outcome assessment:** Regularly scheduled clinic visits on day 1, at week 4, and every 4 weeks thereafter to week 24
GALILEO, 2013 [73-74] **Group1: IAI 2mg; Group2: Sham**	
Basic information	**Design:** double-blind, sham-controlled RCT, phase 3 **Location:** International **Setting:** multicentre, 43 sites in Europe (Austria 3; France 5; Germany 21; Hungary 5; Italy 7; Latvia 2), 20 sites in Asia/Pacific region (Australia 6; Japan 6; Singapore 2; South Korea 6) **Follow-up:** primary end point 24 weeks, up to 12 months (76-weeks follow-up planned) **Clinical trial registration:** NCT01012973 at *clinicaltrials.gov* **Loss to follow-up:** 25 out of 177 (14.1%) lost to follow-up at 24 weeks
Participants and criteria	**Baseline characteristics:** ➢ Age (years): IAI 2mg: 59.9±12.4; Sham: 63.8±13.3 ➢ Gender: IAI 2mg: 56.3% male; Sham: 54.4% male ➢ Baseline VA (letters): IAI 2mg: 53.6±15.8; Sham: 50.9±15.4 ➢ Baseline CRT (μm): IAI 2mg: 683.2±234.5; Sham: 638.7±224.7 ➢ Mean IOP (mmHg): IAI 2mg: 15.1±2.8; Sham: 14.4±2.7 **Inclusion criteria:** ➢ Treatment-naive patients, age ≥18 years ➢ Centre-involved macular oedema secondary to CRVO for a maximum of 9 months ➢ Mean CRT⩾250 μm with OCT ➢ BCVA of 20/40 to 20/320 (73 to 24 letters) in study eye.

	Exclusion criteria: ➢ Pregnant ➢ Uncontrolled glaucoma (IOP≥25 mm Hg), filtration surgery, bilateral manifestation of RVO, iris neovascularization; ➢ Previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, or intraocular corticosteroids.
Interventions	**IAI (n=103):** intravitreal injections of 2 mg aflibercept every 4 weeks for 24 weeks **Sham (n=71):** sham procedure (empty syringe without needle pressed to conjunctival surface) every 4 weeks for 24 weeks **Regimen for all groups:** Pan-retinal photocoagulation was allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus. **Extension:** During weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from weeks 52 to 76, both groups received treatment every 8 weeks
Outcomes	**Primary end point:** Gain of 15 ETDRS letters or more in BCVA from baseline to week 24. **Secondary end points:** Changes from baseline to week 24 in BCVA, CRT, NEI-VFQ-25 total score, and EQ-5D score. proportion of eyes progressing to ocular neovascularization, and National Eye Institute 25-item Visual Function Questionnaire total score. Proportion of patients progressing to anterior segment neovascularisation, neovascularisation of the optic disc, or neovascularisation of the retina elsewhere requiring panretinal photocoagulation at week 24 **Outcome assessment:** week 24 and 52
Epstein, 2012 [75-77] **Group1: IVB 1.25mg; Group2: Sham**	
Basic information	**Design:** double-blind, sham-controlled RCT **Location:** Sweden **Setting:** Single centre **Follow-up:** primary end point 6 months, open-label extension up to 12 months **Clinical trial registratioEpsn:** NCT00906685 at *clinicaltrials.gov* **Loss to follow-up:** no losses reported in 0-6 months; 6-12 months: 1 in sham group, 3 in bevacizumab 1.25 mg group
Participants and criteria	**Baseline characteristics:** ➢ Age (years): IVB 1.25mg: 70.6±12.6; Sham: 70.4±10.4; Total: 70.5±12.6 ➢ Gender: IVB 1.25mg: 63% male; Sham: 57% male; Tatal: 60% male ➢ Baseline VA (letters): IVB 1.25mg: 44.4±15.3; Sham: 43.9±16.0; Total: 44.1±15.5 ➢ Baseline CRT (μm): IVB 1.25mg: 712±330; Sham: 729±195; Total: 721±269 ➢ Time from diagnosis to inclusion: IVB 1.25mg: 8.3±4.8; Sham: 9.4±6.5; Total: 8.8±5.7 **Inclusion criteria:** ➢ CRVO with a duration of 6 months or less ➢ Mean CRT⩾300 μm with OCT ➢ BCVA of 15 to 65 letters in study eye.

	Exclusion criteria: ➢ CRVO with neovascularisation ➢ Any previous treatment for CRVO ➢ Intraocular surgery during the previous 3 months ➢ Vascular retinopathy of other causes ➢ Glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25mmHg despite full therapy ➢ Myocardial infarction or stroke during the last 12 months
Interventions	**IVB 1.25mg (n=30):** 1.25 mg (0.05 ml) bevacizumab (Avastin) injections every 6 weeks for 6 months (total 4 injections) **Sham (n = 30):** sham injection. **Open-label extension:** months 6-12, all patients in both groups received bevacizumab 1.25 mg every 6 weeks (4 injections). **General treatments:** all eyes treated with topical antibiotics 30 minutes prior to injection, topical chlorhexidine, topical anaesthesia with 1% tetracaine
Outcomes	**Primary outcome measure:** proportion of patients gaining ≥15 ETDRS letters **Secondary outcome measures:** BCVA, CRT, and number of patients with neovascular glaucoma defined as increased intraocular pressure due to the formation of new vessels in the angle as diagnosed by gonioscopy. **Outcome assessment:** follow-up every 6 weeks up to 6 months, open-label extension up to 12 months
Wroblewski, 2009 [23, 78-83] **Group1: IVP 0.3mg; Group: IVP 1mg; Group 3mg**	
Basic information	**Design:** dose-ranging, double-masked, parallel group, sham-controlled RCT, phase 2 **Location:** International **Setting:** multicenter (35 centres), practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, and the United States. **Follow-up:** primary end point 30 weeks, follow-up up to 12 months **Clinical trial registration:** NCT00088283 at *clinicaltrials.gov*
Participants and criteria	**Baseline characteristics:** ➢ Age (years): IVP 0.3mg: 64; IVP 1mg: 64; Sham: 59 ➢ Gender: IVP 0.3mg: 45.5% male; IVP 1mg: 54.5% male; Sham: 59.4% male ➢ Baseline VA (letters): IVP 0.3mg: 47.6; IVP 1mg: 48.4; Sham: 48.5 ➢ Baseline CRT (μm): IVP 0.3mg: 675; IVP 1mg: 619; Sham: 656 ➢ Duration from diagnosis: < 6 months **Inclusion criteria:** ➢ age ≥18 years ➢ Mean CRT⩾250 μm with OCT ➢ BCVA of 20 to 65 letters in study eye and better than 35 letters in the fellow eye **Exclusion criteria:** ➢ Signs of old BRVO or CRVO in the study ➢ Subtenon corticosteroid administration for any ophthalmic condition ➢ Prior panretinal or sector scatter photocoagulation ➢ Any other retinal vascular disease including diabetic retinopathy

	➢ Eyes with a brisk afferent pupillary defect
Interventions	**IVP 0.3mg (n=33):** intravitreal 0.3mg pegaptanib sodium every 6 weeks for 24 weeks, for a total of 5 injections. **IVP 1mg (n=33):** intravitreal 1mg pegaptanib sodium every 6 weeks for 24 weeks, for a total of 5 injections. **Sham (n=32):** sham injection (blunt pressure applied to the globe without a needle) **Regimen for all groups:** Antisepsis procedures were the same for all subjects including those receiving sham; all subjects received injected subconjunctival anesthetic. During the study, panretinal photocoagulation was permitted at any time point for neovascularization according to the CRVO protocol; intravitreous steroids were not permitted at any time.
Outcomes	**Primary outcome:** ≥15 ETDRS letters gained **Other outcomes:** ≥15 letters lost, BCVA, CRT, safety **Outcome assessment:** every 6 weeks up to 30 weeks, follow-up to 52 weeks
Ramezani, 2014 [84] **Group1: IVB; Group 2: Tria**	
Basic information	**Design:** a controlled, single-masked, RCT, Phase 2 **Location:** Iran **Setting:**, Single centre, Imam Hossein medical center Tehran, Iran, **Follow-up:** primary end point 6 months **Clinical trial registration:** NCT01178697 at *clinicaltrials.gov*
Participants and criteria	**Baseline characteristics:** ➢ Age (years): IVB: 60±8; Tria: 59±9; Total: 60±9 ➢ Gender: IVB: 55.8% male; Tria : 53.5% male; Total: 54.7% male ➢ Baseline VA (logMAR): IVB: 0.87±0.49; Tria: 0.81±0.45; Total: 0.84±0.47 ➢ Baseline CRT (μm): IVB: 473±223; Tria: 438±202; Total: 455±213 ➢ Duration from diagnosis: < 12 weeks **Inclusion criteria:** ➢ age ≥18 years ➢ patients with recent onset CRVO (<12 weeks), based on the patients' history **Exclusion criteria:** ➢ received previous therapy such as macular laser photocoagulation or intravitreal injection ➢ the history of glaucoma or ocular hypertension ➢ BCVA better than 20/40, CRT of <250 microns, significant media opacity, ➢ any type of neovascularization, accompanying arterial occlusion ➢ signs of chronicity (such as cilioretinal and/or retinal shunt vessels) ➢ existence of other significant retinal diseases and noncompliance.
Interventions	**IVB (n=43):** Intravitreal 1.25 mg (0.05 ml) bevacizumab (Avastin) injections, 3 times, one month apart **Tria (n=43):** Intravitreal injections of 2 mg (0.5 ml) triamcinolone acetonide, 2 times, two months apart **Regimen for all groups:** One eye per participant was enrolled in this trial. Intravitreal injections were carried out in the operating room with application of tetracaine 0.5% drops. All eyes were prepared with 5% povidone iodine. After insertion of eyelid speculum,

	injections were performed by 30 G needles through supratemporal quadrant at 4 mm from the limbus. Patients used topical antibiotics four times per day for 5 days after the injections.
Outcomes	**Primary outcome:** BCVA changes from baseline. **Secondary outcome measures:** CRT changes and intraocular pressure (IOP) changes **Outcome assessment:** up to 6 months
COMRADE-C, 2016 [85] **Group1: IVR; Group2: DEX**	
Basic information	**Design:** a double-masked RCT, phase IIIb **Location:** International **Setting:** multicentre, 66 sites across Germany, Great Britain, Poland, and Hungary **Follow-up:** primary end point 6 months **Clinical trial registration:** NCT01396083 at *clinicaltrials.gov* **Loss to follow-up:** 11 out of 124 (8.9%) lost in the ranibizumab group, 47 out of 117 (39.5%) lost in the dexamethasone completed the 6-month study
Participants and criteria	**Baseline characteristics:** ➢ Age (years): IVR: 65.3±11.4; DEX: 66.9±12.4; Total: 66.1±11.9 ➢ Gender: IVR: 58.1% male; DEX : 61.3% male; Total: 59.7% male ➢ Baseline VA (letters): IVR: 51.7±16.5; DEX: 51.5±15.6; Total: 51.6±16.1 ➢ Baseline CRT (μm): IVR: 723.8±245.9; DEX: 705.2±231.1; Total: 714.6±238.4 ➢ Duration from diagnosis: ⩽6 months **Inclusion criteria:** ➢ male and female patients age ≥18 years ➢ visual impairment due to macular edema secondary to CRVO diagnosed ⩽6 months before screening ➢ BCVA (study eye) of 20/40 to 20/400 (6/12 to 6/120 meters) using Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA testing charts. **Exclusion criteria:** ➢ a history of radial optic neurotomy or sheathotomy in the study eye, presence of either dry or wet age-related macular degeneration (AMD) in the study eye, ocular diseases (uveitis, neovascular glaucoma, diabetic retinopathy, diabetic maculopathy, or ocular ischemic syndrome) associated with increased intraocular VEGF levels, macular detachment/subretinal fluid attributable to causes other than BRVO, hypersensitivity to any of the study drugs or to drugs with similar chemical structures, or allergy to fluorescein; ➢ CRT of <250 mm in the study eye; ➢ prior episode of retinal vein occlusion in the study eye; ➢ anti-VEGF treatment in the study or the fellow eye 3 months before baseline; ➢ panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before baseline or anticipated within the 4 months following randomization; ➢ intraocular corticosteroid use within 6 months before baseline; ➢ IOP of >30 mm Hg or uncontrolled glaucoma; patients could be rescreened after 1 month if they had undergone treatment; ➢ a history of cerebral vascular accident or myocardial infarction within 12 months prior

	to baseline; ➢ a history of pars plana vitrectomy.
Interventions	**IVR (n=124):** Receive intravitreal injections of ranibizumab 0.5mg as per the 2011 European (EU) SmPC, a minimum of 3 consecutive monthly ranibizumab injections or injections until stable VA (no change in VA for 3 consecutive monthly assessments based on investigators' judgment) was reached; **DEX (n=119):** Patients received a single implant of sustained-release intravitreal dexamethasone intravitreal implant 0.7 mg at baseline according to the approved EMA label. **Regimen for all groups:** All patients received treatment in accordance with the European Union summary of product characteristics (SmPC) for ranibizumab or dexamethasone intravitreal implant. As mandated by the study protocol, no adjustments of the ranibizumab or dexamethasone intravitreal implant dosing regimen, or rescue therapy, were allowed.
Outcomes	**Primary outcome:** BCVA changes from baseline to month 1 through month 6. **Secondary outcomes:** CRT changes, proportion of patients with a BCVA gain or loss of ⩾15/⩾10/⩾5 letters at month 6, number of injections, IOP changed, safety over time, National Eye Institute Visual Function Questionnaire (NEI VFQ-25), the Short Form Health Survey (SF-36), the Euro Quality of Life (EQ-5D) questionnaire **Outcome assessment:** every month up to 6 months

Appendix 5 Outcomes of included studies

GENEVA, 2010 [46-48](DEX vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)

6 months

	DEX 0.7mg (n=136)	DEX 0.35mg (n=154)	Sham (n=147)
BCVA (ETDRS letters)	+0.1		-1.8
p value	<0.001 vs sham		
≥15 letters gained	25 (18.4%)	11 (17%)	18 (12.2%)
p value	NS vs sham	NS vs sham	
≥15 letters lost	19 (14.0%)		30 (20.4%)
p value	NS vs sham		
CRT (µm)	-118.2		-125.3
p value	NS vs sham		

12 months

	DEX 0.7mg (n=136)	DEX 0.35mg (n=154)	Sham (n=147)
BCVA (ETDRS letters)	+2 (graph estimated)		-1.4 (ditto)
≥15 letters gained	37 (27%)		31 (21%)

Adverse events

6 months

	DEX 0.7mg (n=133)	DEX 0.35mg (n=154)	Sham (n=147)
Overall of ocular AEs	91 (68.4%)		73 (49.7%)
IOP increased	40 (30.1%)		2 (1.4%)
Cataract AEs	11 (8.3%)		7 (4.8%)

ROVO, 2013 [49] (Tria vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)

