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Research Article

Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis

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Abstract

Background: Proliferative diabetic retinopathy is a major cause of sight loss in people with diabetes, with a high risk of vitreous haemorrhage, tractional retinal detachment and other complications. Panretinal photocoagulation is the primary established treatment for proliferative diabetic retinopathy. Anti-vascular endothelial growth factor drugs are used to treat various eye conditions and may be beneficial for people with proliferative diabetic retinopathy.

Objective: To investigate the efficacy and safety of anti-vascular endothelial growth factor therapy for the treatment of proliferative diabetic retinopathy when compared to panretinal photocoagulation.

Methods: A systematic review and network meta-analysis of randomised controlled trials comparing anti-vascular endothelial growth factor (alone or in combination) to panretinal photocoagulation in people with proliferative diabetic retinopathy. The database searches were updated in May 2023. Trials where the primary focus was treatment of macular oedema or vitreous haemorrhage were excluded. Key outcomes were best corrected visual acuity, diabetic macular oedema and vitreous haemorrhage. Individual participant data were obtained and analysed for three large, high-quality trials in combination with published data from other trials. Network meta-analyses of best corrected visual acuity and meta-analyses of other outcomes combined individual participant data with published data from other trials; regression analyses against patient covariates used just the individual participant data.

Results: Twelve trials were included: one of aflibercept, five of bevacizumab and six of ranibizumab. Individual participant data were available from 1 aflibercept and 2 ranibizumab trials, representing 624 patients (33% of the total).

When considered together, anti-vascular endothelial growth factors produced a modest, but not clinically meaningful, benefit over panretinal photocoagulation in best corrected visual acuity, after 1 year of follow-up (mean difference in logarithm of the minimum angle of resolution −0.116, 95% credible interval −0.183 to −0.038). There was no clear evidence of a difference in effectiveness between the anti-vascular endothelial growth factors. The benefit of

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anti-vascular endothelial growth factor appears to decline over time. Analysis of the individual participant data trials suggested that anti-vascular endothelial growth factor therapy may be more effective in people with poorer visual acuity, in those who have vitreous haemorrhage and, possibly, in people with poorer vision generally.
Anti-vascular endothelial growth factor was superior to panretinal photocoagulation at preventing macular oedema after 1 year (relative risk 0.48, 95% confidence interval 0.28 to 0.83) and possibly at preventing vitreous haemorrhage (relative risk 0.72, 95% confidence interval 0.47 to 1.10). Anti-vascular endothelial growth factor reduced the incidence of retinal detachment when compared to panretinal photocoagulation (relative risk 0.41, 95% confidence interval 0.22 to 0.77). Data on other adverse events were generally too limited to identify any differences between anti-vascular endothelial growth factor and panretinal photocoagulation.
Conclusions: Anti-vascular endothelial growth factor has no clinically meaningful benefit over panretinal photocoagulation for preserving visual acuity. However, anti-vascular endothelial growth factor therapy appears to delay or prevent progression to macular oedema and vitreous haemorrhage. The possibility that anti-vascular endothelial growth factor therapy may be more effective in patients with poorer health and poorer vision merits further clinical investigation. The long-term effectiveness and safety of anti-vascular endothelial growth factor treatment are unclear, particularly as additional panretinal photocoagulation and anti-vascular endothelial growth factor treatment will be required over time.
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Background

Diabetes is a major public health issue, affecting over 4 million people in the UK. Diabetic retinopathy is a 'chronic progressive, potentially sight-threatening disease of the retinal microvasculature'[1,2] and is a major form of diabetes-related sight loss, impairing the sight of more than 1700 people in the UK each year.[3] There are several severity stages of diabetic retinopathy, with proliferative retinopathy being the most severe form. It has a high risk of retinal detachment and vitreous haemorrhage, which may result in severe vision loss.[4,5]

In the UK, proliferative diabetic retinopathy (PDR) is usually treated using a form of laser therapy, called panretinal photocoagulation (PRP), where a laser is applied to the retina to prevent the proliferation of new (abnormal) blood vessels. PRP is delivered over the entire periphery of the retina, by placing 1200–1600 burns per session, usually over two or three treatment sessions. PRP is effective and durable[6] but can have adverse effects such as macular oedema and peripheral visual field loss.[7]

Anti-vascular endothelial growth factor (anti-VEGF) drugs are used to treat various eye conditions. Ranibizumab and aflibercept are approved for the treatment of diabetic macular oedema (DMO) in England and Wales[8,9] and have been the main treatment for wet age-related macular degeneration for several years. Anti-VEGF treatments are injected into the eye, under local anaesthetic, typically at monthly intervals. Anti-VEGF has been proposed for the treatment of proliferative retinopathy, prior to the development of macular oedema. It has been suggested that anti-VEGF could better maintain vision than using PRP and may slow the progression of retinopathy and prevent oedema.[10] However, anti-VEGF use may have rare but potentially serious adverse effects (SAEs), such as retinal detachment or cataracts.[11] Concerns have been raised that the benefits of anti-VEGF may not be long-lasting, and so patients might have worse outcomes than with laser photocoagulation without appropriate re-treatment.[12,13]

International Council of Ophthalmology guidelines on diabetic eye care[14] support laser photocoagulation and 'appropriate use of anti-VEGF drugs' for the management of diabetic retinopathy. National Institute for Health and Care Excellence (NICE) guidance on the treatment of diabetic retinopathy in England and Wales is in development but may only recommend anti-VEGF if retinopathy continues to progress after PRP treatment.[15]

As there is now a sizeable body of evidence on the effectiveness of anti-VEGF drugs, a review and analysis of the evidence are needed. In particular, a review of raw data from key trials is important to examine key issues, such as whether the efficacy of anti-VEGF varies with patient characteristics, or changes over time. This systematic review with individual participant data (IPD) meta-analysis aimed to address these issues and fully examine all the current clinical evidence on the use of anti-VEGFs in diabetic retinopathy. This review formed part of a larger project examining the value of anti-VEGF for treating diabetic retinopathy funded by the National Institute for Health Research (Project number NIHR132948). The review is registered on PROSPERO (CRD42021272642) and the full protocol is available online from the NIHR (https://fundingawards.nihr.ac.uk/award/NIHR132948). The larger project also included a review of trials of

anti-VEGF in non-proliferative retinopathy[16] and an economic analysis of the value of anti-VEGF in treating diabetic retinopathy.

Methods

Systematic review

This review was conducted following Centre for Reviews and Dissemination guidance on undertaking systematic reviews[17] and reported according to the principles of the overarching Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18]

Database searches and trial selection

An Information Specialist (HF) designed a preliminary search strategy in Ovid MEDLINE in consultation with the research team. The final MEDLINE strategy was adapted for use in all resources searched. The searches were performed on 27 August 2021 and were updated on 13 July 2022 and again on 26 May 2023. The following databases were searched: Ovid MEDLINE(R) ALL, EMBASE (Ovid), Science Citation Index Expanded (Web of Science), Conference Proceedings Citation Index Science (Web of Science), Cochrane Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Database of Abstracts of Reviews of Effects [Centre for Reviews and Dissemination (CRD)], PROSPERO (CRD) and Epistemonikos. The following trial registries were searched: World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov and the EU Clinical Trials Registry. Full search strategies are presented in *Appendix 1*, *Database search strategies*.

Two researchers (RW, AL) independently screened all titles and abstracts retrieved for consideration of the full text. The reviewers then screened all papers to determine inclusion. Disagreements were resolved through discussion or with a third reviewer (MS).

A data extraction form was developed and piloted. Data on interventions used, patient characteristics, outcomes reported and all outcome data were extracted for all included randomised controlled trials (RCTs) from included publications by one reviewer and checked by a second (RW, AL). Risk of bias in all included trials was assessed by one reviewer and checked by a second using the RoB 2 tool, focusing on the best corrected visual acuity (BCVA) outcomes.[19]

Inclusion criteria

The systematic review included all RCTs that recruited people with diabetic retinopathy (proliferative and non-proliferative); patients with a principal indication for treatment of DMO or vitreous haemorrhage were excluded. The technologies of interest were any anti-VEGF therapy (including aflibercept, bevacizumab or ranibizumab), on its own or in combination with PRP, when compared to PRP.

A full list of outcomes of interest are reported in the review protocol (https://fundingawards.nihr.ac.uk/award/NIHR132948). This paper focuses on the following outcomes: BCVA using a logarithm of the minimum angle of resolution (log-MAR) chart, reported as either log-MAR or Early Treatment Diabetic Retinopathy Study (ETDRS) letter count; and the incidence of DMO and vitreous haemorrhage. Other outcomes, such as adverse events, were included (see *Appendix 4*), but limited data were available, either in the IPD or in publications.

The patient characteristics considered in the IPD analyses were: age, sex, BCVA at randomisation, central subfield thickness (CST) at randomisation, presence of DMO or vitreous haemorrhage at randomisation, prior use of anti-VEGF or PRP and diabetes status [type and glycated haemoglobin (HbA1c) at randomisation]. Grade and severity of retinopathy and presence of tractional retinal detachment were specified in the protocol but could not be analysed as they were not reported consistently in the IPD.

Collection of individual participant data

In accordance with the project protocol (https://fundingawards.nihr.ac.uk/award/NIHR132948), IPD was not sought for every eligible trial. IPD was sought only from those trials considered to be most informative, based on being of larger size and having low risk of bias. After considering all the eligible trials, the project team and advisory group decided to request IPD from trials of aflibercept or ranibizumab, with at least 80 participants. Of the 14 eligible trials that compared anti-VEGF to PRP laser therapy or sham injection, we sought to obtain IPD from the 6 largest trials of aflibercept and ranibizumab, all of which were conducted in the USA or Europe.

Authors of selected trials were contacted to provide IPD. Where IPD was supplied, it was transferred securely to the project team and held on a secure server. Data were recoded to match the pre-specified AVID project data coding, and checked for randomisation quality, internal consistency and consistency with the trial publications.

Statistical analysis

For BCVA, network meta-analyses (NMAs) were performed using standard Bayesian methods of NMA using the R

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package multinma (version 0.5.1, The R Foundation for Statistical Computing, Vienna, Austria).[20] This extends the standard NMA modelling approach to allow joint modelling of IPD and published data, and to investigate the potential impact of patient factors and timing of assessments on the effectiveness of anti-VEGF therapy, and on the ranking of the different treatments.[20]

Network meta-analyses of visual acuity (BCVA) were performed for both log-MAR results and ETDRS letter counts, as both were reported in trials. Published data were transformed from one scale to the other, as required. This article presents results on the log-MAR scale; ETDRS results are reported in the appendices.

Network meta-analyses were performed using the longest follow-up time in each trial up to 1 year, and at exactly 1 year, for trials of at least 1-year's duration. NMAs were also conducted incorporating a linear interaction between change in BCVA and follow-up time, and with an interaction between change in BCVA and BCVA at randomisation. To further investigate the impact of anti-VEGFs on BCVA, two simplified NMAs were performed by combining treatment arms: comparing anti-VEGF (of any type), anti-VEGF (any type) combined with PRP and PRP alone; and comparing aflibercept, ranibizumab (with or without PRP), bevacizumab (with or without PRP) and PRP alone.

