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Comparative efficacy and safety of different Anti-VEGF combined with different delivery methods for neovascular glaucoma: systematic review and Bayesian network meta-analysis

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ABSTRACT

Objective: The efficacy and safety of Anti-VEGF combined with different delivery methods for NVG were investigated by Bayesian network meta-analysis (NMA), and the cumulative ranking curve (SUCRA) was used to rank the efficacy of anti-VEGF regimens in management of NVG.

Methods: Electronic databases were retrieved from their inception to September 5, 2022. All randomized controlled trials (RCTs) were screened into EndNote X9, and the Bayesian NMA was performed using STATA15.0 and OpenBUGS 3.2.3. The source of heterogeneity and the related factors affecting the stability of the results have as well been explored.

Results: Seventeen RCTs, comprising 1311 eyes from 1228 patients, were included in the analysis. Five treatment regimens involving three anti-VEGF drugs were examined. In effective group, simultaneous intravitreal and intracameral injection of conbercept (ICCIVC) (MD = - 11.56, 95% CrI -20.8 ~ -2.24), intravitreal injection of conbercept (IVC) (MD = -8.88, 95% CrI -13.93 ~ -3.78), intravitreal injection of ranibizumab (IVR) (MD = -7.62, 95% CrI -10.91 ~ -4.33) and intravitreal injection of bevacizumab (IVB) (MD = -5.51, 95% CrI -10.79 ~ -0.35) had lower intraocular pressure (IOP) at 1 month after glaucoma surgery than the blank control group. The SUCRA indicated ICCIVC (82.0%) may be the best regimens to reduce IOP. Safety group analysis found no statistically significant differences among interventions, according to the SUCRA, ICCIVC (68.0%) was the safest choice with the least complications. Subgroup or meta-regression analyses were performed, which showed mean age is the main source of heterogeneity. The sensitivity analysis proved that the results of this study are robust.

Conclusion: ICCIVC were more effective and safer than the other regimens for NVG. Simultaneous intravitreal and intracameral injection is the best method in terms of route of administration, and conbercept was found to be superior to ranibizumab and bevacizumab in terms of selecting drug.

PROSPERO registration number: CRD42022309676.

Strengths and limitations of this study

- To our knowledge， the study is the first to analyze the efficacy and safety of different anti-VEGF drugs combined with different injection methods in the treatment of NVG, and to prioritize different anti-VEGF regimens.
- Network meta-analysis is the best method to compare interventions in the absence of head-to-head trials.
- Subgroup and meta-regression analyses were conducted to investigate the heterogeneity; sensitivity analysis was used to explore the influence of small sample sizes and large heterogeneity on the results.
- Most of the included studies were conducted in Asia, so the conbercept accounted for the majority which could produced partial selection bias on the results

Word count: 6327 words

INTRODUCTION

Neovascular glaucoma (NVG) is a potentially blinding secondary glaucoma, stemming from the development of abnormal new blood vessels that obstruct the normal drainage of aqueous humor.[1] It is typically associated with ocular ischemic diseases, such as diabetic retinopathy (DR), central retinal vein occlusion (CRVO) and ocular ischaemic syndrome (OIS).[2] NVG is a rare pathology, and the prevalence in the population reaches only 0.01–0.12%. The incidence of NVG is 3.9% of all glaucoma cases (9–14.7% of all secondary glaucoma).[3]

The therapy for NVG is twofold which consists of decreasing the vascular drive and controlling intraocular pressure (IOP).[4,5] For the first part, to mitigate neovascularization, panretinal photocoagulation (PRP) or intravitreal vascular endothelial growth factor (VEGF) inhibitors are commonly used. Simultaneously, effective IOP control is achieved through topical and systemic medications or surgical interventions to avoid damaging the optic nerve.

Initially utilized in ophthalmology for the treatment of choroidal neovascularization in age-related macular degeneration (nAMD), the application of anti-VEGF medications has expanded rapidly to encompass the treatment of various other conditions.[6,7] The currently available anti-VEGF inhibitors, including bevacizumab (Avastin), ranibizumab (Lucentis), aflibercept (Eylea), and conbercept (Lumitin), have been proven to be effective suppressing anterior segment neovascularization and lowering IOP.[3,8,9] These medications have been administered via intravitreal, intracameral, and, less frequently, simultaneous intravitreal and intracameral routes for NVG treatment.[10-13] Numerous researchers also verified the effectiveness of these delivery modalities.[14-16]

Consequently, we conducted a comparative analysis of diverse anti-VEGF regimens for NVG utilizing data obtained from randomized controlled trials (RCTs)

and ranked their priority to furnish statistical evidence guiding clinical practice.

MATERIAL AND METHODS

The methodology of this network meta-analysis (NMA) was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) extension statement for reporting network meta-analysis.[17] The final version of this protocol was registered with PROSPERO, number CRD42022309676. The full dataset is available online.

Search strategy

Two authors independently searched the PubMed, EMBASE, the Cochrane library, Web of Science, ClinicalTrials.gov, ISRCNT and Chinese databases, including the China National Knowledge Infrastructure, the China Science Periodical Database (the Wanfang Database), the VIP Journal Integration Platform, and the China Biology Medicine database from the inception to September 5 2022 with no language restrictions. The Chinese literature mainly selects high quality studies including Chinese Medical Association or core journals. A detailed process has been provided in supplemental materials 1.

Inclusion and exclusion criteria

We included studies based on the following criteria: (1) study type: RCTs; (2) population: patients were diagnosed as NVG; (3) intervention: controlled study of different therapeutic strategies related to anti-VEGF regimens, as well as, PRP was performed in all patients enrolled, but there was not restriction on the types of anti-

glaucoma surgery; (4) outcome variables: the results of the included studies need to meet at least one outcome measure of this NMA.

Studies that met any of the following criteria were excluded: (1) conference abstracts, reviews, meta-analyses, or case reports; (2) unknown or other types of glaucoma patients; (3) history of anti-VEGF or steroid injection, studies related to drug dosage, studies related to comparison of surgical methods, and studies related to unplanned PRP; (4) poor quality Chinese studies.

Outcome measures

We took the IOP (mmHg) at 1 month after anti-glaucoma surgery (IOP 1 month, a) and the incidence of postoperative complications during the follow-up period (complications, b) as our primary efficacy and safety, respectively. Complications encompassed hypotony, choroidal detachment/effusion and bleeding-associated complications such as hyphema, vitreous hemorrhage, or suprachoroidal hemorrhage.

The secondary efficacy outcomes included the success rate of anti-glaucoma surgery (success rate, c), using the definitions by authors of individual studies; visual retention rate after anti-glaucoma surgery (visual retention rate, d), visual retention = improved visual acuity + unchanged visual acuity; and IOP at 6 months after anti-glaucoma surgery (IOP 6 months, e). In order to reduce bias, we preferably selected the common follow-up time point for above outcomes, in case there was no common time point of data, we used available information during the follow-up period. For controllable NVG, IOP at 1 month after anti-VEGF treatment was evaluated (non-surgical IOP 1 month, f).

Study screening process

Studies were independently selected by two review authors to ensure reliability. We resolved discrepancies through discussion. Disagreements were resolved by a third review author.

Data extraction

Two authors independently extracted the following data: study characteristics (including randomization method and masking of treatment allocation), patient characteristics (mean age, sex, primary disease, stage of NVG, baseline IOP, visual acuity), intervention measures (anti-VEGF drug types and administration methods, anti-glaucoma surgery methods) and outcome variables.

Risk of bias assessment

Two authors used the revised Cochrane risk-of-bias tool for randomized trials (RoB2) to assess the risk of bias, disagreements were resolved by discussion with a third investigator.[18]

Statistical analysis

For outcomes with at least 2 direct comparative studies available, pairwise random-effect meta-analysis was conducted by STATA (version 15.0). Categorical outcomes were assessed using Odds Ratios (OR) with corresponding 95% Confidence Intervals (CIs), while continuous outcomes were evaluated using Mean Differences (MD) with 95% CIs.

Whenever the evidence formed a connected network diagram, a random-effect Bayesian NMA was conducted in OpenBUGS (version 3.2.3).[19] We calculated OR and 95% credible intervals (CrI) for categorical outcomes, along with MD and 95% CrI for

continuous outcomes to estimate the regimens effect size, respectively. The summarized estimates were calculated using Markov Chains Monte Carlo (MCMC) methods.[19] To estimate the posterior distribution for each model, three Markov chain Monte Carlo simulations were initialized using 200000 iterations for each simulation. However, the results are reported after excluding the first 100000 iterations. Convergence was assessed by visually inspecting history and trace plots.

In standard pairwise meta-analyses, we estimated heterogeneity variances for each direct comparison, which was conducted by I^2 and the between-studies variance estimate obtained by τ^2 (Profile likelihood estimator).[20] A heterogeneity variance σ – an estimated between-studies standard deviation (SD) in NMA – was used for each outcome.[21]

We used the 'design-by-treatment' interaction method and the node-splitting method to examine global and local consistency, respectively.[22,23] Additionally, we also used the node-splitting method to examine the loop-closed inconsistency.[24]

The regimens were ranked based on the surface under the cumulative ranking curve (SUCRA).[25] The higher ranking means better treatment efficacy.[26,27] To summarize the efficacy and safety of all regimens, the resultant rankings are presented by clustered ranking plot.

Reporting bias assessment

We plotted the comparison-adjusted funnel plot to investigate small-study bias and the possibility of publication bias at the network level.[28]

Subgroup, meta-regression and sensitivity analysis

Subgroup, meta-regression analysis were conducted to explore the source of heterogeneity when there were more than 10 studies and when the number of studies included in the analysis was greater than the number of treatments, the study investigated whether the surgical methods of anti-glaucoma, the proportion of retinal vein occlusion in the primary disease and mean age are significant sources of heterogeneity. Sensitivity analyses that examine robustness of the results were performed by removing studies that fall outside the funnel plot and small sample studies at the bottom of the funnel plot.

Confidence in cumulative evidence

The overall quality of evidence were assessed by the Confidence in Network Meta-Analysis (CINeMA) approach,[29] which were downgraded based on the evaluation results, and confidence is finally rated as high, moderate, low and very low.

RESULTS

Literature search

A total of 1112 records were identified by the electronic database and trial registration platform in our initial search, from which 524 articles were excluded for duplications, and 548 were excluded by reading titles and abstracts, 40 potentially eligible citations were selected for full-text review. After excluding 23 reports, 17 trials with 1228 participants with 1311 eyes fulfilled our inclusion criteria.[30-35] The process is illustrated by a flow diagram (Figure 1). References for Chinese trials are given in the Supplemental Material 2.

Characteristics of the included studies

A total of 17 RCTs are all two-arm studies. There are 13 studies involving anti-glaucoma surgery involving 821 eyes. There are 6 studies involving 490 eyes that did not participate in anti-glaucoma surgery. However, among them, there are two studies included both anti-glaucoma surgery group and no anti-glaucoma surgery.

Our studies covered blank control group (Blank) and 5 different regimens for three anti-VEGF drugs, which are intravitreal injection of conbercept (IVC), intravitreal injection of ranibizumab (IVR), intravitreal injection of bevacizumab (IVB), intracameral injection of conbercept (ICC) and simultaneous intravitreal and intracameral injection of conbercept (ICCIVC). Of 15 possible comparisons between included treatments, 6 were compared directly. The baseline characteristics of each study are presented in Supplemental Material 3.

Risk of bias results

The overall bias of the included RCTs was as follows: low risk 0%, some concerns risk 41.2%, high risk 58.8%. Due to the severe clinical symptoms and complications of NVG, studies on this disease cannot be completely double-blind, resulting in high overall bias in the included literature. The details of the risk of bias assessment has been shown in Supplemental Material 4.

Pairwise meta-analysis

IVR ($I^2 = 0\%$, $\tau^2 = 0$, OR = 0.25, 95% CI 0.10 to 0.68, P = 0.006) was higher than Blank in terms of success rate. In terms of IOP 1 month, IVR ($I^2 = 99\%$, $\tau^2 = 24.86$, MD = 7.28, 95% CI 2.83 to 11.74, P = 0.001) and IVB ($I^2 = 76.4\%$, $\tau^2 = 10.39$, MD = 5.37, 95% CI 0.87 to 9.88, P = 0.019) were lower than Blank; about IOP 6 months, IVR ($I^2 = 98.2\%$, $\tau^2 = 41.28$, MD = 8.42, 95% CI 1.97 to 14.86, P = 0.011) was lower than Blank;

in the non-surgical IOP 1 month group, the effect of IVR (I^2 = 99%, τ^2 = 26.17, MD = 13.54, 95% CI 6.41 to 20.66, P < 0.001) was better than Blank. However, these studies all have significant heterogeneity. And no statistical differences were found for the group of visual retention rate and complications. Results from pairwise meta-analysis for each outcome were presented in Supplemental Material 5.

Network meta-analysis

Primary efficacy outcome: IOP 1 month

Thirteen studies involving 821 eyes and six regimens reported IOP 1month after surgery, and there were 15 treatment comparisons. The network plot is shown in Figure 2. When compared with Blank, ICCIVC (MD = -11.56, 95% CrI -20.8 to -2.24), IVC (MD = -8.88, 95% CrI -13.93 to -3.78), IVR (MD = -7.62, 95% CrI -10.91 to -4.33) and IVB (MD = -5.51, 95% CrI -10.79 to -0.35) showed a favorable effect in IOP 1 month after surgery. However, no statistical difference was found in the remaining comparisons (Figure 3). According to the ranking probabilities based on SUCRA, ICCIVC ranked first (82.0%), followed by ICC (65.8%), IVC (64.4%), IVR (51.7%), IVB (35.0%) and Blank (1.1%) (Supplemental Material 6a).

CINeMA assessment was mostly very low. The comparison-adjusted funnel plot was drawn (Supplemental Material 7a). Four studies fell outside the funnel plot and one study was at the bottom of the funnel plot, indicating potential report bias and small sample size. Meta-regression revealed significantly association between effect size and mean age (0.68, 95% CrI 0.11 to 1.21), however, no association between effect size and the proportion of RVO (18.96, 95% CrI -12.38 to 50.04). Meanwhile, no statistical significance was found in subgroup analysis between different types of anti-glaucoma surgical and effect size (2.44, 95% CrI -0.58 to 5.57). For sensitivity analysis, after

excluding the five studies outside and at the bottom of the funnel plot, the results showed that the effectiveness of ICC (MD = -9.41, 95% CrI -16.62 to -1.98) was higher than Blank, however, the other regimens did not change significantly, Figure 4 for details.

Primary safety outcome: complications

Eleven studies involving 702 eyes and six regimens reported complications after surgery, and there were 15 treatment comparisons (Figure 2). In regard to all regimens, no significant difference was found in complications after surgery (Figure 3). With respect to ranking probabilities, ICCIVC ranked first (68.0%), followed by IVR (64.5%), IVC (58.2%), ICC (47.8%), IVB (35.4%) and Blank (26.0%) (Supplemental Material 6b).

CINeMA assessment was mostly very low. The comparison-adjusted funnel plot was drawn (Supplemental Material 7b). Two studies fell outside the funnel plot, which showed the potential report bias and small sample size. The results of meta-regression and subgroup analysis were consistent with the result of the primary efficacy. For sensitivity analysis, after excluding two studies NMA was performed for the remaining nine studies, and the results showed that IVB (OR = 0.12, 95% CrI 0.03 to 0.50) was safer than Blank, however, the other regimens did not change significantly. (Figure 4).

Secondary efficacy outcomes: success rate

Seven studies involving 417 eyes and four regimens reported success rate after surgery, and there were six treatment comparisons. There were no significant differences between the treatment regimens. According to ranking probabilities based on SUCRA, IVC ranked first (74.8%), followed by IVR (63.3%), IVB (59.1%) and Blank (2.8%).

The assessment of CINeMA was mostly very low. (Supplemental Material 6c, 7c, 8a, and 9a).

Secondary efficacy outcomes: visual retention rate

Six studies involving 331 eyes and five regimens reported visual retention rate after surgery, and there were ten treatment comparisons. The model did not converge when we analyzed data using Bayesian methods, so we conducted a random-effects network meta-analysis by a frequentist framework, with STATA (version 15.0). There were no significant differences between the treatment regimens. According to ranking probabilities based on SUCRA, IVC ranked first (94.1%), followed by ICCIVC (77.5%), Blank (43.1%), IVR (22.5%) and IVB (12.8%). The assessment of CINeMA was mostly very low (Supplemental Material 6d, 7d, 8b, and 9b).

Secondary efficacy outcomes: IOP 6 months

Nine studies involving 549 eyes and five regimens reported IOP 6 months after surgery, and there were ten treatment comparisons. When compared with Blank, IVC (MD = -8.94, 95% CrI -15.8 to -2.08) and IVR (MD = -8.37, 95% CrI -12.42 to -4.35) showed significantly lower IOP 6 months after surgery. However, no statistical difference was found in the remaining comparisons. According to ranking probabilities based on SUCRA, ICC ranked first (77.9%), followed by IVC (72.2%), IVR (67.9%), IVB (24.1%) and Blank (8.0%). The assessment of CINeMA was mostly very low (Supplemental Material 6e, 7e, 8c, and 9c).

Secondary outcomes: non-surgical IOP 1 month

Six studies involving 490 eyes and six regimens reported non-surgical IOP 1 month, and there were 15 treatment comparisons. When compared with Blank, IVR (MD = -13.5, 95% CrI -18.98 to -8.03) showed a significantly lower IOP. However, no statistical difference was found in the remaining comparisons. According to ranking probabilities based on SUCRA, IVR ranked first (91.7%), followed by ICCIVC (67.9%), ICC (58.0%), IVC (44.0%) IVB (23.6%) and Blank (14.9%). The assessment of CINeMA was mostly very low (Supplemental Material 6f, 7f, 8d, and 9d).

Efficacy versus safety in network analysis

A clustered ranking plot for both primary efficacy and safety results suggested that ICCIVC is the most efficacious and safest regimen in this analysis, as this regimen located on the upper right corner of the figure (Figure 5).

Inconsistency

The heterogeneity σ was 3.77 (95% CI 2.441–4.918) for IOP 1 month, 3.16 (95% CI 1.443–4.869) for complications. The test of global and local inconsistency did not detect any evidence of statistically significant inconsistency for primary and secondary outcomes (global inconsistency: $p = 0.15–0.79$). Among six outcomes, three outcomes covered loop-closed, all of which showed no significant inconsistency.

DISCUSSION

To our knowledge, this study is the first to analyze the efficacy and safety of different anti-VEGF drugs combined with different delivery methods for NVG using Bayesian network meta-analysis, and to prioritize different anti-VEGF regimens. At present, two network meta-analyses on NVG can be retrieved.[36,37] DONG Z et al.'s results in 2018

and LIN P et al.'s study in 2022, which only compared the clinical efficacy and safety of various surgical interventions for NVG. However, combined with a large number of literature research and clinical evidence, it is found that different anti-VEGF drugs and their different routes of administration for the treatment of NVG also have differences in clinical efficacy and safety. For studies on anti-VEGF drugs in the treatment of NVG, Simha A's review in 2020 including four RCTs indicated that the use of anti-VEGF drugs in patients with NVG resulted in better resolution of iris neovascularization in the short-term, but the long-term benefits have not been conclusively concluded, and there is insufficient evidence to assess the difference in adverse events with or without anti-VEGF drugs;[1] a meta-analysis by Hyung Bin Hwang in 2021 showed that the success rate of AGV+IVB treatment was higher than that of AGV treatment alone.[38] The above studies only prove that the combination of anti-VEGF injections can produce positive impact on NVG, but it does not analyze the efficacy of NVG treatment according to the different types of anti-VEGF and the different routes of administration.