12 months

	Tria 4mg (n=25)	RON (n=38)	Sham (n=20)
BCVA (ETDRS letters)	-8	-35.5	0

p value	NS vs sham		
VA improvement	5 (20%)	18 (47.3%)	2 (10%)
p value	NS vs sham		
VA deterioration	NR	3 (7.9%)	7 (35%)
CRT (μm)	-235	-263	-206
p value	NS vs sham		
Adverse events			
12 months			
	Tria 4mg (n=25)	**RON (n=38)**	**Sham (n=20)**
IOP increased	8 (32%)		0
Cataract progression	6 (24%)	5 (13.2%)	3 (15%)
Neovscular glaucoma	3 (12%)	2 (5.3%)	3 (15%)
Rubeosis iridis	0		3 (15%)
SCORE, 2009 [50-66] (Tria vs sham)			
Efficiency outcomes (changes from baseline at follow-up time points)			
6 months (weight mean and SD of 4 and 8 months)			
	Tria 4mg (n=85)	**Tria 1mg(n=84)**	**Obs (n=75)**
BCVA (letters)	-0.15±20.67	-3.93±23.42	-9.66±18.04
p value	NR	NR	
≥15 letters gained	17 (19.5%)	15(17.5%)	3 (4%)
p value	NR	NR	
≥15 letters lost	19 (20.5%)	21 (25.0%)	31 (35.5%)
p value	NR	NR	
12 months			
	Tria 4mg (n=82)	**Tria 1mg(n=83)**	**Obs (n=73)**
BCVA (letters, 95%CI)	-1.2±24.82 (-6.3 to +4.0)	-1.2±25.45 (-6.4 to +4.1)	-12.1±23.93 (-17.1 to -7.1)
p value	<0.05 vs obs	<0.05 vs obs	
≥15 letters gained	21 (25.6%)	22 (26.5%)	5 (6.8%)
p value	0.001 vs obs	0.001 vs obs	

≥15 letters lost	21 (25.6%)	21 (25.3%)	32 (43.8%)
p value	NR	NR	
CRT (µm) (median, IQR)	-261 (-407 to -79) n=78	-196 (-390 to -62) n=72	-277 (-418 to -40) n=68
p value	NR	NR	
24 months			
	Tria 4mg (n=50)	**Tria 1mg(n=55)**	**Obs (n=46)**
BCVA (letters, 95%CI)	-2.4±24.89 (-9.3 to +4.4)	-4.4±26.87 (-11.5 to +2.8)	-10.7±22.84 (-17.4 to -4.1)
p value	NR		
≥15 letters gained	13 (26%)	17 (30.9%)	4 (8.7%)
p value	NR		
≥15 letters lost	13 (26%)	17 (30.9%)	22 (47.8%)
p value	NS, p=0.06 tria vs obs		
CRT (µm) (median, IQR)	-236 (-421 to -63) n=45	-286 (-458 to -119) n=48	-304 (-465 to -108) n=43
p value	NR		
Adverse events			
12 months			
	Tria 4mg (n=91)	**Tria 1mg(n=92)**	**Obs (n=88)**
Initiation of IOP-lowering medication	32 (35.2%)	18 (19.6%)	7 (8.0%)
Iris neovascularization or neovascular glaucoma	4 (4.4%)	9 (9.8%)	2 (2.3%)
Retinal neovascularization	2 (2.2%)	2 (2.2%)	4 (4.6%)
Vitreous hemorrhage	0	4 (4.3%)	4 (4.6%)
CRUISE, 2010 [67-69] (IVR vs sham)			
Efficiency outcomes (changes from baseline at follow-up time points)			
6 months			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=130)**	**Sham (n=130)**
BCVA (letters, 95%CI)	+12.7±15.9 (9.9, 15.4)	+14.9±13.2 (12.6, 17.2)	+0.8±16.2 (-2.0, 3.6)
p value	<0.0001 vs sham	<0.0001 vs sham	

≥15 letters gained	61 (46.2%)	62 (47.7%)	22 (16.9%)
p value	<0.0001 vs sham	<0.0001 vs sham	
≥15 letters lost	5 (3.8%)	2 (1.5%)	20 (15.4%)
p value	NR		
CRT (µm, 95%CI)	-433.7 (-484.9, -382.6) n=131	-452.3(-497.0, -407.6) n=130	-167.7 (-221.5, -114.0) n=129
p value	<0.0001 vs sham	<0.0001 vs sham	
NEI-VFQ (95%CI)	+7.1 (5.2, 9.0)	+6.2 (4.3, 8.0)	+2.8 (0.8, 4.7)
p value	<0.05 vs sham	<0.05 vs sham	
12 months (IVR PRN)			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=130)**	**Sham (n=130)**
BCVA (letters, 95%CI)	+13.9±15.2 (11.2, 16.5)	+13.9±14.2 (11.5, 16.4)	+7.3±15.9 (4.5, 10.0)
p value	0.0007 vs sham	0.0006 vs sham	
≥15 letters gained	62 (47.0%)	66 (50.8%)	43 (33.1%)
p value	NR		
≥15 letters lost	5 (3.8%)	3 (2.3%)	13 (10.0%)
p value	NR		
CRT (µm)	-462.1	-452.8	-427.2
p value	NS vs sham	NS vs sham	
NEI-VFQ	+7.1	+6.6	+5.0
p value	NR	NR	
Adverse events			
6 months			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=129)**	**Sham (n=129)**
Any intraocular inflammation event	3 (2.3%)	2 (1.6%)	5 (3.9%)
Cataract	2 (1.5%)	2 (1.6%)	0
Neovascular glaucoma	0	0	2 (1.6%)
Vitreous haemorrhage	5 (3.8%)	7 (5.4%)	9 (7.0%)
12 months			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=129)**	**Sham (n=110)**

Any intraocular inflammation event	3 (2.3%)	2 (1.6%)	2 (1.8%)
Cataract	5 (3.8%)	9 (7.0%)	2 (1.8%)
Neovascular glaucoma	0	1 (0.8%)	0
Vitreous haemorrhage	7 (5.3%)	7 (5.4%)	2 (1.8%)
Iris neovascularization	2 (1.5%)	5 (3.9%)	2 (1.8%)
Retinal tear	0	2 (1.6%)	2 (1.8%)

ROCC, 2010 [70] (IVR vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVR 0.5mg (n=15)	**Sham (n=14)**
BCVA (letters)	+12±20	-1±17
p value	0.067 vs sham	
CRT (µm)	-304±194	-151±205
p value	0.05 vs sham	

Adverse events		
6 months		
	IVR 0.5mg (n=15)	**Sham (n=14)**
Vitreous hemorrhage	2 (13.3%)	0
Retinal tear	0	1 (7.1%)
Neovascular disease	0	1 (7.1%)

COPERNICUS, 2012 [71-72] (IAI vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IAI 2mg (n=114)	**Sham (n=73)**
BCVA (letters)	+17.3±12.8	-4.0±18
p value	<0.001	
≥15 letters gained	64 (56.1%)	9 (12.3%)
p value	<0.001	

≥15 letters lost	2 (1.8%)	20 (27.4%)
p value	NR	
CRT (µm)	-457.2	-144.8
p value	<0.001	
NEI VFQ-25	+7.2±12.1	+0.8±9.8
p value	0.001	
12 months (all IAI PRN)		
	IAI 2mg (n=114)	**Sham (n=73)**
BCVA (letters)	+16.2	+3.8
p value	<0.001	
≥15 letters gained	63 (55.3%)	22 (30.1%)
p value	<0.001	
≥15 letters lost	6 (5.3%)	11 (15.1%)
p value	NR	
CRT (µm)	-413.0	-381.8
p value	NS	
NEI VFQ-25	+7.5	+5.1
p value	NS	
Adverse events		
6 months		
	IAI 2mg (n=114)	**Sham (n=74)**
Patients with at least one serious adverse events	4 (3.5%)	10 (13.5%)
Vitreous hemorrhage	0	4 (5.4%)
Neovascular glaucoma	0	2 (2.7%)
Iris neovascularization	0	2 (2.7%)
Retinal hemorrhage	0	2 (2.7%)
Retinal tear	0	1 (1.4%)
Endophthalmitis	1 (0.9%)	0
6 to 12months		

	IAI 2mg + PRN (n=110)	Sham + PRN (n=60)
Patients with at least one serious adverse events	3 (2.7%)	2 (3.3%)
Vitreous hemorrhage	1 (0.9%)	1 (1.7%)
Glaucoma	0	1 (1.7%)
Retinal tear	0	1 (1.7%)
Cataract	1 (0.9%)	1 (1.7%)

GALILEO, 2013 [73-74] (IAI vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)

6 months

	IAI 2mg (n=103)	Sham (n=68)
BCVA (letters)	+18.0±12.2	+3.3±14.1
p value	<0.0001	
≥15 letters gained	62 (60.2%)	15 (22.1%)
p value	<0.0001	
≥15 letters lost	8 (7.8%)	15 (22.1%)
p value	0.0033	
CRT (µm)	-448.6	-169.3
p value	<0.0001	
NEI-VFQ-25	+7.5	+3.5
p value	0.0013	

Adverse events

6 months

	IAI 2mg (n=104)	Sham (n=68)
Eye pain	12 (11.5%)	3 (4.4%)
Conjunctival haemorrhage	9 (8.7%)	3 (4.4%)
Ocular hyperaemia	5 (4.8%)	4 (5.9%)
Vitreous floaters	5 (4.8%)	0
Macular ischaemia	4 (3.8%)	3 (4.4%)

Eye irritation	3 (2.9%)	7 (10.3%)
Retinal ischaemia	1 (1.0%)	3 (4.4%)
IOP increased	10 (9.6%)	4 (5.9%)

Epstein, 2012 [75-76] (IVB vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVB 1.25mg (n=30)	**Sham (n=30)**
BCVA (letters)	+14.1±18.7	-2.0±20.5
p value	<0.01	
≥15 letters gained	18 (60%)	6 (20%)
p value	0.003	
≥15 letters lost	2 (6.7%)	7 (23.3%)
p value	NS, 0.146	
CRT (µm)	-426	-102
p value	<0.0001	
12 months		
	IVB 1.25mg (n=30)	**Sham (n=30)**
BCVA (letters)	+16.1	+4.6
p value	<0.05	
≥15 letters gained	18 (60%)	10 (33.3%)
p value	<0.05	
≥15 letters lost	2 (6.7%)	2 (6.7%)
p value	NS	
CRT (µm)	-435	-404
p value	>0.05	
Adverse events		
6 months		
	IVB 1.25mg (n=30)	**Sham (n=30)**
Iris rubeosis	0	5 (16.7%)

Wroblewski, 2009 [23, 77-83] (IVP vs Sham)			
Efficiency outcomes (changes from baseline at follow-up time points)			
6 months (~30weeks)			
	IVP 0.3mg (n=33)	**IVP 1mg (n=33)**	**Sham (n=32)**
BCVA (letters)	+7.1	+9.9	-3.2
p value	0.09 vs sham	0.02 vs sham	
≥15 letters gained	12 (36.4%)	13 (36.1%)	9 (28.1%)
p value	0.48		
≥15 letters lost	3 (9.1%)	2 (6.1%)	10 (31.3%)
p value	0.03 vs sham	0.01 vs sham	
CRT (µm)	-243	-179	-148
p value	0.13	0.06	
12 months			
	IVP 0.3mg (n=33)	**IVP 1mg (n=33)**	**Sham (n=32)**
BCVA (letters)	+7.5	+6.3	-2.4
p value	NS vs sham	NS vs sham	
CRT (µm)	-295	-216	-183
p value	<0.05 vs sham		
Adverse events			
No serious ocular adverse events up to 30 weeks. No evidence of increased risk of systemic adverse events up to 30 weeks.			

Ramezani, 2014 [84] (IVB vs Tria)		
Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVB (n=43)	**Tria (n=43)**
BCVA (letters)	+23±11.5	+9.5±11.5
p value	<0.001	<0.001
CRT (µm)	-151±122	-75±89
p value	<0.001	<0.001

Adverse events		
6 months		
	IVB (n=43)	**Tria (n=43)**
IOP changes (mmHg)	-1.0±2.2	+2.2±2.7

COMRADE-C, 2016 [85] (IVR vs DEX)		
Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVR (n=124)	**DEX (n=119)**
BCVA (letters)	+16.9±13.6	-0.7±22.5
p value	<0.0001 vs DEX	
≥15 letters gained	73 (58.9%)	22 (18.5%)
p value	<0.0001 vs DEX	
≥15 letters lost	1 (0.8%)	31 (26.1%)
p value	<0.0001 vs DEX	
CRT (μm)	-376.7±274.9	-168.7±288.3
p value	NR	
Adverse events		
6 months		
	IVR (n=124)	**DEX (n=119)**
IOP increased	7 (5.6%)	38 (31.9%)
Macular edema	14 (11.3%)	21 (17.6%)
Eye pain	15 (12.1%)	15 (12.6%)
VA reduced	8 (6.5%)	22 (18.5%)
Conjunctival hemorrhage	16 (12.9%)	13 (10.9%)
Vitreous floaters	5 (4.0%)	11 (9.2%)
Iris neovascularization	0 (0.0%)	9 (7.6%)
Dry eye	4 (3.2%)	4 (3.4%)
Glaucoma	0 (0.0%)	8 (6.7%)
Visual impairment	2 (1.6%)	6 (5.0%)

Vitreous detachment	5 (4.0%)	3 (2.5%)
Eye irritation	4 (3.2%)	3 (2.5%)
Retinal ischemia	1 (0.8%)	6 (5.0%)
Retinal vascular disorder	2 (1.6%)	5 (4.2%)
Ocular hypertension	0	6 (5.0%)
Retinal exudates	2 (1.6%)	4 (3.4%)
Optic disc vascular disorder	5 (4.0)	0

Appendix 6 Risk of bias of individual studies

Trials	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
GENEVA, 2010 [46-48]	Low	Low	High: Personel administering treatments were not masked. Participants were masked to dose of implant, but not to treatment (steroid implant versus no implant).	Low	High: Macular thickness was described as a secondary outcome in the trial registry for one trial only, but the 6-month reported results used the pooled data from both trials to analyze this outcome at 6 months	Low	Unclear
ROVO, 2013 [49]	Low	Low	Unclear	Unclear	Low	Low	Unclear
SCORE, 2009 [50-66]	Low	Low	High: physicians and patients masked to dose but not triamcinolone versus observation	Low	High: In the observation arm, 17% of participants had missing data compared with the 6.8% observed risk for the primary outcome. Reasons for missing data were not reported	Low	Unclear

Trials	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CRUISE, 2010 [67-69]	Low	Unclear	Low	Low	Unclear	Low	Unclear
ROCC, 2010 [70]	Unclear	Low	Low	Low	Unclear	Low	Unclear
COPERNICUS, 2012 [71-72]	Low	Unclear	Low	Low	Unclear	Low	Low
GALILEO, 2013 [73-74]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
EPSTEIN, 2012 [75-77]	Unclear	Low	Low	Low	Low	Low	Low
Wroblewski, 2009 [23, 78-83]	Low	Low	Low	Low	Unclear	Low	Unclear
Ramezani, 2014 [84]	Low	Low	High: Because IVT might cause floaters, we did not consider this study as a double-blind one.	Low	Low	Low	Unclear
COMRADE-C, 2016 [85]	Low	Low	Low	Low	Unclear	Low	Unclear

BMJ Open

Comparison of the efficacy and safety of different drug therapies for macular edema secondary to central retinal vein occlusion: a systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022700.R1
Article Type:	Research
Date Submitted by the Author:	21-Jun-2018
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Ophthalmology
Keywords:	Central retinal vein occlusion, macular edema, anti-VEGF, corticosteroid, network meta-analysis

Comparison of the efficacy and safety of different drug therapies for macular edema secondary to central retinal vein occlusion: a systematic review and network meta-analysis

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ABSTRACT

Objectives: To evaluate the efficacy and safety of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids for the treatment of macular edema (ME) secondary to central retinal vein occlusion (CRVO).