The potential impact that future trials could have on the NMAs was investigated using threshold analysis. Threshold analysis investigates where in a NMA results might not be robust to future changes in the observed evidence.[21]

For all other outcomes, there were insufficient data to perform a full NMA. Instead, summary data [such as number of events or mean outcome and its standard deviation (SD) in each trial arm] were extracted from the IPD and combined with equivalent summary data from publications of trials where we did not have IPD, using standard random-effects meta-analysis. These meta-analyses assumed that all types of anti-VEGF had the same effectiveness.

To investigate the impact of patient characteristics on the effectiveness of anti-VEGFs and to further investigate the impact of follow-up time on effectiveness, regression models were fitted using only the trials that supplied IPD. Mixed-effect linear and logistic regression was used to investigate the interactions between anti-VEGF use and all participant characteristics. Repeated-measures models were used to account for multiple assessments per patient over time. Random effects across trials were applied for trial intercept and treatment terms, to account for possible heterogeneity; all other model parameters were fixed effects. For a full description of the IPD models, see the statistical appendix (see *Appendix 6*).

All analyses were conducted in R version 4.3. The R code for all analyses is available via Github (github.com/marksimmondsyork/AVID).

Patient and public involvement

Patient and clinical representatives were involved in all stages of this project as part of our advisory group including: the funding application, protocol development, discussing the review and its findings, and writing this paper. Further patient and stakeholder involvement was engaged through the NICE committee currently developing guidance on diabetic retinopathy management.

Equality, diversity and inclusion

As this was a review project of existing trial data, we could not account for equality issues in this field beyond what was reported in included publications or data. We note that reporting on potential equality areas such as ethnicity or socioeconomics was limited.

Results

Included trials

Figure 1 shows the PRISMA flow chart for this review. Overall, 14 RCTs were included. Excluded studies are listed in *Appendix 1*, *List of excluded studies*. The searches also identified 21 other RCTs, which were unsuitable for meta-analyses. These included trials reported only as conference abstracts, not in English, published before 2011 (and judged to be out of date), or that used types of anti-VEGF not in widespread use. Those trials therefore could not be reasonably included in the NMAs. These are summarised in *Appendix 1*, *Trials in narrative synthesis*.

Individual participant data were available for three trials (CLARITY,[22] PROTEUS[23] and PROTOCOL S[24]) of the six contacted. One trial (PRIDE[25]) was unable to provide IPD at the time of the request, as analyses had not been completed. Two trials recruited patients with non-proliferative retinopathy; both evaluated aflibercept.[19,20] One (PANORAMA[10]) declined to provide IPD as the data holders did not wish data on non-proliferative diabetic retinopathy (NPDR) to be analysed alongside data on PDR, and the other (PROTOCOL W[26]) stated it would make its IPD public later in 2023. As IPD were not available from either of the two trials of patients with NPDR, this article considers only trials of patients with PDR where anti-VEGF was compared to PRP. Results of the NPDR trials have been reported elsewhere.[16]

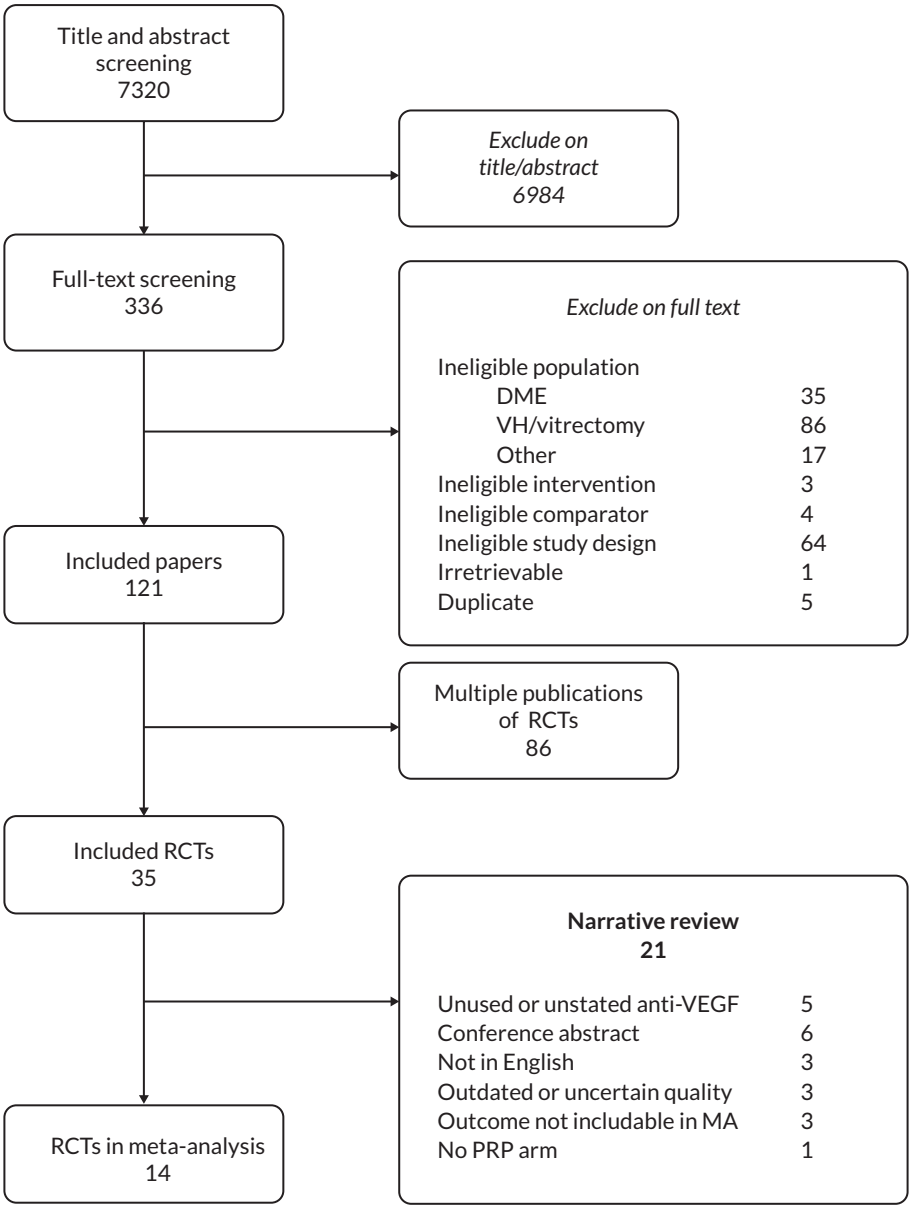

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. DME, diabetic macular oedema; MA, meta-analysis; VH, vitreous haemorrhage.

The 12 included RCTs are summarised in *Table 1*. Trials varied substantially in sample size from only 40 eyes up to just over 300 persons. There were six trials of ranibizumab, five of bevacizumab, and one trial of aflibercept. Five trials used anti-VEGF alone as the intervention, but others used anti-VEGF combined with PRP. Twelve trials were of patients with proliferative retinopathy. Trials of aflibercept and ranibizumab were conducted in Europe, North America or Brazil, and all trials of bevacizumab were conducted in the Middle East or South Asia. BCVA was the only outcome reported consistently in all trials.

The dosing regimens varied across trials and are summarised in *Appendix 2*, *Table 10*. Anti-VEGF was typically given either in a single injection or in three injections (one every 4 weeks). PRP was usually given in two sessions at time of randomisation, and not repeated. Grounds for additional treatment with either anti-VEGF or PRP at later follow-up times varied substantially across trials, and was usually based on clinical judgement of progression of retinopathy.

Risk of bias

For the risk-of-bias assessment of the included trials, see *Appendix 1*, *Risk-of-bias assessment*. The trials varied in their potential risk of bias. Where possible and appropriate, IPD provided by the trialists informed the risk-of-bias assessment. Overall, two trials were classed at low risk of bias, three moderate and seven at

TABLE 1 Properties of the included trials

Trial	Year	Anti-VEGF	Comparator	Location	Sample size	Population	Duration	IPD inclusion
CLARITY[22]	2017	Aflibercept	PRP	UK	232 persons	PDR	1 year	Included
DRCRN PROTOCOL S[27,28]	2018	Ranibizumab	PRP	USA	305 persons	PDR	5 years	Included
Ferraz[29]	2015	Ranibizumab + PRP	PRP	Brazil	60 eyes	PDR	6 months	Not sought
PRIDE[25]	2019	Ranibizumab + PRP	PRP	Germany	106 persons	PDR	1 year	Unavailable
PROTEUS[23]	2018	Ranibizumab + PRP	PRP	Europe	87 persons	PDR	1 year	Included
Sao Paulo B[30]	2011	Ranibizumab + PRP	PRP	Brazil	40 persons	PDR	1 year	Not sought
Sao Paulo A[31]	2018	Ranibizumab + PRP, ETRDS	Ranibizumab + PRP, PASCAL	Brazil	40 eyes	PDR	1 year	Not sought
Marashi[32]	2017	Bevacizumab	PRP	Jordan/Syria	30 persons	PDR	1 year	Not sought
Ahmad[33]	2012	Bevacizumab (+ PRP)	PRP	Pakistan	54 eyes	PDR	3 months	Not sought
Ali[34]	2018	Bevacizumab (+ PRP)	PRP	Pakistan	60 eyes	PDR	1 month	Not sought
Rebecca[35]	2021	Bevacizumab (+ PRP)	PRP	Pakistan	76 eyes	PDR	6 months	Not sought
Roohipour[36]	2016	Bevacizumab (+ PRP)	PRP	Iran	64 eyes	PDR	10 months	Not sought

DRCRN, Diabetic Retinopathy Clinical Research Network.

high risk of bias. Risk of bias across individual domains was predominately of 'some concerns', primarily due to poor reporting, although larger trials tended to be better reported. Concerns were most common for the outcome measurement domain, due to the lack of masking of participants and outcome assessors. Other concerns included limited description of randomisation and allocation concealment processes, and missing participants and outcome data. The direction of bias was generally unpredictable. Overall, all the trials of bevacizumab were judged to be at high risk of bias. This was a key factor in our decision to request IPD only from the aflibercept and ranibizumab trials.

Network meta-analysis of vision (best corrected visual acuity)

We first consider the analyses combining IPD with published aggregate data from trials where IPD were not available. For full results of these analyses, see *Appendix 2* and *Appendix 3*.

Two NMAs of BCVA were performed: one including the longest follow-up in all trials, up to 1 year, to include all trials. The second analysis included only follow-up at exactly or almost exactly 1 year (defined as 45–60 weeks follow-up), to exclude trials of very short duration. As only one trial (PROTOCOL S) reported outcomes beyond 1 year, NMAs with longer follow-up times were not feasible. The network diagram for the analysis at longest follow-up up to 1 year is shown in *Figure 2*. The green lines show the trials where IPD were available; blue lines represent trials where published data were used. For the diagram at exactly 1 year, see *Appendix 2*, *Analyses at exactly 1 year follow-up*.