In recent years, there have been more and more RCTs on anti-VEGF drugs for NVG. However, some anti-VEGF therapies often lack head-to-head studies, which makes it difficult to directly compare the effectiveness. This study provides indirect comparative evidence through the transmission of NMA, and the results obtained from direct and indirect evidence are compared.

A total of 17 RCTs involving 1311 eyes of 1228 patients were included in this study. Three anti-VEGF drugs were analyzed involving five treatment regimens, which were ICCIVC, IVC, ICC, IVB and IVR.

The primary efficacy outcome (IOP 1 month) shows that ICCIVC, IVC, IVR and IVB are significantly higher than Blank, there are direct controlled studies between IVC, IVR, IVB and Blank, while there are no direct controlled studies between ICCIVC and

Blank, the evidence stems from indirect comparisons. Using SUCRA value as the effect size, cluster analysis suggested that ICCIVC had the most significant effect, followed by ICC, IVC, IVR, and IVB. From the above ranking, it can be seen that conbercept was superior to ranibizumab and bevacizumab in terms of efficacy. Recent controlled clinical studies also showed that conbercept has more advantages than ranibizumab in controlling IOP and improving visual acuity, and has fewer postoperative complications. Analysis of the reasons suggested that conbercept is formed by fusion of partial immunoglobulin regions of VEGFR-1 and VEGFR-2 with Fc fragment of human immunoglobulin G1, so its affinity for VEGF-A and PIGF was higher than ranibizumab and bevacizumab.[39] According to different delivery routes of conbercept, the priority of efficacy proved that combined injection had the best effect, and then intracameral injection was superior to intravitreal injection. Bhagat et al have reported that the intracameral injection route was the most effective in controlling IOP,[40] possibly because the drug could directly reach the new blood vessels of iris and angle after the intracameral injection. Moreover, the concentration of local anti-VEGF drugs in the anterior chamber was higher than that of intravitreal injection.

The primary safety outcome (complications) showed no statistical difference among all interventions, from the perspective of cumulative ranking probability, ICCIVC may be the safest, but its SUCRA value was only slightly higher than IVR. The safety SUCRA value of these five anti-VEGF regimens were not significantly different from the Blank, which indicated that the effect of anti-VEGF injection on reducing postoperative complications was not very significant. A retrospective study demonstrated no significant correlation between IVB and hyphema after anti-glaucoma surgery,[41] which is consistent with our results. Sugimoto et al. believed that injection of anti-VEGF only reduced the neovascularization on the surface of the iris, but did not

completely remove the neovascularization in the interstitium of the iris,[42] which still had no easing effect on postoperative hemorrhagic complications.

Reporting bias assessment of the efficacy and safety of the primary outcome showed that publication bias and small sample effect existed in both groups. Sensitivity analysis was carried out by eliminating the studies with large heterogeneity outside the funnel plot and the studies with small sample at the bottom of the funnel plot. The results did not change significantly, which indicated that the results of the primary outcome were stable. In order to explore the heterogeneity of efficacy and safety, subgroup and meta-regression analyses were conducted on them respectively. The results showed that mean age had an influence on the effect size of the two groups.

In this study, only three anti-VEGF regimens were included in the success rate group. According to the results of SUCRA value, IVC ranked the highest, followed by IVR and IVB, which were consistent with the results of efficacy in the primary outcome, namely the priority of conbercept was higher than that of ranibizumab, and finally bevasizumab. However, the criterion of postoperative success in this outcome cannot be set uniformly, and can only be evaluated according to the definition of each study, which inevitably increases the bias.

The group of IOP 6 months represents the long-term efficacy of anti-VEGF for NVG. The results showed that IVC and IVR were significantly different from the Blank. IVR was similar to the results of Pairwise meta-analysis, while IVC was obtained by indirect comparison. ICC ranked highest according to SUCRA, followed by IVC, IVR and finally IVB, which was similar to the efficacy results of the primary outcome.

For the non-surgical group, the analysis of the results showed that IVR was significantly different from the Blank, according to the priority of SUCRA value, the best treatment was IVR, followed by ICCIVC. However, previous studies have

confirmed that for the treatment of iris and chamber angle neovascularization, intracameral combined with intravitreal can cause rapid regression of neovascularization, and this rapid regression time is shorter than intravitreal or intracameral injection alone.[43,44] Therefore, the rank is different from the published studies, and we speculate that the possible reasons are as follows: A total of 6 RCTs were included in this outcome index, among which 3 had baseline average IOP > 40mmHg, belonging to uncontrolled NVG. Anti-glaucoma surgery was required according to the treatment principle, but anti-glaucoma surgery was not performed in the original study, so they were also included in the non-surgical group in this NMA, which would cause a certain bias in the results.

The advantage of this study is that it is the first to analyze the efficacy and safety of different anti-VEGF drugs combined with different injection methods in the treatment of NVG, and to prioritize different anti-VEGF regimens. At the same time, the method of network meta-analysis is applied, which is the optimal alternative method for the lack of head-to-head intervention analysis. In this study, subgroup and meta-regression analyses were conducted for the primary outcome to investigate the heterogeneity of the study. In addition, sensitivity analysis was used to explore the influence of small sample sizes and large heterogeneity on the results.

However, the results of the NMA should be interpreted with caution due to the following limitations: (a) As NVG is a rare disease, there is a lack of large-scale, multi-center RCTs, and the number of included literature studies and sample size are small; (b) In this NMA, the credibility evaluation of CINeMA are all low or very low, and the quality evaluation of included studies is not ideal, and funnel plot results show that this study has report bias; (c) Most of the included studies were conducted in Asia, so the conbercept accounted for the majority which could produced partial selection bias on

the results; (d) For the analysis of complications, success rate and vision retention rate, no definite time point data could be obtained, so the data close to the specified time point was selected, but there may still be some bias; In terms of success rate , due to the direct use of the author's definition of surgical success criteria in the original study, the results are inevitably biased.

Therefore, more high-quality, large-scale, multicenter clinical randomized controlled studies need to be carried out in the future, especially the intervention measures of other anti-VEGF drug regimens not mentioned in this study, in order to provide more objective and rigorous evidence for NVG.

CONCLUSION

This NMA provides substantial evidence for the clinical application of anti-VEGF drug regimens for NVG. In conclusion, our review suggested ICCIVC were more effective and safer than the other four interventions. Simultaneous intravitreal and intracameral injection is the best method in terms of route of administration, and with the aspect of selecting drug, conbercept is preferred to ranibizumab and bevacizumab.

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Contributions JQW conceived the study, drafted the protocol, collected data, performed the statistical analysis and wrote the manuscript. YMG participated in data extraction and data analysis. YMG, JHW and JM contributed to assembly of data, the

quality assessment and data interpretation. LY revised the manuscript, acquired funding, accepted full responsibility for the work of the study, had access to the data, and controlled the decision to publish as the guarantor. All authors have read and approved the final version of the manuscript.

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Figure legends

Figure 1. Flow chart of the study selection procedure

RCT, randomized controlled trial; NMA, network meta-analysis

Figure 2. Network plot of available treatment comparisons for primary outcome. Size of node represent the number of patients randomized to each regimen. Line width represent the number of RCTs comparing each pair of regimens directly

Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

Figure 3. Network meta-analysis of primary efficacy and safety outcomes. Regimens are reported in order of patients' IOP 1month after surgery ranking according to SUCRAs.

Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

Figure 4. Sensitivity network meta-analyses for primary efficacy and safety outcomes. Regimens are reported in order of patients' IOP 1month after surgery ranking according to SUCRAs.

Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

Figure 5. Clustered ranking plot of anti-VEGF regimens for NVG based on primary efficacy and safety outcomes. Each color represents a group of regimens that belong to the same cluster.

Regimens lying in the upper right corner are the most efficacious and safest regimen.

Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection

of conbercept.

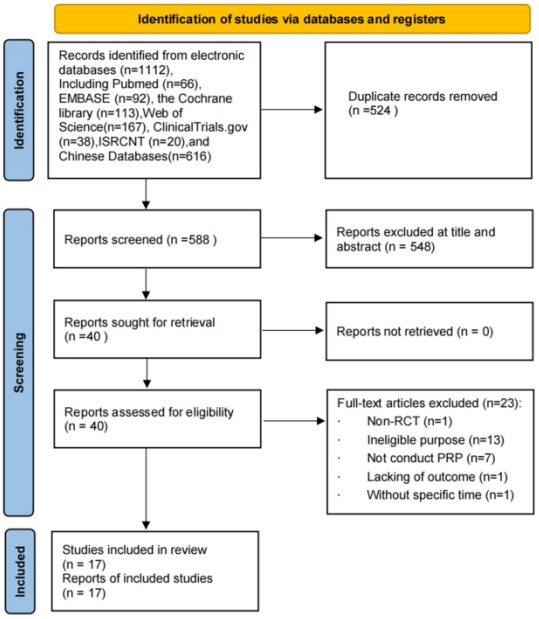

Figure 1. Flow chart of the study selection procedure
RCT, randomized controlled trial; NMA, network meta-analysis

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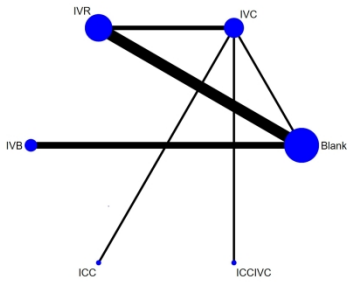

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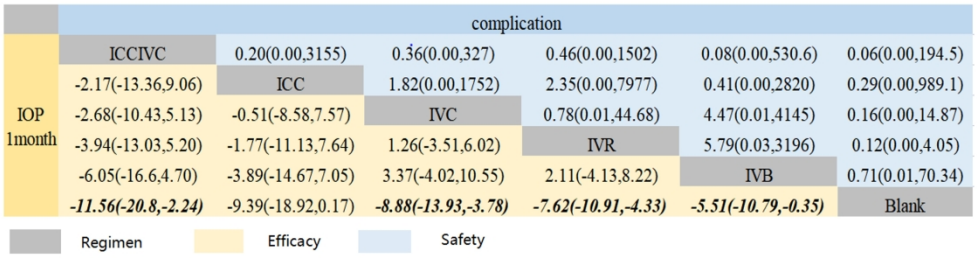

Figure 3. Network meta-analysis of primary efficacy and safety outcomes. Regimens are reported in order of patients' IOP 1month after surgery ranking according to SUCRAs.
Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

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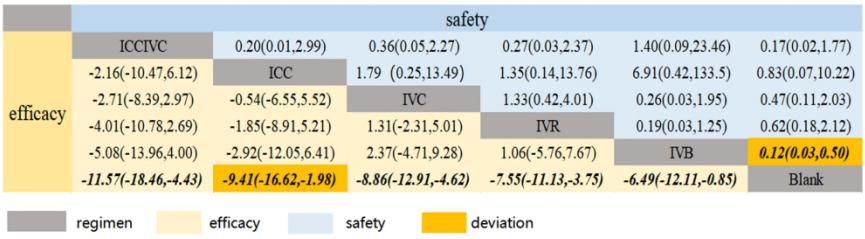

Figure 4. Sensitivity network meta-analyses for primary efficacy and safety outcomes. Regimens are reported in order of patients' IOP 1month after surgery ranking according to SUCRAs.
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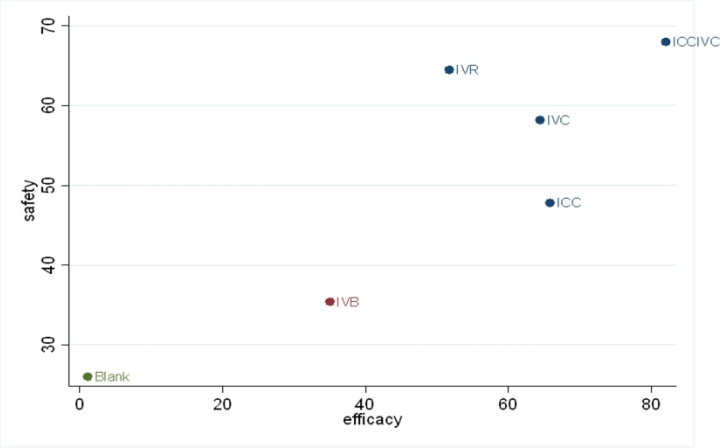

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881x661mm (144 x 144 DPI)

1, Search strategy and results

A. PubMed(n=66)

Search: ((Glaucoma*, Neovascular OR Neovascular Glaucoma* OR NVG OR refractory glaucoma OR iris neovascularization OR chamber angle neovascularization) AND (Bevacizumab OR Conbercept OR ranibizumab OR Aflibercept OR Vascular Endothelial Growth Factor OR VEGF)) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])

B. Embase(n=92)

No.	Query	Results	Date
#15.	#1 AND #7 AND #14	92	5 Sep 2022
#14.	#8 OR #9 OR #10 OR #11 OR #12 OR #13	163,424	5 Sep 2022
#13.	'vegf':ab,ti	111,190	5 Sep 2022
#12.	'vascular endothelial growth factor':ab,ti	83,366	5 Sep 2022
#11.	'aflibercept':ab,ti	4,372	5 Sep 2022
#10.	'ranibizumab':ab,ti	6,941	5 Sep 2022
#9.	'conbercept':ab,ti	400	5 Sep 2022
#8.	'bevacizumab':ab,ti	33,688	5 Sep 2022
#7.	#2 OR #3 OR #4 OR #5 OR #6	3,687	5 Sep 2022
#6.	'chamber angle neovascularization':ab,ti	12	5 Sep 2022
#5.	'iris neovascularization':ab,ti	516	5 Sep 2022
#4.	'nvg':ab,ti	695	5 Sep 2022
#3.	'refractory glaucoma':ab,ti	838	5 Sep 2022
#2.	'neovascular glaucoma':ab,ti	2,466	5 Sep 2022
#1.	random* OR placebo* OR 'double blind*'	2,327,259	5 Sep 2022

G. the Cochrane library(n=113)

ID	Search	Hits
#1	MeSH descriptor: [Glaucoma, Neovascular] explode all trees	57
#2	(Glaucomas, Neovascular or Neovascular Glaucoma or Neovascular Glaucomas or Glaucoma, Neovascular OR NVG):ti,ab,kw (Word variations have been searched)	355
#3	(iris neovascularization or chamber angle neovascularization or refractory glaucoma):ti,ab,kw (Word variations have been searched)	277
#4	#1 or #2 or #3	534
#5	(Bevacizumab or Conbercept or ranibizumab or Aflibercept or Vascular Endothelial Growth Factor or VEGF):ti,ab,kw (Word variations have been searched)	13992
#6	MeSH descriptor: [Bevacizumab] explode all trees	2242
#7	(Mvasi or Avastin or Bevacizumab-awwb or Bevacizumab awwb):ti,ab,kw (Word variations have been searched)	912
#8	MeSH descriptor: [Ranibizumab] explode all trees	965
#9	(Lucentis or V2, RhuFab or RhuFab V2):ti,ab,kw (Word variations have been searched)	446
#10	MeSH descriptor: [Vascular Endothelial Growth Factor A] explode all trees	1394
#11	#5 or #6 or #7 or #8 or #9 or #10	14064
#12	MeSH descriptor: [Randomized Controlled Trial] explode all trees	118
#13	(Randomized Controlled Trial or randomly or randomized) (Word variations have been	

searched) 1345977

#14 #12 or #13 1324842

#15 #4 and #11 and #14 117

C. Web of Science(n=167), ClinicalTrials.gov (n=38), ISRCNT (n=20)

D. Chinese databases: the China Science Periodical Database (the Wanfang Database, n=213), the China National Knowledge Infrastructure (n=143), VIP journal integration platform (n=133) and China Biology Medicine database (n=127)

using the following keywords: Neovascular Glaucoma, NVG, refractory glaucoma, iris neovascularization, chamber angle neovascularization, Bevacizumab, Conbercept, ranibizumab, Aflibercept, Vascular Endothelial Growth Factor, VEGF and random

2, References for Chinese included trials

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3, The characteristics of the included studies in this network meta-analysis

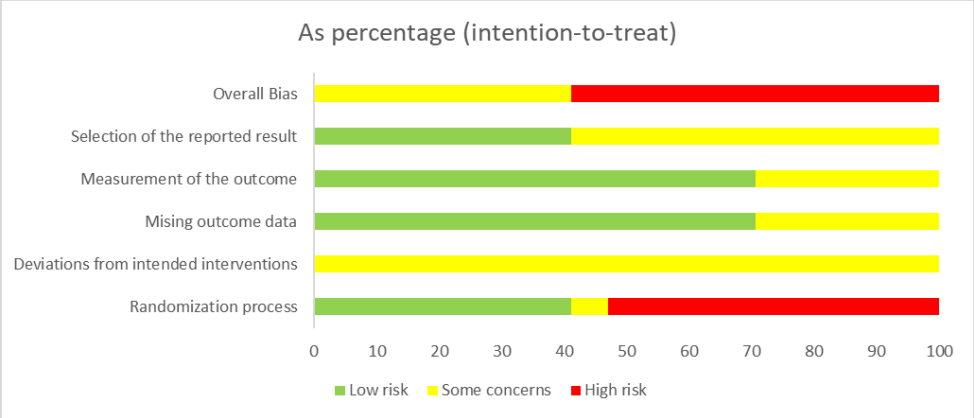
The characteristics of the included studies												
Author	Year	Region	Bias	Age（MD±SD）	Sample		Gender	Primary disease		Intervention	Other therapy	Follow-up	outcome
					P	E	Male/Female	RVO	DR				
Zhou et al	2016	China	High	45.15±2.47	57	57	31/26	26.32%	59.65%	Blank vs IVR	PRP+Trab(MMC)	6M	a,b,c,d,e
Yan et al	2019	China	Some	57.76±4.42	80	80	45/35	NA	NA	Blank vs IVR	PRP+CPC	6M	a,b,d,e
Guo et al	2021	China	High	61.59±17.32	160	160	92/68	24.38%	65%	IVC vs IVR	PRP+Trab(MMC)	12M	a,b,e
Arcieri et al	2014	Brazil	Some	60.83±10.09	40	40	24/16	47.5%	52.5%	Blank vs IVB	PRP+AGV	24M	a,b,c,e
Yazdani et al	2007	Iran	Some	60±14.9	26	26	21/5	34.62%	61.54%	Blank vs IVB	PRP+Surgery（Type unknown）	6M	a,b,d,e
Bai et al	2022	China	Some	64.2	74	81	51/23	38.3%	61.7%	IVC vs ICC	PRP+Trab(MMC) PRP	6M	a, b, e
Xu et al	2015	China	High	52.94±2.52	37	37	26/11	45.95%	48.65%	Blank vs IVR	PRP+CPC	6M	a, e
Guo et al	2017	China	Some	53.32±5.89	68	68	48/20	77.94%	14.71%	IVC vs IVR	PRP+Trab(MMC)	12M	a,b,c,d,e
Li et al	2020	China	High	58.6±2.34	90	90	54/36	NA	NA	Blank vs IVC	PRP+Trab(MMC)	3M	a, b, c
Zhang et al	2020	China	High	62.59±10.49	106	106	55/51	48.33%	51.67%	IVC vs ICCIVC	PRP+Trab(MMC) PRP	12M	a, b, d