Design: Systematic review and network meta-analysis.

Participants: Patients from previously reported randomized controlled trials (RCTs) comparing anti-VEGF and corticosteroids for the treatment of ME secondary to CRVO.

Methods: Literature searches were conducted using PubMed, Medline, Embase, Cochrane Library, and *clinicaltrials.gov* until March 2017. Therapeutic effects were estimated using the proportions of patients gaining/losing ⩾15 letters, best-corrected visual acuity (BCVA), and central retinal thickness (CRT). Treatment safety was estimated using the proportions of adverse events, namely increased intraocular pressure (IOP), cataracts, vitreous hemorrhage (VH), and retinal tear. The software ADDIS (version 1.16.8) was used for analysis. Treatment effect and safety of different drugs could be ranked based on simulation.

Results: Eleven RCTs comprising 2060 patients were identified. Regarding patients gaining ⩾15 letters, aflibercept and ranibizumab were significantly more effective than sham/placebo at 6 months. Regarding patients losing ⩾15 letters at 6 months, ranibizumab showed significant improvement compared to dexamethasone. Aflibercept, bevacizumab, or ranibizumab showed greater improvements in BCVA than sham/placebo at 6 months. Intravitreal ranibizumab injection demonstrated greater CRT reduction than both sham and dexamethasone did. Dexamethasone had a higher risk of increased IOP than aflibercept and ranibizumab. Ranibizumab demonstrated a greater risk of cataracts than dexamethasone. Aflibercept and ranibizumab demonstrated low incidence of VH and retinal tear, respectively. Aflibercept had a slight advantage over ranibizumab as assessed by benefit-risk analysis.

Conclusions: Anti-VEGF agents have advantages in the treatment of ME secondary to CRVO. Aflibercept and ranibizumab showed marked BCVA improvement and CRT reduction. Aflibercept may have a slight advantage over ranibizumab. The results of this study can serve as a reference for clinicians to provide patient-tailored treatment.

Review registration

PROSPERO CRD42017064076

Strengths and limitations of this study

- This meta-analysis included the most recent reports.
- Strict inclusion and exclusion criteria were used to perform a comprehensive comparison of aflibercept, ranibizumab, bevacizumab, pegaptanib, dexamethasone, and triamcinolone treatments.
- Our data contained some biases that might have influenced our results. In the 11 literature included, three of them did not illustrate blinding of participants and two of them reported incomplete outcome data.
- Detailed data at long-term follow-up time points are required to improve the accuracy and robustness of our findings.
- The details of adverse events were not always reported in each study.

Keywords: Central retinal vein occlusion (CRVO), macular edema, anti-VEGF, corticosteroid, network meta-analysis

INTRODUCTION

Central retinal vein occlusion (CRVO), a common retinal vascular disorder, is characterized by dilated and tortuous retinal veins with hemorrhages in all four quadrants of the retina.[1,2] CRVO can reduce vision severely,[3,4] and its prevalence is estimated at 0.80 per 1000 persons, indicating that approximately 2.5 million adults are affected by CRVO globally.[1] CRVO is caused by a combination of risk factors, including advanced age, atherosclerosis, hypertension, diabetes mellitus, thrombophilia, hyperlipidemia, glaucoma, and other vessel wall changes or hemodynamic abnormalities.[5,6] Macular edema (ME) is the most common complication in CRVO that can lead to impaired central vision,[7] and ME secondary to CRVO is the second most common retinal vascular disease after diabetic retinopathy.[1,8,9]

The serious consequences of CRVO and its increasing prevalence make effective and widely applicable treatments necessary. Preventing ME and improving visual acuity (VA) are the two most important goals of treatment of ME secondary to CRVO. During the past several decades, various therapeutic approaches have been advocated for CRVO. The Central Vein Occlusion Study (CVOS) demonstrated that macular grid photocoagulation could decrease ME in patients with CRVO; however, it failed to improve VA when compared with that in the observation group.[10,11] Although intravitreal corticosteroid agents (e.g., triamcinolone acetonide injections and dexamethasone implants), which have anti-inflammatory, antiangiogenic, and anti-edematous properties,[12] demonstrate some adverse events (AEs), they have been used to treat ME and improve VA in CRVO patients. Intravitreal triamcinolone has recently been shown to have a beneficial effect on ME secondary to CRVO and a preventive effect on neovascularization. [13-15] Kuppermann *et al*. also reported that dexamethasone implants might be a potential treatment option for persistent ME.[16]

Vascular endothelial growth factor (VEGF) is a homodimeric protein that can stimulate vascular endothelial cell growth and induce vascular permeability.[17] It plays a crucial role in the pathophysiology process of ME,[18] and its levels were elevated in the ocular fluids of patients with CRVO.[19] Therefore, several anti-VEGF agents, including aflibercept, ranibizumab, bevacizumab, and pegaptanib, have been widely used for treating ME secondary to CRVO, because they significantly improve visual and anatomic outcomes in CRVO patients.[20-23]

Currently, intravitreal corticosteroid agents and intravitreal anti-VEGF agents are the common clinical therapies for ME secondary to CRVO. Nevertheless, these different drug treatment strategies

have not been comprehensively compared, and there are no head-to-head trials or clear guidance to determine the best treatment strategy for CRVO patients. Therefore, a systematic review of randomized controlled trials (RCTs) is needed to indirectly compare the efficacies of anti-VEGF agents and intravitreal corticosteroids agents for treating ME secondary to CRVO.

A previous network meta-analysis of RCTs that examined CRVO treatments had mainly focused on the efficacy outcomes at 6 months and failed to include pegaptanib. [24] In addition, it only considered the functional outcomes (e.g., letters gained and VA improvement) as therapeutic effects without consideration of anatomical outcomes and AEs. Therefore, the current systematic review and network meta-analysis was performed to overcome the shortcomings of the previous study and to include data from the latest RCTs. In the present study, we aimed to indirectly compare the clinical efficacy and safety of aflibercept, ranibizumab, bevacizumab, pegaptanib, dexamethasone, and triamcinolone for the treatment of ME secondary to CRVO. The clinical efficacy outcomes include best-corrected visual acuity (BCVA) improvement, central retinal thickness (CRT) reduction, and the proportion of $\geqslant$15 letters gained or lost. The safety outcomes include the proportion of common AEs, such as increased intraocular pressure (IOP), cataracts, neovascular glaucoma, and vitreous hemorrhage (VH). We hope that our findings will aid ophthalmologists in choosing the best treatment options for their patients.

METHODS

This systematic review was performed according to the PRISMA Statement, and the review was conducted and reported according to the PRISMA NMA Checklist of items (Appendix 1).[25-26] We developed a systematic review protocol and registered it with PROSPERO (CRD42017064076). (Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064076).

Patient and Public Involvement

We used secondary data from peer-reviewed published articles, so no patients or public were not involved in this network meta-analysis.

Literature search

Literature searches were performed using five databases (Embase, Medline, Pubmed Central,

Cochrane Library, and *ClinicalTrials.gov*) to identify relevant articles published until the end of March 2017. The following terms were searched in each database: central retinal vein occlusion (CRVO), anti-VEGF agents, corticosteroids, and randomized controlled trials (RCTs). The full search strategies are described in supplementary Appendix 2. In addition, supplementary searches were performed to search for other relevant studies in the World Health Organization (WHO) International Clinical Trials Registry Platform, Google Scholar, and other websites of professional associations. Language or study design restrictions were not used. When titles or abstracts or both fit our search terms, abstracts were reviewed to exclude irrelevant studies (e.g., case reports, reviews, or experimental treatments). We then carefully read all the remaining articles to determine if they contained data that were applicable to our study.

Article inclusion/exclusion criteria

In this network meta-analysis, studies were selected based on the following inclusion criteria: 1) The study was an RCT. 2) Ranibizumab, bevacizumab, aflibercept, pegaptanib dexamethasone, or triamcinolone was used. 3) Subjects were adults (≥ 18 years) of either sex with ME secondary to CRVO. 4) Studies had to report at least one of the following outcomes: proportions of patients gaining/losing ≥ 15 letters (3 lines) from baseline to 6 or 12 months, the mean change in BCVA from baseline to 6 or 12 months, the mean change in CRT from baseline to 6 or 12 months, or the proportions of patients with AEs at 6 or 12 months. Studies that met any of the following criteria were excluded from our meta-analysis: 1) review article; 2) duplicate publication; 3) sufficient information not published (e.g., full text not accessible, full text did not contain raw data, or inconsistent or erroneous data provided), and 4) subjects with CRVO did not have ME prior to treatment.

Risk of bias assessment

The included studies were examined independently for biases by two authors using *Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions*.[27] The following study characteristics were assessed for biases: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting

(reporting bias), and other factors that contribute to biases (e.g., extreme baseline imbalance, study design, and trial stopped early because of data-dependent developments). The status of each of the above items was listed as "yes" to indicate a low risk, "no" to indicate a high risk, or "unclear" to indicate an unknown risk of bias.

Data extraction

The following information on study characteristics and clinical treatments were collected from all included studies:

1) Basic information

   Name of first author, year of publication, design of trial, location of study, setting, follow-up time, clinical trial registration

2) Participants and criteria

   Baseline characteristics (age, gender, baseline VA, baseline CRT, duration of ME, etc.), inclusion criteria, exclusion criteria

3) Interventions

   Different treatment groups and number of patients included

4) Outcomes

   Primary outcomes, other outcomes, outcome assessment

Some data that were not reported in articles were published online at *ClinicalTrials.gov* or other meta-analyses. T. Qian and M. Zhao carried out search and extracted data. If disagreements occurred, X. Xu would check the data again.

Evaluation indicator

The indicators of treatment efficacy included the proportions of patients gaining/losing $\geqslant$ 15 letters from baseline to 6 or 12 months and the mean changes in BCVA and CRT. The safety indicators included the proportions of patients with various AEs.

Statistical analyses

Our analysis classified anti-VEGF agents and corticosteroids used in monotherapy as separate treatment nodes irrespective of their doses: aflibercept, ranibizumab, bevacizumab, pegaptanib,

dexamethasone, triamcinolone, and placebo or sham (i.e., conventional therapy/usual care).

Network meta-analysis allows the integration of data from both direct and indirect evidence, and it can be used to estimate comparisons between pairs of treatments that have not been compared in individual studies.[28,29] The network meta-analysis was performed within a Bayesian framework by using the Markov Chain Monte Carlo (MCMC) method.[30] The measures of treatment effects were relative risk (RR) for dichotomous outcomes and the weighted mean difference (WMD) for continuous outcomes. Bayesian statistical inference provides probability distributions for treatment effect parameters, with 95% credible intervals (95% CrI), which can be interpreted as a 95% probability that the parameter takes a value within the specified range.[31,32] If 1.0 was not included in the 95% CrI, the results were considered statistically significant. Consistency analysis could be performed in the presence of similarity and homogeneity, and on this basis, it is possible to rank the effect of different treatment strategies. The higher ranking means the better the treatment is. But when considering the adverse events, the higher ranking means the more probability of adverse events. When performing this network meta-analysis, we relied on the assumptions of transitivity and consistency.[33] The consistency of results was qualitatively examined if sufficient evidence was available. If both direct and indirect evidences existed, node-splitting and pairwise meta-analyses were used to evaluate the inconsistency of direct comparisons in indirect evidences in the network meta-analysis.[34] In order to analyze the direct and indirect evidences in accordance in the split node, the node-splitting assessment is necessary. And $P < 0.05$ indicates significant heterogeneity in this assessment.

The data of the included studies were analyzed using the STATA 14® (StataCorp LP, College Station, TX)[35] and the Aggregate Data Drug Information System (ADDIS v1.16.8, Drugis, Groningen, NL).[36] The risk of bias graph was drawn using Review Manager 5.3.5 software. During data analysis, four parallel chains were used and 50,000 samples were obtained after a 20,000-sample burn-in in each chain.[37] Convergence was assessed using the Brooks-Gelman-Rubin method. This method compares within-chain and between-chain variance to calculate the Potential Scale Reduction Factor (PSRF). A PSRF close to one indicates that approximate convergence has been reached.[38]

RESULTS

Literature search results

The PRISMA flowchart of the selection process of studies included in this network meta-analysis is illustrated in Figure 1. In total, 1032 articles were initially identified in our literature searches. Of these, 556 articles were potentially relevant and screened after duplicates had been removed. A title and abstract review eliminated an additional 508 articles. Full-text examinations excluded seven additional articles[39-45] (7 studies) owing to various reasons. Finally, 41 articles[23, 46-85] (11 studies) were included in this systematic review and network meta-analysis. The specific literature of both included and excluded studies is shown in Appendix 3.

Characteristics and outcomes of included studies

Eleven studies comprising 2060 patients with ME secondary to CRVO were included in this meta-analysis. A network graph was constructed to show the network of eligible comparisons for the network meta-analysis (Figure 2). Briefly, the follow-up duration was at least 6 months and the patients' ages and gender distributions did not vary significantly among different drug treatment groups. The median sample size was 174 individuals (range 29–437). The main characteristics of the 11 included studies are presented in Table 1. The detailed study results are presented in Appendix 4.

Methodological quality of included studies

The biases of the 11 included studies were assessed using the Cochrane Collaboration's tool as listed in Appendix 5. Each risk of bias item is expressed as a percentage across all included studies in Figure 3. In terms of methodological quality, three trials (27.3%) had a high risk of bias.