Figure 3 shows the results of all treatment comparisons from the NMA for data up to 1 year, and *Figure 4* for data at exactly 1 year. In both figures, negative relative effects (to the left of the vertical line) indicate favouring the first-named intervention. For the primary comparisons with PRP, all anti-VEGF agents favour anti-VEGF over PRP and improved vision. Reductions in log-MAR when

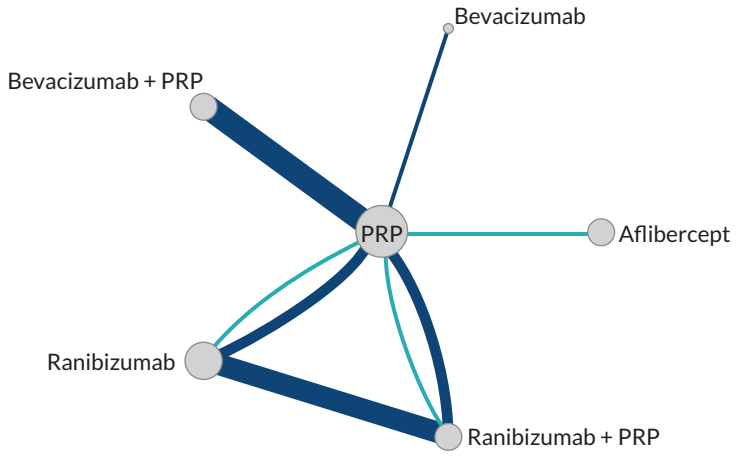

FIGURE 2 Network diagram at up to 1 year of follow-up.

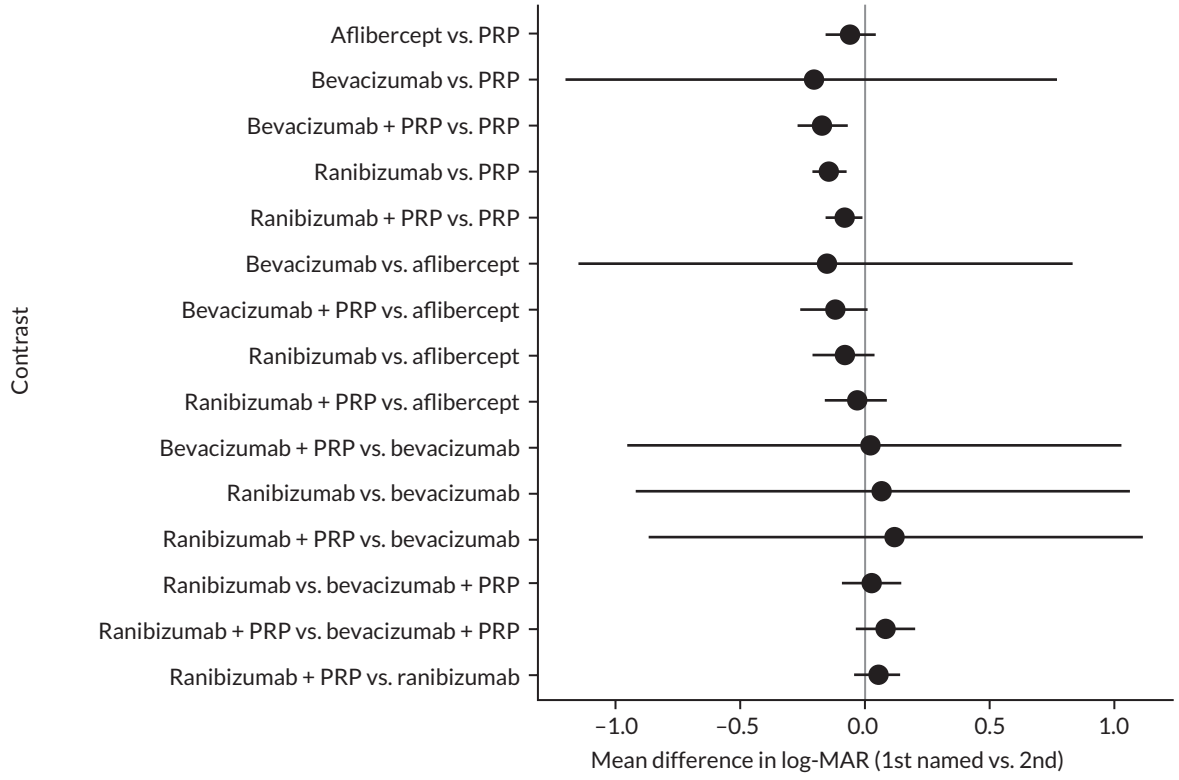

FIGURE 3 Comparison of interventions from NMA of BCVA up to 1 year. Note: Points on left-hand side of the plot favour the first-named treatment.

compared to PRP ranged from −0.055 (or 2.6 ETDRS letters) for aflibercept to −0.172 (or 6.8 ETDRS letters) for bevacizumab with PRP. However, for aflibercept no difference between aflibercept and PRP remains within the credible interval (CrI). Results are broadly similar across anti-VEGF agents in both analyses. Results for bevacizumab (without PRP) are inconclusive because of the very limited data on this treatment group. Indirect comparisons between anti-VEGFs found no conclusive evidence that any one anti-VEGF was superior to the others. Heterogeneity across the network appeared to be modest, with an estimated heterogeneity standard error (τ) of 0.04 (95% CrI 0 to 0.12). For full results of both analyses, see *Appendix 2*, *Analyses at up to 1 year of follow-up* and *Analyses at exactly 1 year follow-up*.

Impact of follow-up time and vision at randomisation

A NMA was fitted to allow the effectiveness of anti-VEGFs to vary with follow-up time in each trial and with BCVA at randomisation, using the individual baseline BCVA scores for the IPD alongside the

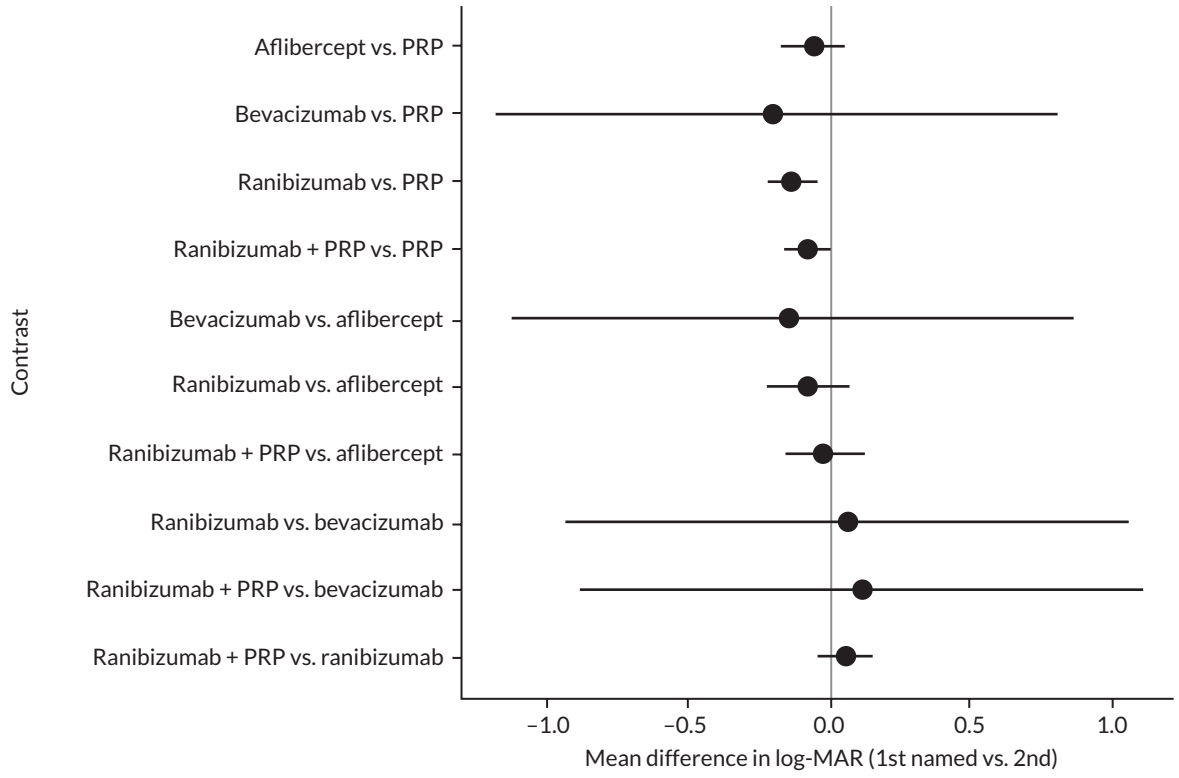

FIGURE 4 Comparison of interventions from NMA of BCVA at exactly 1 year. Note: Points on left-hand side of the plot favour the first-named treatment.

trial-level averages from published data where IPD were unavailable. The results of this analysis are shown in *Figure 5* at 1 year of follow-up and the average baseline BCVA across IPD trials (which was 75 ETDRS letters). Effect estimates are broadly similar for this analysis as for the unadjusted analyses in *Figure 4*. Improvements in log-MAR scores when compared to PRP ranged from −0.067 for bevacizumab with PRP to −0.112 for ranibizumab. However, confidence intervals (CIs) are wider, generating uncertainty as to the effectiveness of anti-VEGFs. We note that the relative effect of aflibercept compared to PRP is larger than in previous analyses (e.g. *Figure 3*), and for bevacizumab it is smaller, perhaps because most bevacizumab trials were of short duration and mostly recruited patients with poorer vison, while the CLARITY trial of aflibercept included patients with generally good vison at randomisation.

The analysis found no conclusive evidence that the effectiveness of anti-VEGF varied with time (up to 1 year). There was evidence that anti-VEGFs were more effective at preserving vision in people with poorer BCVA at randomisation (by 0.42 ETDRS letters per letter worse at randomisation, 95% CrI 0.33 to 0.49). There was evidence of some residual heterogeneity ($\tau = 0.08$, 95% CrI 0 to 0.21), so follow-up duration and BCVA at randomisation do not appear to fully account for the heterogeneity.

Further network meta-analyses of best corrected visual acuity

To further investigate the impact of anti-VEGFs on BCVA, two simplified NMAs were performed by combining treatment arms. Both incorporated interactions with time and BCVA at randomisation:

1. Comparing anti-VEGF (of any type), anti-VEGF (any type) combined with PRP and PRP alone.
2. Comparing aflibercept, ranibizumab (with or without PRP), bevacizumab (with or without PRP) and PRP alone.

Results for these NMAs are presented in *Table 2* and given in full in *Appendix 2*, *Network meta-analyses of reduced networks*. In summary, there was good evidence that, when all types of anti-VEGF were combined, anti-VEGF in general improved BCVA when compared to PRP at 1 year [mean difference (MD) in log-MAR −0.116 (or 4.46 ETDRS letters), 95% CrI −0.183 to −0.038]. When comparing anti-VEGF combined with PRP to anti-VEGF alone, there was no evidence of any difference [MD in log-MAR 0.042 (or −1.47 ETDRS letters), 95% CrI −0.057 to 0.127]. Removing the trials of bevacizumab, which were generally at higher risk of bias, had no substantial impact on the results. When comparing the three anti-VEGFs (with or without concomitant PRP), there was no conclusive evidence of any difference between the three anti-VEGFs.