Xi et al	2018	China	High	53.96±2.23	74	82	39/35	35.14%	25.68%	Blank vs IVR	PRP+CPC	3M	a, c
Feng et al	2018	China	High	54.9±8.3	38	40	22/16	32.5%	67.5%	Blank vs IVR	PRP+CPC	6M	a,b,c,e
Mahdy et al	2012	Egypt	High	55.5±3.18	40	40	23/17	20%	77.5%	Blank vs IVB	PRP+AGV	18M	a,b,c,d
Gou et al	2020	China	Some	53.5±5.92	50	50	27/23	0	100%	Blank vs IVC	PRP	9M	f
Lin et al	2017	China	Some	45.92±6.49	176	242	93/83	NA	NA	Blank vs IVR	PRP	1M	f
Deng et al	2018	China	High	57.87±4.96	93	93	50/43	27.96%	63.44%	Blank vs IVR	PRP	1M	f
Wittström et al	2011	Sweden	High	78.4±8	19	19	7/12	100%	0	Blank vs IVB	PRP	6M	f

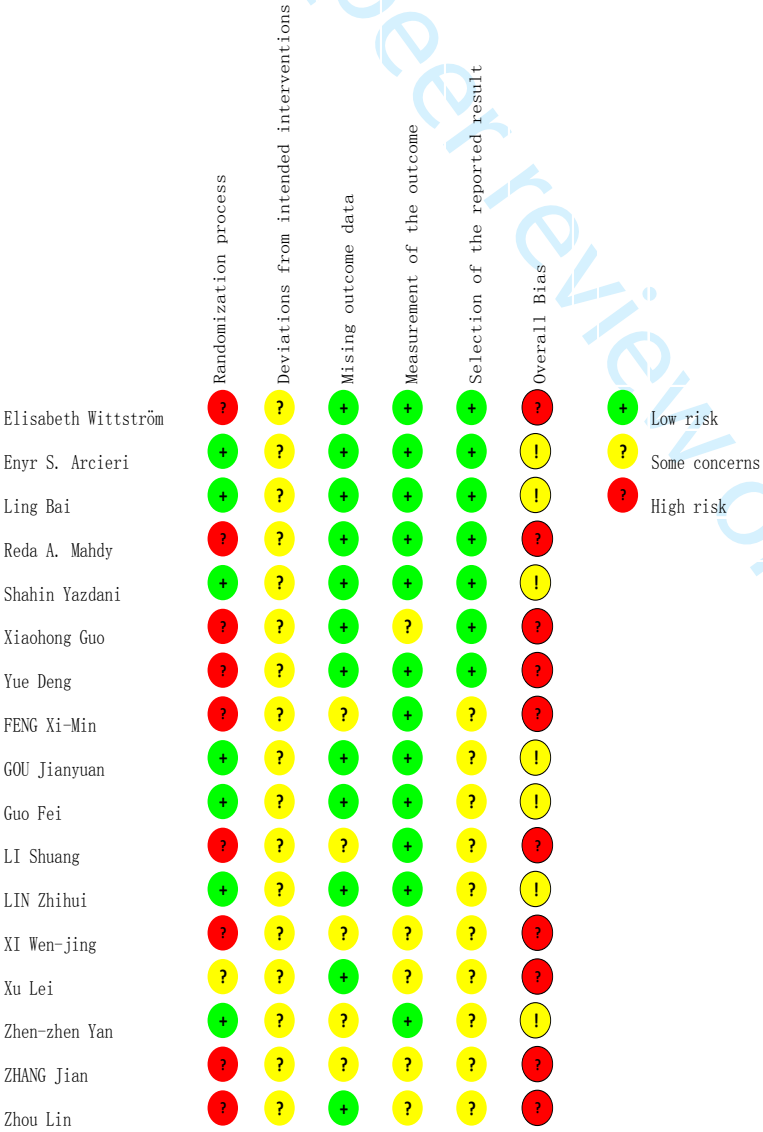
NA=not available; RVO=retinal vein occlusion; DR=diabetic retinopathy; P=people; E=eye; M=month; Trab (MMC)= trabeculectomy with mitomycin;AGV=Ahmed glaucoma valve;CPC=cyclophotocoagulation;PRP=panretinal photocoagulation;(a) IOP 1month, (b) complications, (c) success rate, (d) visual retention rate, (e) IOP 6months, (f) non-surgical IOP 1month; Blank=blank control group; IVC =intravitreal injection of conbercept; IVR=intravitreal injection of ranibizumab; IVB=intravitreal injection of bevacizumab; ICC=intracameral injection of conbercept; ICCIVC=simultaneous intravitreal and intracameral injection of conbercept.

4, Risk of bias assessment (the revised Cochrane risk-of-bias tool for randomized trials (RoB2))

Risk of bias graph



Risk of bias summary: it is a summary table of review authors' judgments for each risk of bias entriy for each study



5, Results from pairwise meta-analysis for each outcome: numbers, estimates and heterogeneity

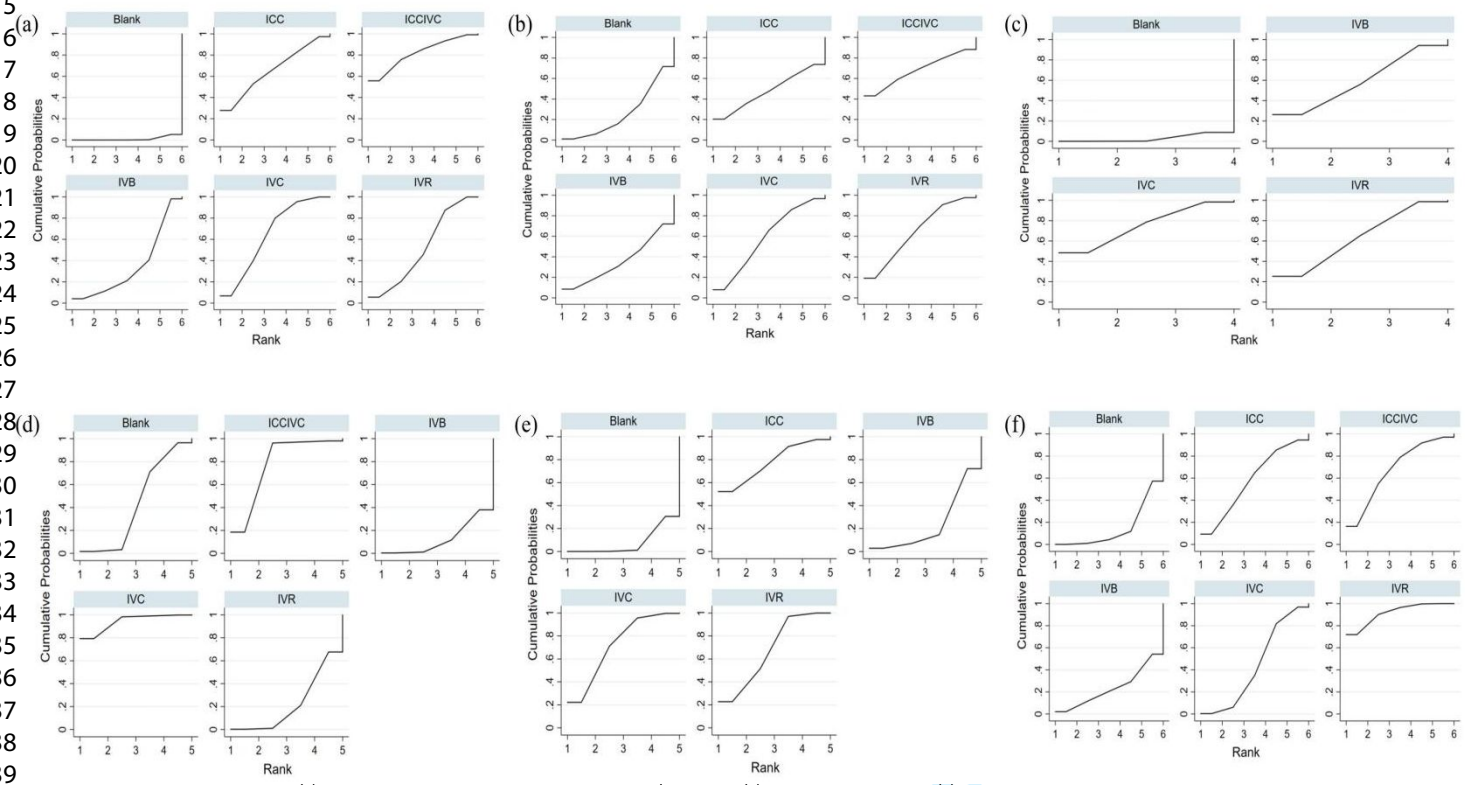
IOP 1month								
study	**I^2**	**τ^2**	**MD**	**LL**	**UL**	**P**	**NO.(i)**	**sample**
Blank vs IVR	99%	24.86	7.28	2.83	11.74	**0.001**	5	296
Blank vs IVB	76.4%	10.39	5.37	0.87	9.88	**0.019**	3	106
Blank vs IVC	NA	NA	10.50	8.83	12.17	**0.000**	1	90
IVC vs IVR	0	0	-0.25	-1.50	1.01	0.701	2	228
IVC vs ICC	NA	NA	0.53	-2.22	3.28	0.705	1	41
IVC vs ICCIVC	NA	NA	2.71	1.08	4.34	**0.001**	1	60
complications								
study	**I^2**	**τ^2**	**OR**	**LL**	**UL**	**P**	**NO.(i)**	**sample**
Blank vs IVR	78.9%	2.41	5.12	0.67	39.15	0.115	3	177
Blank vs IVB	77.9%	3.01	2.59	0.27	25.01	0.412	3	106
Blank vs IVC	NA	NA	1.54	0.24	9.66	0.65	1	90
IVC vs IVR	0	0	0.72	0.39	1.32	0.283	2	228
IVC vs ICC	NA	NA	0.57	0.16	2.07	0.395	1	41
IVC vs ICCIVC	NA	NA	2.68	0.91	7.94	0.075	1	60
Success rate								
study	**I^2**	**τ^2**	**OR**	**LL**	**UL**	**P**	**No.(i)**	**sample**
Blank vs IVR	0	0	0.25	0.10	0.68	**0.006**	3	179
Blank vs IVB	74%	2.61	0.23	0.02	3.01	0.26	2	80
Blank vs IVC	NA	NA	0.24	0.07	0.81	**0.021**	1	90
IVC vs IVR	NA	NA	3.09	0.12	78.55	0.494	1	68

IVC vs ICC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs ICCIVC	NA	NA	NA	NA	NA	NA	NA	NA
Visual retention rate								
study	**I^2**	**τ^2**	**OR**	**LL**	**UL**	**P**	**No.(i)**	**Sample**
Blank vs IVR	0	0	0.41	0.16	1.03	0.056	2	134
Blank vs IVB	73.7%	2.67	0.23	0.02	3.14	0.268	2	66
Blank vs IVC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs IVR	NA	NA	0.32	0.01	8.23	0.494	1	68
IVC vs ICC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs ICCIVC	NA	NA	0.24	0.06	0.99	**0.049**	1	60
IOP 6month								
study	**I^2**	**τ^2**	**MD**	**LL**	**UL**	**P**	**No.(i)**	**sample**
Blank vs IVR	98.2%	41.28	8.42	1.97	14.86	**0.011**	4	214
Blank vs IVB	56.7%	21.70	2.46	-5.62	10.54	0.551	2	66
Blank vs IVC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs IVR	0	0	-0.48	-1.69	0.73	0.436	2	228
IVC vs ICC	NA	NA	1.04	-0.31	2.39	0.132	1	41
IVC vs ICCIVC	NA	NA	NA	NA	NA	NA	NA	NA
Non-surgery IOP 1month								
study	**I^2**	**τ^2**	**MD**	**LL**	**UL**	**P**	**No.(i)**	**sample**
Blank vs IVR	99%	26.17	13.54	6.41	20.66	**0.000**	2	335
Blank vs IVB	NA	NA	0.30	-9.98	10.58	0.95	1	19
Blank vs IVC	NA	NA	5.24	2.64	7.84	**0.000**	1	50

IVC vs ICC	NA	NA	1.81	-0.09	3.71	0.062	1	40
IVC vs ICCIVC	NA	NA	3.33	1.45	5.21	**0.001**	1	46

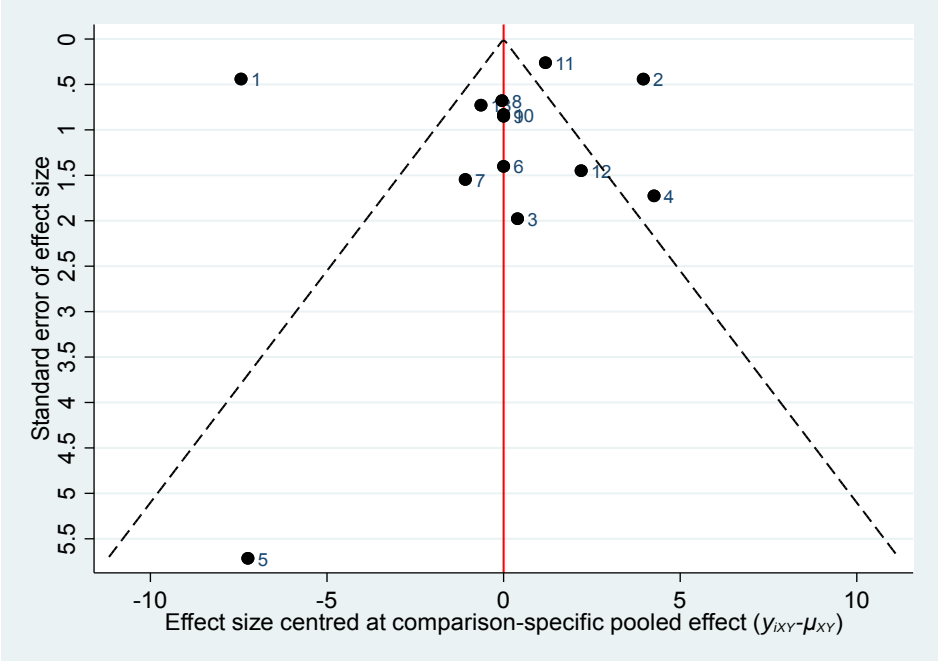
No.(i)= the number of interventions

6, Plots of SUCRA for primary and secondary outcomes.

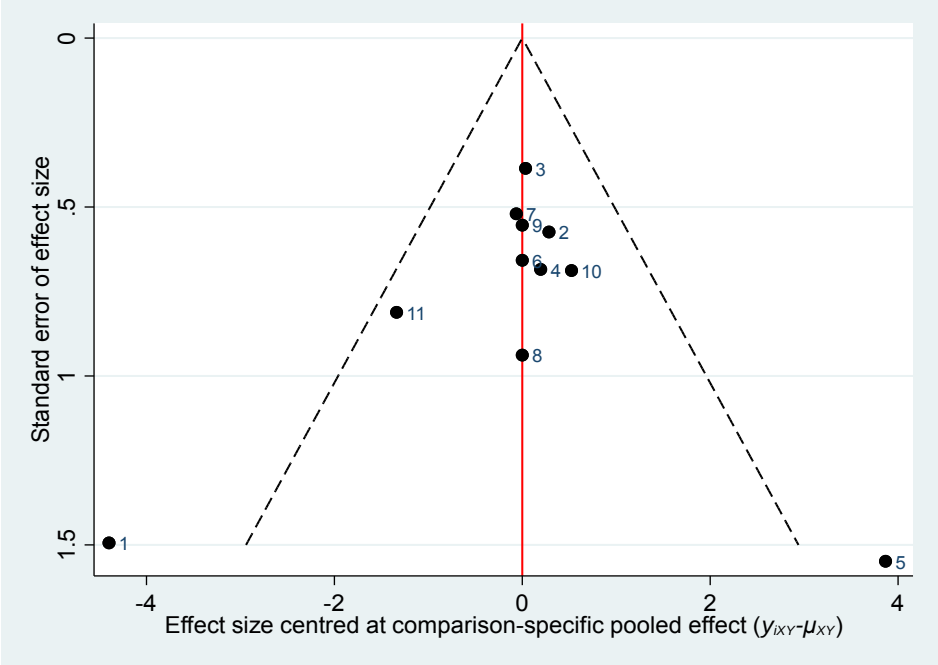


7, Comparison-adjusted funnel plot for primary and secondary outcome from the network meta-analysis