Table 1 Study Characteristics of the Eleven RCTs Enrolled

Trials year	Location	Interventions (Number of patients)	Age (Mean±SD)	Baseline VA (ETDRS, letters)	Follow-up (Months)
GENEVA[46-48] 2010	International	DEX 0.7mg (n=136) DEX 0.35mg (n=154) Sham (n=147)	mean 62.7 to 65.2 years	52.4±10.6 NA 53.3±10.8	6, 12
ROVO [49] 2015	Austria	Tria 4mg (n=25) RON (n=38) Pla (n=20)	NA	46.5 (overall)	12
SCORE [50-56] 2013	United State	Tria 4mg (n=91) Tria 1mg (n=92)	67.5±12.0 67.4±12.4	51.0±14.4 50.6±14.9	Every 4 months for

CRUISE [67-69] 2010	United State	Obs (n=88)	69.2±12.8	52.1±13.1	36 months
		IVR 0.3mg (n=132)	69.7±11.6	47.4±14.8	Monthly
		IVR 0.5mg (n=130)	67.6±12.4	48.1±14.6	visits up to
		Sham (n=130)	65.4±13.1	49.2±14.7	12 months
ROCC [70] 2010	Norway	IVR 0.5mg (n=15)	72	45±23	6
		Sham (n=14)		41±22	
COPERNICUS [71-72] 2012	International	IAI 2mg (n=114)	65.5±13.5	50.7±13.9	6
		Sham (n=73)	67.5±14.3	48.9±14.4	
GALILEO [73-74] 2013	International	IAI 2mg (n=103)	59.9±12.4	53.6±15.8	6,12
		Sham (n=71)	63.8±13.3	50.9±15.4	
Epstein [75-77] 2012	Sweden	IVB 0.25mg (n=30)	70.6±12.6	70.6±12.6	6,12
		Sham (n=30)	70.4±10.4	70.4±10.4	
Wroblewski [23, 78-83] 2009	International	IVP 0.3mg (n=33)	64	47.6	12
		IVP 1mg (n=33)	64	48.4	
		Sham (n=32)	59	48.5	
Ramezani [84] 2014	Iran	IVB 1.25mg (n=43)	60±8	0.87±0.49logMAR	6
		Tria 2mg (n=43)	59±9	0.81±0.45logMAR	
COMRADE-C [86] 2016	International	IVR 0.5mg (n=124)	65.3±11.4	61.7±16.5	1, 6
		DEX (n=119)	66.9±12.4	51.5±15.6	

SD: Standard deviation; VA: Visual acuity; DEX: Dexamethasone; Tria: Triamcinolone; RON: radial optical neurotomy; Pla: Placebo; Obs: Observation; IVR: Intravitreal ranibizumab injections; IAI: intravitreal aflibercept injections; IVB: Intravitreal bevacizumab injections; IVP: Intravitreal pegaptanib injections

Efficacy of interventions on the proportions of patients with gaining/losing ⩾ 15 letters at 6 or 12 months

The improvement of VA was the most important functional measure of treatment efficacy. The proportions of patients gaining ⩾ 15 letters were considered the primary outcome in many included studies. Table 2 shows the RR and 95% CrI in the proportions of patients gaining and losing ⩾ 15 letters from baseline for all possible comparisons at 6 months using the consistency model.

Table 2 Network meta-analysis results in ≥15 letters gained (lower part) and lost (upper part) at 6 months

Treatment

with statistically significant effect **Relative risk (95% CrI) in proportions of losing ≥15 letters**

Aflibercept	1.67 (0.01, 321.97)	8.34 (0.14, 746.87)	1.61 (0.01,289.03)	0.30 (0.00, 30.02)	8.48 (0.49, 176.53)	3.42 (0.03，534.31)
1.06 (0.07,13.87)	Bevacizumab	5.08 (0.03, 1194.75)	0.99 (0.00, 367.38)	0.18 (0.00, 51.64)	5.15 (0.07, 385.18)	2.05 (0.01, 626.99)
5.67 (0.73, 13.87)	5.12 (0.38, 76.39)	Dexamethasone	0.19 (0.00, 33.43)	0.04 (0.00, 0.99)	1.01 (0.03, 23.86)	0.40 (0.00, 64.91)

4.44 (0.34, 58.62)	4.10 (0.20, 88.77)	0.81 (0.06, 11.76)	Pegaptanib	0.19 (0.00,43.40)	5.21 (0.09, 386.38)	2.11 (0.01, 672.55)
1.17 (0.14, 10.25)	1.04 (0.08, 16.70)	0.20 (0.04, 1.07)	0.25 (0.02, 4.08)	Ranibizumab	28.43 (0.95,921.74)	11.32 (0.06, 2413.4)
6.97 (1.73, 29.70)	6.23 (0.76, 59.04)	1.22 (0.24, 5.85)	1.54 (0.18, 13.37)	6.04 (1.15, 29.10)	Sham/Placebo	0.41 (0.01, 20.59)
1.04 (0.06, 13.91)	0.94 (0.04, 21.87)	0.18 (0.01, 2.67)	0.24 (0.01, 4.65)	0.88 (0.05, 13.74)	0.15 (0.01, 1.31)	Triamcinolone

Relative risk (95% CrI) in proportions of gaining ≥15 letters

In terms of the proportions of patients gaining ⩾ 15 letters, aflibercept (RR: 6.97, 95% CrI: 1.73–29.70), bevacizumab (RR: 6.23, 95% CrI: 0.76–59.04), dexamethasone (RR: 1.22, 95% CrI: 0.24–5.85), pegaptanib (RR: 1.54, 95% CrI: 0.18–13.37), ranibizumab (RR: 6.04, 95% CrI: 1.15–29.10), and triamcinolone (RR: 6.97, 95% CrI: 1.73–29.70) are more likely to have a positive effect in treatment of CRVO than sham/placebo treatment at 6 months. Among them, aflibercept and ranibizumab were significantly superior to the sham/placebo group. Ranibizumab was significantly superior to dexamethasone (p = 0.04, 95% CrI: 0.00–0.09) in terms of the proportions of patients losing ⩾ 15 letters. Table 3 shows the rank probabilities of these drugs for the treatment of CRVO according to the proportions of patients gaining ⩾ 15 letters at 6 months, while Table 4 shows the rank probabilities of the proportions of patients losing ⩾ 15 letters at 6 months.

Table 3 Ranking based on simulations for gaining ≥15 letters at 6 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Aflibercept	0.22	0.31	0.27	0.15	0.03	0.01	0.00
Bevacizumab	0.27	0.22	0.20	0.20	0.07	0.03	0.02
Dexamethasone	0.00	0.01	0.02	0.06	0.29	0.36	0.25
Pegaptanib	0.02	0.03	0.05	0.12	0.35	0.18	0.24
Ranibizumab	0.17	0.25	0.29	0.24	0.04	0.01	0.00
Sham/Placebo	0.00	0.00	0.00	0.02	0.14	0.39	0.46
Triamcinolone	0.32	0.18	0.17	0.21	0.07	0.03	0.02

Table 4 Ranking based on simulations for losing ≥15 letters at 6 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Aflibercept	0.02	0.04	0.08	0.18	0.27	0.29	0.13
Bevacizumab	0.10	0.09	0.13	0.18	0.19	0.18	0.14

Dexamethasone	0.37	0.24	0.18	0.12	0.06	0.03	0.00
Pegaptanib	0.09	0.08	0.13	0.18	0.20	0.18	0.13
Ranibizumab	0.00	0.01	0.03	0.06	0.12	0.23	0.53
Sham/Placebo	0.27	0.40	0.23	0.08	0.01	0.00	0.00
Triamcinolone	0.16	0.13	0.23	0.20	0.14	0.09	0.06

Because some specific data were not extracted or reported, the outcomes of the proportions of patients gaining/losing ⩾ 15 letters at 12 months did not involve all drugs. Table 5 shows the RR and 95% CrI in proportions of patients gaining and losing ⩾ 15 letters from baseline for all possible comparisons at 12 months using the consistency model.

Table 5 Network meta-analysis results in ≥15 letters gained (lower part) and lost (upper part) at 12 months

■ **Treatment**

■ **with statistically significant effect** **Relative risk (95% CrI) in proportions of losing ≥15 letters**

Aflibercept	3.45 (0.10, 91.91)	-	-	0.64 (0.04, 10.37)	3.35 (0.44, 24.39)	1.48 (0.09, 21.82)
0.93 (0.13, 7.06)	Bevacizumab	-	-	0.18 (0.01, 5.93)	0.99 (0.07, 16.67)	0.43 (0.02, 12.71)
2.22 (0.34, 13.46)	2.34 (0.23, 23.20)	Dexamethasone	-	-	-	-
-	-	-	Pegaptanib	-	-	-
1.45 (0.21, 9.28)	1.56 (0.15, 15.34)	0.65 (0.07, 5.76)	-	Ranibizumab	5.32 (0.68,50.28)	2.41 (0.14, 41.26)
3.08 (0.99, 8.85)	3.26 (0.56, 17.47)	1.40 (0.32, 6.14)	-	2.08 (0.45, 10.09)	Sham/Placebo	0.45 (0.07, 2.68)
0.59 (0.07, 4.52)	0.63 (0.05, 7.43)	0.27 (0.03, 2.60)	-	0.40 (0.04, 4.22)	0.19 (0.03, 1.10)	Triamcinolone

Relative risk (95% CrI) in proportions of gaining ≥15 letters

In terms of the proportions of patients gaining ⩾ 15 letters at 12 months, aflibercept (RR: 3.08, 95% CrI: 0.99–8.85), bevacizumab (RR: 3.26, 95% CrI: 0.56–17.47), dexamethasone (RR: 1.40, 95% CrI: 0.32–6.14), ranibizumab (RR: 2.08, 95% CrI: 0.45–10.09), and triamcinolone (RR: 5.21, 95% CrI: 0.91–31.67) are more likely to have a positive effect in treatment of CRVO than sham/placebo treatment at 12 months; however, the differences were not significantly different. Table 6 shows the rank probabilities of these drugs for the treatment of CRVO according to the proportions of patients gaining ⩾ 15 letters at 12 months, while Table 7 shows the rank probabilities of the proportions of

patients losing ⩾ 15 letters at 12 months.

Table 6 Ranking based on simulations for gaining ≥15 letters at 12 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Aflibercept	0.12	0.33	0.34	0.15	0.04	0.01
Bevacizumab	0.24	0.29	0.20	0.15	0.07	0.05
Dexamethasone	0.02	0.05	0.10	0.20	0.39	0.23
Ranibizumab	0.06	0.13	0.22	0.35	0.15	0.08
Sham/Placebo	0.00	0.00	0.01	0.07	0.31	0.61
Triamcinolone	0.55	0.20	0.12	0.08	0.03	0.02

Table 7 Ranking based on simulations for losing ≥15 letters at 12 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Aflibercept	0.05	0.10	0.22	0.35	0.27
Bevacizumab	0.47	0.18	0.15	0.11	0.08
Ranibizumab	0.03	0.05	0.13	0.28	0.52
Sham/Placebo	0.37	0.50	0.12	0.01	0.00
Triamcinolone	0.09	0.17	0.38	0.24	0.12

Efficacy of interventions on the mean changes in BCVA from baseline at 6 months

Table 8 shows the mean changes and 95% CrI of BCVA improvement for all possible comparisons by the network meta-analysis using the consistency model. Patients treated with aflibercept (RR: 17.88, 95% CrI: 7.59–29.11), bevacizumab (RR: 19.32, 95% CrI: 5.17–33.11), and ranibizumab (RR: 13.78, 95% CrI: 1.58–24.91) showed greater improvements in BCVA than those treated with sham/placebo group at 6 months, and the differences were significant. Triamcinolone (RR: 7.48, 95% CrI: -6.05–20.78) was also superior to sham injection, but the difference was not significant. Overall, patients treated with anti-VEGF agents (aflibercept, ranibizumab, or bevacizumab) had a higher probability of improvement in BCVA than those treated with corticosteroid agents (triamcinolone or dexamethasone).

Table 8 Network meta-analysis results in BCVA changes (lower part) and CRT changes (upper part) at 6 months

■ Treatment ■ with statistically significant effect	Weighted mean difference (95% CrI) in CRT change, mm				
Aflibercept	-	-	-	-	-

-1.42 (-18.40, 17.85)	Bevacizumab	-	-	-	-
21.60 (-0.36, 44.17)	22.89 (-1.36, 46.69)	Dexamethasone	205.30 (-64.62, 470.88)	46.08 (-345.04, 447.19)	-
4.04 (-11.09, 21.23)	5.51 (-12.60, 24.12)	-17.42 (-32.78, -1.28)	Ranibizumab	-156.80 (-452.68, 144.63)	-
17.88 (7.59, 29.11)	19.32 (5.17, 33.11)	-3.72 (-23.60, 15.43)	13.78 (1.58, 24.91)	Sham/Placebo	-
10.37 (-6.22, 28.27)	11.94 (-1.35, 24.40)	-11.08 (-34.93, 12.35)	6.42 (-11.52, 23.89)	-7.48 (-20.78, 6.05)	Triamcinolone

Weighted mean difference (95% CrI) in BCVA changes, letters

Table 9 shows the rank probability of these drugs for the treatment of CRVO according to the BCVA improvement at 6 months.

Table 9 Ranking based on simulations for BCVA changes from baseline at 6 months

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Aflibercept	0.34	0.45	0.16	0.04	0.01	0.00
Bevacizumab	0.54	0.28	0.14	0.02	0.01	0.00
Dexamethasone	0.01	0.01	0.02	0.07	0.19	0.70
Ranibizumab	0.10	0.21	0.53	0.14	0.02	0.00
Sham/Placebo	0.00	0.00	0.01	0.06	0.68	0.25
Triamcinolone	0.01	0.05	0.14	0.66	0.10	0.04

Efficacy of interventions on mean changes in CRT from baseline at 6 months

The CRT represents anatomic changes in the fovea after treatment. As certain studies did not report CRT changes after treatment, the evaluation of CRT only involved ranibizumab, dexamethasone, and sham injections. Intravitreal ranibizumab injections showed greater reduction in CRT than both sham injection (RR: -156.80, 95% CrI: -452.68–144.63) and dexamethasone (RR: -205.30, 95% CrI: -470.88–64.62). Table 10 shows the rank probability of these three drugs for the treatment of CRVO according to CRT reductions at 6 months.

Table 10 Ranking based on simulations for CRT changes from baseline at 6 months

Drug	Rank 1	Rank 2	Rank 3
Dexamethasone	0.61	0.34	0.05
Ranibizumab	0.01	0.16	0.83
Sham/Placebo	0.37	0.51	0.12

Adverse events

Many adverse events (AEs) were reported after drug treatment in the 11 studies, which comprised 2060 patients (Table 11). The most common ocular AE reported in more than two studies that could be compared by network meta-analysis were increased IOP, cataracts, VH, and retinal tear.

Table 11 Main adverse events after drug treatment reported according to the included studies

Drugs / Adverse events	Aflibercept	Ranibizumab	Bevacizumab	Dexamethasone	Triamcinolone	Sham/ Placebo
IOP increased	10/104	7/124		78/252	8/125	6/235
Cataract				13/263		7/176
Neovscular glaucoma	0/114	0/129			3/25	7/223
Conjunctival hemorrhage	9/104	16/125		13/119		3/68
Vitreous hemorrhage	0/114	9/144				13/217
Eye irritation	3/104					7/68
Eye pain	12/104	15/124		15/119		3/68
Retinal hemorrhage	0/114					2/74
Retinal tear	0/114	0/15				2/88
Iris neovascularization	0/114	0/124		9/119		2/74
Endophthalmitis	1/114					0/74
Retinal ischemia	1/104	1/124		6/119		3/68
Iris rubeosis			0/30			5/30

Consistency analysis of network model

Based on direct versus indirect evidence, we compared the effect estimate twice using node-splitting, considering that direct and indirect evidences existed together. The first was the comparison of ranibizumab, dexamethasone, and sham/placebo, while the second was bevacizumab, triamcinolone, and sham/placebo. Table 12 shows the comparisons of the estimated quantiles for the direct and indirect evidence, as well as the combined evidence. No inconsistencies were observed (P>0.05). These data suggest that our model is relatively robust.