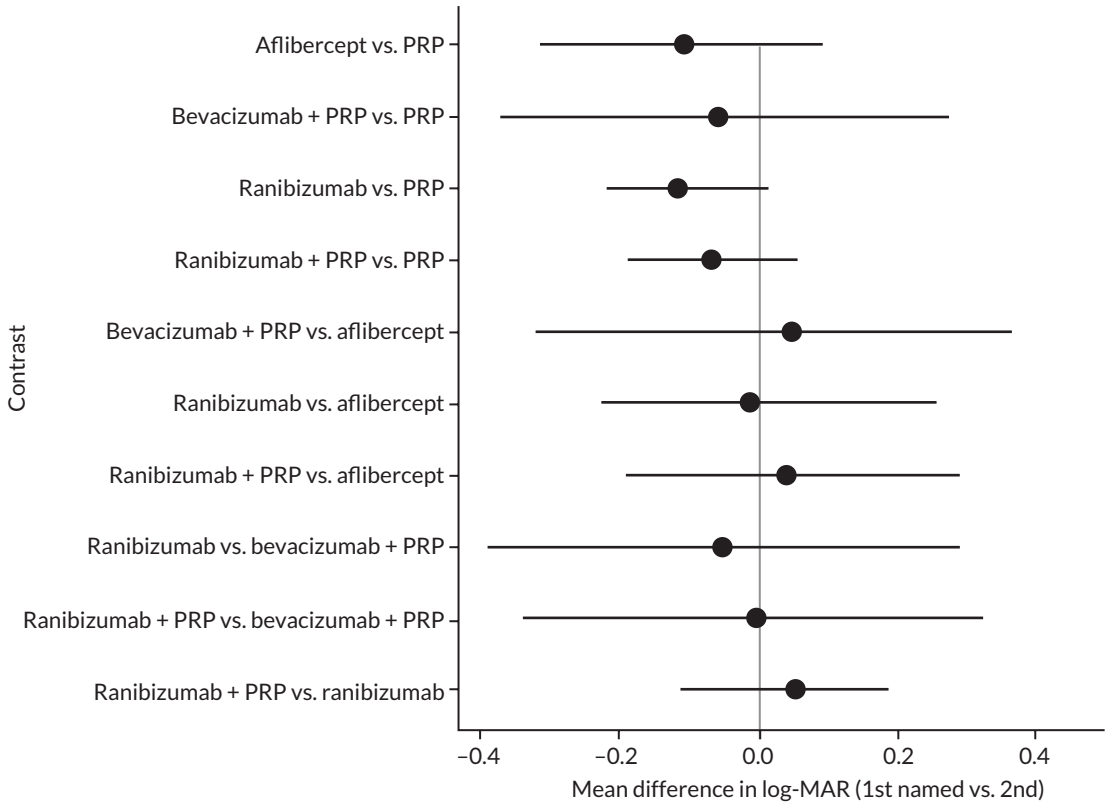

FIGURE 5 Network meta-analysis of log-MAR with adjustment for follow-up time and BCVA at baseline. Note: Points on left-hand side of the plot favour the first-named treatment.

TABLE 2 Results of NMAs of reduced networks (log-MAR BCVA at 1 year follow-up)

Treatment	Comparator	MD	95% CrI
Anti-VEGF (any type) vs. anti-VEGF + PRP ***vs.*** PRP ***alone***			
Anti-VEGF (any)	PRP	−0.116	−0.183 to −0.038
Anti-VEGF + PRP	PRP	−0.074	−0.149 to −0.004
Anti-VEGF + PRP	Anti-VEGF	0.042	−0.057 to 0.127
Anti-VEGF (excluding bevacizumab) vs. anti-VEGF + PRP ***vs.*** PRP ***alone***			
Anti-VEGF *(ranibizumab or aflibercept)*	PRP	−0.117	−0.175 to −0.044
Anti-VEGF + PRP	PRP	−0.068	−0.147 to 0.007
Anti-VEGF + PRP	Anti-VEGF	0.048	−0.049 to 0.132
Aflibercept vs. ranibizumab (with or without PRP) vs. bevacizumab (with or without PRP) vs. PRP			
Aflibercept	PRP	−0.108	−0.310 to 0.090
Bevacizumab	PRP	−0.086	−0.239 to 0.058
Ranibizumab	PRP	−0.091	−0.184 to 0.012
Bevacizumab	Aflibercept	0.023	−0.224 to 0.265
Ranibizumab	Aflibercept	0.017	−0.197 to 0.250
Ranibizumab	Bevacizumab	−0.005	−0.174 to 0.183

Note
Negative MDs favour the treatment over comparator.

Threshold analyses

Results of the threshold analyses to test the robustness of the NMAs are presented in *Appendix 2*, *Threshold analyses*. In general, the threshold analyses found that the ordering of effectiveness of the anti-VEGFs is not robust, given the small differences in effect between the anti-VEGFs and the wide CrIs. This suggests that there is not currently enough robust evidence to conclude if any one of the three anti-VEGFs is superior to the others.

Other outcomes

Results on outcomes other than BCVA were inconsistently reported, with most being reported in no more than three trials. Given limited reporting both in publications and IPD, NMAs were not feasible for these outcomes. *Appendix 4* gives full results for these analyses; forest plots for all outcomes are given in *Appendix 4*, *Forest plots of outcomes*. Analyses were based on number of events reported at exactly 1 year of follow-up, excluding patients with the outcome at randomisation for the IPD trials, so numbers may not exactly match publications of those trials. Meta-analyses could be performed for DMO, vitreous haemorrhage and use of vitrectomy by assuming that all three types of anti-VEGF are equally effective. *Table 3* summarises the results of random-effects meta-analyses of those outcomes. Some data were available for neovascularisation, but mostly from trials where we did not have IPD.

These meta-analyses show that anti-VEGF reduces the incidence of DMO after 1 year by half when compared to using PRP. Using anti-VEGF also appears to reduce the incidence of vitreous haemorrhage by around 28%, but this was not conclusive. It also appears to reduce the need for vitrectomy, but this is uncertain due to the small number of vitrectomies performed and heterogeneity across trials.

Adverse events

As with other non-BCVA outcomes, adverse events were not widely reported, with little consistency across trials as to which adverse events were reported. Full data for all reported adverse events are given in *Appendix 4*, *Adverse event outcomes*. Meta-analyses were performed for adverse event types reported in two or more trials by assuming that the impact of anti-VEGFs is the same for all types of anti-VEGF.

The meta-analysis results are shown in *Figure 6*. Due to the small numbers of events, and limited numbers of trials reported each adverse event, most results are inconclusive. Anti-VEGF appears to reduce the incidence of retinal detachment. For all other adverse event types, there was no conclusive evidence of any difference between anti-VEGFs and PRP, largely because adverse events were too rare to draw any conclusions.

TABLE 3 Random-effects meta-analyses of non-BCVA outcomes

Outcome	No. of trials	No. of events	Relative risk (anti-VEGF vs. PRP)	95% CI	I^2
DMO	4	120	0.48	0.28 to 0.83	29%
Vitreous haemorrhage	6	77	0.72	0.47 to 1.10	0
Vitrectomy	4	18	0.63	0.16 to 2.42	31%

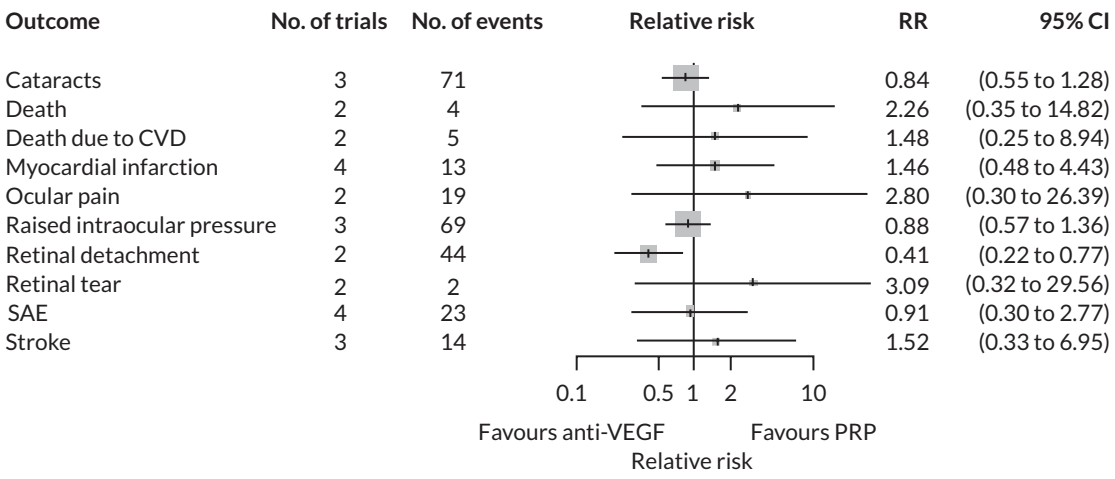

FIGURE 6 Meta-analysis summary for adverse events. CVD, cardiovascular disease; RR, relative risk.

Analysis of individual participant data trials

Individual participant data were available for three trials: PROTOCOL S (ranibizumab vs. PRP, 305 patients), CLARITY (aflibercept vs. PRP, 202 patients), and PROTEUS (ranibizumab + PRP vs. PRP, 87 patients). As the three trials use different types of anti-VEGF, all analyses of the IPD assumed that there was no difference in effectiveness across the different anti-VEGFs. Given the results of the NMAs, this seems to be a reasonable assumption.

As data on BCVA were available at multiple follow-up times, repeated-measures analysis was used to investigate the impact of anti-VEGF on BCVA. Analyses were performed using follow-up times up to 1 year of follow-up (3, 7, 9 and 12 months, to accord with follow-up times in the three trials), all data up to 2 years (every 6 months) and all data up to 5 years (every year after 1 year). As PROTOCOL S was the only trial reporting data beyond 1 year, it dominates analyses at longer follow-up times. Complete results of the combined analysis of the IPD are presented in *Appendix 5*.

Best corrected visual acuity

The potential impact of follow-up duration on the effectiveness of anti-VEGF was investigated by fitting a repeated-measures model with a linear interaction between anti-VEGF effect and follow-up time. Results of these repeated-measures analyses are shown in *Table 4* . All three analyses show that anti-VEGF improves vision when compared to PRP by 0.062–0.074 log-MAR after 1 year, which is equivalent to 3.1–3.7 ETDRS letters. Heterogeneity was modest ($\tau = 0.03$), and similar to heterogeneity observed in the NMAs.

At 1- and 2-year follow-up, there was no evidence that vision varies with follow-up duration, as the time–treatment interaction terms were not statistically significant. However, at 5 years, there was evidence that vision on PRP improves with increasing follow-up duration (−0.013 log-MAR or 0.64 ETDRS letters per year), whereas vision with anti-VEGF declines by comparison (0.037 log-MAR or 1.86 ETDRS letters per year). This would suggest that any benefit in vison with anti-VEGF may be lost within 3 years. This is a consequence of the PROTOCOL S trial finding no evidence of difference between ranibizumab and PRP after 5 years of follow-up (log-MAR 0.02, 95% CI −0.059 to 0.098).