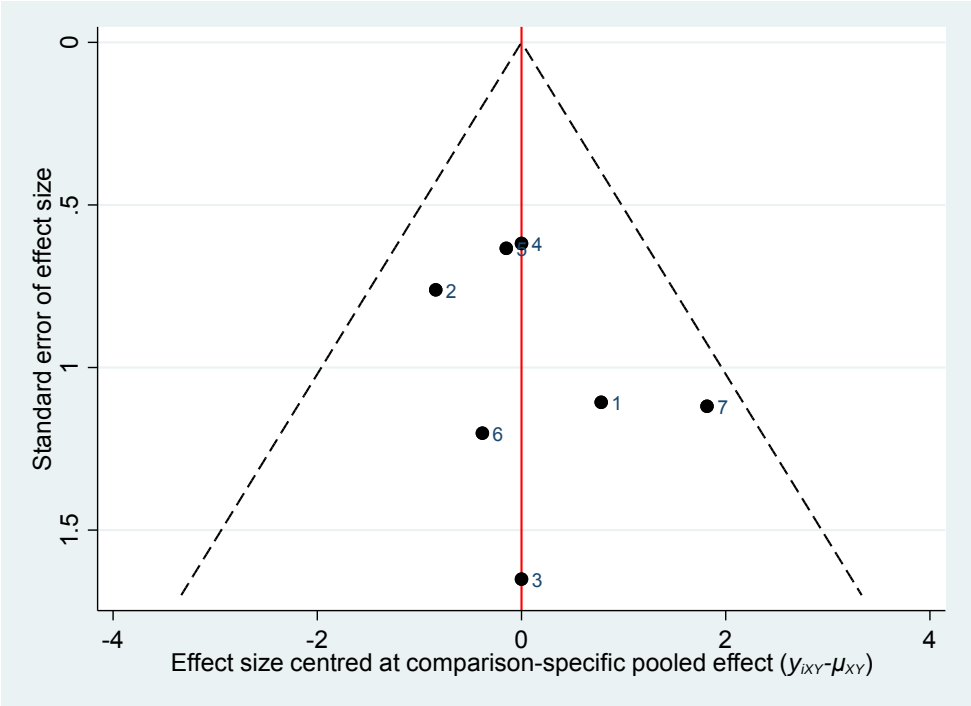
a. IOP 1month



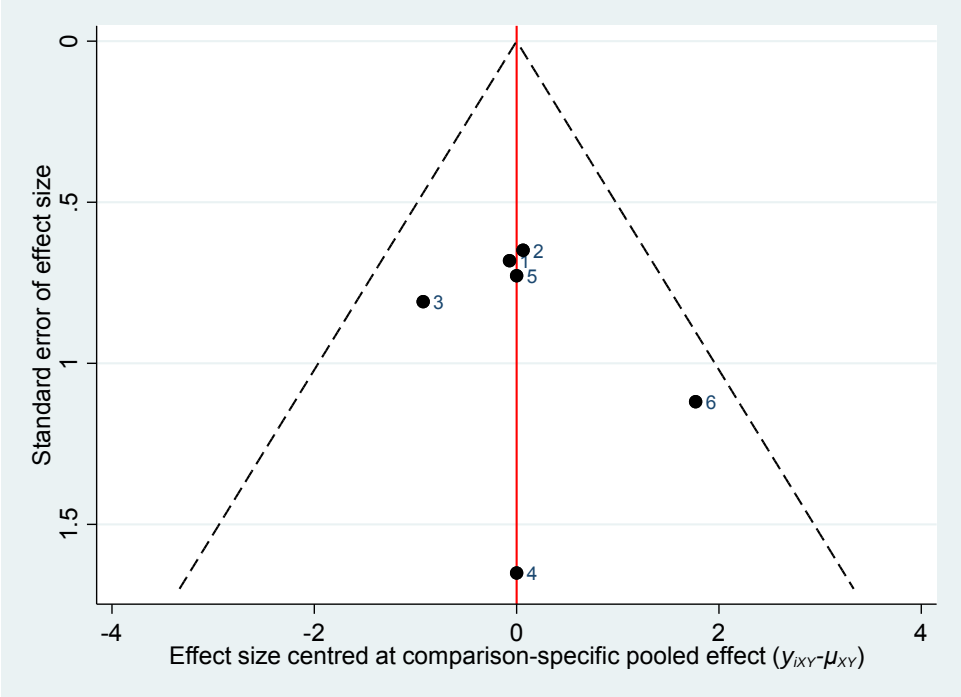
b. Complication



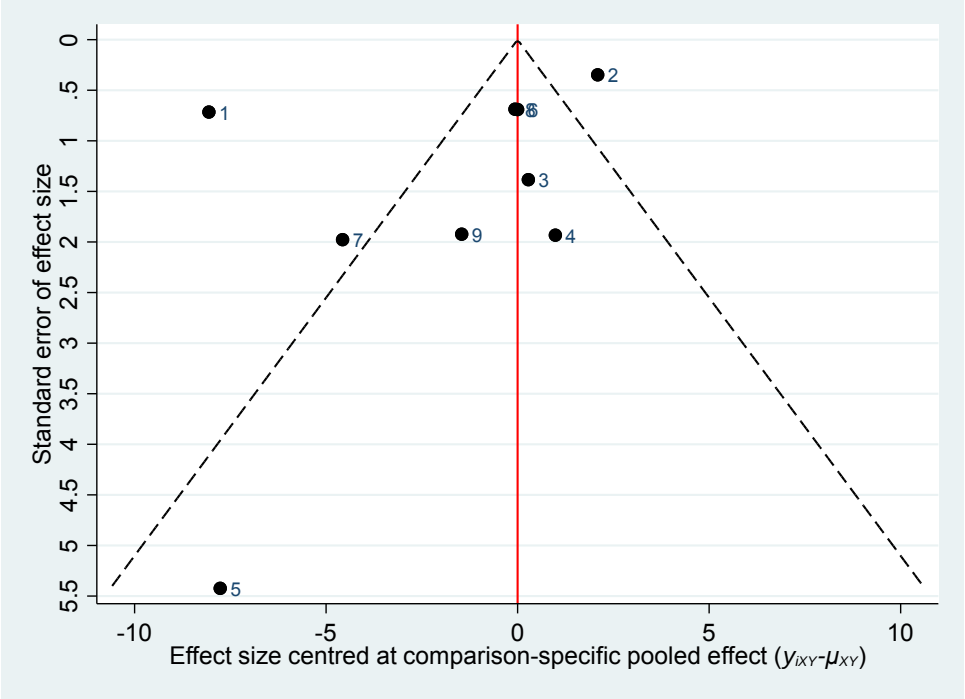
c.Success rate



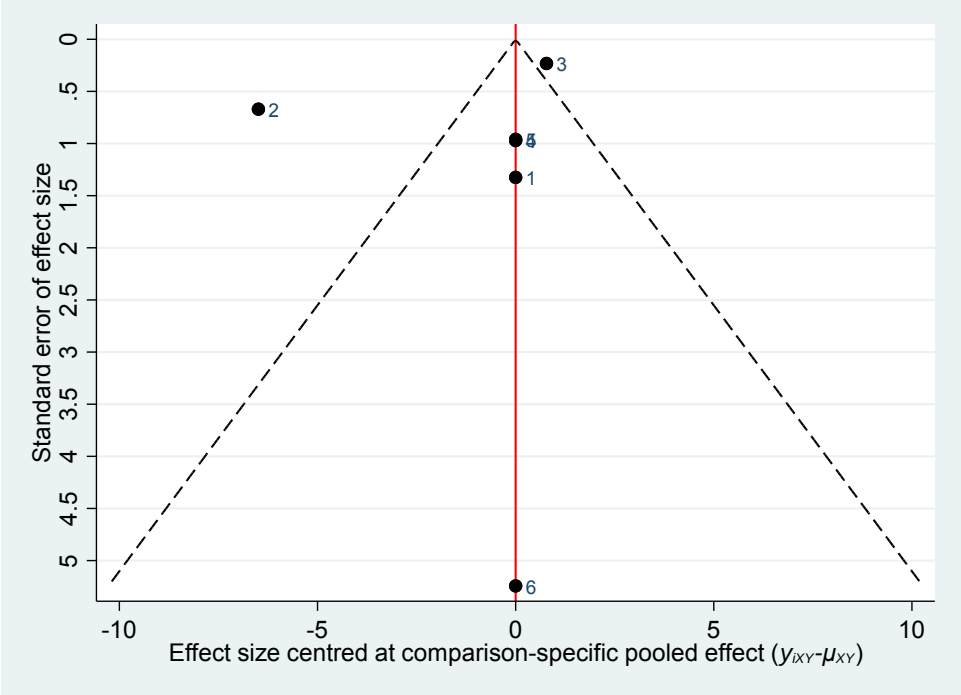
d.Visual retention rate



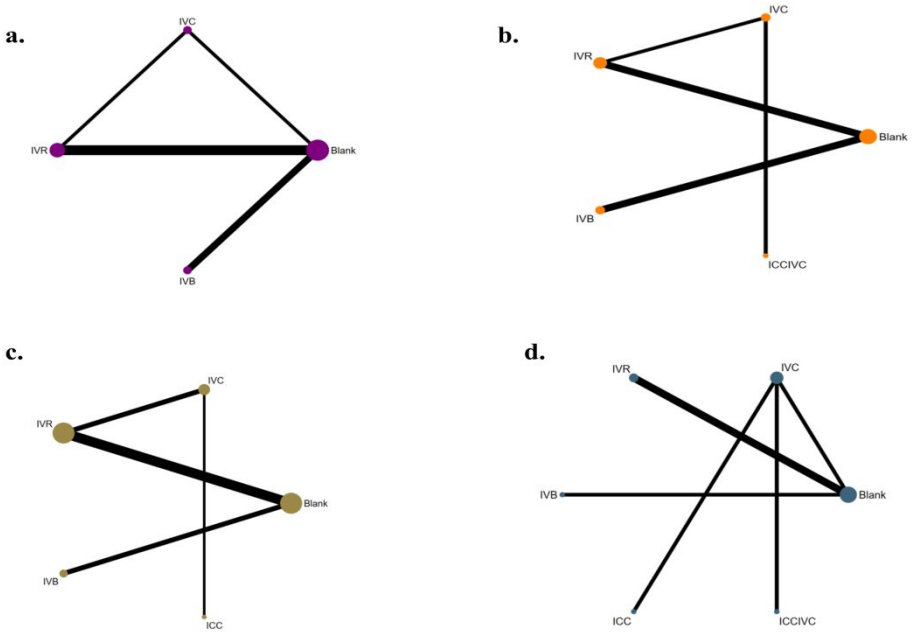
e.IOP 6month



f. Non-surgery IOP 1month



8, Network plot of available treatment comparisons for secondary outcome.



9, The results of network meta-analysis for secondary outcomes

a. Success rate

IVC	0.32(0.013,8.33)	NA	***4.17(1.23,14.29)***
0.47(0.00,12.28)	IVR	NA	***4(1.47,10)***
0.60(0.00,49.75)	1.31(0.03,125.9)	IVB	4.35(0.33,50)
8.20(0.40,1177)	3.83(0.24,43.69)	4.99(0.22,164)	Blank

b. Visual retention rate

IVC	***4.17(1.01,16.67)***	NA	3.13(0.12,100)	NA
4.20 (0.59,29.91)	ICCIVC	NA	NA	NA
1.26 (0.03,53.55)	3.33 (0.05,228.84)	Blank	2.44(0.97,6.25)	4.35(0.32,50)
3.09 (0.09,102.86)	1.36 (0.02,75.54)	2.45 (0.65,9.22)	IVR	NA
4.70 (0.08,291.49)	1.12 (0.01,108.11)	3.73 (0.66,20.93)	1.52 (0.17,13.44)	IVB

c. IOP 6month

ICC	-1.04(-2.39,0.31)	NA	NA	NA
-1.02(-8.78,6.70)	IVC	0.48(-0.73,1.69)	NA	NA
-1.59(-11.12,7.92)	0.57(-4.99,6.14)	IVR	NA	***-8.42(-14.86,-1.97)***
-7.90(-20.2,4.76)	6.88(-3.08,16.58)	6.31(-1.95,14.30)	IVB	-2.46(-10.54,5.62)
-9.95(-20.29,0.39)	***-8.94(-15.8,-2.08)***	***-8.37(-12.42,-4.35)***	-2.06(-9.25,4.90)	Blank

d. Non-surgery IOP 1month

IVR	NA	NA	NA	NA	***-13.54(-20.66,-6.41)***
4.99(-7.55，17.57)	ICCIVC	NA	***-3.33(-5.21,-1.45)***	NA	NA
6.51(-5.99，19.07)	-1.51(-12.68，9.66)	ICC	-1.81(-3.71,0.09)	NA	NA
-8.30(-18.06，1.42)	-3.30(-11.19，4.61)	-1.79(-9.66，6.08)	IVC	NA	***-5.24(-7.84,-2.64)***
13.23(-0.46，27.03)	-8.24(-25.20，8.73)	-6.73(-23.69，10.29)	4.94(-10.13，19.90)	IVB	-0.30(-10.58,9.98)
-13.5(-18.98,-8.03)	-8.50(-19.79，2.76)	-6.99(-18.28,4.31)	-5.20(-13.27,2.86)	-0.26(-12.92,12.45)	Blank

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page7

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Page8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page8-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page8-9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page12-13
	23b	Discuss any limitations of the evidence included in the review.	Page14
	23c	Discuss any limitations of the review processes used.	Page14
	23d	Discuss implications of the results for practice, policy, and future research.	Page14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page15
Competing interests	26	Declare any competing interests of review authors.	Page15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page16

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71

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Comparative efficacy and safety of different anti-VEGF agents combined with different delivery methods for neovascular glaucoma: a systematic review and Bayesian network meta-analysis

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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Glaucoma < OPHTHALMOLOGY, Medical ophthalmology < OPHTHALMOLOGY, Ophthalmology < SURGERY

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Comparative efficacy and safety of different anti-VEGF agents combined with different delivery methods for neovascular glaucoma: a systematic review and Bayesian network meta-analysis

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ABSTRACT

Objective To compare the efficacy and safety of different anti-vascular endothelial growth factor (VEGF) agents combined with different delivery methods for neovascular glaucoma (NVG).

Design Systematic review and Bayesian network meta-analysis (NMA).

Data sources PubMed, Embase, Cochrane Library, Web of Science, ClinicalTrials.gov, ISRCTN, and Chinese databases including the China National Knowledge Infrastructure, the China Science Periodical Database (Wanfang Database), the VIP Journal Integration Platform, and the China Biology Medicine database were searched from inception to September 5th, 2022.

Eligibility criteria We included randomised controlled trials (RCTs) that investigated the treatment of neovascular glaucoma (NVG) using different anti-VEGF agents combined with various methods of drug administration, without any language limitations. All patients included underwent panretinal laser photocoagulation (PRP) and no restrictions on prior glaucoma surgery.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias. Random-effect Bayesian NMA was conducted to compare efficacy and safety and rank priority of anti-VEGF regimens. The source of heterogeneity and the related factors affecting the stability of the results were also explored. CINeMA was used to assess the certainty of the evidence.

Results Our analysis included seventeen RCTs involving a total of 1311 eyes from 1228 patients. We examined five different treatment regimens, which utilised three different anti-VEGF drugs. The following treatments showed a significant decrease in intraocular pressure (IOP) compared with the control group at 1 month after glaucoma surgery: simultaneous intravitreal and intracameral injection of conbercept (ICCIVC)

(mean difference [MD] = -11.56, 95% credible interval [CrI] -20.8 to -2.24), intravitreal injection of conbercept (IVC) (MD = -8.88, 95% CrI -13.93 to -3.78), intravitreal injection of ranibizumab (IVR) (MD = -7.62, 95% CrI -10.91 to -4.33), and intravitreal injection of bevacizumab (IVB) (MD = -5.51, 95% CrI -10.79 to -0.35). The SUCRA analysis indicated that ICCIVC (82.0%) may be the most effective regimen in reducing IOP. In terms of safety, there were no statistically significant differences among the interventions. According to the SUCRA analysis, ICCIVC (68.0%) was considered the safest choice with the fewest complications. Subgroup and meta-regression analyses showed that mean age was the main source of heterogeneity. Sensitivity analysis demonstrated the robustness of the study results.

Conclusion ICCIVC was more effective and safer than other anti-VEGF regimens for NVG. Simultaneous intravitreal and intracameral injection was found to be the best route of administration, and conbercept was found to be the superior drug selection when compared with ranibizumab and bevacizumab.

Study registration PROSPERO, CRD42022309676.

Strengths and limitations of this study

- Network meta-analysis is the best method to compare interventions in the absence of head-to-head trials.
- To the best of our knowledge, this study is the most comprehensive network meta-analysis conducted to date, as it includes all the available data from comparative studies.
- Subgroup and meta-regression analyses were performed to examine the heterogeneity within the included studies; additionally, sensitivity analysis was

conducted to assess the impact of small sample sizes and significant heterogeneity on the study results.

- Most of the included studies were conducted in Asia, and as a result, conbercept was the most commonly used anti-VEGF agent, which could potentially have introduced a selection bias that may have influenced the results.

INTRODUCTION

Neovascular glaucoma (NVG) is a secondary type of glaucoma that has the potential to cause vision loss. It occurs when abnormal new blood vessels form and obstruct the normal drainage of aqueous humour in the eye.[1] It is typically associated with ocular ischemic diseases, such as diabetic retinopathy (DR), central retinal vein occlusion (CRVO) and ocular ischaemic syndrome (OIS).[2] Although NVG is a relatively rare condition, with a prevalence ranging from 0.01% to 0.12% in the population, it accounts for approximately 3.9% of all glaucoma cases and 9-14.7% of all cases of secondary glaucoma.[3]

The treatment approach for NVG typically involves two main aspects: reducing vascular drive and controlling intraocular pressure (IOP).[4, 5]To address neovascularisation, common therapeutic options include panretinal photocoagulation (PRP) or the administration of vascular endothelial growth factor (VEGF) inhibitors. At the same time, effective control of IOP is vital to prevent damage to the optic nerve and is achieved through the use of topical and systemic medications or surgical interventions.

Initially utilised in ophthalmology for the treatment of choroidal neovascularisation in age-related macular degeneration (nAMD), the application of anti-VEGF medications has expanded rapidly to encompass the treatment of various

other conditions.[6, 7] The currently available VEGF inhibitors including bevacizumab (Avastin), ranibizumab (Lucentis), aflibercept (Eylea), and conbercept (Lumitin), have been proven to be effective in suppressing anterior segment neovascularisation and lowering IOP.[3, 8-10] These medications are administered via intravitreal, intracameral, and, less frequently, simultaneous intravitreal and intracameral routes for NVG treatment.[11-14] Numerous researchers also verified the effectiveness of these delivery modalities.[15-17]

We conducted a comparative analysis of different available anti-VEGF regimens (agents and delivery methods) for NVG utilising data obtained from randomised controlled trials (RCTs) in order to rank their priority with the aim of guiding clinical practice.

METHODS

This network meta-analysis (NMA) is reported following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) extension statement for reporting network meta-analysis.[18] The protocol for this study has been registered with PROSPERO under the registration number CRD42022309676.

Search strategy

Two authors independently searched the PubMed, EMBASE, the Cochrane library, Web of Science, ClinicalTrials.gov, ISRCTN and Chinese databases including the China National Knowledge Infrastructure, the China Science Periodical Database (the Wanfang Database), the VIP Journal Integration Platform, and the China Biology Medicine database from the inception of the databases to September 5 2022, with no

language restrictions. The Chinese literature mainly selects high quality studies such as Chinese Medical Association or core journals. A detailed process has been provided in Supplemental Material 1.

Inclusion and exclusion criteria

We included studies based on the following criteria: (1) participants: patients with a diagnosis of NVG; (2) interventions: anti-VEGF agents were administered in combination with diverse treatment regimens featuring different delivery modes. All eligible patients underwent PRP and no restrictions on prior glaucoma surgery; (3) comparators: placebo control, no-treatment control and positive control; (4) outcomes: the results of the included studies need to meet at least one outcome measure as defined in this NMA; (5) study type: RCTs.

Studies that met any of the following criteria were excluded: (1) conference abstracts, reviews, meta-analyses, or case reports; (2) unknown or other types of glaucoma patients; (3) history of anti-VEGF or steroid injection, studies related to drug dosage, studies related to comparison of surgical methods, and studies related to unplanned PRP; (4) poor quality Chinese studies.

Outcome measures

We took the IOP (mmHg) at 1 month after anti-glaucoma surgery (IOP 1 month, a) and the incidence of postoperative complications during the follow-up period (complications, b) as our primary efficacy and safety, respectively. Complications encompassed bleeding-associated complications such as hyphema, vitreous haemorrhage, or suprachoroidal haemorrhage.

The secondary efficacy outcomes included the success rate of anti-glaucoma surgery (success rate, c), using the definitions by authors of individual studies; the visual retention rate after anti-glaucoma surgery (visual retention rate, d), where visual retention was determined by improved or unchanged visual acuity; and IOP at 6 months after anti-glaucoma surgery (IOP 6 months, e). In order to minimise bias, we preferably selected a common follow-up time point for above outcomes. If a common time point was not available in the data, we utilised the available information during the follow-up period. Additionally, for controllable NVG cases which did not require glaucoma surgery, the IOP at 1 month after anti-VEGF treatment was evaluated (non-surgical IOP 1 month, f).

Study screening process

The selection of studies was independently conducted by two review authors to ensure reliability. Any discrepancies or disagreements were resolved through discussion between the two authors. Disagreements were resolved by a third review author.

Data extraction

Two authors independently extracted the following data: study characteristics (including randomisation method and masking of treatment allocation), patient characteristics (mean age, sex, primary disease, stage of NVG, baseline IOP, visual acuity), intervention measures (anti-VEGF drug types and administration methods, anti-glaucoma surgery methods) and outcome variables.

Risk of bias assessment

Two authors utilised the revised Cochrane risk-of-bias tool for randomised trials (RoB2) to assess the risk of bias, disagreements were resolved through discussion with a third investigator.[19]

Statistical analysis

For outcomes with at least 2 direct comparative studies available, we conducted a pairwise random-effects meta-analysis using STATA (version 15.0). Categorical outcomes were assessed using odds ratios (OR) with corresponding 95% confidence intervals (CIs), while continuous outcomes were evaluated using mean differences (MD) with 95% CIs.

Whenever the evidence formed a connected network diagram, a random-effect Bayesian NMA was conducted in OpenBUGS (version 3.2.3).[20] We calculated OR and 95% credible intervals (CrI) for categorical outcomes, along with MD and 95% CrI for continuous outcomes to estimate the regimens effect size, respectively. The summarised estimates were calculated using Markov Chains Monte Carlo (MCMC) methods.[20] To estimate the posterior distribution for each model, three Markov chain Monte Carlo simulations were initialised using 200000 iterations for each simulation. However, the results are reported after excluding the first 100000 iterations. Convergence was assessed by visually inspecting history and trace plots.