Table 12 Node-splitting meta-analysis of two comparison

Name	Direct Effect	Indirect Effect	Overall	P-Value
≥15 letters gained (6 months)				
IVR, Sham	-1.50 (-3.92, 0.83)	-2.35 (-5.58, 1.10)	-1.80 (-3.37, -0.14)	0.50
IVR, DEX	-1.87 (-4.13, 0.43)	-1.05 (-4.42, 2.25)	-1.61 (-3.18, 0.07)	0.50
DEX, Sham	-0.46 (-2.73, 1.88)	0.33 (-2.88, 3.63)	-0.20 (-1.77, 1.42)	0.49
≥15 letters lost (6 months)				

IVR, Sham	2.70 (-1.55, 7.04)	4.63 (-1.35, 11.10)	3.35 (-0.05, 6.83)	0.51
IVR, DEX	4.23 (-0.34, 9.40)	2.20 (-3.79, 8.57)	3.35 (0.01, 7.02)	0.51
DEX, Sham	0.48 (-3.75, 4.78)	-1.52 (-8.23, 4.84)	0.01 (-3.42, 3.17)	0.52
BCVA changes (6 months)				
IVB, Sham	-16.48 (-37.18, 3.97)	-23.22 (-50.85, 5.12)	-19.78 (-31.99, -5.60)	0.54
IVB, Tria	-13.57 (-31.94, 5.21)	-6.61 (-34.12, 20.15)	-12.13 (-23.87, 1.28)	0.57
Tria, Sham	-9.49(-29.15, 9.89)	-2.71 (-31.65, 25.52)	-7.36 (-19.70, 4.64)	0.58

BCVA, mean change in best corrected visual acuity; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; DEX, Dexamethasone; Tria, triamcinolone

Benefit-risk analysis between anti-VEGF agents and dexamethasone

For the purpose of the proposed methods, benefit-risk analysis is defined as the quantitative synthesis of drug efficacy (or effectiveness) and AE profile.[86] Based on the existing data from the included studies, benefit-risk analysis could be performed if efficacy outcomes and safety outcomes were both reported at the same time. When considering gaining $\geqslant$ 15 letters at 6 months as a benefit index and increased IOP as a risk index, aflibercept and ranibizumab were superior to dexamethasone in the treatment of ME secondary to CRVO (Figure 4). When considering gaining $\geqslant$ 15 letters at 6 months as a benefit index and cataracts as a risk index, ranibizumab exhibited a greater benefit of visual improvement as well as a higher risk of cataracts than dexamethasone (Figure 5).

Benefit-risk analysis of aflibercept versus ranibizumab

Aflibercept and ranibizumab are the two most widely used anti-VEGF agents in the treatment of CRVO worldwide. However, there are few head-to-head RCTs comparing the efficacy and safety of aflibercept and ranibizumab directly. Gaining $\geqslant$ 15 letters at 6 months was considered a benefit index were considered a risk index; increased IOP, vitreous hemorrhage, and retinal tear were considered risk indices separately. Thus, aflibercept exhibited slightly better visual improvement and a lower risk of the latter three adverse events than ranibizumab (Figure 6).

DISCUSSION

Intravitreal corticosteroids [12] (triamcinolone or dexamethasone) and intravitreal anti-VEGF drugs [87-88] are both therapeutic options for CRVO patients despite their limitations. It is important that comparisons of the efficacy and safety of intravitreal anti-VEGF injection and intravitreal corticosteroids are needed in patients with ME secondary to CRVO.

In terms of the proportions of patients gaining ⩾ 15 letters at 6 months, our results showed that only aflibercept and ranibizumab had a significantly better efficacy than the sham/placebo group. Between the four main anti-VEGF agents and the two corticosteroids, our results showed no evidence of differences in effectiveness at both 6 and 12 months. According to the rank probability of the existing data, aflibercept, bevacizumab, and triamcinolone are the best three drugs, with no statistical significance, in gaining ⩾ 15 letters at 6 and 12 months. However, bevacizumab and triamcinolone were used off-label and lacked safety data. Therefore, aflibercept would be considered the first choice to improve VA in the treatment of ME secondary to CRVO. Aflibercept targets a wider range of cytokines and may have a stronger binding affinity,[89] which could explain the greater efficacy in visual improvement, than ranibizumab, bevacizumab, and pegaptanib. Unlike corticosteroids, anti-VEGF could decrease the vitreal levels of VEGF. Aflibercept and ranibizumab exhibited significantly better efficacy at 6 months but not at 12 months, indicating that the effects of aflibercept and ranibizumab were less obvious than the effects of the sham/placebo group as the follow-up time progressed.

In terms of the proportion of patients that lost ⩾ 15 letters at 6 or 12 months, the pooled result showed that only ranibizumab was superior to dexamethasone, with a significant difference at 6 months. Although no significant difference was found among the other drug treatment groups, anti-VEGF agents showed a tendency toward better efficacy in visual improvement than corticosteroids did. Among the anti-VEGF agents, ranibizumab had the lowest risk of patients losing ⩾15 letters.

Apart from the ⩾ 15 letters gained or lost, BCVA changes from baseline could reflect visual recovery. At 6 months, aflibercept, bevacizumab, and ranibizumab showed a greater improvement in BCVA than the sham/placebo group, with a statistically significant difference. The results support the efficacy of anti-VEGF agents for VA improvement to some extent, which is consistent with the aforementioned results of ⩾ 15 letters gained or lost. In the case of visual improvement, anti-VEGF agents, especially ranibizumab and aflibercept, were better than corticosteroids.

CRT, an anatomical index reflecting macular, was also considered as an important outcome to estimate the efficacy of these drugs. Only three RCTs reported a CRT reduction. According to the outcomes reported, ranibizumab afforded more reduction in CRT at 6 months than dexamethasone, and bevacizumab afforded more reduction than triamcinolone. As for intravitreal anti-VEGF injections, the resolution of exudative fluid and retinal edema is important for the favorable treatment of BCVA.[90]

A low incidence of AEs should also be considered besides the better efficacy of different drug treatments. In this network meta-analysis, increased IOP, cataracts, VH, and retinal tear are the four most frequently reported AEs from the included studies. More reported data can lead to more accurate analyses. As shown in Table 11, dexamethasone has a higher risk of increased IOP compared to that of aflibercept and ranibizumab. In contrast, ranibizumab was associated with a higher probability of cataracts than dexamethasone. Cataracts are associated with injection frequency, and dexamethasone needs fewer injections than anti-VEGF agents. Gu *et al*. reported that the advantages of dexamethasone are fewer number of injections and long-term efficacy, while the advantages of ranibizumab include lower incidence of increased IOP,[91] which is similar to the results of our pooled data. A head-to-head trial called COMRADE-B demonstrated that elevated IOP occurred more frequently with dexamethasone than with ranibizumab treatment, similar to BRVO.[92] In addition, aflibercept showed lower incidence of VH and ranibizumab showed lower incidence of retinal tear. AEs mainly arise from the disease process itself or as a result of the side effects during the course of treatment. Intravitreal anti-VEGF or corticosteroid injections and traumatic procedures sometimes cause AEs such as endophthalmitis. Safety is as important as efficacy after treatment, and both must be considered comprehensively in the selection of drugs for CRVO.

When comparing ranibizumab, dexamethasone, and sham/placebo, as well as bevacizumab, triamcinolone, and sham/placebo, node-splitting and pairwise meta-analysis could be used to estimate the efficacy based on direct versus indirect evidence. If direct and indirect evidence existed together, the consistencies could be tested. Since no inconsistencies were observed in this network meta-analysis, we performed sensitivity analysis of the comparison of random and fixed effects models, which was more accurate.[34] The unchanged outcome suggests that our model was robust according to known data, and therefore, the results of this network meta-analysis would be useful in

clinical practice.

As mentioned above, both dexamethasone and ranibizumab have their own advantages and disadvantages.[91] Broadly speaking, each drug has benefits and risks; therefore, estimating benefits and risks consistently is necessary. Although anti-VEGF agents can avoid the increased IOP caused by dexamethasone, the high risk of developing cataracts after anti-VEGF treatment, especially ranibizumab, cannot be ignored.

Aflibercept and ranibizumab are the two, on-label maximum dosage drugs recently approved in Europe and America. According to the data of benefit-risk analysis between the two drugs from the included studies, aflibercept had a slight advantage over ranibizumab. However, this does not mean that aflibercept is effective for all patients. Patients need to choose medications according to their actual situation. During our clinical practice, some patients were not responsive to anti-VEGF agents, but instead responded to dexamethasone.

Considering that intravitreal anti-VEGF agents are expensive, intravitreal corticosteroids should be considered to reduce the overall treatment cost. However, care should be taken when using these treatments because elevated IOP is seen more frequently with corticosteroid therapy than with anti-VEGF therapy, as demonstrated by our network meta-analysis. Regardless of the treatment administered, all patients with CRVO should be closely monitored for IOP changes and VA.

This is the second network meta-analysis providing an indirect comparison of drugs to treat ME secondary to CRVO, and our study possesses several strengths when compared to previous systematic reviews.[24] First, our meta-analysis included the most recent reports, analyzing studies published as late as May 1, 2017. Second, we performed a comprehensive comparison of aflibercept, ranibizumab, bevacizumab, pegaptanib, dexamethasone, and triamcinolone treatment using strict inclusion and exclusion criteria. Third, the 12-month follow-up time point was also considered in addition to 6 months, because the outcome at 12 months could better show the duration of efficacy after treatment.

Although the results of this work may be important for clinical treatment, there are certain limitations that need to be considered. First, our data contained some biases, which may have influenced our results. Second, more detailed data at long-term follow-up time points (e.g., 24 months) are required to improve the accuracy and robustness of our findings for clinical applications. Third, the details of adverse events (AEs) were not always reported in each study, and the data available can only indicate

the relative safety of every intervention for CRVO. To assess the efficacy of these treatments more accurately, additional high-quality RCTs with comprehensive safety data will be necessary.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab, pegaptanib, dexamethasone, and triamcinolone are needed. Further long-term, prospective studies are needed to examine and compare the safety and efficacy of CRVO-associated ME treatment strategies. Including data from future studies in subsequent meta-analyses will improve conclusion accuracy and robustness and provide better clinical guidance. In addition, as patients can be concerned about the cost of treatment, clinicians may prefer aflibercept because it requires fewer injections.[24]

CONCLUSION

Our analysis confirms that anti-VEGF agents have more advantages than corticosteroids in the treatment of ME secondary to CRVO. A higher proportion of the patients who received intravitreal anti-VEGF injections gained $\geqslant$ 15 letters than those treated with corticosteroids at both 6 and 12 months. Among these anti-VEGF agents, aflibercept and ranibizumab were the best drugs for BCVA improvement and CRT reduction. In terms of adverse events, the results of network meta-analysis showed that 1) dexamethasone was associated with a higher risk of increased IOP than aflibercept and ranibizumab, 2) ranibizumab had a higher probability of cataract formation than dexamethasone, 3) aflibercept exhibited superiority in terms of low incidence of VH, and 4) ranibizumab exhibited superiority in terms of low incidence of retinal tear. Aflibercept was shown to have a slight advantage over ranibizumab by benefit-risk analysis, but with no statistical difference. More high-quality RCTs will be necessary as the results of this study provide only a reference for clinicians. Each patient must be evaluated individually for the appropriate treatment regimen.

ACKNOWLEDGMENTS

The authors thank the researchers whose studies were included in this network meta-analysis and provided useful data to us.

FOOTNOTES

Funding: This study was funded by the National Key Research and Development Program of China (Grant No. 2016YFC0904800) and the National Natural Science Foundation of China (Grant No.

81570851).

Conflicts of interest: None declared.

Author contributions: T. Qian: study conception, study design, data collection, data analysis, manuscript writing, and final manuscript approval; M. Zhao: study design, data collection, and critical manuscript revision; Y. Wan: statistical analysis; M. Li: statistical analysis; X. Xu: study conception, study design, critical manuscript revision, and final manuscript approval.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.p1qq2r1

Figure 1. Study selection flow diagram

Figure 2. Network graph of all treatment comparisons for all studies
Each node represents one drug. The size of nodes is proportional to the number of randomized participants (sample size). Lines represent direct comparisons within randomized controlled trials, and the width of the lines is proportional to the number of trials comparing each pair of treatments.

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item are presented as percentages across all included studies.

Figure 4. Benefit-risk analysis of aflibercept and ranibizumab versus dexamethasone considering gaining ⩾ 15 letters and increased IOP (intraocular pressure): a) Aflibercept *vs.* dexamethasone; b) Ranibizumab *vs.* dexamethasone.
Key benefit-risk summary with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Aflibercept/Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

Figure 5. Benefit-risk analysis of ranibizumab versus dexamethasone considering gaining ⩾ 15 letters and cataracts.
Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

Figure 6. Benefit-risk analysis of aflibercept versus ranibizumab considering gaining ⩾ 15 letters at 6 months and the three main adverse events: a) increased IOP (intraocular pressure); b) vitreous hemorrhage; c) retinal tear.
Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Ranibizumab (red) or Aflibercept (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