Further analyses were conducted to investigate the impact of protocol-specified patient characteristics on the effectiveness of anti-VEGF. The values of these characteristics at baseline in each trial is reported in *Appendix 5*, *Tables 35* and *36*. A repeated-measures analysis was performed on all data up to 1 year of follow-up, including an interaction between anti-VEGF and the protocol-specified patient covariate. Results are summarised in *Table 5* for the analysis at 1 year of follow-up.

The overall effect of anti-VEGF on BCVA was consistent across analyses, with an improvement in BCVA for anti-VEGF versus PRP or around −0.08 log-MAR (or four ETDRS letters). Statistically significant interactions between anti-VEGF and patient characteristics were identified for the following:

Sex, where men benefit more than women by 0.07 log-MAR (95% CI 0.014 to 0.127, or 3.5 ETDRS letters). Vision at randomisation, where people with poorer vision before treatment have greater benefits from anti-VEGF (by 0.137 log-MAR per whole log-MAR unit at baseline; or 0.14 ETDRS letters per letter poorer at baseline). Vitreous

TABLE 4 Individual participant data repeated-measures analysis of effectiveness of anti-VEGF over time

Follow-up time	Parameter	MD	95% CI
1 year	Anti-VEGF vs. PRP (at 1 year)	−0.074	−0.13 to −0.018
	Time (PRP arm)	−0.005	−0.039 to 0.029
	Time × anti-VEGF interaction	0.007	−0.041 to 0.054
2 years	Anti-VEGF vs. PRP (at 1 year)	−0.073	−0.128 to −0.017
	Time (PRP arm)	−0.003	−0.023 to 0.018
	Time × anti-VEGF interaction	0.014	−0.015 to 0.042
5 years	Anti-VEGF vs. PRP (at 1 year)	−0.062	−0.115 to −0.01
	Time (PRP arm)	−0.013	−0.022 to −0.004
	Time × anti-VEGF interaction	0.037	0.025 to 0.05

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Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

haemorrhage at baseline, where people with haemorrhage benefit more from anti-VEGF (by 0.127 log-MAR, 95% CI 0.058 to 0.197, or 6.4 ETDRS letters). HbA1c, where people with higher HbA1c benefit more from anti-VEGF (by 0.002 log-MAR per unit HbA1c, or 0.1 ETDRS letters).

Some caution is required in interpreting these results, given the number of analyses performed and associated risk of finding false-positive results. Also, when analyses were performed at a follow-up of exactly 1 year, excluding earlier reported times, these treatment–covariate interactions were not statistically significant (see *Appendix 5*, *Analyses of best corrected visual acuity*).

Other outcomes

The IPD were analysed to investigate the effectiveness of anti-VEGF on DMO and vitreous haemorrhage (see *Appendix 5*, *Analyses of other outcomes*). There were insufficient data to perform meta-regressions for any other outcomes. Results were consistent with those from the full data analysis. At 1 year, anti-VEGF reduced DMO incidence when compared to PRP [odds ratio (OR) 0.471, 95% CI 0.254 to 0.874] and was in the direction of reduced incidence of vitreous haemorrhage (OR 0.700, 95% CI 0.408 to 1.199).

As data were available at multiple time points, Cox proportional hazards models were also fitted to the DMO and vitreous haemorrhage data. These found less clear evidence of a benefit of anti-VEGF. For DMO, the hazard ratio for anti-VEGF versus PRP was 0.82 (95% CI 0.60 to 1.17); for vitreous haemorrhage, the hazard ratio was 0.89 (95% CI 0.83 to 1.49).

The impact of patient characteristics on the effectiveness of anti-VEGF was investigated using meta-regression, but models were unreliable, and some did not converge, due to the limited data. Few statistically significant interactions between patient characteristics and anti-VEGF were found for either DMO incidence or vitreous haemorrhage

TABLE 5 Individual participant data meta-regression of anti-VEGF interacting with patient characteristics

Covariate	Parameter	MD (log-MAR)	95% CI
Age	Anti-VEGF vs. PRP	−0.076	−0.13 to −0.022
	Anti-VEGF × covariate interaction	0.002	−0.001 to 0.004
Sex (male)	Anti-VEGF vs. PRP	−0.073	−0.132 to −0.014
	Anti-VEGF × covariate interaction	−0.07	−0.127 to −0.014
BCVA at randomisation	Anti-VEGF vs. PRP	−0.076	−0.124 to −0.028
	Anti-VEGF × covariate interaction	−0.137	−0.246 to −0.028
Diabetes (type 2)	Anti-VEGF vs. PRP	−0.077	−0.158 to 0.004
	Anti-VEGF × covariate interaction	−0.023	−0.089 to 0.042
Prior anti-VEGF use	Anti-VEGF vs. PRP	−0.052	−0.123 to 0.02
	Anti-VEGF × covariate interaction	−0.027	−0.14 to 0.087
Prior PRP use	Anti-VEGF vs. PRP	−0.094	−0.148 to −0.04
	Anti-VEGF × covariate interaction	0.065	−0.001 to 0.13
Vitreous haemorrhage at randomisation	Anti-VEGF vs. PRP	−0.064	−0.1 to −0.028
	Anti-VEGF × covariate interaction	−0.127	−0.197 to −0.058
DMO at randomisation	Anti-VEGF vs. PRP	−0.094	−0.17 to −0.018
	Anti-VEGF × covariate interaction	0.04	−0.02 to 0.1
HbA1c	Anti-VEGF vs. PRP	−0.078	−0.124 to −0.031
	Anti-VEGF × covariate interaction	−0.002	−0.003 to −0.001
CST at randomisation	Anti-VEGF vs. PRP	−0.073	−0.129 to −0.018
	Anti-VEGF × covariate interaction	0	0 to 0.001

incidence. There was statistically significant evidence that anti-VEGF produced a greater reduction in vitreous haemorrhage incidence in men (OR 0.161, 95% CI 0.038 to 0.681).

Some other outcomes were reported only in one of the IPD trials. Diabetic retinopathy severity score (DRSS) was reported in PROTOCOL S, where there was strong evidence that ranibizumab led to improved DRSS after 1 year (Mann–Whitney U-test *p*-value 0.0002).

Data on reading ability, driving ability and employment status were also reported in PROTOCOL S, with no clear evidence that ranibizumab improved any of these when compared to PRP. The CLARITY trial reported some quality-of-life data [EuroQol-5 Dimensions (EQ-5D) and NEI scales], with no evidence that aflibercept improved quality of life when compared to PRP.

Additional treatment

All three IPD trials reported additional rounds of anti-VEGF or PRP treatment received. In CLARITY and PROTEUS, most patients received a least one further round of the treatment to which they were randomised within 1 year of follow-up. There was no evidence that rates of treatment were different between the trial arms. In PROTOCOL S, over 5 years of follow-up, most patients received additional treatment. In the ranibizumab arm, this was predominantly further anti-VEGF treatment. In the PRP arm however, it appeared that most patients received anti-VEGF treatment at some point during follow-up, mostly for treatment of macular oedema. This imbalance between arms in additional treatments might partly explain why there was no difference in visual acuity between trial arms after 5 years.

Discussion

This meta-analysis included 12 trials of anti-VEGFs used to treat PDR, with a total of 1145 participants. IPD were available from 3 trials (624 participants). The evidence base is therefore small overall, and the size of the IPD database is limited, which restricted our ability to fully investigate the efficacy of anti-VEGF therapy. We did not have any IPD from bevacizumab trials, and only one aflibercept trial was eligible for inclusion. This limited our ability to reliably compare the three types of anti-VEGF.

The NMAs found evidence that all anti-VEGF therapies are better at maintaining vision than PRP therapy at up to 1 year of follow-up. However, this benefit appears to be small. On average, across the three types of anti-VEGF, it was −0.116 log-MAR (95% CI −0.183 to −0.038) or, equivalently, around 4.5 ETDRS letters. This is within the region of variation that might be expected between visual acuity measurements without any intervention.[37] Evidence from the PROTOCOL S trial suggests that even this benefit may disappear within 5 years.[24] There was no evidence to suggest that the three anti-VEGFs (aflibercept, ranibizumab and bevacizumab) differ in effectiveness; in particular, aflibercept and ranibizumab appear to have very similar effectiveness. There was also no evidence that combining anti-VEGF injection with PRP therapy is more effective at improving vision than anti-VEGF alone.

Both the NMAs and analysis of the IPD found evidence that anti-VEGF was more effective at maintaining vison in people with poorer vision at time of treatment. The IPD analyses also found evidence that anti-VEGF may be more effective in men, in people with vitreous haemorrhage at randomisation, and people with higher HbA1c levels. This suggests that there may be benefits in targeting anti-VEGF use to people with poorer health and vision. This may be clinically plausible, given that anti-VEGF is an accepted treatment for more severe eye conditions such as DMO, and so this would benefit from further investigation. However, these findings must be interpreted with caution as they are based on regression analyses from only three trials.

Numbers of adverse events in the trials were small, and generally too few to detect any differences in incidence between ani-VEGF and PRP. There was evidence that anti-VEGF may reduce the rate of retinal detachment when compared to PRP [relative risk (RR) 0.41, 95% CI 0.22 to 0.77].

Data on outcomes other than visual acuity were limited, so NMAs were not feasible. Our analysis found that anti-VEGF reduced the incidence of macular oedema within 1 year when compared to PRP (RR 0.48, 95% CI 0.28 to 0.83), suggesting an absolute risk reduction from around 25% to 12% after 1 year. Anti-VEGF may also reduce the incidence of vitreous haemorrhage (RR 0.72, 95% CI 0.47 to 1.10), suggesting an absolute risk reduction from around 6% to 4% after 1 year, although this was inconclusive. Therefore, although anti-VEGF has limited impact on visual acuity directly, anti-VEGF may be valuable in preventing the onset of macular oedema. This preventive benefit should be balanced against the fact that people who develop oedema will generally be treated with anti-VEGF, so delaying onset of oedema may not lead to long-term benefit to vision.

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Patient and public perspectives

Patient representatives noted several key areas of continued concern. Most critically was that most trials of anti-VEGF used BCVA as their primary outcome, without any consideration of how that impacted on quality of life, ability to work, drive or care for family. The lack of long-term evidence also raised concerns because there is substantial uncertainty about how PDR will be managed and treated long term. Patients treated with anti-VEGF often require many repeated anti-VEGF eye injections over time. By comparison, treatment with PRP was usually complete in one or two treatment rounds. Hence, anti-VEGF treatment places a heavier burden on patient time given the larger number of regular clinic visits that are required.

Conclusion

Anti-VEGF injection is only marginally better than PRP at maintaining vision and the benefit is not clinically meaningful. There was no evidence of a difference in effectiveness between aflibercept, ranibizumab and bevacizumab, although data to compare these therapies were limited. There was no evidence to show that that combining anti-VEGF with PRP improves effectiveness. Anti-VEGF may prevent, or delay, progression of macular oedema and vitreous haemorrhage. As trial data on these outcomes are more limited than for visual acuity, we suggest that any further trials should focus on the preventive potential of anti-VEGF rather than its impact on visual acuity.