For standard pairwise meta-analyses, we estimated heterogeneity variances for each direct comparison, which was conducted by I^2 and the between-studies variance estimate obtained by τ^2 (Profile likelihood estimator).[21] The heterogeneity variance, denoted as σ, represented the estimated standard deviation (SD) between studies in the NMA for each outcome.[22]

We used the 'design-by-treatment' interaction method and the node-splitting method to examine global and local consistency, respectively.[23, 24] Additionally, we also used the node-splitting method to examine the loop-closed inconsistency.[25]

The regimens were ranked based on the surface under the cumulative ranking curve (SUCRA).[26] A higher SUCRA indicates better treatment efficacy.[27, 28] To summarise the efficacy and safety of all regimens, the resultant rankings are presented by clustered ranking plot.

Reporting bias assessment

We plotted the comparison-adjusted funnel plot to investigate small-study bias and the possibility of publication bias at the network level.[29]

Subgroup, meta-regression and sensitivity analysis

Subgroup, meta-regression analysis were conducted to explore the source of heterogeneity when there were more than 10 studies, or when the number of studies included in the analysis was greater than the number of treatments. Specifically, we investigated whether the surgical methods of anti-glaucoma, the proportion of retinal vein occlusion in the primary disease and mean age were significant sources of heterogeneity. We also performed sensitivity analyses to examine the robustness of our results. Specifically, we removed studies that fell outside the funnel plot, as well as small sample studies at the bottom of the funnel plot. These analyses helped us assess the impact of potential sources of bias on the overall results of our study.

Confidence in cumulative evidence

The overall quality of evidence was assessed by the Confidence in Network

Meta-Analysis (CINeMA) approach.[30]This method involves evaluating the quality of the evidence for each outcome, considering factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on the evaluation results, we downgraded the quality of the evidence when appropriate, and assigned a final confidence rating of high, moderate, low, or very low.

Patient and public involvement

None.

RESULTS

Literature search

The initial search of electronic databases and trial registration platforms yielded a total of 1,112 records. After excluding 524 articles due to duplications and another 548 articles based on reading the titles and abstracts, we selected 40 potentially eligible citations for full-text review. After a careful review of these full-text articles, we excluded 23 reports, resulting in 17 trials that met our inclusion criteria. These 17 trials involved 1,228 participants, with a total of 1,311 eyes.[31-47] An outline of the study selection process is shown in Figure 1.

Characteristics of the included studies

A total of 17 RCTs are all two-arm studies. Of these, 13 studies involved anti-glaucoma surgery and involved a total of 821 eyes. The remaining six studies, which involved 490 eyes, did not include anti-glaucoma surgery. However, among them, there are two studies included both anti-glaucoma surgery group and no anti-glaucoma surgery.

Our studies covered blank control group (Blank) and 5 different regimens for three anti-VEGF drugs, which are intravitreal injection of conbercept (IVC), intravitreal injection of ranibizumab (IVR), intravitreal injection of bevacizumab (IVB), intracameral injection of conbercept (ICC) and simultaneous intravitreal and intracameral injection of conbercept (ICCIVC). In total, there were 15 possible comparisons between these treatments. Of these, six comparisons were made directly in the included studies. The baseline characteristics of each study are presented in Supplemental Material 2.

Risk of bias results

The overall bias of the included RCTs was as follows: low risk 0%, some concerns risk 41.2%, high risk 58.8%. It is important to note that due to the severe clinical symptoms and complications associated with NVG, it is challenging to conduct completely double-blind studies in this field. This limitation often leads to a higher overall risk of bias in the included literature. The details of the risk of bias assessment are shown in Supplemental Material 3.

Pairwise meta-analysis

In terms of success rate, IVR (I^2 = 0%, τ^2 = 0, OR = 0.25, 95% CI 0.10 to 0.68, P = 0.006) was higher than Blank. Regarding IOP, we found that after 1 month, both IVR (I^2 = 99%, τ^2 = 24.86, MD = 7.28, 95% CI 2.83 to 11.74, P = 0.001) and IVB (I^2 = 76.4%, τ^2 = 10.39, MD = 5.37, 95% CI 0.87 to 9.88, P = 0.019) were lower than Blank. After 6 months, IVR (I^2 = 98.2%, τ^2 = 41.28, MD = 8.42, 95% CI 1.97 to 14.86, P = 0.011) was lower than Blank. In the non-surgical IOP 1 month group, the effect of IVR (I^2 = 99%, τ^2 = 26.17, MD = 13.54, 95% CI 6.41 to 20.66, P < 0.001)

was found to be more effective than Blank. However, these studies all have significant heterogeneity. And no any statistically significant differences were found between treatment groups in terms of visual retention rate and complications. Results from pairwise meta-analysis for each outcome were presented in Supplemental Material 4.

Network meta-analysis

Primary efficacy outcome: IOP at 1 month

Thirteen studies involving 821 eyes and six regimens reported IOP 1 month after surgery, and there were 15 treatment comparisons. The network plot is shown in Figure 2. Comparing the treatments to the Blank control, ICCIVC (MD = -11.56, 95% CrI -20.8 to -2.24), IVC (MD = -8.88, 95% CrI -13.93 to -3.78), IVR (MD = -7.62, 95% CrI -10.91 to -4.33) and IVB (MD = -5.51, 95% CrI -10.79 to -0.35) demonstrated a favourable effect on IOP 1 month after surgery. However, no statistical difference was found in the remaining comparisons (Figure 3). ICCIVC had the highest rank (82.0%) for efficacy in reducing IOP after 1 month. Following that, ICC (65.8%), IVC (64.4%), IVR (51.7%), IVB (35.0%), and finally, the Blank control (1.1%) were ranked accordingly (Supplemental Material 5a).

The CINeMA assessment of the evidence in our study mostly rated the quality as very low. In the comparison-adjusted funnel plot (Supplemental Material 5b), four studies were observed to fall outside the funnel plot, suggesting potential report bias, while one study was at the bottom of the funnel plot, indicating a small sample size. In the meta-regression analysis, revealing significantly association between effect size and mean age (0.68, 95% CrI 0.11 to 1.21). However, no association between effect size and the proportion of RVO (18.96, 95% CrI -12.38 to 50.04). Additionally, no statistical significance was found in subgroup analysis between different types of anti-

glaucoma surgical and effect size (2.44, 95% CrI -0.58 to 5.57). In the sensitivity analysis, we excluded the five studies that fell outside and at the bottom of the funnel plot, the results showed that the effectiveness of ICC (MD = -9.41, 95% CrI -16.62 to -1.98) was higher than Blank. However, the other regimens did not exhibit significant changes in their effectiveness, Figure 4 for details.

Primary safety outcome: complications

Eleven studies involving 702 eyes and six different treatment regimens reported complications after surgery, leading to 15 treatment comparisons (Figure 2). No significant differences were found in complications after surgery when considering all regimens (Figure 3). With respect to ranking probabilities, ICCIVC ranked first (68.0%), followed by IVR (64.5%), IVC (58.2%), ICC (47.8%), IVB (35.4%) and Blank (26.0%) (Supplemental Material 6a).

Similar to the findings on efficacy, the CINeMA assessment indicated that the evidence quality for complications after surgery was mostly rated as very low. The comparison-adjusted funnel plot revealed that two studies fell outside the funnel plot, suggesting potential report bias and small sample size (Supplemental Material 6b). The results of both meta-regression and subgroup analysis were consistent with the primary efficacy findings. Sensitivity analysis was performed by excluding two studies. After this exclusion, the remaining nine studies were subjected to NMA. The results indicated that, compared to the Blank control, IVB (OR = 0.12, 95% CrI 0.03 to 0.50) was found to be safer. However, the other treatment regimens did not exhibit significant changes in terms of safety (Figure 4).

Secondary efficacy outcomes: success rate

Seven studies involving 417 eyes and four regimens reported success rate after surgery, leading to six treatment comparisons. No significant differences were found between the treatment regimens in terms of success rate. According to ranking probabilities based on SUCRA, IVC ranked first (74.8%), followed by IVR (63.3%), IVB (59.1%) and Blank (2.8%). The assessment of CINeMA was mostly rated as very low (Supplemental Material 7).

Secondary efficacy outcomes: visual retention rate

Six studies involving 331 eyes and five regimens reported visual retention rate after surgery, resulting in ten treatment comparisons. Due to the inability of the Bayesian methods to converge, we utilised a random-effects network meta-analysis within a frequentist framework, specifically using STATA (version 15.0). No significant differences were found between the treatment regimens. According to ranking probabilities based on SUCRA, IVC ranked first (94.1%), followed by ICCIVC (77.5%), Blank (43.1%), IVR (22.5%) and IVB (12.8%). The assessment of CINeMA was mostly very low (Supplemental Material 8).

Secondary efficacy outcomes: IOP at 6 months

Nine studies involving 549 eyes and five regimens reported IOP 6 months after surgery, leading to ten treatment comparisons. When compared with Blank, IVC (MD = -8.94, 95% CrI -15.8 to -2.08) and IVR (MD = -8.37, 95% CrI -12.42 to -4.35) exhibited significantly lower IOP 6 months after surgery. However, no statistical difference was found in the remainder of the treatment comparisons. According to ranking probabilities based on SUCRA, ICC ranked first (77.9%), followed by IVC

(72.2%), IVR (67.9%), IVB (24.1%) and Blank (8.0%). The assessment of CINeMA was largely rated as very low (Supplemental Material 9).

Secondary outcomes: non-surgical IOP at 1 month

Six studies involving 490 eyes and six regimens reported non-surgical IOP 1 month after treatment, resulting in15 treatment comparisons. When compared with the Blank, IVR (MD = -13.5, 95% CrI -18.98 to -8.03) showed a significantly lower IOP. However, no statistical difference was found in the remaining comparisons. According to ranking probabilities based on SUCRA, IVR ranked first (91.7%), followed by ICCIVC (67.9%), ICC (58.0%), IVC (44.0%) IVB (23.6%) and Blank (14.9%). The assessment of CINeMA was mostly rated as very low (Supplemental Material 10).

Efficacy versus safety in network analysis

The clustered ranking plot, which compares the results of primary efficacy and safety results, indicated that ICCIVC was the most efficacious and safest regimen in this analysis. This was shown by the position of this regimen on the upper right corner of the plot in Figure 5.

Inconsistency

The heterogeneity, as represented by the standard deviation (σ), was estimated at 3.77 (95% CI 2.441–4.918) for IOP 1 month and 3.16 (95% CI 1.443–4.869) for complications. The test of global and local inconsistency did not detect any evidence of statistically significant inconsistency for primary and secondary outcomes (global

inconsistency: p = 0.15–0.79). Among six outcomes, three outcomes covered loop-closed, all of which showed no significant inconsistency.

DISCUSSION

To our knowledge, this study is the first to analyse the efficacy and safety of different anti-VEGF drugs combined with different delivery methods for NVG using Bayesian network meta-analysis, and to prioritise different anti-VEGF regimens. At present, two network meta-analyses on NVG can be retrieved.[48, 49] DONG Z et al.'s results in 2018 and LIN P et al.'s study in 2022, which only compared the clinical efficacy and safety of various surgical interventions for NVG. However, combined with a large number of literature research and clinical evidence, it is found that different anti-VEGF drugs and their different routes of administration for the treatment of NVG also have differences in clinical efficacy and safety. For studies on anti-VEGF drugs in the treatment of NVG, Simha A's review in 2020 including four RCTs indicated that the use of anti-VEGF drugs in patients with NVG resulted in better resolution of iris neovascularisation in the short-term, but the long-term benefits have not been conclusively concluded, and there is insufficient evidence to assess the difference in adverse events with or without anti-VEGF drugs;[1] a meta-analysis by Hyung Bin Hwang in 2021 showed that the success rate of AGV+IVB treatment was higher than that of AGV treatment alone.[50] The above studies only prove that the combination of anti-VEGF injections can produce positive impact on NVG, but it does not analyse the efficacy of NVG treatment according to the different types of anti-VEGF and the different routes of administration.

In recent years, there has been an increase in the number of RCTs investigating the use of anti-VEGF drugs for NVG. However, some anti-VEGF therapies often lack

head-to-head studies, which makes it difficult to directly compare their effectiveness. This study provides indirect comparative evidence through the transmission of NMA, and the results obtained from direct and indirect evidence are compared.

A total of 17 RCTs involving 1311 eyes of 1228 patients were included in this study. Three anti-VEGF drugs were analysed involving five treatment regimens, which were ICCIVC, IVC, ICC, IVB and IVR.

The primary efficacy outcome (IOP 1 month) shows that ICCIVC, IVC, IVR and IVB are significantly more effective than Blank, direct controlled studies were available for comparing IVC, IVR, IVB and Blank. While there were no direct controlled studies comparing ICCIVC and Blank, so the evidence supporting this comparison comes from indirect comparisons. Using SUCRA value as the effect size, cluster analysis suggested that ICCIVC had the most significant effect, followed by ICC, IVC, IVR, and IVB. From the above ranking, it can be seen that conbercept was superior efficacy compared to ranibizumab and bevacizumab. Recent controlled clinical studies have also shown that conbercept has more advantages than ranibizumab in controlling IOP and improving visual acuity and has fewer postoperative complications. The analysis suggests that conbercept, formed by fusion of partial immunoglobulin regions of VEGFR-1 and VEGFR-2 with Fc fragment of human immunoglobulin G1, has a higher affinity for VEGF-A and PIGF compared to ranibizumab and bevacizumab.[51] Considering different delivery routes of conbercept, the analysis suggests that combined injection yields the best treatment effect, followed by intracameral injection, which is superior to intravitreal injection. Bhagat et al have reported that the intracameral injection route is the more effective in controlling IOP,[52] possibly because the drug can directly reach the neovascularised blood vessels of iris and angle after the intracameral injection. Moreover, the local

concentration of anti-VEGF drugs in the anterior chamber is higher with intracameral injection compared to intravitreal injection.

The primary safety outcome (complications) showed no statistical difference among all interventions, from the perspective of cumulative ranking probability, ICCIVC may be the safest among the anti-VEGF regimens analysed, but its SUCRA value was only slightly higher than that of IVR. The safety SUCRA value for all five anti-VEGF regimens were not significantly different from the Blank, which indicated that the effect of anti-VEGF injection on reducing postoperative complications was not very significant. A retrospective study demonstrated no significant correlation between IVB and hyphema after anti-glaucoma surgery,[53] which is consistent with our results. Sugimoto et al. believed that injection of anti-VEGF only reduce the neovascularisation on the surface of the iris, but may not completely eliminate the neovascularisation in the interstitium of the iris,[54] which may explain why there was no significant effect on postoperative haemorrhagic complications.

The study conducted a reporting bias assessment for both the efficacy and safety of the primary outcome. It revealed the presence of publication bias and small sample size effects in both groups. Sensitivity analysis was carried out by eliminating the studies with large heterogeneity outside the funnel plot and the studies with small sample at the bottom of the funnel plot. The results did not change significantly, indicating that the results of the primary outcome were stable. In order to explore the heterogeneity of efficacy and safety, subgroup and meta-regression analyses were conducted on them respectively. The results showed that mean age of the participants had an influence on the effect size of both groups.

In this study, only three anti-VEGF regimens were included in the success rate group. According to the results of SUCRA value, IVC had the highest ranking,

followed by IVR and IVB. This ranking is consistent with the efficacy results observed in the primary outcome, indicating that conbercept had a higher priority compared to ranibizumab and bevacizumab. It is important to note that the criterion for determining postoperative success in this outcome could not be uniformly established and had to be evaluated based on the definition used in each individual study. This variation in defining success may introduce some degree of bias in the analysis.

The group of IOP 6 months represents the long-term efficacy of anti-VEGF for NVG. The results showed that IVC and IVR were significantly different from the Blank. These findings for IVR were consistent with previous pairwise meta-analyses. However, for IVC, the evidence was obtained through indirect comparison. ICC ranked highest according to SUCRA, followed by IVC, IVR and IVB. These rankings were similar to the efficacy results obtained in the primary outcome. This indicates that conbercept demonstrated superior efficacy compared to ranibizumab and bevacizumab for long-term IOP control in NVG patients.

For the non-surgical group, the analysis of the results revealed that IVR was significantly more effective than the Blank, according to the priority of SUCRA value, the best treatment was IVR, followed by ICCIVC. However, previous studies have confirmed that intracameral combined with intravitreal injection can lead to rapid regression of iris and chamber angle neovascularisation, with a shorter regression time than intracameral or intravitreal injection alone.[55, 56] Therefore, the rank is different from the published studies, and we speculate that the possible reasons are as follows: A total of 6 RCTs were included in this outcome index, 3 of which had a baseline average IOP > 40mmHg, representing uncontrolled NVG. According to treatment guidelines, anti-glaucoma surgery should be considered for such cases,

however, in the original studies, anti-glaucoma surgery was not performed, and they were included in the non-surgical group in this NMA, which could have biased the results to some extent.

This study offers several notable advantages. Firstly, it is the first study to comprehensively analyse the efficacy and safety of different anti-VEGF drugs in combination with different injection methods in the treatment of NVG. This allows for a comparison and prioritisation of different anti-VEGF regimens, providing valuable insights for clinical decision-making. Moreover, the study employs network meta-analysis, which is an optimal approach when direct head-to-head intervention analyses are lacking. To address heterogeneity in the primary outcome, the study conducts subgroup and meta-regression analyses. These analyses help investigate potential sources of variation and explore how factors like mean age may influence treatment outcomes. Additionally, sensitivity analysis is employed to assess the impact of small sample sizes and large heterogeneity on the results. This analysis helps evaluate the stability and consistency of the findings, even when considering potentially influential studies. Overall, the methodological approaches used in this study, including network meta-analysis, subgroup analysis, meta-regression analysis, and sensitivity analysis, contribute to a comprehensive and well-rounded analysis of the efficacy and safety of different anti-VEGF drugs and injection methods for NVG treatment.

However, the results of the NMA should be interpreted with caution due to the following limitations: (a) As NVG is a rare disease, there is a lack of large-scale, multicentre RCTs, leading to a small sample size and limited number of included studies; (b) In this NMA, the credibility evaluation of CINeMA was generally low or very low, and the quality evaluation of included studies is not ideal, the report bias

identified through funnel plots suggests that publication bias may exist; (c) Most of the included studies were conducted in Asia, resulting in a higher prevalence of conbercept use, which could potentially introduce partial selection bias on the results; (d) For the analysis of complications, success rate and vision retention rate, the absence of definite time point data meant that data close to the specified time point was selected, leading to potential bias. In terms of success rate, the study used the original author's definition of surgical success criteria, which may have introduced bias and made direct comparison between studies difficult.

In summary, future research efforts should focus on conducting high-quality, large-scale, multicentre clinical RCTs that encompass a wider range of anti-VEGF drug regimens, thus generating more robust evidence to inform clinical practice and improve outcomes for patients with NVG.

CONCLUSION

This NMA provides substantial evidence for the clinical application of anti-VEGF drug regimens for NVG. Our findings suggest that ICCIVC was more effective and safer than the other four interventions included in the analysis. Simultaneous intravitreal and intracameral injection is the preferred route of administration. With regards to selecting a specific drug, conbercept is recommended over ranibizumab and bevacizumab.

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extraction and data analysis. YMG, JHW and JM contributed to assembly of data, the quality assessment and data interpretation. LY revised the manuscript, acquired funding, accepted full responsibility for the work of the study, had access to the data, and controlled the decision to publish as the guarantor. All authors have read and approved the final version of the manuscript.

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Figure titles and legends

Figure 1. Flowchart of the study selection process. RCT, randomised controlled trial; NMA, network meta-analysis.