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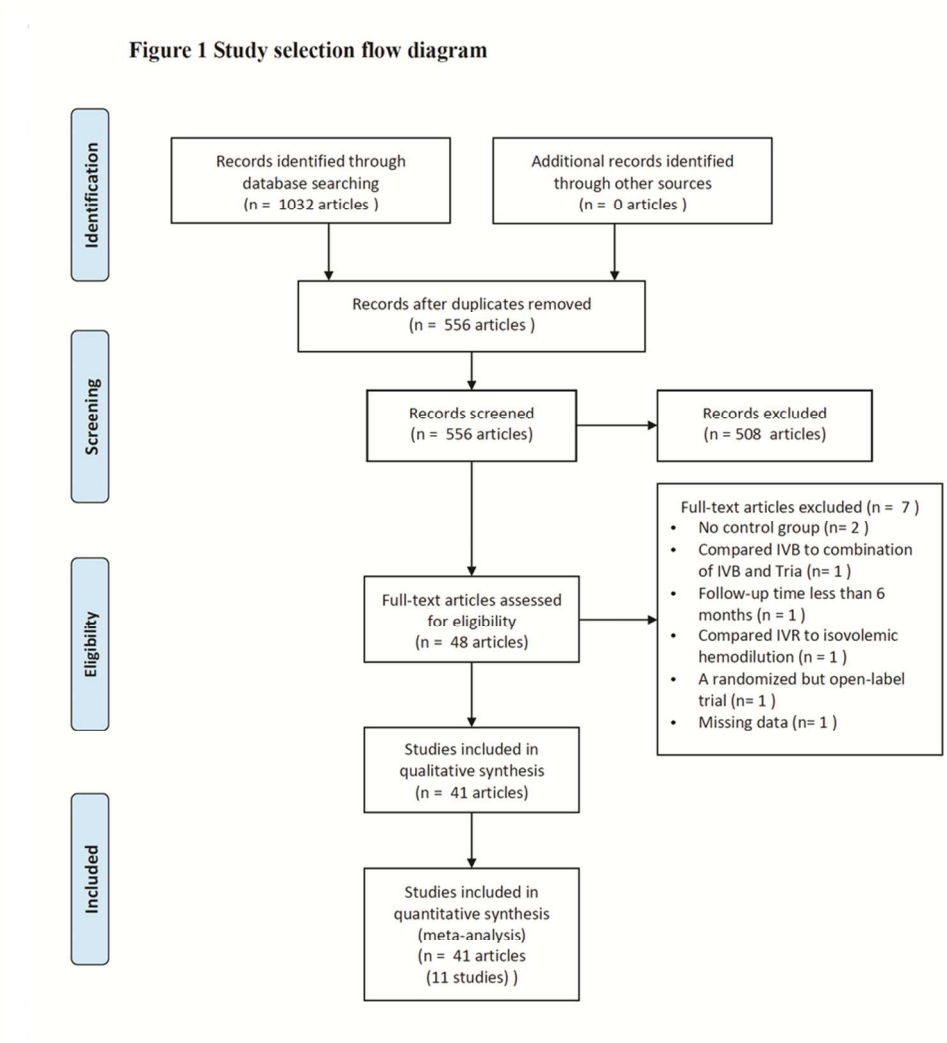
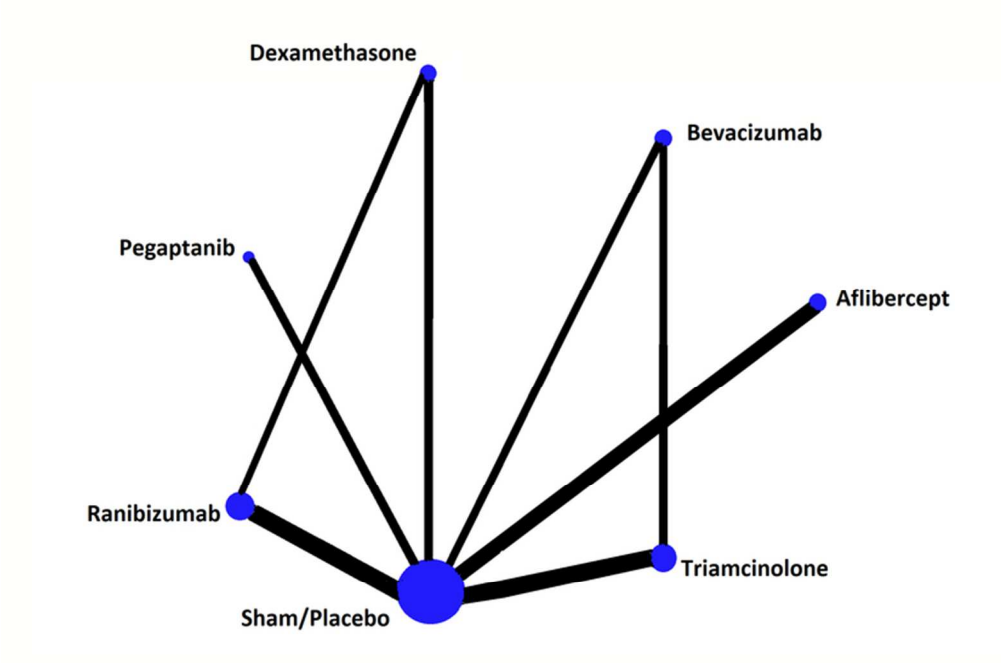


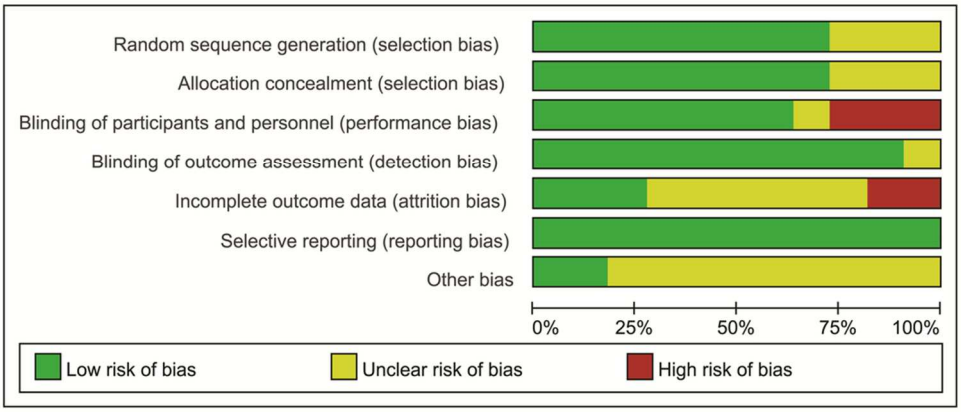
Study selection flow diagram

85x89mm (300 x 300 DPI)



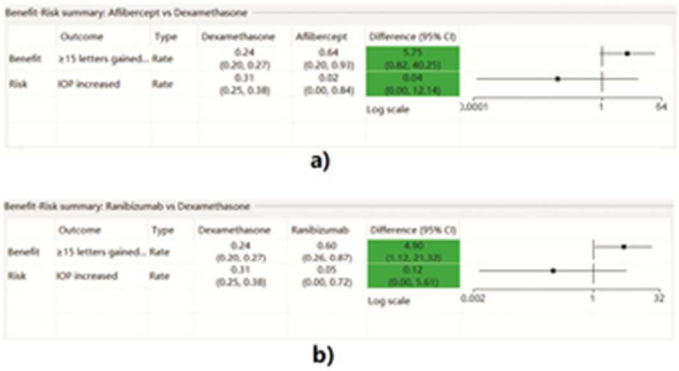
Network graph of all treatment comparisons for all studies
Each node represents one drug. The size of nodes is proportional to the number of randomized participants (sample size). Lines represent direct comparisons within randomized controlled trials, and the width of the lines is proportional to the number of trials comparing each pair of treatments.

69x47mm (300 x 300 DPI)



Risk of bias graph: review authors' judgments about each risk of bias item are presented as percentages across all included studies

93x42mm (300 x 300 DPI)

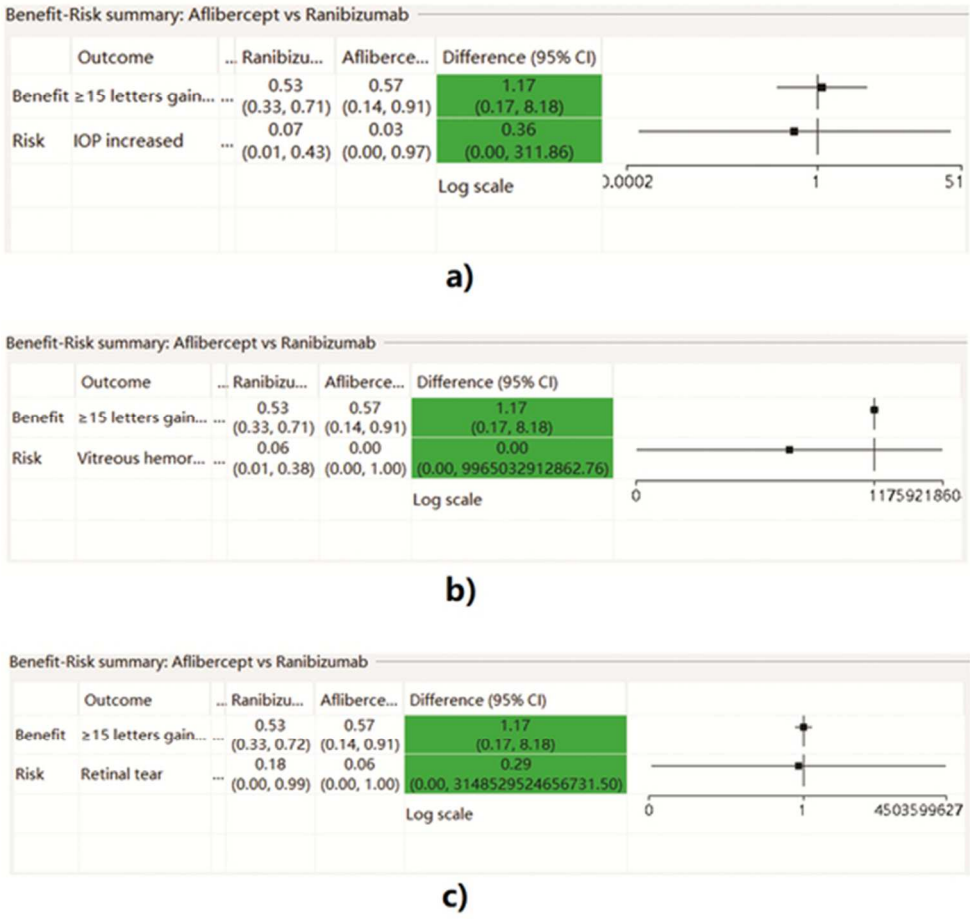


Benefit-risk analysis of aflibercept and ranibizumab versus dexamethasone considering gaining ≥ 15 letters and increased IOP (intraocular pressure): a) Aflibercept vs. dexamethasone; b) Ranibizumab vs. dexamethasone.
Key benefit-risk summary with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Aflibercept/Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

29x16mm (300 x 300 DPI)

Benefit-risk analysis of ranibizumab versus dexamethasone considering gaining ≥ 15 letters and cataracts. Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Dexamethasone (red) or Ranibizumab (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

13x3mm (300 x 300 DPI)



Benefit-risk analysis of aflibercept versus ranibizumab considering gaining ≥ 15 letters at 6 months and the three main adverse events: a) increased IOP (intraocular pressure); b) vitreous hemorrhage; c) retinal tear. Key benefit-risk summary table with embedded relative effect forest plot. The color in the "difference" column indicates whether the point estimate favors Ranibizumab (red) or Aflibercept (green). The symbol in the forest plot indicates whether the logarithmic (square) or linear (diamond) scale is used.

49x47mm (300 x 300 DPI)

Appendix 1. PRISMA NMA Checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	P4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P4-5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	P5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	P5-P6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P5-P6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P7

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P6
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	P6-P7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P6-P7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	P7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • Handling of multi-arm trials; • Selection of variance structure; • Selection of prior distributions in Bayesian analyses; and • Assessment of model fit.	P7-P8
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	P8-P9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P6-P7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • Alternative formulations of the treatment network; and • Use of alternative prior distributions for Bayesian analyses (if applicable).	P7-P8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P8
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Table1-3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P9, Table3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise	P9-P12

		comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	P11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	Figure11-14, P11-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	P16-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	P18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	P20

PICOS = population, intervention, comparators, outcomes, study design.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix 2. Search strategies

We searched the Embase, Medline, EMBASE, Cochrane Library and *clinicaltrials.gov* by the end of March 2017. We provided below the search strategies of the five database.

Embase search strategy

1. exp Central retinal vein occlusion/
2. exp Central vein occlusion/
3. exp Retinal vein occlusion/
4. exp Retinal vein/
5. ((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).tw.
6. (CRVO or CVO or RVO or VO).tw.
7. or/1-6
8. exp retina macula edema/
9. exp cystoid/
10. (macula$ adj3 oedema).tw.
11. (macula$ adj3 edema).tw.
12. (CME or CMO).tw.
13. or/8-12
14. exp Anti-Vascular Endothelial Growth Factors/
15. exp Vascular Endothelial Growth Factors/

16. exp anti-VEGF Agents/
17. exp Endothelial Growth Factors/
18. exp Angiogenesis Inducing Agents/
19. exp Angiogenesis Inhibitors/
20. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or vastin or aflibercept$ or Eylea or VEGF-Trap).tw.
21. (anti adj2 VEGF$).tw.
22. (endothelial adj2 growth adj2 factor$).tw.
23. or/14-22
24. exp corticosteroids/
25. exp Glucocorticoid/
26. exp Steroids/
27. (dexamethasone$ or Ozurdex or triamcinolone$).tw.
28. or/24-27
29. exp randomized controlled trial/
30. exp controlled clinical trial/
31. exp randomized/
32. exp randomized/
33. or/29-32
34. exp Sham/
35. or/23, 28, 33, 34
36. 7 and 13 and 35

CENTRAL search strategy

#1 MeSH descriptor Central Retinal Vein Occlusion

#2 MeSH descriptor Central Vein Occlusion

#3 MeSH descriptor Retinal Vein Occlusion

#4 MeSH descriptor Retinal Vein

#5 retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)

#6 CRVO or CVO or RVO or RV

#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

#8 MeSH descriptor Macular Edema

#9 MeSH descriptor Edema Oedema

#10 macula* near/3 oedema

#11 macula* near/3 edema

#12 CME or CMO

#13 (#8 OR #9 OR #10 OR #11 OR #12)

#14 MeSH descriptor Anti-Vascular Endothelial Growth Factors

#15 MeSH descriptor Vascular Endothelial Growth Factors

#16 MeSH descriptor anti-VEGF Agents

#17 MeSH descriptor Endothelial Growth Factors

#18 MeSH descriptor Angiogenesis Inducing Agents

#19 MeSH descriptor Angiogenesis Inhibitors

#20 macugen* or pegaptanib* or lucentis* or rhufab* or ranibizumab* or bevacizumab* or vastin or aflibercept* or Eylea or VEGF-Trap

#21 anti near/2 VEGF*

#22 endothelial near/2 growth near/2 factor*

#23 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)

#24 MeSH descriptor corticosteroids

#25 MeSH descriptor Glucocorticoid

#26 MeSH descriptor Steroids

#27 dexamethasone* or Ozurdex or triamcinolone*

#28 (#24 OR #25 OR #26 OR #27)

#29 MeSH descriptor randomized controlled trial

#30 MeSH descriptor controlled clinical trial

#31 MeSH descriptor randomized

#32 MeSH descriptor randomised

#33 (#29 OR #30 OR #31 OR #32)

#34 Sham injection

#35 (#23 OR #28 OR #33 OR #34)

#36 (#7 AND #13 AND #35)

MEDLINE search strategy

1. exp Central retinal vein occlusion/

2. exp Central vein occlusion/
3. exp Retinal vein occlusion/
4. exp Retinal vein/
5. ((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).tw.
6. (CRVO or CVO or RVO or VO).tw.
7. or/1-6
8. exp retina macula edema/
9. exp cystoid/
10. (macula$ adj3 oedema).tw.
11. (macula$ adj3 edema).tw.
12. (CME or CMO).tw.
13. or/8-12
14. exp Anti-Vascular Endothelial Growth Factors/
15. exp Vascular Endothelial Growth Factors/
16. exp anti-VEGF Agents/
17. exp Endothelial Growth Factors/
18. exp Angiogenesis Inducing Agents/
19. exp Angiogenesis Inhibitors/
20. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or vastin or aflibercept$ or Eylea or VEGF-Trap).tw.
21. (anti adj2 VEGF$).tw.