Our analyses found some evidence that anti-VEGFs are more effective at maintaining visual acuity in people with poorer vision or health. Therefore, it may be beneficial for future trials or observational studies to focus on using anti-VEGF in patients with more severe retinopathy or poorer vision to determine whether our findings are supported by future evidence, and to identify exactly which patients might benefit most from receiving anti-VEGF therapy.

A key area of uncertainty is the effectiveness of anti-VEGFs long term, particularly the impacts of the requirement for repeated treatment. With most trials only following up patients for 1 year, the long-term benefits of anti-VEGF are unclear. Trial evidence suggests that most patients will receive additional anti-VEGF or PRP therapy over time. Patients initially treated with PRP may receive anti-VEGF later if their retinopathy worsens or they progress to macular oedema. Evidence on effectiveness of early treatment with anti-VEGF, rather than waiting until retinopathy worsens, remains limited, and further clinical trials or observational evidence in this area is needed.

Additional information

CRediT contribution statement

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Data-sharing statement

Data and code to reproduce the meta-analyses using published data are available on Git Hub (https://github.com/marksimmondsyork/AVID). The IPD analysed cannot be shared on confidentiality grounds. For all other data requests, please contact the corresponding author.

Ethics statement

As this was a systematic review of existing data, no ethics approval was required.

Information governance statement

The University of York is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under Data Protection legislation the University of York is the Data Processor; the trialists who hold the trial data supplied are the Data Controllers, and we process personal data in agreement with them.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/MJYP6578.

Primary conflicts of interest: João Pereira Figueira and Sobha Sivaprasad were chief investigators for the PROTEUS and CLARITY trials, respectively; they supplied IPD from those trials to the AVID team; both have received funding or honoraria from related pharmaceutical companies. Laura Bojke declares that she was on the HS&DR Researcher-Led awards panel (December 2019–December 2022). All other authors have no conflicts of interest to declare.

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List of abbreviations

ANTI-VEGF	anti-vascular endothelial growth factor
BCVA	best corrected visual acuity

CRD	Centre for Reviews and Dissemination
CST	central subfield thickness
DMO	diabetic macular oedema
DRSS	diabetic retinopathy severity score
EQ-5D	EuroQol-5 Dimensions
ETDRS	Early Treatment Diabetic Retinopathy Study
HBA1C	glycated haemoglobin
IPD	individual participant data
LOG-MAR	logarithm of the minimum angle of resolution
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NPDR	non-proliferative diabetic retinopathy
PDR	proliferative diabetic retinopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	panretinal photocoagulation
RCT	randomised controlled trial
SAE	serious adverse event

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34. Ali W, Abbasi KZ, Raza A. Panretinal photocoagulation plus intravitreal bevacizumab versus panretinal photocoagulation alone for proliferative diabetic retinopathy. *J Coll Physicians Surg Pak* 2018;**28**:923–7.

35. Shaikh FF, Jatoi SM. Comparison of efficacy of combination therapy of an intravitreal injection of bevacizumab and photocoagulation versus pan retinal photocoagulation alone in high risk proliferative diabetic retinopathy. *Pak J Med Sci* 2021;**37**:157–61.

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38. Public Health England. *Official Statistics: Public Health Outcomes Framework – Statistical Commentary*. 2020. URL: www.gov.uk/government/publications/public-health-outcomes-framework-may-2020-data-update/public-health-outcomes-framework-statistical-commentary-may-2020 (accessed 2 September 2020).

Appendix 1 Systematic review processes

Database search strategies

Ovid MEDLINE(R) ALL

(includes Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid http://ovidsp.ovid.com/

Date range searched: <1946–25 May 2023>

Date searched: 26 May 2023

Records retrieved: 3172

The MEDLINE strategy below includes a search filter to limit retrieval to RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, *et al*. Technical Supplement to Chapter 4: Searching for and Selecting Studies. In Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook

1 (*Diabetes Mellitus/ or *Diabetes Complications/) and exp *Retinal Diseases/(3199)
2 Diabetic Retinopathy/ (29304)
3 ((diabet* or DM) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath* or maculopath*)).ti,ab,kw. (30685)
4 (((proliferat* or PDR or pre-proliferat* or preproliferat* or non-proliferat* or nonproliferat* or NPDR or background) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath*)) and (diabet* or DM)).ti,ab,kw. (7895)
5 (new blood vessel* and diabet*).ti,ab,kw. (273)
6 (((retin* or subretina* or sub-retina* or interretina* or inter-retina* or vitreoretin* or vitreo-retin* or chorioretin* or chorio-retin* or choroid* or macula* or intraocular or intra-ocular or intravitreal or intra-vitreal) adj4 (damage* or deteriorat* or degnerat* or disease* or edema or oedema or neovascularі?ation*)) and diabet*).ti,ab,kw. (13654)
7 ((retinal vein* adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*).ti,ab,kw. (1473)
8 or/1-7 (44519)
9 exp Vascular Endothelial Growth Factors/ai (9366)
10 exp Receptors, Vascular Endothelial Growth Factor/ai (3393)
11 (anti adj2 VEGF*).ti,ab,kw. (9210)
12 (anti-VEGF* or antiVEGF*).ti,ab,kw. (9455)
13 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor*).ti,ab,kw. (5745)
14 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).ti,ab,kw. (11005)
15 (vascular proliferation adj4 inhibit*).ti,ab,kw. (38)
16 or/9-15 (28125)

17 Angiogenesis Inhibitors/ (28876)
18 exp Angiogenesis Inducing Agents/ai (118)
19 (angiogen* adj2 (antagonist* or inhibit*)).ti,ab,kw. (14831)
20 ((antiangiogen* or anti angiogen* or anti-angiogen*) adj2 (agent* or drug* or effect*)).ti,ab,kw. (10949)
21 (angiostatic adj2 (agent* or drug*)).ti,ab,kw. (103)
22 ((neovasculari?ation or vasculari?ation) adj2 inhibit*).ti,ab,kw. (1243)
23 or/17-22 (45139)
24 Aflibercept*.ti,ab,kw,rn. (3315)
25 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,kw. (316)
26 Bevacizumab/ (14139)
27 Bevacizumab*.ti,ab,kw,rn. (22533)
28 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw. (1675)
29 (IVB adj2 inject*).ti,ab,kw. (316)
30 Ranibizumab/ (4684)
31 Ranibizumab*.ti,ab,kw,rn. (6307)
32 (Lucentis or "rhuFab V2").ti,ab,kw. (456)
33 (IVR adj2 inject*).ti,ab,kw. (139)
34 Pegaptanib*.ti,ab,kw,rn. (671)
35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw. (140)
36 or/24-35 (28353)
37 8 and (16 or 23 or 36) (4979)
38 randomized controlled trial.pt. (593242)
39 controlled clinical trial.pt. (95314)
40 randomized.ab. (604126)
41 placebo.ab. (238387)
42 drug therapy.fs. (2592996)
43 randomly.ab. (408822)
44 trial.ab. (649200)
45 groups.ab. (2520111)
46 or/38-45 (5663345)
47 37 and 46 (3308)
48 exp animals/ not humans.sh. (5123796)
49 47 not 48 (3190)
50 limit 49 to yr="2000-Current" (3182)
51 remove duplicates from 50 (3172)

Key:

/ or.sh. = indexing term (Medical Subject Heading: MeSH)

/ai = indexing term with subheading for antagonists & inhibitors

exp = exploded indexing term (MeSH)

* or $ = truncation

? = adds up to 1 additional character

ti,ab,kw = terms in either title, abstract or keyword fields

rn = registry number/name of substance

adj3 = terms within three words of each other (any order).

pt = publication type

fs = floating sub-heading

EMBASE

via Ovid http://ovidsp.ovid.com/

Date range searched: <1974–2023 May 25>

Date searched: 26 May 2023

Records retrieved: 2558

The Embase strategy below includes the Cochrane Embase RCT filter (Ovid format).

Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. *Health Info Libr J*. 2019 July 22. https://doi.org/10.1111/hir.12269

1 *diabetes mellitus/ and exp *retina disease/ (4826)
2 exp diabetic retinopathy/ (53891)
3 ((diabet* or DM) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath* or maculopath*)).ti,ab,kw. (43573)
4 (((proliferat* or PDR or pre-proliferat* or preproliferat* or non-proliferat* or nonproliferat* or NPDR or background) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath*)) and (diabet* or DM)).ti,ab,kw. (11148)
5 (new blood vessel* and diabet*).ti,ab,kw. (391)
6 (((retin* or subretina* or sub-retina* or interretina* or inter-retina* or vitreoretin* or vitreo-retin* or chorioretin* or chorio-retin* or choroid* or macula* or intraocular or intra-ocular or intravitreal or intra-vitreal) adj4 (damage* or deteriorat* or degnerat* or disease* or edema or oedema or neovasculari?ation*)) and diabet*).ti,ab,kw. (20734)
7 ((retinal vein* adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*).ti,ab,kw. (2199)

8 or/1-7 (70501)
9 vasculotropin inhibitor/ (7663)
10 (anti adj2 VEGF*).ti,ab,kw. (15751)
11 (anti-VEGF* or antiVEGF*).ti,ab,kw. (16291)
12 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor*).ti,ab,kw. (7400)
13 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).ti,ab,kw. (17346)
14 (vascular proliferation adj4 inhibit*).ti,ab,kw. (50)
15 or/9-14 (38838)
16 angiogenesis inhibitor/ (20415)
17 (angiogen* adj2 (antagonist* or inhibit*)).ti,ab,kw. (20444)
18 ((antiangiogen* or anti angiogen* or anti-angiogen*) adj2 (agent* or drug* or effect*)).ti,ab,kw. (15734)
19 (angiostatic adj2 (agent* or drug*)).ti,ab,kw. (125)
20 ((neovasculari?ation or vasculari?ation) adj2 inhibit*).ti,ab,kw. (1718)
21 or/16-20 (45260)
22 aflibercept/ (8877)
23 Aflibercept*.ti,ab,kw,dy,tn. (9141)
24 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,dy,tn. (1741)
25 bevacizumab/ (72890)
26 Bevacizumab*.ti,ab,kw,dy,tn. (75152)
27 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw,dy,tn. (11007)
28 (IVB adj2 inject*).ti,ab,kw. (395)
29 ranibizumab/ (12442)
30 Ranibizumab*.ti,ab,kw,dy,tn. (12826)
31 (Lucentis or "rhuFab V2").ti,ab,kw,dy,tn. (3216)
32 (IVR adj2 inject*).ti,ab,kw. (197)
33 pegaptanib.dy,tn. (2470)
34 Pegaptanib*.ti,ab,kw,dy,tn. (2544)
35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw,dy,tn. (1266)
36 or/22-35 (85594)
37 8 and (15 or 21 or 36) (8778)
38 randomized controlled trial/ (785964)
39 controlled clinical trial/ (469252)
40 Random$.ti,ab,ot. (1968994)
41 randomization/ (99178)
42 intermethod comparison/ (297283)
43 placebo.ti,ab,ot. (366311)
44 (compare or compared or comparison).ti,ot. (604093)
45 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2766233)
46 (open adj label).ti,ab,ot. (109016)
47 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,ot. (274477)
48 double blind procedure/ (210575)
49 parallel group$1.ti,ab,ot. (32223)
50 (crossover or cross over).ti,ab,ot. (124540)
51 ((assign$ or match or matched or allocation) adj5 (alternate or group or groups or intervention or interventions or patient or patients or subject or subjects or participant or participants)).ti,ab,ot. (415063)
52 (assigned or allocated).ti,ab,ot. (489023)
53 (controlled adj7 (study or design or trial)).ti,ab,ot. (450984)
54 (volunteer or volunteers).ti,ab,ot. (282270)
55 human experiment/ (650911)
56 trial.ti,ot. (403295)
57 or/38-56 (6311902)
58 37 and 57 (2810)
59 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$).ti,ot. and animal experiment/ (1227092)
60 animal experiment/ not (human experiment/ or human/) (2577203)
61 59 or 60 (2645661)
62 58 not 61 (2689)
63 limit 62 to yr="2000-Current" (2686)
64 remove duplicates from 63 (2558)