Figure 2. Network plot of available treatment comparisons for primary outcome. The size of the node represents the number of patients randomised to each regimen. Line width represents the number of RCTs comparing each pair of regimens directly. Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

Figure 3. Network meta-analysis of primary efficacy and safety outcomes. Regimens are reported in order of patients' IOP 1 month after surgery ranking according to SUCRAs. Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

Figure 4. Sensitivity network meta-analyses for primary efficacy and safety outcomes. Regimens are reported in order of patients' IOP 1 month after surgery ranking according to SUCRAs. Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection

of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

Figure 5. Clustered ranking plot of anti-VEGF regimens for NVG based on primary efficacy and safety outcomes. Each colour represents a group of regimens that belong to the same cluster. Regimens lying in the upper right corner are the most efficacious and safest. Blank, blank control group; IVC, intravitreal injection of conbercept; IVR, intravitreal injection of ranibizumab; IVB, intravitreal injection of bevacizumab; ICC, intracameral injection of conbercept; ICCIVC, simultaneous intravitreal and intracameral injection of conbercept.

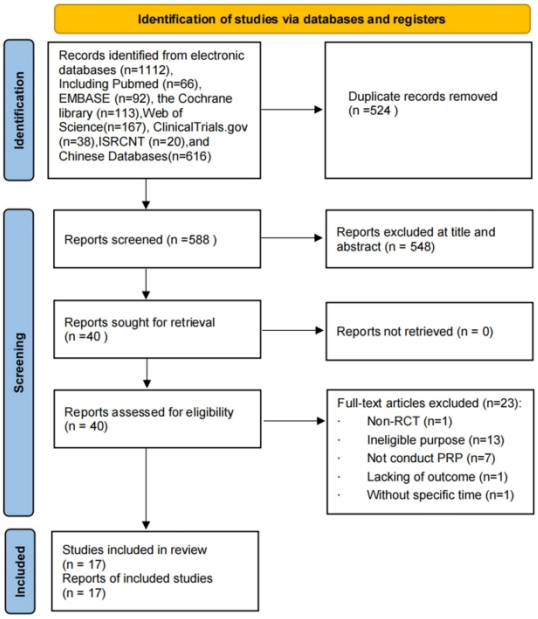

Figure 1. Flow chart of the study selection procedure
RCT, randomized controlled trial; NMA, network meta-analysis

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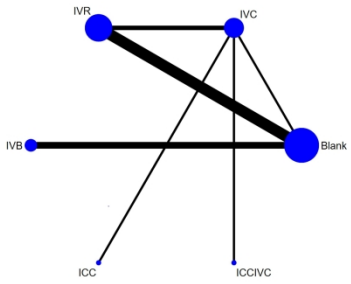

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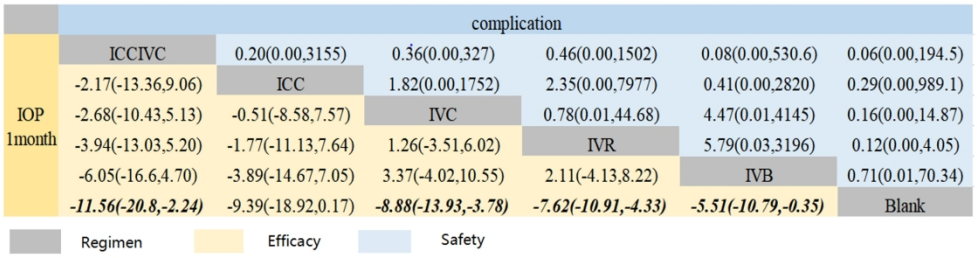

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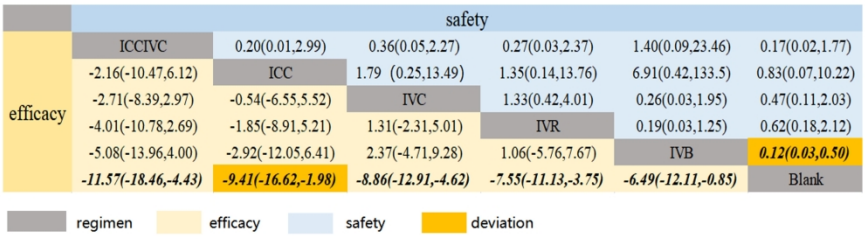

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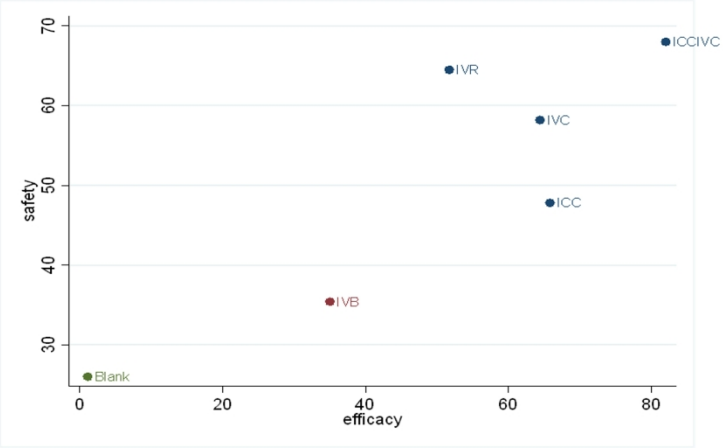

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881x661mm (144 x 144 DPI)

1, Search strategy and results

A. PubMed(n=66)

Search: ((Glaucoma*, Neovascular OR Neovascular Glaucoma* OR NVG OR refractory glaucoma OR iris neovascularization OR chamber angle neovascularization) AND (Bevacizumab OR Conbercept OR ranibizumab OR Aflibercept OR Vascular Endothelial Growth Factor OR VEGF)) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])

B. Embase(n=92)

No.	Query	Results	Date
#15.	#1 AND #7 AND #14	92	5 Sep 2022
#14.	#8 OR #9 OR #10 OR #11 OR #12 OR #13	163,424	5 Sep 2022
#13.	'vegf':ab,ti	111,190	5 Sep 2022
#12.	'vascular endothelial growth factor':ab,ti	83,366	5 Sep 2022
#11.	'aflibercept':ab,ti	4,372	5 Sep 2022
#10.	'ranibizumab':ab,ti	6,941	5 Sep 2022
#9.	'conbercept':ab,ti	400	5 Sep 2022
#8.	'bevacizumab':ab,ti	33,688	5 Sep 2022
#7.	#2 OR #3 OR #4 OR #5 OR #6	3,687	5 Sep 2022
#6.	'chamber angle neovascularization':ab,ti	12	5 Sep 2022
#5.	'iris neovascularization':ab,ti	516	5 Sep 2022
#4.	'nvg':ab,ti	695	5 Sep 2022
#3.	'refractory glaucoma':ab,ti	838	5 Sep 2022
#2.	'neovascular glaucoma':ab,ti	2,466	5 Sep 2022
#1.	random* OR placebo* OR 'double blind*'	2,327,259	5 Sep 2022

G. the Cochrane library(n=113)

ID	Search	Hits
#1	MeSH descriptor: [Glaucoma, Neovascular] explode all trees	57
#2	(Glaucomas, Neovascular or Neovascular Glaucoma or Neovascular Glaucomas or Glaucoma, Neovascular OR NVG):ti,ab,kw (Word variations have been searched)	355
#3	(iris neovascularization or chamber angle neovascularization or refractory glaucoma):ti,ab,kw (Word variations have been searched)	277
#4	#1 or #2 or #3	534
#5	(Bevacizumab or Conbercept or ranibizumab or Aflibercept or Vascular Endothelial Growth Factor or VEGF):ti,ab,kw (Word variations have been searched)	13992
#6	MeSH descriptor: [Bevacizumab] explode all trees	2242
#7	(Mvasi or Avastin or Bevacizumab-awwb or Bevacizumab awwb):ti,ab,kw (Word variations have been searched)	912
#8	MeSH descriptor: [Ranibizumab] explode all trees	965
#9	(Lucentis or V2, RhuFab or RhuFab V2):ti,ab,kw (Word variations have been searched)	446
#10	MeSH descriptor: [Vascular Endothelial Growth Factor A] explode all trees	1394
#11	#5 or #6 or #7 or #8 or #9 or #10	14064
#12	MeSH descriptor: [Randomized Controlled Trial] explode all trees	118

#13 (Randomized Controlled Trial or randomly or randomized) (Word variations have been searched) 1345977

#14 #12 or #13 1324842

#15 #4 and #11 and #14 117

C. Web of Science(n=167), ClinicalTrials.gov (n=38), ISRCNT (n=20)

D. Chinese databases: the China Science Periodical Database (the Wanfang Database, n=213), the China National Knowledge Infrastructure (n=143), VIP journal integration platform (n=133) and China Biology Medicine database (n=127)

using the following keywords: Neovascular Glaucoma, NVG, refractory glaucoma, iris neovascularization, chamber angle neovascularization, Bevacizumab, Conbercept, ranibizumab, Aflibercept, Vascular Endothelial Growth Factor, VEGF and rand

2, The characteristics of the included studies in this network meta-analysis

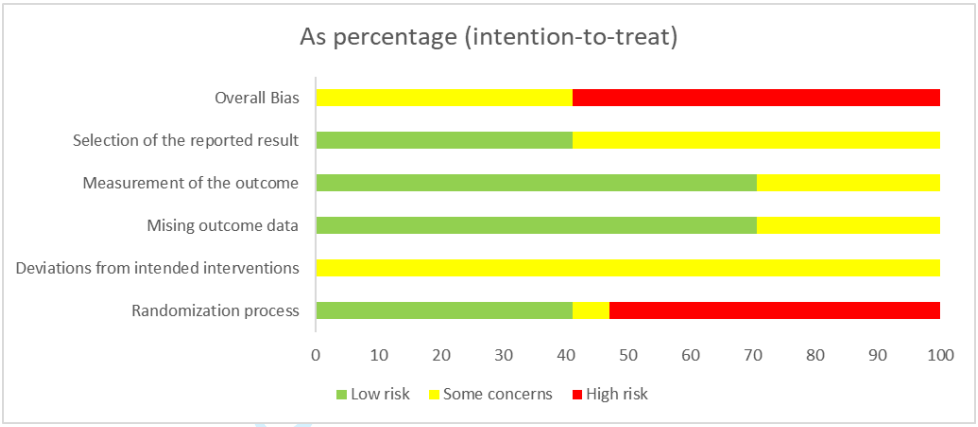
The characteristics of the included studies												
Author	Year	Region	Bias	Age (MD±SD)	Sample		Gender	Primary disease		Intervention	Other therapy	Follow-up	outcome
					P	E	Male/Female	RVO	DR				
Zhou et al	2016	China	High	45.15±2.47	57	57	31/26	26.32%	59.65%	Blank-IVR	PRP+Trab(MMC)	6M	a,b,c,d,e
Yan et al	2019	China	Some	57.76±4.42	80	80	45/35	NA	NA	Blank-IVR	PRP+CPC	6M	a,b,d,e
Guo et al	2021	China	High	61.59±17.32	160	160	92/68	24.38%	65%	IVC-IVR	PRP+Trab(MMC)	12M	a,b,e
Arcieri et al	2014	Brazil	Some	60.83±10.09	40	40	24/16	47.5%	52.5%	Blank-IVB	PRP+AGV	24M	a,b,c,e
Yazdani et al	2007	Iran	Some	60±14.9	26	26	21/5	34.62%	61.54%	Blank-IVB	PRP+Surgery (Type unknown)	6M	a,b,d,e
Bai et al	2022	China	Some	64.2	74	81	51/23	38.3%	61.7%	IVC-ICC	PRP+Trab(MMC) PRP	6M	a, b, e
Xu et al	2015	China	High	52.94±2.52	37	37	26/11	45.95%	48.65%	Blank-IVR	PRP+CPC	6M	a, e
Guo et al	2017	China	Some	53.32±5.89	68	68	48/20	77.94%	14.71%	IVC-IVR	PRP+Trab(MMC)	12M	a,b,c,d,e
Li et al	2020	China	High	58.6±2.34	90	90	54/36	NA	NA	Blank-IVC	PRP+Trab(MMC)	3M	a, b, c
Zhang et al	2020	China	High	62.59±10.49	106	106	55/51	48.33%	51.67%	IVC-ICCIVC	PRP+Trab(MMC) PRP	12M	a, b, d

Xi et al	2018	China	High	53.96±2.23	74	82	39/35	35.14%	25.68%	Blank-IVR	PRP+CPC	3M	a, c
Feng et al	2018	China	High	54.9±8.3	38	40	22/16	32.5%	67.5%	Blank-IVR	PRP+CPC	6M	a,b,c,e
Mahdy et al	2012	Egypt	High	55.5±3.18	40	40	23/17	20%	77.5%	Blank-IVB	PRP+AGV	18M	a,b,c,d
Gou et al	2020	China	Some	53.5±5.92	50	50	27/23	0	100%	Blank-IVC	PRP	9M	f
Lin et al	2017	China	Some	45.92±6.49	176	242	93/83	NA	NA	Blank-IVR	PRP	1M	f
Deng et al	2018	China	High	57.87±4.96	93	93	50/43	27.96%	63.44%	Blank-IVR	PRP	1M	f
Wittström et al	2011	Sweden	High	78.4±8	19	19	7/12	100%	0	Blank-IVB	PRP	6M	f

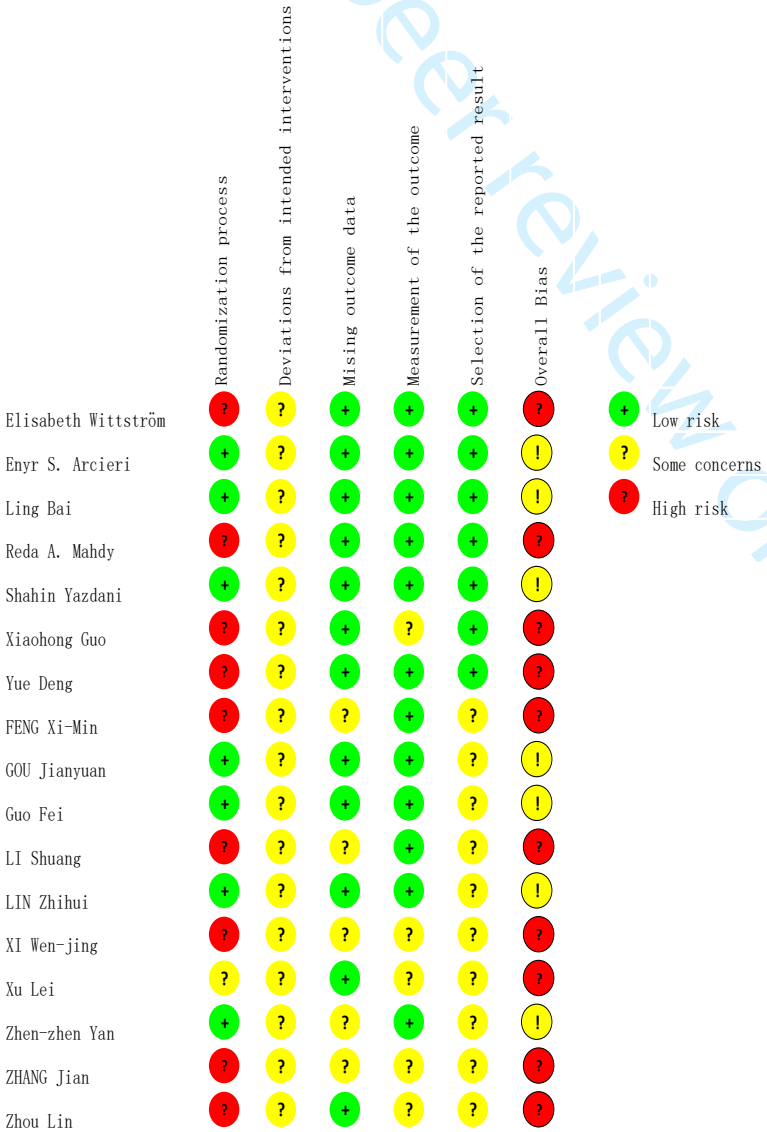
NA=not available; RVO=retinal vein occlusion; DR=diabetic retinopathy; P=people; E=eye; M=month; Trab (MMC)= trabeculectomy with mitomycin;AGV=Ahmed glaucoma valve;CPC=cyclophotocoagulation;PRP=panretinal photocoagulation;(a) IOP 1month, (b) complications, (c) success rate, (d) visual retention rate, (e) IOP 6months, (f) non-surgical IOP 1month; Blank=blank control group; IVC =intravitreal injection of conbercept; IVR=intravitreal injection of ranibizumab; IVB=intravitreal injection of bevacizumab; ICC=intracameral injection of conbercept; ICCIVC=simultaneous intravitreal and intracameral injection of conbercept.

3, Risk of bias assessment (the revised Cochrane risk-of-bias tool for randomized trials (RoB2))

Risk of bias graph



Risk of bias summary: it is a summary table of review authors' judgments for each risk of bias entriy for each study



4, Results from pairwise meta-analysis for each outcome: numbers, estimates and heterogeneity

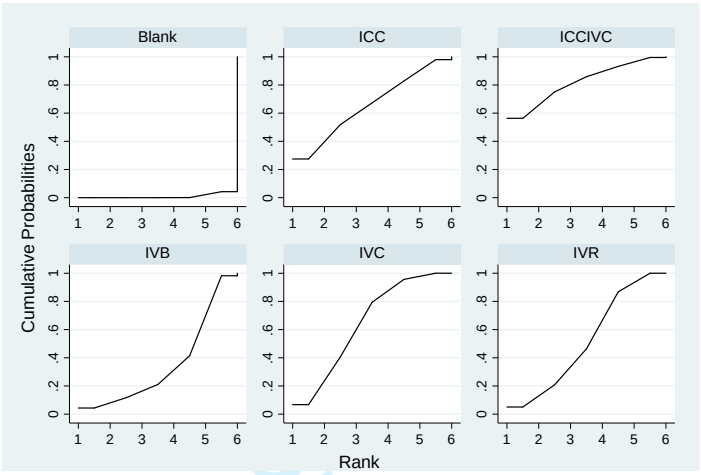
IOP 1month								
study	**I^2**	**τ^2**	**MD**	**LL**	**UL**	**P**	**NO.(i)**	**sample**
Blank vs IVR	99%	24.86	7.28	2.83	11.74	**0.001**	5	296
Blank vs IVB	76.4%	10.39	5.37	0.87	9.88	**0.019**	3	106
Blank vs IVC	NA	NA	10.50	8.83	12.17	**0.000**	1	90
IVC vs IVR	0	0	-0.25	-1.50	1.01	0.701	2	228
IVC vs ICC	NA	NA	0.53	-2.22	3.28	0.705	1	41
IVC vs ICCIVC	NA	NA	2.71	1.08	4.34	**0.001**	1	60
complications								
study	**I^2**	**τ^2**	**OR**	**LL**	**UL**	**P**	**NO.(i)**	**sample**
Blank vs IVR	78.9%	2.41	5.12	0.67	39.15	0.115	3	177
Blank vs IVB	77.9%	3.01	2.59	0.27	25.01	0.412	3	106
Blank vs IVC	NA	NA	1.54	0.24	9.66	0.65	1	90
IVC vs IVR	0	0	0.72	0.39	1.32	0.283	2	228
IVC vs ICC	NA	NA	0.57	0.16	2.07	0.395	1	41
IVC vs ICCIVC	NA	NA	2.68	0.91	7.94	0.075	1	60
Success rate								
study	**I^2**	**τ^2**	**OR**	**LL**	**UL**	**P**	**No.(i)**	**sample**
Blank vs IVR	0	0	0.25	0.10	0.68	**0.006**	3	179
Blank vs IVB	74%	2.61	0.23	0.02	3.01	0.26	2	80
Blank vs IVC	NA	NA	0.24	0.07	0.81	**0.021**	1	90
IVC vs IVR	NA	NA	3.09	0.12	78.55	0.494	1	68