22. (endothelial adj2 growth adj2 factor$).tw.
23. or/14-22
24. exp corticosteroids/
25. exp Glucocorticoid/
26. exp Steroids/
27. (dexamethasone$ or Ozurdex or triamcinolone$).tw.
28. or/24-27
29. randomized controlled trial.pt
30. controlled clinical trial.pt
31. randomized.ab,ti
32. randomized/ab.ti
33. or/29-32
34. exp Sham/
35. or/23, 28, 33, 34
36. 7 and 13 and 35

Cochrane Library search strategy

#1 MeSH descriptor: [Central Retinal Vein Occlusion] explode all trees

#2 MeSH descriptor: [Central Vein Occlusion] explode all trees

#3 MeSH descriptor: [Retinal Vein Occlusion] explode all trees

#4 MeSH descriptor: [Retinal Vein] explode all trees

#5 (retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or

steno* or block* or embolism*))

#6 MeSH descriptor: [CRVO or CVO or RVO or RV] explode all trees

#7 {or #1-#6}

#8 MeSH descriptor: [Macular Edema] explode all trees

#9 MeSH descriptor: [Edema Oedema] explode all trees

#10 (macula* near/3 oedema)

#11 (macula* near/3 edema)

#12 (CME or CMO)

#13 {or #8-#12}

#14 MeSH descriptor: [Anti-Vascular Endothelial Growth Factors] explode all trees

#15 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees

#16 MeSH descriptor: [anti-VEGF Agents] explode all trees

#17 MeSH descriptor: [Endothelial Growth Factors] explode all trees

#18 MeSH descriptor: [Angiogenesis Inducing Agents] explode all trees

#19 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees

#20 macugen*

#21 pegaptanib*

#22 lucentis*

#23 rhufab*

#24 ranibizumab*

#25 bevacizumab*

#26 vastin

#27 aflibercept*

#28 Eylea

#29 VEGF-Trap

#30 (anti near/2 VEGF*)

#31 (endothelial) near/2 (factor*)

#32 {or #14-#31}

#33 MeSH descriptor: [corticosteroids] explode all trees

#34 MeSH descriptor: [Glucocorticoid] explode all trees

#35 MeSH descriptor: [Steroids] explode all trees

#36 (dexamethasone* or Ozurdex or triamcinolone*)

#37 {or #33-#36}

#38 MeSH descriptor: [randomized controlled trial] explode all trees

#39 MeSH descriptor: [controlled clinical trial] explode all trees

#40 MeSH descriptor: [randomized] explode all trees

#41 MeSH descriptor: [randomised] explode all trees

#42 {or #38-#41}

#43 MeSH descriptor: [Sham] explode all trees

#44 #32 or #37 or #42 or #43

#45 #7 AND #13 AND #44

ClinicalTrials.gov search strategy

(Angiogenesis or Vascular Endothelial Growth Factors or Anti-VEGF or pegaptanib or lucentis or rhufab or ranibizumab or bevacizumab or vastin or aflibercept or Eylea or VEGF-Trap) OR (Steroids or dexamethasone or Ozurdex or triamcinolone) AND (Macula Oedema or Macula Edema) AND (Central retinal vein occlusion or Retinal vein occlusion)

Appendix 3 Specific literatures of included and excluded studies

Included studies

GENEVA, 2010

- Haller J A, Bandello F, Belfort R, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion[J]. Ophthalmology, 2010, 117(6): 1134-1146. e3.
- Haller J A, Bandello F, Belfort R, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: twelve-month study results[J]. Ophthalmology, 2011, 118(12): 2453-2460.
- Yeh W S, Haller J A, Lanzetta P, et al. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant[J]. Ophthalmology, 2012, 119(6): 1190-1198.

ROVO, 2013

- Aggermann T, Brunner S, Krebs I, et al. A prospective, randomised, multicenter trial for surgical treatment of central retinal vein occlusion: results of the Radial Optic Neurotomy for Central Vein Occlusion (ROVO) study group[J]. Graefe's Archive for Clinical and Experimental Ophthalmology, 2013, 251(4): 1065-1072.

SCORE, 2009

- Myers D, Blodi B, Ip M, et al. Reading center evaluation of OCT images from patients enrolled in the standard care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study[J]. Investigative Ophthalmology & Visual Science, 2006, 47(13): 5194-5194.
- Bhavsar A R, Ip M S, Glassman A R. The risk of endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE clinical trials[J]. American journal of ophthalmology, 2007, 144(3): 454-456.
- Oden N L, VanVeldhuisen P C, Scott I U, et al. Temporal variability of OCT in retinal vein occlusion participants in the SCORE study[J]. Investigative Ophthalmology & Visual Science, 2007, 48(13): 107-107.
- Ip M, Oden N, VanVeldhuisen P, et al. The standard care vs. corticosteroid for retinal vein occlusion study: design and baseline characteristics[J]. Am Acad Ophthalmol, 2008, 260.
- Scott I U, VanVeldhuisen P C, Oden N L, et al. SCORE Study report 1: baseline associations between central retinal thickness and visual acuity in patients with retinal vein occlusion[J]. Ophthalmology, 2009, 116(3): 504-512.
- Scott I U, Blodi B A, Ip M S, et al. SCORE Study Report 2: interobserver

agreement between investigator and reading center classification of retinal vein occlusion type[J]. Ophthalmology, 2009, 116(4): 756-761.

- Ip M S, Oden N L, Scott I U, et al. SCORE Study report 3: study design and baseline characteristics[J]. Ophthalmology, 2009, 116(9): 1770-1777. e1.
- Domalpally A, Blodi B A, Scott I U, et al. The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study system for evaluation of optical coherence tomograms: SCORE study report 4[J]. Archives of ophthalmology, 2009, 127(11): 1461-1467.
- Ip M S, Scott I U, VanVeldhuisen P C, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5[J]. Archives of ophthalmology, 2009, 127(9): 1101.
- Scott I U, Ip M S, VanVeldhuisen P C, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6[J]. Archives of ophthalmology, 2009, 127(9): 1115.
- Scott I U, Oden N L, VanVeldhuisen P C, et al. SCORE Study Report 7: incidence of intravitreal silicone oil droplets associated with staked-on vs luer cone syringe design[J]. American journal of ophthalmology, 2009, 148(5): 725-732. e7.
- Blodi B A, Domalpally A, Scott I U, et al. Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study system for evaluation of stereoscopic color fundus photographs and fluorescein angiograms: SCORE Study Report 9[J]. Archives of ophthalmology, 2010, 128(9): 1140-1145.
- Scott I U, VanVeldhuisen P C, Oden N L, et al. Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus COrticosteroid for REtinal Vein Occlusion Study report 10[J]. Ophthalmology, 2011, 118(2): 345-352.
- Chan C K, Ip M S, VanVeldhuisen P C, et al. SCORE Study report# 11: incidences of neovascular events in eyes with retinal vein occlusion[J]. Ophthalmology, 2011, 118(7): 1364-1372.
- Weinberg D V, Wahle A E, Ip M S, et al. Score Study report 12: development of venous collaterals in the Score Study[J]. Retina, 2013, 33(2): 287-295.
- Domalpally A, Peng Q, Danis R, et al. Association of outer retinal layer morphology with visual acuity in patients with retinal vein occlusion: SCORE Study Report 13[J]. Eye, 2012, 26(7): 919-924.
- Scott I U, VanVeldhuisen P C, Oden N L, et al. Baseline characteristics and response to treatment of participants with hemiretinal compared with branch retinal or central retinal vein occlusion in the Standard Care vs COrticosteroid for REtinal Vein Occlusion (SCORE) study: SCORE Study report 14[J]. Archives of Ophthalmology, 2012, 130(12): 1517-1524.

CRUISE, 2010

- Brown D M, Campochiaro P A, Singh R P, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study[J]. Ophthalmology, 2010, 117(6): 1124-1133. e1.
- Campochiaro P A, Brown D M, Awh C C, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study[J]. Ophthalmology, 2011, 118(10): 2041-2049.
- Heier J S, Campochiaro P A, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial[J]. Ophthalmology, 2012, 119(4): 802-809.

ROCC, 2010

- Kinge B, Stordahl P B, Forsaa V, et al. Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study[J]. American journal of ophthalmology, 2010, 150(3): 310-314.

COPERNICUS, 2012

- Boyer D, Heier J, Brown D M, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study[J]. Ophthalmology, 2012, 119(5): 1024-1032.
- Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study[J]. American journal of ophthalmology, 2013, 155(3): 429-437. e7.

GALILEO, 2013

- Gillies M. Intravitreal Vegf Trap-eye In Central Retinal Vein Occlusion: Results Of The Phase 3 Copernicus And Galileo Studies[J]. Clinical & Experimental Ophthalmology, 2012, 40: 44.
- Holz F G, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study[J]. British Journal of Ophthalmology, 2013; 97(3):278-284.

Epstein, 2012

- Epstein D, Algvere P, von Wendt G, et al. Long-term benefit from bevacizumab for macular edema in central retinal vein occlusion: 12-month results of a prospective study[J]. Acta Ophthalmologica, 2012, 90: 48.
- Epstein D L J, Algvere P V, von Wendt G, et al. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study[J]. Ophthalmology, 2012, 119(6): 1184-1189.

- Epstein D L, Algvere P V, von Wendt G, et al. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study[J]. Ophthalmology, 2012, 119(12): 2587-2591.

Wroblewski, 2009

- Wells III J A. Pegabtanib sodium for treatment of macular edema secondary to Central Retinal Vein Occlusion (CRVO)[J]. Investigative Ophthalmology & Visual Science, 2006, 47(13): 4279-4279.
- Wells J A. Safety and efficacy of pegaptanib sodium in treating macular edema secondary to Central Retinal Vein Occlusion[J]. Am Acad Ophthalmol, 2006.
- Ciulla T A. Treatment of macular edema following central retinal vein occlusion with pegaptanib sodium (macugen): a one-year study[J]. Am Acad Ophthalmol, 2007.
- Csaky K G. Pegaptanib (Macugen) for Macular edema in Central Retinal Vein Occlusion: early OCT results and effect of therapy reinitiation[J]. American Academy of Ophthamology, 2007.
- Wells III J A, Wroblewski J J, Macugen in CRVO Study Group. Pegaptanib sodium for the treatment of macular edema following Central Retinal Vein Occlusion (CRVO): functional outcomes[J]. Investigative Ophthalmology & Visual Science, 2007, 48(13): 1544-1544.
- Patel S S, Macugen in CRVO Study Group. Pegaptanib sodium for the treatment of macular edema following Central Retinal Vein Occlusion (CRVO): anatomical outcomes[J]. Investigative Ophthalmology & Visual Science, 2007, 48(13): 311
- Wroblewski J J, Wells J A, Adamis A P, et al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion[J]. Archives of ophthalmology, 2009, 127(4): 374-380.

Ramezani, 2014

- Ramezani A, Esfandiari H, Entezari M, et al. Three intravitreal bevacizumab versus two intravitreal triamcinolone injections in recent onset central retinal vein occlusion[J]. Acta ophthalmologica, 2014, 92(7).

COMRADE-C, 2016

- Hoerauf H, Feltgen N, Weiss C, et al. Clinical efficacy and safety of ranibizumab versus dexamethasone for central retinal vein occlusion (COMRADE C): a European label study[J]. American journal of ophthalmology, 2016, 169: 258-267.

Excluded studies

Exclusion reason 1: No control group (n= 1)

- Larsen M, Waldstein S M, Boscia F, et al. Individualized ranibizumab regimen driven by stabilization criteria for central retinal vein occlusion: twelve-month results of the CRYSTAL study[J]. Ophthalmology, 2016, 123(5): 1101-1111.
- Spaide R F, Chang L K, Klancnik J M, et al. Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion[J]. American journal of ophthalmology, 2009, 147(2): 298-306.

Exclusion reason 2: Compared IVB to combination of IVB and Tria (n= 1)

- Wang H Y, Li X, Wang Y S, et al. Intravitreal injection of bevacizumab alone or with triamcinolone acetonide for treatment of macular edema caused by central retinal vein occlusion[J]. International journal of ophthalmology, 2011, 4(1): 89.

Exclusion reason 3: Follow-up time less than 6 months (n = 1)

- Ramezani A, Entezari M, Moradian S, et al. Intravitreal triamcinolone for acute central retinal vein occlusion; a randomized clinical trial[J]. Graefe's Archive for Clinical and Experimental Ophthalmology, 2006, 244(12): 1601-1606.

Exclusion reason 4: Compared IVR to isovolemic hemodilution (n = 1)

- Kreutzer T C, Wolf A, Dirisamer M, et al. Intravitreal ranibizumab versus isovolemic hemodilution in the treatment of macular edema secondary to central retinal vein occlusion: twelve-month results of a prospective, randomized, multicenter trial[J]. Ophthalmologica, 2015, 233(1): 8-17.

Exclusion reason 5: A randomized but open-label trial (n= 1)

- Ding X, Li J, Hu X, et al. Prospective study of intravitreal triamcinolone acetonide versus bevacizumab for macular edema secondary to central retinal vein occlusion[J]. Retina, 2011, 31(5): 838-845.

Exclusion reason 6: Missing data (n= 1)

- Gado A S, Macky T A. Dexamethasone intravitreous implant versus bevacizumab for central retinal vein occlusion-related macular oedema: a prospective randomized comparison[J]. Clinical & experimental ophthalmology, 2014, 42(7): 650-655.