Key:

/ or.sh. = indexing term (Emtree Subject Heading)

exp = exploded indexing term (Emtree)

* or $ = truncation

? = adds up to 1 additional character

ti,ab,kw = terms in either title or abstract fields

dy,tn = drug index terms word or drug trade name fields

adj3 = terms within three words of each other (any order).

pt = publication type

ot = original title

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Date range searched: issue 5 of 12 May 2023

Date searched: 26 May 2023

Records retrieved: 1825

#1 ([mh ^"Diabetes Mellitus"] or [mh ^"Diabetes Complications"]) and [mh "Retinal Diseases"]250
#2 [mh ^"Diabetic Retinopathy"]1934
#3 ((diabet* or DM) NEAR/3 (retinopath* or vitreoretinopath* or chorioretinopath* or maculopath*)):ti,ab,kw4547
#4 (((proliferat* or PDR or preproliferat* or nonproliferat* or NPDR or background) NEAR/3 (retinopath* or vitreoretinopath* or chorioretinopath*)) and (diabet* or DM)):ti,ab,kw1326
#5 ("new blood" NEXT vessel* and diabet*):ti,ab,kw32
#6 (((retin* or subretina* or interretina* or vitreoretin* or chorioretin* or choroid* or macula* or intraocular or intravitreal) NEAR/4 (damage* or deteriorat* or degenerat* or disease* or edema or oedema or neovascularis?ation*)) and diabet*):ti,ab,kw3457
#7 ((retinal NEXT vein* NEAR/3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*):ti,ab,kw254
#8 [38-#7]5751
#9 [mh "Vascular Endothelial Growth Factors"/ai]758
#10 [mh "Receptors, Vascular Endothelial Growth Factor"/ai]154
#11 (anti NEAR/2 VEGF*):ti,ab,kw1610
#12 (antiVEGF*):ti,ab,kw1523
#13 ((anti NEXT vascular or antivascular) NEAR/2 "endothelial growth" NEXT factor*):ti,ab,kw699
#14 ((("vascular endothelial" NEAR/2 growth NEXT factor*) or vasculotropin or VEGF* or "vascular permeability" NEXT factor* or VPF) NEAR/2 (trap* or inhibit* or antagonist*)):ti,ab,kw2048
#15 ("vascular proliferation" NEAR/4 inhibit*):ti,ab,kw1
#16 {OR #9-#15}3671
#17 [mh ^"Angiogenesis Inhibitors"]1681
#18 [mh "Angiogenesis Inducing Agents"/ai]0
#19 (angiogen* NEAR/2 (antagonist* or inhibit*)):ti,ab,kw2126
#20 ((antiangiogen* or anti NEXT angiogen*) NEAR/2 (agent* or drug* or effect*)):ti,ab,kw717
#21 (angiostatic NEAR/2 (agent* or drug*)):ti,ab,kw10
#22 ((neovascularis?ation or vascularis?ation) NEAR/2 inhibit*):ti,ab,kw37
#23 {OR #17-#22}2691
#24 Aflibercept*:ti,ab,kw1081
#25 (Eylea or Zaltrap or Ziv NEXT Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw252
#26 [mh ^Bevacizumab]2633
#27 Bevacizumab*:ti,ab,kw7386
#28 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb NEXT VEGF or "NSC 704865" or NSC704865):ti,ab,kw941
#29 (IVB NEAR/2 inject*):ti,ab,kw89
#30 [mh ^Ranibizumab]1049
#31 Ranibizumab*:ti,ab,kw2266
#32 (Lucentis or "rhuFab V2"):ti,ab,kw451
#33 (IVR NEAR/2 inject*):ti,ab,kw32
#34 Pegaptanib*:ti,ab,kw166
#35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw82
#36 {OR #24-#35}10087
#37 #8 and (#16 or #23 or #36)1847
#38 (rat or rats or rodent* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or bovine or sheep or ovine or "ovis aries" or porcine):ti,ab,kw17188
#39 #37 not #38 with Publication Year from 2000 to 2023, in Trials1825

Science Citation Index Expanded

via Web of Science, Clarivate Analytics https://clarivate.com/

Date range searched: 1900–26 May 2023

Date searched: 26 May 2023

Records retrieved: 2394

32 #29 NOT #302,394Limited by 2000-01-01 to 2023-05-26
31 #29 NOT #302,410
30 TI=(animal or animals or rat or rats or rodent* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or porcine or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or sheep or ovine or "ovis aries" or lamb or lambs or ewe or ewes or rabbit or rabbits or leporide or leporidae or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or bovine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)3,259,653
29 #27 AND #282,524

28 TS=(random* or control* or trial* or "single blind" or "double blind" or "triple blind" or placebo)8,083,064
27 #6 AND #266,121
26 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #2583,065
25 TS=("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838)142
24 TS=(Pegaptanib*)716
23 TS=(IVR NEAR/2 inject*)177
22 TS=(Lucentis or "rhuFab V2")564
21 TS=(Ranibizumab*)9,347
20 TS=(IVB NEAR/2 inject*)307
19 TS=(Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or "rhuMAb VEGF" or "NSC 704865" or NSC704865)3,355
18 TS=(Bevacizumab*)36,279
17 TS=(Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005)320
16 TS=(Aflibercept*)4,076
15 TS=((neovascularisation or neovascularization or vascularisation or vascularization) NEAR/2 inhibit*)1,858
14 TS=(angiostatic NEAR/2 (agent* or drug*))105
13 TS=((antiangiogen* or "anti angiogen*" or anti-angiogen*) NEAR/2 (agent* or drug* or effect*))11,802
12 TS=(angiogen* NEAR/2 (antagonist* or inhibit*))19,846
11 TS=("vascular proliferation" NEAR/4 inhibit*)44
10 TS=((("vascular endothelial" NEAR/2 "growth factor*") or vasculotropin or VEGF* or "vascular permeability factor*" or VPF) NEAR/2 (trap* or inhibit* or antagonist*))14,540
9 TS=(("anti vascular" or anti-vascular or antivascular) NEAR/2 "endothelial growth factor*")5,018
8 TS=(anti-VEGF* or antiVEGF*)10,111
7 TS=(anti NEAR/2 VEGF*)10,549
6 #1 OR #2 OR #3 OR #4 OR #543,073
5 TS=(("retinal vein*" NEAR/3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*)1,546
4 TS=(((retin* or subretina* or sub-retina* or interretina* or inter-retina* or vitreoretin* or vitreo-retin* or chorioretin* or chorio-retin* or choroid* or macula* or intraocular or intra-ocular or intravitreal or intra-vitreal) NEAR/4 (damage* or deteriorat* or degenerat* or disease* or edema or oedema or neovasculari?ation*)) and diabet*)16,980
3 TS=("new blood vessel*" and diabet*)288
2 TS=(((proliferat* or PDR or pre-proliferat* or preproliferat* or non-proliferat* or nonproliferat* or NPDR or background) NEAR/3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath*)) and (diabet* or DM))7,763
1 TS=((diabet* or DM) NEAR/3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath* or maculopath*))36,053

Key:

TS = terms in either title, abstract, author keywords, and keywords plus fields

TI = search in title field

NEAR/3 = terms within three words of each other (any order).

* = truncation

Conference Proceedings Citation Index – Science

via Web of Science, Clarivate Analytics https://clarivate.com/

Date range searched: 1990–26 May 2023

Date searched: 26 May 2023

Records retrieved: 86

32 #29 NOT #3086Limited by 2000-01-01 to 2023-05-26
31 #29 NOT #3089
30 TI=(animal or animals or rat or rats or rodent* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or porcine or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or sheep or ovine or "ovis aries" or lamb or lambs or ewe or ewes or rabbit or rabbits or leporide or leporidae or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or bovine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)295,290
29 #27 AND #2892
28 TS=(random* or control* or trial* or "single blind" or "double blind" or "triple blind" or placebo)1,616,551
27 #6 AND #26458
26 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #258,998

25 TS=("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838)14
24 TS=(Pegaptanib*)39
23 TS=(IVR NEAR/2 inject*)1
22 TS=(Lucentis or "rhuFab V2")29
21 TS=(Ranibizumab*)564
20 TS=(IVB NEAR/2 inject*)7
19 TS=(Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or "rhuMAb VEGF" or "NSC 704865" or NSC704865)196
18 TS=(Bevacizumab*)4,659
17 TS=(Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005)60
16 TS=(Aflibercept*)577
15 TS=((neovascularisation or neovascularization or vascularisation or vascularization) NEAR/2 inhibit*)177
14 TS=(angiostatic NEAR/2 (agent* or drug*))6
13 TS=((antiangiogen* or "anti angiogen*" or anti-angiogen*) NEAR/2 (agent* or drug* or effect*))634
12 TS=(angiogen* NEAR/2 (antagonist* or inhibit*))1,209
11 TS=("vascular proliferation" NEAR/4 inhibit*)6
10 TS=(((("vascular endothelial" NEAR/2 "growth factor*") or vasculotropin or VEGF* or "vascular permeability factor*" or VPF) NEAR/2 (trap* or inhibit* or antagonist*))1,025
9 TS=(("anti vascular" or anti-vascular or antivascular) NEAR/2 "endothelial growth factor*")224
8 TS=(anti-VEGF* or antiVEGF*)836
7 TS=(anti NEAR/2 VEGF*)869
6 #1 OR #2 OR #3 OR #4 OR #55,826
5 TS=(("retinal vein*" NEAR/3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*)74
4 TS=(((retin* or subretina* or sub-retina* or interretina* or inter-retina* or vitreoretin* or vitreo-retin* or chorioretin* or chorio-retin* or choroid* or macula* or intraocular or intra-ocular or intravitreal or intra-vitreal) NEAR/4 (damage* or deteriorat* or degenerat* or disease* or edema or oedema or neovasculari?ation*)) and diabet*)2,140
3 TS=("new blood vessel*" and diabet*)29
2 TS=(((proliferat* or PDR or pre-proliferat* or preproliferat* or non-proliferat* or nonproliferat* or NPDR or background) NEAR/3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath*)) and (diabet* or DM))642
1 TS=((diabet* or DM) NEAR/3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath* or maculopath*))4,723

Key:

TS = terms in either title, abstract, author keywords, and keywords plus fields

TI = search in title field

NEAR/3 = terms within three words of each other (any order).