IVC vs ICC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs ICCIVC	NA	NA	NA	NA	NA	NA	NA	NA
Visual retention rate								
study	**I^2**	**τ^2**	**OR**	**LL**	**UL**	**P**	**No.(i)**	**Sample**
Blank vs IVR	0	0	0.41	0.16	1.03	0.056	2	134
Blank vs IVB	73.7%	2.67	0.23	0.02	3.14	0.268	2	66
Blank vs IVC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs IVR	NA	NA	0.32	0.01	8.23	0.494	1	68
IVC vs ICC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs ICCIVC	NA	NA	0.24	0.06	0.99	**0.049**	1	60
IOP 6month								
study	**I^2**	**τ^2**	**MD**	**LL**	**UL**	**P**	**No.(i)**	**sample**
Blank vs IVR	98.2%	41.28	8.42	1.97	14.86	**0.011**	4	214
Blank vs IVB	56.7%	21.70	2.46	-5.62	10.54	0.551	2	66
Blank vs IVC	NA	NA	NA	NA	NA	NA	NA	NA
IVC vs IVR	0	0	-0.48	-1.69	0.73	0.436	2	228
IVC vs ICC	NA	NA	1.04	-0.31	2.39	0.132	1	41
IVC vs ICCIVC	NA	NA	NA	NA	NA	NA	NA	NA
Non-surgery IOP 1month								
study	**I^2**	**τ^2**	**MD**	**LL**	**UL**	**P**	**No.(i)**	**sample**
Blank vs IVR	99%	26.17	13.54	6.41	20.66	**0.000**	2	335
Blank vs IVB	NA	NA	0.30	-9.98	10.58	0.95	1	19
Blank vs IVC	NA	NA	5.24	2.64	7.84	**0.000**	1	50
IVC vs ICC	NA	NA	1.81	-0.09	3.71	0.062	1	40

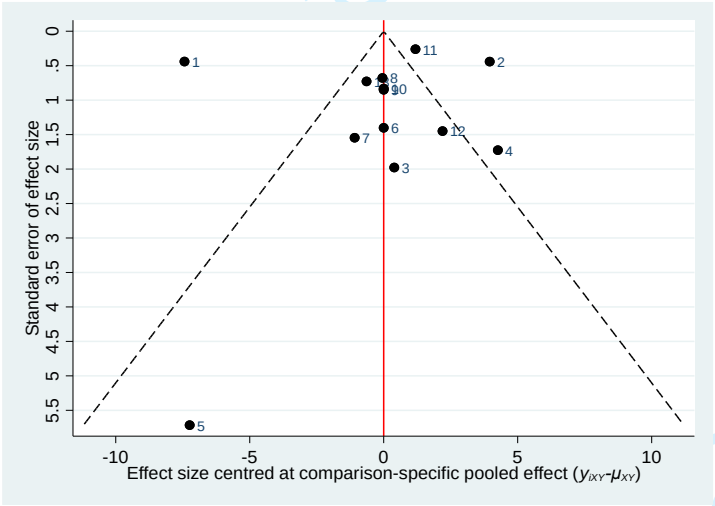
IVC vs ICCIVC	NA	NA	3.33	1.45	5.21	**0.001**	1	46

No.(i)= the number of interventions

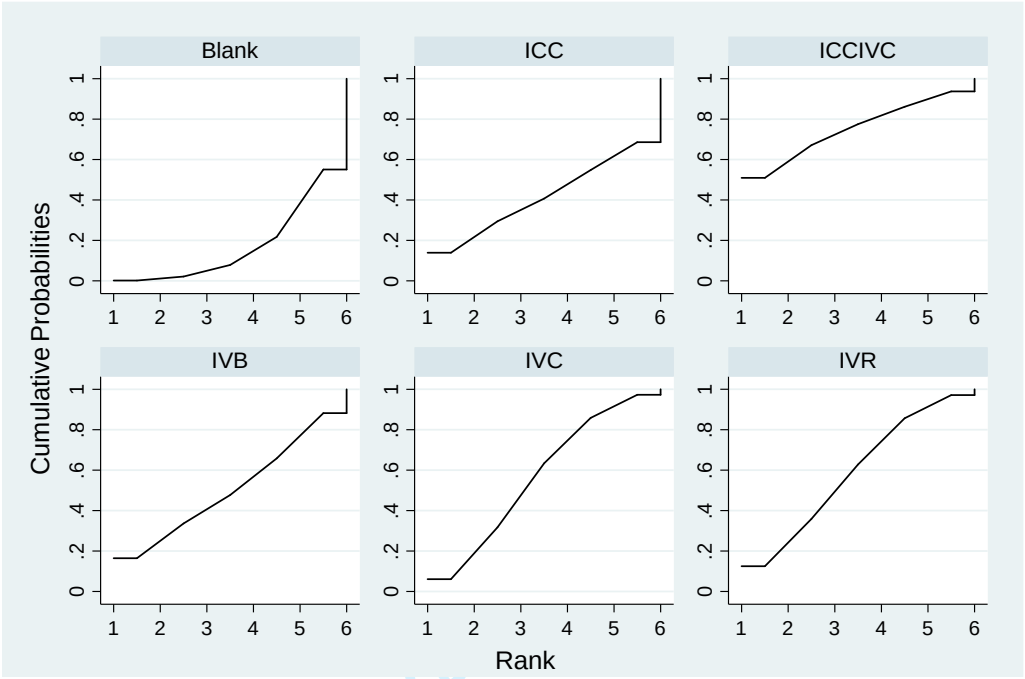
5a-Plots of SUCRA for the primary efficacy outcome (IOP at 1 month), the larger the area under the curve, the higher the ranking.



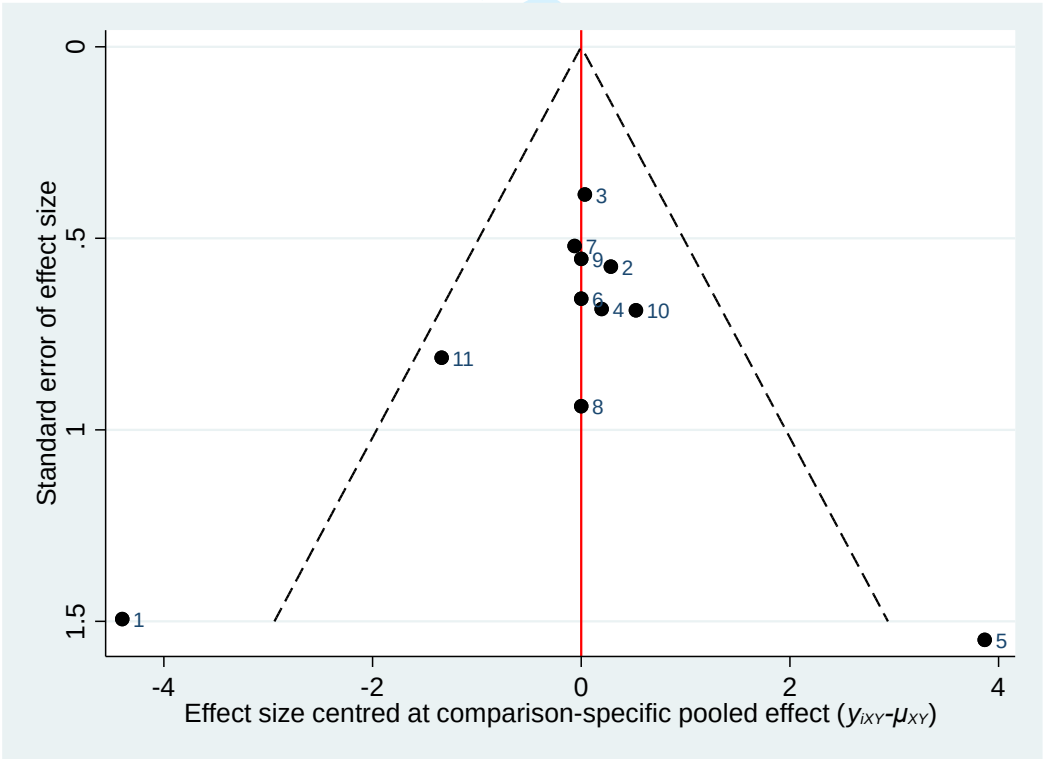
5b-Comparison-adjusted funnel plot for the primary efficacy outcome (IOP 1month) from the network meta-analysis



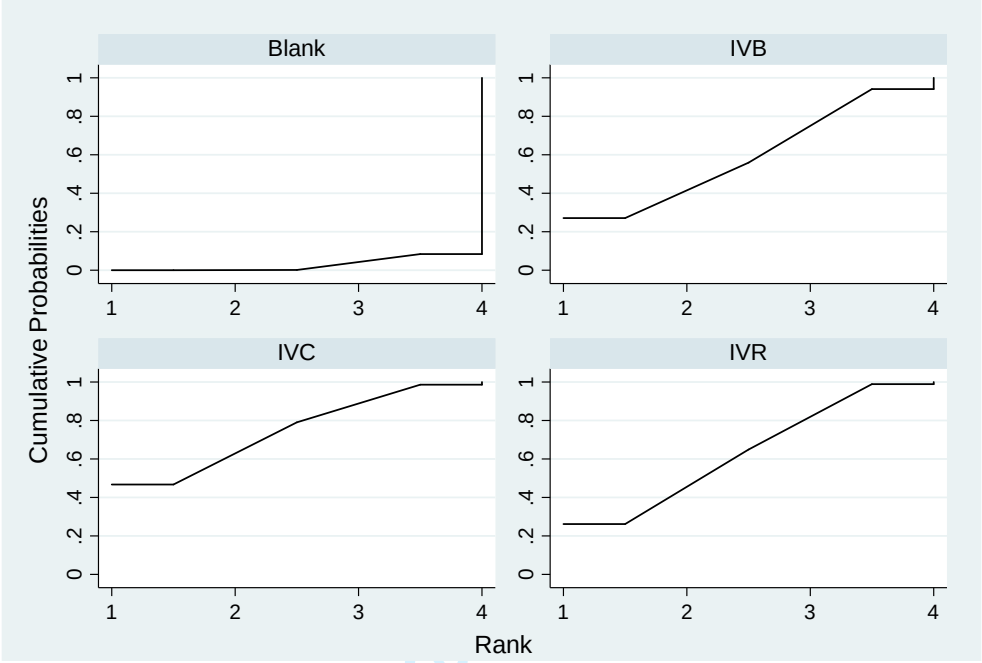
6a-Plots of SUCRA for the primary safety outcome (complications), the larger the area under the curve, the higher the ranking.



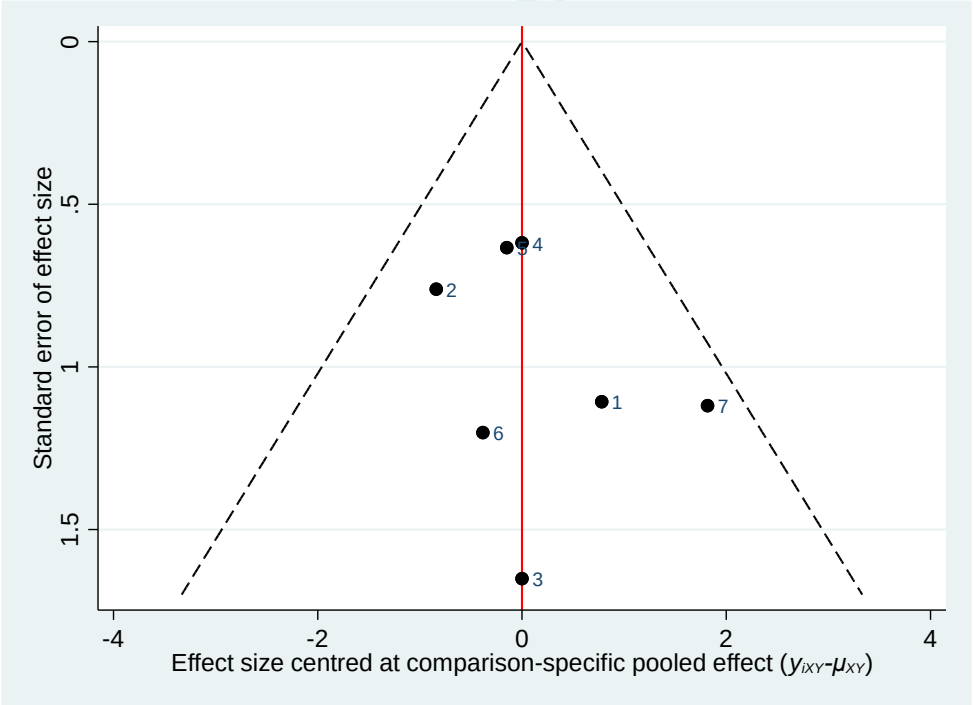
6b-Comparison-adjusted funnel plot for the primary safety outcome (complications) from the network meta-analysis



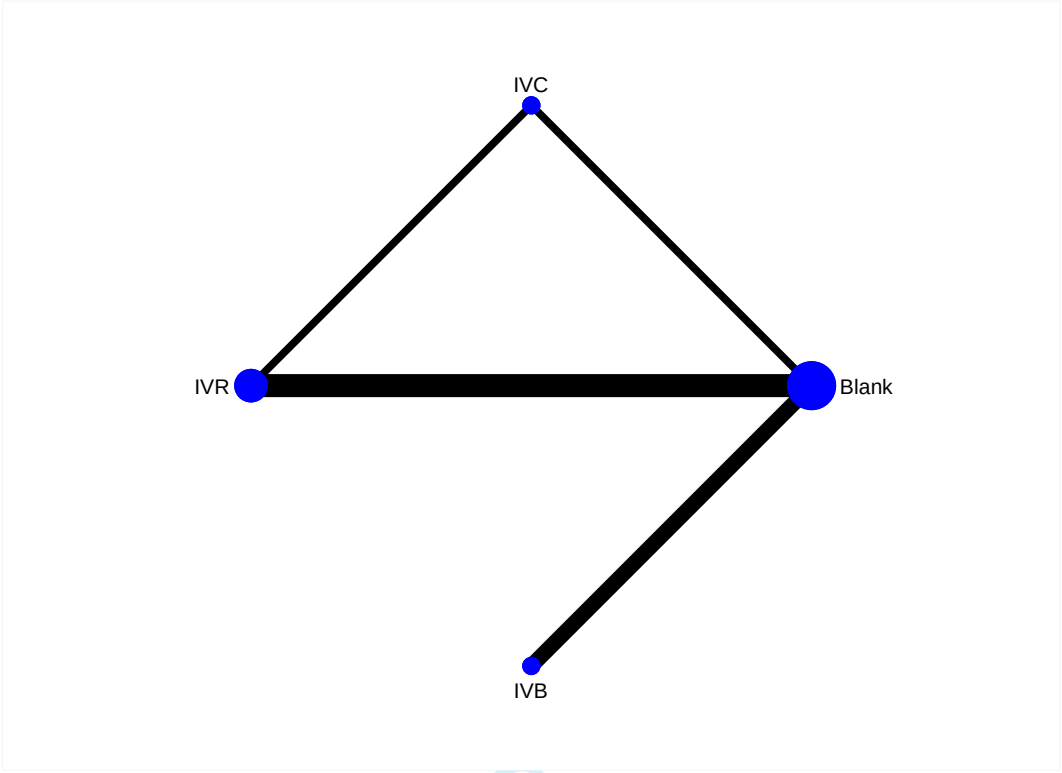
7a-Plots of SUCRA for the secondary efficacy outcomes (success rate), the larger the area under the curve, the higher the ranking.



7b-Comparison-adjusted funnel plot for the secondary efficacy outcomes (success rate) from the network meta-analysis



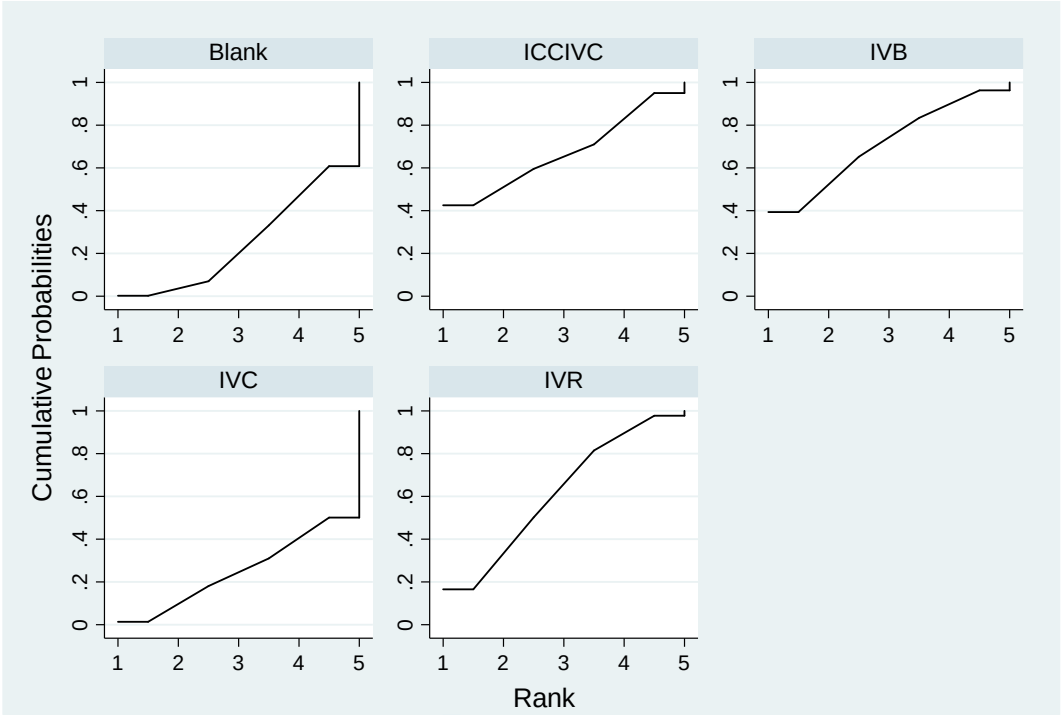
7c-Network plot of available treatment comparisons for the secondary efficacy outcomes (success rate).



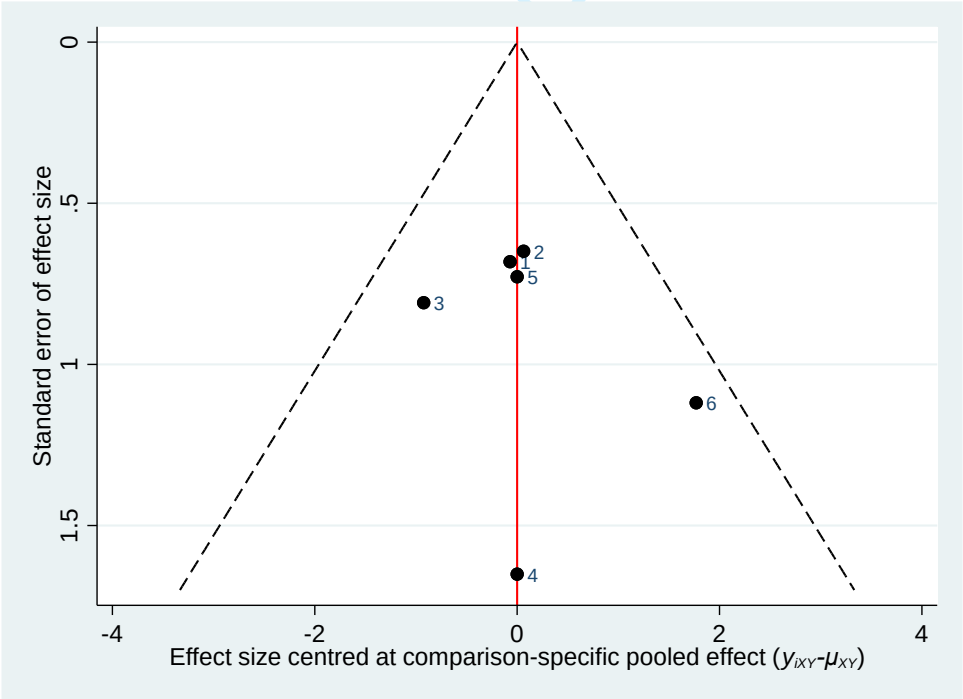
7d-The results of network meta-analysis for the secondary efficacy outcomes (success rate).