Appendix 4 Outcomes of included studies

GENEVA, 2010 [46-48] (DEX vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)

6 months

	DEX 0.7mg (n=136)	DEX 0.35mg (n=154)	Sham (n=147)
BCVA (ETDRS letters)	+0.1		-1.8
p value	<0.001 vs sham		
≥15 letters gained	25 (18.4%)	11 (17%)	18 (12.2%)
p value	NS vs sham	NS vs sham	
≥15 letters lost	19 (14.0%)		30 (20.4%)
p value	NS vs sham		
CRT (µm)	-118.2		-125.3
p value	NS vs sham		

12 months

	DEX 0.7mg (n=136)	DEX 0.35mg (n=154)	Sham (n=147)
BCVA (ETDRS letters)	+2 (graph estimated)		-1.4 (ditto)
≥15 letters gained	37 (27%)		31 (21%)

Adverse events

6 months

	DEX 0.7mg (n=133)	DEX 0.35mg (n=154)	Sham (n=147)
Overall of ocular AEs	91 (68.4%)		73 (49.7%)
IOP increased	40 (30.1%)		2 (1.4%)
Cataract AEs	11 (8.3%)		7 (4.8%)

ROVO, 2013 [49] (Tria vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)

12 months

	Tria 4mg (n=25)	RON (n=38)	Sham (n=20)
BCVA (ETDRS letters)	-8	-35.5	0

p value	NS vs sham		
VA improvement	5 (20%)	18 (47.3%)	2 (10%)
p value	NS vs sham		
VA deterioration	NR	3 (7.9%)	7 (35%)
CRT (µm)	-235	-263	-206
p value	NS vs sham		
Adverse events			
12 months			
	Tria 4mg (n=25)	**RON (n=38)**	**Sham (n=20)**
IOP increased	8 (32%)		0
Cataract progression	6 (24%)	5 (13.2%)	3 (15%)
Neovscular glaucoma	3 (12%)	2 (5.3%)	3 (15%)
Rubeosis iridis	0		3 (15%)

SCORE, 2009 [50-66] (Tria vs sham)			
Efficiency outcomes (changes from baseline at follow-up time points)			
6 months (weight mean and SD of 4 and 8 months)			
	Tria 4mg (n=85)	**Tria 1mg(n=84)**	**Obs (n=75)**
BCVA (letters)	-0.15±20.67	-3.93±23.42	-9.66±18.04
p value	NR	NR	
≥15 letters gained	17 (19.5%)	15(17.5%)	3 (4%)
p value	NR	NR	
≥15 letters lost	19 (20.5%)	21 (25.0%)	31 (35.5%)
p value	NR	NR	
12 months			
	Tria 4mg (n=82)	**Tria 1mg(n=83)**	**Obs (n=73)**
BCVA (letters, 95%CI)	-1.2±24.82 (-6.3 to +4.0)	-1.2±25.45 (-6.4 to +4.1)	-12.1±23.93 (-17.1 to -7.1)
p value	<0.05 vs obs	<0.05 vs obs	
≥15 letters gained	21 (25.6%)	22 (26.5%)	5 (6.8%)
p value	0.001 vs obs	0.001 vs obs	

≥15 letters lost	21 (25.6%)	21 (25.3%)	32 (43.8%)
p value	NR	NR	
CRT (µm) (median, IQR)	-261 (-407 to -79) n=78	-196 (-390 to -62) n=72	-277 (-418 to -40) n=68
p value	NR	NR	
24 months			
	Tria 4mg (n=50)	**Tria 1mg(n=55)**	**Obs (n=46)**
BCVA (letters, 95%CI)	-2.4±24.89 (-9.3 to +4.4)	-4.4±26.87 (-11.5 to +2.8)	-10.7±22.84 (-17.4 to -4.1)
p value	NR		
≥15 letters gained	13 (26%)	17 (30.9%)	4 (8.7%)
p value	NR		
≥15 letters lost	13 (26%)	17 (30.9%)	22 (47.8%)
p value	NS, p=0.06 tria vs obs		
CRT (µm) (median, IQR)	-236 (-421 to -63) n=45	-286 (-458 to -119) n=48	-304 (-465 to -108) n=43
p value	NR		
Adverse events			
12 months			
	Tria 4mg (n=91)	**Tria 1mg(n=92)**	**Obs (n=88)**
Initiation of IOP-lowering medication	32 (35.2%)	18 (19.6%)	7 (8.0%)
Iris neovascularization or neovascular glaucoma	4 (4.4%)	9 (9.8%)	2 (2.3%)
Retinal neovascularization	2 (2.2%)	2 (2.2%)	4 (4.6%)
Vitreous hemorrhage	0	4 (4.3%)	4 (4.6%)
CRUISE, 2010 [67-69] (IVR vs sham)			
Efficiency outcomes (changes from baseline at follow-up time points)			
6 months			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=130)**	**Sham (n=130)**
BCVA (letters, 95%CI)	+12.7±15.9 (9.9, 15.4)	+14.9±13.2 (12.6, 17.2)	+0.8±16.2 (-2.0, 3.6)
p value	<0.0001 vs sham	<0.0001 vs sham	

≥15 letters gained	61 (46.2%)	62 (47.7%)	22 (16.9%)
p value	<0.0001 vs sham	<0.0001 vs sham	
≥15 letters lost	5 (3.8%)	2 (1.5%)	20 (15.4%)
p value	NR		
CRT (µm, 95%CI)	-433.7 (-484.9, -382.6) n=131	-452.3(-497.0, -407.6) n=130	-167.7 (-221.5, -114.0) n=129
p value	<0.0001 vs sham	<0.0001 vs sham	
NEI-VFQ (95%CI)	+7.1 (5.2, 9.0)	+6.2 (4.3, 8.0)	+2.8 (0.8, 4.7)
p value	<0.05 vs sham	<0.05 vs sham	
12 months (IVR PRN)			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=130)**	**Sham (n=130)**
BCVA (letters, 95%CI)	+13.9±15.2 (11.2, 16.5)	+13.9±14.2 (11.5, 16.4)	+7.3±15.9 (4.5, 10.0)
p value	0.0007 vs sham	0.0006 vs sham	
≥15 letters gained	62 (47.0%)	66 (50.8%)	43 (33.1%)
p value	NR		
≥15 letters lost	5 (3.8%)	3 (2.3%)	13 (10.0%)
p value	NR		
CRT (µm)	-462.1	-452.8	-427.2
p value	NS vs sham	NS vs sham	
NEI-VFQ	+7.1	+6.6	+5.0
p value	NR	NR	
Adverse events			
6 months			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=129)**	**Sham (n=129)**
Any intraocular inflammation event	3 (2.3%)	2 (1.6%)	5 (3.9%)
Cataract	2 (1.5%)	2 (1.6%)	0
Neovascular glaucoma	0	0	2 (1.6%)
Vitreous haemorrhage	5 (3.8%)	7 (5.4%)	9 (7.0%)
12 months			
	IVR 0.3mg (n=132)	**IVR 0.5mg (n=129)**	**Sham (n=110)**

Any intraocular inflammation event	3 (2.3%)	2 (1.6%)	2 (1.8%)
Cataract	5 (3.8%)	9 (7.0%)	2 (1.8%)
Neovascular glaucoma	0	1 (0.8%)	0
Vitreous haemorrhage	7 (5.3%)	7 (5.4%)	2 (1.8%)
Iris neovascularization	2 (1.5%)	5 (3.9%)	2 (1.8%)
Retinal tear	0	2 (1.6%)	2 (1.8%)

ROCC, 2010 [70] (IVR vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVR 0.5mg (n=15)	**Sham (n=14)**
BCVA (letters)	+12±20	-1±17
p value	0.067 vs sham	
CRT (µm)	-304±194	-151±205
p value	0.05 vs sham	

Adverse events		
6 months		
	IVR 0.5mg (n=15)	**Sham (n=14)**
Vitreous hemorrhage	2 (13.3%)	0
Retinal tear	0	1 (7.1%)
Neovascular disease	0	1 (7.1%)

COPERNICUS, 2012 [71-72] (IAI vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IAI 2mg (n=114)	**Sham (n=73)**
BCVA (letters)	+17.3±12.8	-4.0±18
p value	<0.001	
≥15 letters gained	64 (56.1%)	9 (12.3%)
p value	<0.001	

≥15 letters lost	2 (1.8%)	20 (27.4%)
p value	NR	
CRT (µm)	-457.2	-144.8
p value	<0.001	
NEI VFQ-25	+7.2±12.1	+0.8±9.8
p value	0.001	
12 months (all IAI PRN)		
	IAI 2mg (n=114)	**Sham (n=73)**
BCVA (letters)	+16.2	+3.8
p value	<0.001	
≥15 letters gained	63 (55.3%)	22 (30.1%)
p value	<0.001	
≥15 letters lost	6 (5.3%)	11 (15.1%)
p value	NR	
CRT (µm)	-413.0	-381.8
p value	NS	
NEI VFQ-25	+7.5	+5.1
p value	NS	
Adverse events		
6 months		
	IAI 2mg (n=114)	**Sham (n=74)**
Patients with at least one serious adverse events	4 (3.5%)	10 (13.5%)
Vitreous hemorrhage	0	4 (5.4%)
Neovascular glaucoma	0	2 (2.7%)
Iris neovascularization	0	2 (2.7%)
Retinal hemorrhage	0	2 (2.7%)
Retinal tear	0	1 (1.4%)
Endophthalmitis	1 (0.9%)	0
6 to 12months		

	IAI 2mg + PRN (n=110)	Sham + PRN (n=60)
Patients with at least one serious adverse events	3 (2.7%)	2 (3.3%)
Vitreous hemorrhage	1 (0.9%)	1 (1.7%)
Glaucoma	0	1 (1.7%)
Retinal tear	0	1 (1.7%)
Cataract	1 (0.9%)	1 (1.7%)

GALILEO, 2013 [73-74] (IAI vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IAI 2mg (n=103)	**Sham (n=68)**
BCVA (letters)	+18.0±12.2	+3.3±14.1
p value	<0.0001	
≥15 letters gained	62 (60.2%)	15 (22.1%)
p value	<0.0001	
≥15 letters lost	8 (7.8%)	15 (22.1%)
p value	0.0033	
CRT (µm)	-448.6	-169.3
p value	<0.0001	
NEI-VFQ-25	+7.5	+3.5
p value	0.0013	
Adverse events		
6 months		
	IAI 2mg (n=104)	**Sham (n=68)**
Eye pain	12 (11.5%)	3 (4.4%)
Conjunctival haemorrhage	9 (8.7%)	3 (4.4%)
Ocular hyperaemia	5 (4.8%)	4 (5.9%)
Vitreous floaters	5 (4.8%)	0
Macular ischaemia	4 (3.8%)	3 (4.4%)

Eye irritation	3 (2.9%)	7 (10.3%)
Retinal ischaemia	1 (1.0%)	3 (4.4%)
IOP increased	10 (9.6%)	4 (5.9%)

Epstein, 2012 [75-76] (IVB vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVB 1.25mg (n=30)	**Sham (n=30)**
BCVA (letters)	+14.1±18.7	-2.0±20.5
p value	<0.01	
≥15 letters gained	18 (60%)	6 (20%)
p value	0.003	
≥15 letters lost	2 (6.7%)	7 (23.3%)
p value	NS, 0.146	
CRT (µm)	-426	-102
p value	<0.0001	
12 months		
	IVB 1.25mg (n=30)	**Sham (n=30)**
BCVA (letters)	+16.1	+4.6
p value	<0.05	
≥15 letters gained	18 (60%)	10 (33.3%)
p value	<0.05	
≥15 letters lost	2 (6.7%)	2 (6.7%)
p value	NS	
CRT (µm)	-435	-404
p value	>0.05	
Adverse events		
6 months		
	IVB 1.25mg (n=30)	**Sham (n=30)**
Iris rubeosis	0	5 (16.7%)

Wroblewski, 2009 [23, 77-83] (IVP vs Sham)

Efficiency outcomes (changes from baseline at follow-up time points)			
6 months (~30weeks)			
	IVP 0.3mg (n=33)	**IVP 1mg (n=33)**	**Sham (n=32)**
BCVA (letters)	+7.1	+9.9	-3.2
p value	0.09 vs sham	0.02 vs sham	
≥15 letters gained	12 (36.4%)	13 (36.1%)	9 (28.1%)
p value	0.48		
≥15 letters lost	3 (9.1%)	2 (6.1%)	10 (31.3%)
p value	0.03 vs sham	0.01 vs sham	
CRT (µm)	-243	-179	-148
p value	0.13	0.06	
12 months			
	IVP 0.3mg (n=33)	**IVP 1mg (n=33)**	**Sham (n=32)**
BCVA (letters)	+7.5	+6.3	-2.4
p value	NS vs sham	NS vs sham	
CRT (µm)	-295	-216	-183
p value	<0.05 vs sham		
Adverse events			
No serious ocular adverse events up to 30 weeks. No evidence of increased risk of systemic adverse events up to 30 weeks.			

Ramezani, 2014 [84] (IVB vs Tria)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVB (n=43)	**Tria (n=43)**
BCVA (letters)	+23±11.5	+9.5±11.5
p value	<0.001	<0.001
CRT (µm)	-151±122	-75±89
p value	<0.001	<0.001

Adverse events		
6 months		
	IVB (n=43)	**Tria (n=43)**
IOP changes (mmHg)	-1.0±2.2	+2.2±2.7

COMRADE-C, 2016 [85] (IVR vs DEX)

Efficiency outcomes (changes from baseline at follow-up time points)		
6 months		
	IVR (n=124)	**DEX (n=119)**
BCVA (letters)	+16.9±13.6	-0.7±22.5
p value	<0.0001 vs DEX	
≥15 letters gained	73 (58.9%)	22 (18.5%)
p value	<0.0001 vs DEX	
≥15 letters lost	1 (0.8%)	31 (26.1%)
p value	<0.0001 vs DEX	
CRT (μm)	-376.7±274.9	-168.7±288.3
p value	NR	
Adverse events		
6 months		
	IVR (n=124)	**DEX (n=119)**
IOP increased	7 (5.6%)	38 (31.9%)
Macular edema	14 (11.3%)	21 (17.6%)
Eye pain	15 (12.1%)	15 (12.6%)
VA reduced	8 (6.5%)	22 (18.5%)
Conjunctival hemorrhage	16 (12.9%)	13 (10.9%)
Vitreous floaters	5 (4.0%)	11 (9.2%)
Iris neovascularization	0 (0.0%)	9 (7.6%)
Dry eye	4 (3.2%)	4 (3.4%)
Glaucoma	0 (0.0%)	8 (6.7%)
Visual impairment	2 (1.6%)	6 (5.0%)

Vitreous detachment	5(4.0%)	3 (2.5%)
Eye irritation	4(3.2%)	3 (2.5%)
Retinal ischemia	1(0.8%)	6 (5.0%)
Retinal vascular disorder	2(1.6%)	5 (4.2%)
Ocular hypertension	0	6 (5.0%)
Retinal exudates	2(1.6%)	4 (3.4%)
Optic disc vascular disorder	5(4.0)	0

Appendix 5 Risk of bias of individual studies

Trials	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
GENEVA, 2010 [46-48]	Low	Low	High: Personel administering treatments were not masked. Participants were masked to dose of implant, but not to treatment (steroid implant versus no implant).	Low	High: Macular thickness was described as a secondary outcome in the trial registry for one trial only, but the 6-month reported results used the pooled data from both trials to analyze this outcome at 6 months	Low	Unclear
ROVO, 2013 [49]	Low	Low	Unclear	Unclear	Low	Low	Unclear
SCORE, 2009 [50-66]	Low	Low	High: physicians and patients masked to dose but not triamcinolone versus observation	Low	High: In the observation arm, 17% of participants had missing data compared with the 6.8% observed risk for the primary outcome. Reasons for missing data were not reported	Low	Unclear

Trials	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CRUISE, 2010 [67-69]	Low	Unclear	Low	Low	Unclear	Low	Unclear
ROCC, 2010 [70]	Unclear	Low	Low	Low	Unclear	Low	Unclear
COPERNICUS, 2012 [71-72]	Low	Unclear	Low	Low	Unclear	Low	Low
GALILEO , 2013 [73-74]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
EPSTEIN, 2012 [75-77]	Unclear	Low	Low	Low	Low	Low	Low
Wroblewski, 2009 [23, 78-83]	Low	Low	Low	Low	Unclear	Low	Unclear
Ramezani, 2014 [84]	Low	Low	High: Because IVT might cause floaters, we did not consider this study as a double-blind one.	Low	Low	Low	Unclear
COMRADE-C, 2016 [85]	Low	Low	Low	Low	Unclear	Low	Unclear