IVC	0.32(0.013,8.33)	NA	***4.17(1.23,14.29)***
0.47(0.00,12.28)	IVR	NA	***4(1.47,10)***
0.60(0.00,49.75)	1.31(0.03,125.9)	IVB	4.35(0.33,50)
8.20(0.40,1177)	3.83(0.24,43.69)	4.99(0.22,164)	Blank

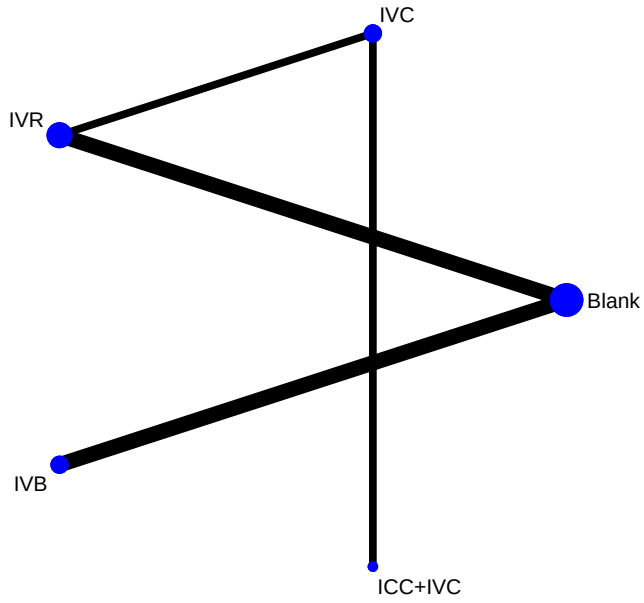
8a-Plots of SUCRA for the secondary efficacy outcomes (visual retention rate), the larger the area under the curve, the higher the ranking.



8b-Comparison-adjusted funnel plot for the secondary efficacy outcomes (visual retention rate) from the network meta-analysis



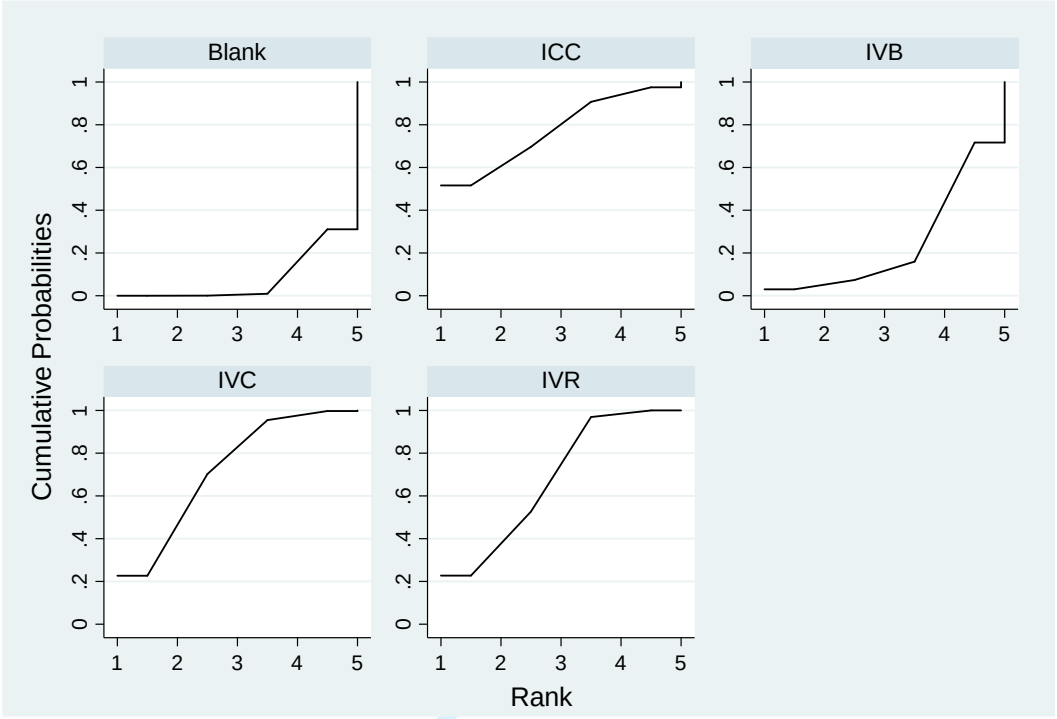
8c-Network plot of available treatment comparisons for the secondary efficacy outcomes (visual retention rate).



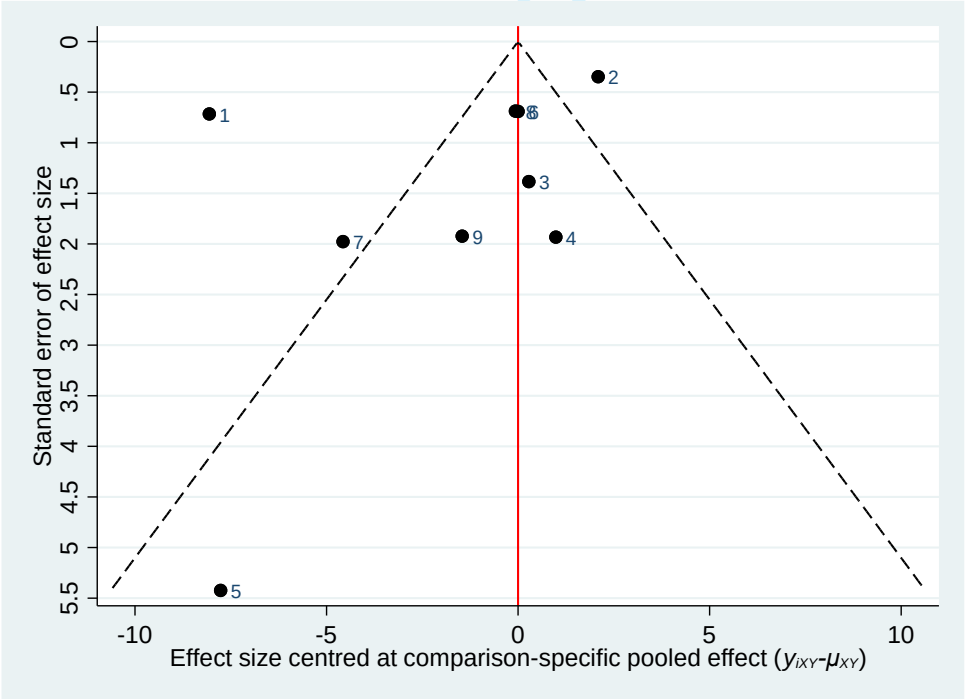
8d-The results of network meta-analysis for the secondary efficacy outcomes (visual retention rate).

IVC	***4.17(1.01,16.67)***	NA	3.13(0.12,100)	NA
4.20 (0.59,29.91)	ICCIVC	NA	NA	NA
1.26 (0.03,53.55)	3.33 (0.05,228.84)	Blank	2.44(0.97,6.25)	4.35(0.32,50)
3.09 (0.09,102.86)	1.36 (0.02,75.54)	2.45 (0.65,9.22)	IVR	NA
4.70 (0.08,291.49)	1.12 (0.01,108.11)	3.73 (0.66,20.93)	1.52 (0.17,13.44)	IVB

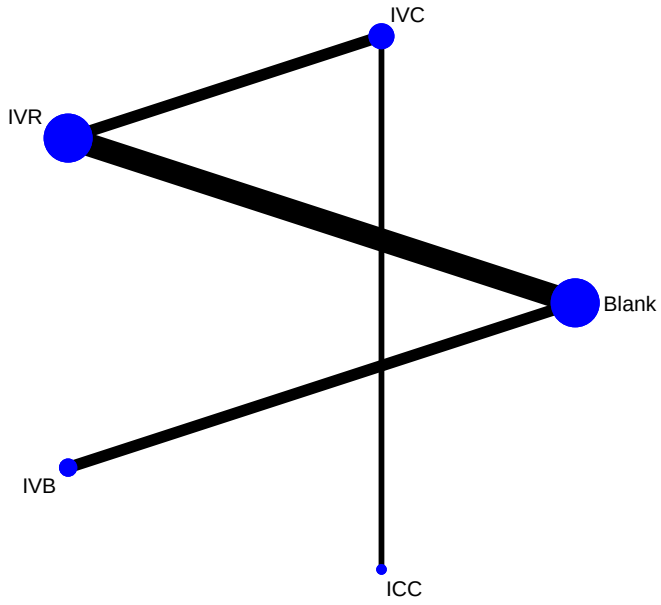
9a-Plots of SUCRA for the secondary efficacy outcomes (IOP at 6 months), the larger the area under the curve, the higher the ranking.



9b-Comparison-adjusted funnel plot for the secondary efficacy outcomes (IOP at 6 months) from the network meta-analysis



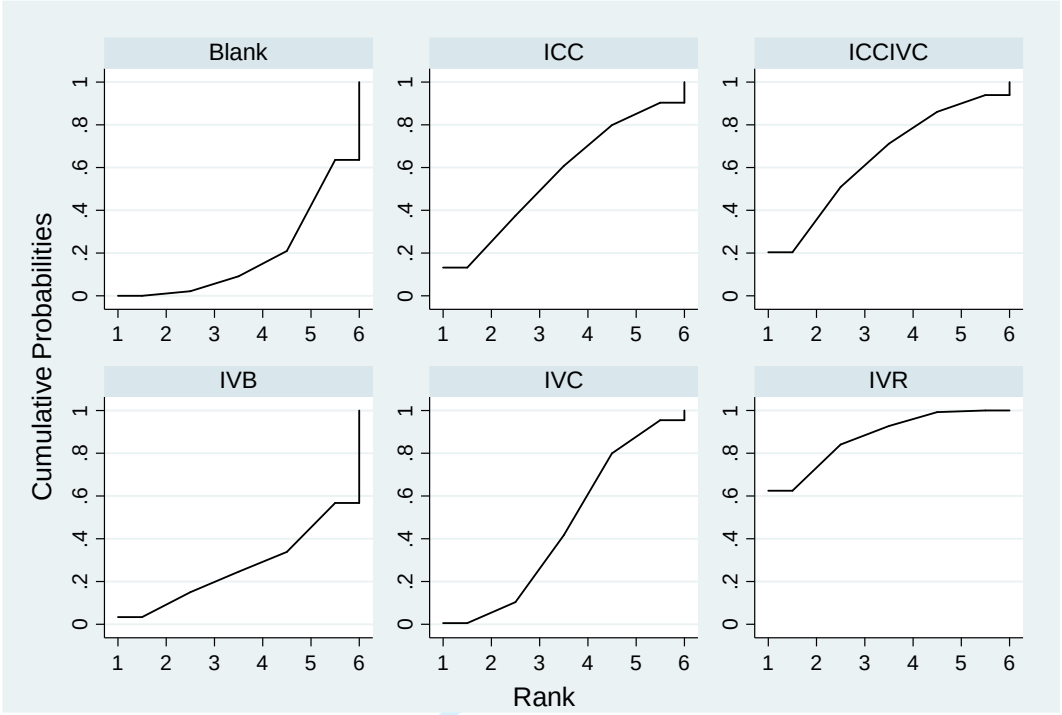
9c-Network plot of available treatment comparisons for the secondary efficacy outcomes (IOP at 6 months).



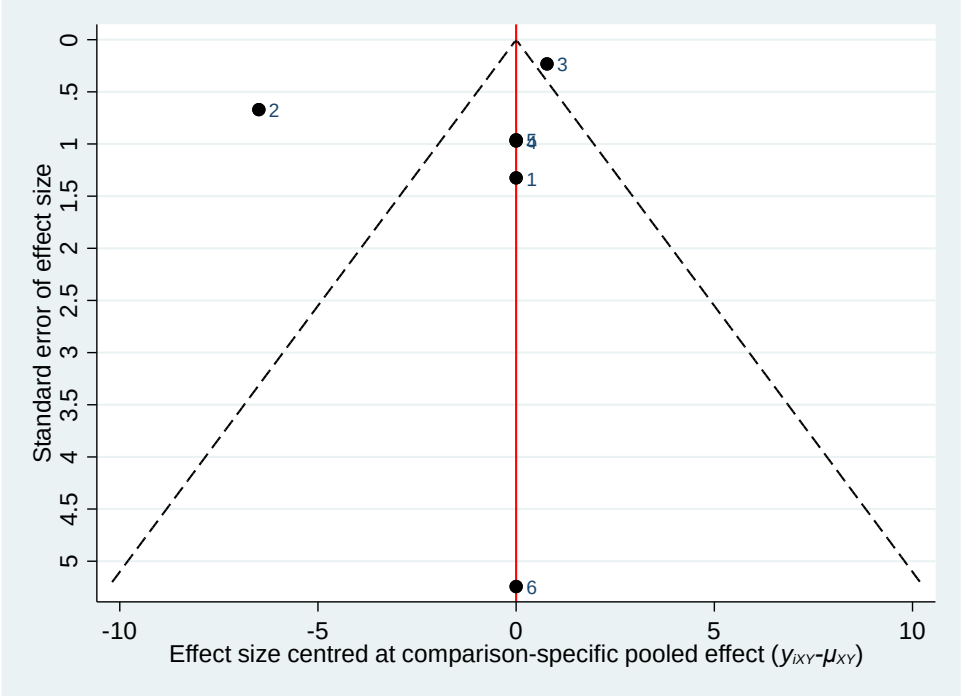
9d-The results of network meta-analysis for the secondary efficacy outcomes (IOP at 6 months).

ICC	-1.04(-2.39,0.31)	NA	NA	NA
-1.02(-8.78,6.70)	IVC	0.48(-0.73,1.69)	NA	NA
-1.59(-11.12,7.92)	0.57(-4.99,6.14)	IVR	NA	***-8.42(-14.86,-1.97)***
-7.90(-20.2,4.76)	6.88(-3.08,16.58)	6.31(-1.95,14.30)	IVB	-2.46(-10.54,5.62)
-9.95(-20.29,0.39)	***-8.94(-15.8,-2.08)***	***-8.37(-12.42,-4.35)***	-2.06(-9.25,4.90)	Blank

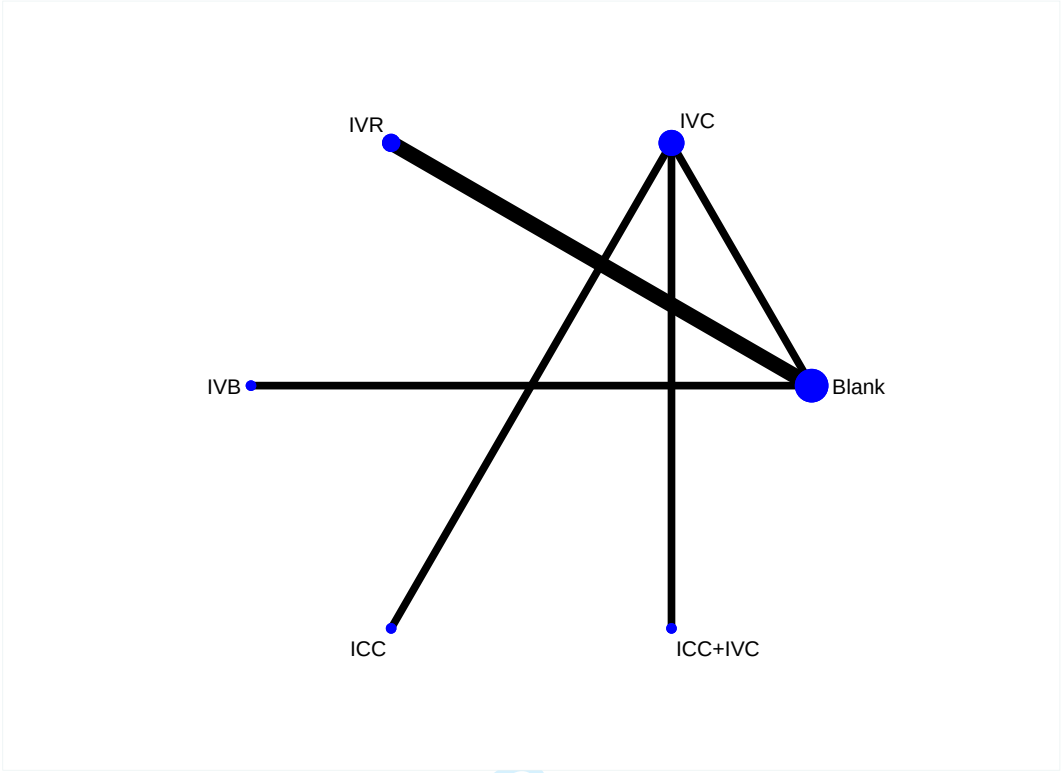
10a-Plots of SUCRA for the secondary outcomes (non-surgical IOP at 1 month), the larger the area under the curve, the higher the ranking.



10b-Comparison-adjusted funnel plot for the secondary outcomes (non-surgical IOP at 1 month) from the network meta-analysis



10c-Network plot of available treatment comparisons for the secondary outcomes (non-surgical IOP at 1 month).



10d-The results of network meta-analysis for the secondary outcomes (non-surgical IOP at 1 month).

IVR	NA	NA	NA	NA	***-13.54(-20.66,-6.41)***
4.99(-7.55，17.57)	ICCIVC	NA	***-3.33(-5.21,-1.45)***	NA	NA
6.51(-5.99，19.07)	-1.51(-12.68，9.66)	ICC	-1.81(-3.71,0.09)	NA	NA
-8.30(-18.06，1.42)	-3.30(-11.19，4.61)	-1.79(-9.66，6.08)	IVC	NA	***-5.24(-7.84,-2.64)***
13.23(-0.46，27.03)	-8.24(-25.20，8.73)	-6.73(-23.69，10.29)	4.94(-10.13，19.90)	IVB	-0.30(-10.58,9.98)
-13.5(-18.98,-8.03)	-8.50(-19.79，2.76)	-6.99(-18.28,4.31)	-5.20(-13.27,2.86)	-0.26(-12.92,12.45)	Blank

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	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).*	***Page 2***
ABSTRACT			***Page 3-4***
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.	
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.*	***Page 5-6***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6 Line 31-36
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.	Page 6 Line 40-52
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).*	***Page 7*** ***Line 24-52***
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.	Page 7 Line 3-20
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement Section 1

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).	Page 8
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.	Page 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 8-9
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.	***Page 9-10***
Risk of bias within 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.	Page 9
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.*	Page 10
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.*	Page 9-10
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.	Page 10
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).	**Page 10 Line 29-33**
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).*	***Page 10-11***

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.	Page 11 Line 30-48
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***Figure 1***
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.	***Page 13-16***
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.	Page 11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 12
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.*	***Page 12-16***
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 comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***Page 12-16***
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.	***Page 16-17***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 13-16
Results of additional analyses	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).	***Page 13-16***
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).	Page 17-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of	Page 21-22

		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).*	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 22 Line 33-47
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.	***Page 23 Line 23-25***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.