* = truncation

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Date range searched: Issue 5 of 12, May 2023

Date searched: 26 May 2023

Records retrieved: 14

#1 ([mh ^"Diabetes Mellitus"] or [mh ^"Diabetes Complications"]) and [mh "Retinal Diseases"]250
#2 [mh ^"Diabetic Retinopathy"]1934
#3 ((diabet* or DM) NEAR/3 (retinopath* or vitreoretinopath* or chorioretinopath* or maculopath*)):ti,ab,kw4547
#4 (((proliferat* or PDR or preproliferat* or nonproliferat* or NPDR or background) NEAR/3 (retinopath* or vitreoretinopath* or chorioretinopath*)) and (diabet* or DM)):ti,ab,kw1326
#5 ("new blood" NEXT vessel* and diabet*):ti,ab,kw32
#6 (((retin* or subretina* or interretina* or vitreoretin* or chorioretin* or choroid* or macula* or intraocular or intravitreal) NEAR/4 (damage* or deteriorat* or degenerat* or disease* or edema or oedema or neovasculari?ation*)) and diabet*):ti,ab,kw3457
#7 ((retinal NEXT vein* NEAR/3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*):ti,ab,kw254
#8 {OR #1-#7}5751
#9 [mh "Vascular Endothelial Growth Factors"/ai]758
#10 [mh "Receptors, Vascular Endothelial Growth Factor"/ai]154
#11 (anti NEAR/2 VEGF*):ti,ab,kw1610
#12 (antiVEGF*):ti,ab,kw1523
#13 ((anti NEXT vascular or antivascular) NEAR/2 "endothelial growth" NEXT factor*):ti,ab,kw699
#14 (((("vascular endothelial" NEAR/2 growth NEXT factor*) or vasculotropin or VEGF* or "vascular permeability" NEXT factor* or VPF) NEAR/2 (trap* or inhibit* or antagonist*)):ti,ab,kw2048

#15 ("vascular proliferation" NEAR/4 inhibit*):ti,ab,kw1
#16 {OR #9-#15}3671
#17 [mh ^"Angiogenesis Inhibitors"]1681
#18 [mh "Angiogenesis Inducing Agents"/ai]0
#19 (angiogen* NEAR/2 (antagonist* or inhibit*)):ti,ab,kw2126
#20 ((antiangiogen* or anti NEXT angiogen*) NEAR/2 (agent* or drug* or effect*)):ti,ab,kw717
#21 (angiostatic NEAR/2 (agent* or drug*)):ti,ab,kw10
#22 ((neovasculari?ation or vasculari?ation) NEAR/2 inhibit*):ti,ab,kw37
#23 {OR #17-#22}2691
#24 Aflibercept*:ti,ab,kw1081
#25 (Eylea or Zaltrap or Ziv NEXT Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw252
#26 [mh ^Bevacizumab]2633
#27 Bevacizumab*:ti,ab,kw7386
#28 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb NEXT VEGF or "NSC 704865" or NSC704865):ti,ab,kw941
#29 (IVB NEAR/2 inject*):ti,ab,kw89
#30 [mh ^Ranibizumab]1049
#31 Ranibizumab*:ti,ab,kw2266
#32 (Lucentis or "rhuFab V2"):ti,ab,kw451
#33 (IVR NEAR/2 inject*):ti,ab,kw32
#34 Pegaptanib*:ti,ab,kw166
#35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw82
#36 {OR #24-#35}10087
#37 #8 and (#16 or #23 or #36)1847
#38 (rat or rats or rodent* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or bovine or sheep or ovine or "ovis aries" or porcine):ti,ab,kw17188
#39 #37 not #38 with Cochrane Library publication date Between Jan 2000 and May 2023, in Cochrane Reviews14

Key:

mh = exploded indexing term (MeSH)

mh ^ = unexploded indexing term (MeSH)

/ai = indexing term with subheading for antagonists & inhibitors

* = truncation or additional characters within a word

? = adds up to 1 additional character

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

Epistemonikos

via www.epistemonikos.org/

Date range searched: inception – 26 May 2023

Date searched: 26 May 2023

Records retrieved: 1026

((title:((title:(((diabet* OR proliferat* OR PDR OR pre-proliferat* OR preproliferat* OR non-proliferat* OR nonproliferat* OR NPDR OR background) AND retinopath*)) OR abstract:(((diabet* OR proliferat* OR PDR OR pre-proliferat* OR preproliferat* OR non-proliferat* OR nonproliferat* OR NPDR OR background) AND retinopath*))) OR (title:((new blood vessel* AND diabet*)) OR abstract:((new blood vessel* AND diabet*)))) OR abstract:((title:(((diabet* OR proliferat* OR PDR OR pre-proliferat* OR preproliferat* OR non-proliferat* OR nonproliferat* OR NPDR OR background) AND retinopath*)) OR abstract:(((diabet* OR proliferat* OR PDR OR pre-proliferat* OR preproliferat* OR non-proliferat* OR nonproliferat* OR NPDR OR background) AND retinopath*))) OR (title:((new blood vessel* AND diabet*)) OR abstract:((new blood vessel* AND diabet*))))) AND (title:((anti AND VEGF*)) OR abstract:((anti AND VEGF*))) OR (title:((anti-VEGF* OR antiVEGF*)) OR abstract:((anti-VEGF* OR antiVEGF*))) OR (title:((("anti vascular" OR anti-vascular OR antivascular) AND "endothelial growth factor")) OR abstract:((("anti vascular" OR anti-vascular OR antivascular) AND "endothelial growth factor"))) OR (title:((("vascular endothelial growth factor" OR vasculotropin OR VEGF* OR "vascular permeability factor" OR VPF) AND (trap* OR inhibit* OR antagonist*))) OR abstract:((("vascular endothelial growth factor" OR vasculotropin OR VEGF* OR "vascular permeability factor" OR VPF) AND (trap* OR inhibit* OR antagonist*)))) OR (title:((angiogen* AND (antagonist* OR inhibit*))) OR abstract:((angiogen* AND (antagonist* OR inhibit*)))) OR (title:(((antiangiogen* OR "anti angiogen" OR anti-angiogen* OR angiostatic) AND (agent* OR drug* OR effect*))) OR abstract:(((antiangiogen* OR "anti angiogen" OR anti-angiogen* OR angiostatic) AND (agent* OR drug* OR effect*)))) OR (title:((Aflibercept* OR Eylea OR Zaltrap OR Ziv-Aflibercept OR "AVE 0005" OR AVE0005 OR "AVE 005" OR AVE005 OR Bevacizumab* OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAbVEGF OR rhuMAb-VEGF OR "rhuMAb VEGF" OR "NSC 704865" OR NSC704865 OR Ranibizumab* OR Lucentis OR "rhuFab V2" OR

Pegaptanib* OR "EYE 001" OR EYE001 OR Macugen OR "NX 1838" OR NX1838)) OR abstract:((Aflibercept* OR Eylea OR Zaltrap OR Ziv-Aflibercept OR "AVE 0005" OR AVE0005 OR "AVE 005" OR AVE005 OR Bevacizumab* OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAbVEGF OR rhuMAb-VEGF OR "rhuMAb VEGF" OR "NSC 704865" OR NSC704865 OR Ranibizumab* OR Lucentis OR "rhuFab V2" OR Pegaptanib* OR "EYE 001" OR EYE001 OR Macugen OR "NX 1838" OR NX1838))) OR (title:(((IVB OR IVR) AND inject*)) OR abstract:(((IVB OR IVR) AND inject*))))

Filter: Publication year 2000–23

Publication type: Systematic Reviews

= 1026

Key:

* = truncation

title: = searches in title field

abstract: = searches in abstract field

PROSPERO

via www.crd.york.ac.uk/prospero/

Date range: inception – 26 May 2023

Date searched: 26 May 2023

Records retrieved: 159

#1 MeSH DESCRIPTOR Diabetic Retinopathy107
#2 ((diabet* or DM) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath* or maculopath*))609
#3 (((proliferat* or PDR or pre-proliferat* or preproliferat* or non-proliferat* or nonproliferat* or NPDR or background) adj3 (retinopath* or vitreoretinopath* or vitreo-retinopath* or chorioretinopath* or chorio-retinopath*)) and (diabet* or DM))110
#4 (new blood vessel* and diabet*)9
#5 (((retin* or subretina* or sub-retina* or interretina* or inter-retina* or vitreoretin* or vitreo-retin* or chorioretin* or chorio-retin* or choroid* or macula* or intraocular or intra-ocular or intravitreal or intravitreal) adj4 (damage* or deteriorat* or degenerat* or disease* or edema or oedema or neovascularisation* or neovascularization*)) AND diabet*)373
#6 ((retinal vein* adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*)64
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6740
#8 MeSH DESCRIPTOR Vascular Endothelial Growth Factors EXPLODE ALL TREES WITH QUALIFIER AI0
#9 MeSH DESCRIPTOR Receptors, Vascular Endothelial Growth Factor EXPLODE ALL TREES WITH QUALIFIER AI0
#10 (anti adj2 VEGF*)327
#11 (anti-VEGF* or antiVEGF*)327
#12 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor*)153
#13 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*))96
#14 (vascular proliferation adj4 inhibit*)0
#15 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14412
#16 MeSH DESCRIPTOR Angiogenesis Inhibitors40
#17 MeSH DESCRIPTOR Angiogenesis Inducing Agents EXPLODE ALL TREES WITH QUALIFIER AI0
#18 (angiogen* adj2 (antagonist* or inhibit*))74
#19 ((antiangiogen* or anti angiogen* or anti-angiogen*) adj2 (agent* or drug* or effect*))145
#20 (angiostatic adj2 (agent* or drug*))0
#21 ((neovascularisation* or neovascularization* or vascularisation* or vascularization*) adj2 inhibit*)0
#22 #16 OR #17 OR #18 OR #19 OR #20 OR #21224
#23 (Aflibercept*)141
#24 (Eylea or Zaltrap or Ziv-Aflibercept or AVE 0005 or AVE0005 or AVE 005 or AVE005)22
#25 MeSH DESCRIPTOR Bevacizumab46
#26 (Bevacizumab*)445
#27 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or NSC 704865 or NSC704865)59
#28 (IVB adj2 inject*)0
#29 MeSH DESCRIPTOR Ranibizumab7
#30 (Ranibizumab*)142
#31 (Lucentis or rhuFab V2)23
#32 (IVR adj2 inject*)0
#33 (Pegaptanib*)30
#34 (EYE 001 or EYE001 or Macugen or NX 1838 or NX1838)5
#35 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34500
#36 #15 OR #22 OR #35839
#37 #7 AND #36159

Key:

MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)

QUALIFIER AI = indexing term subheading for antagonists & inhibitors

EXPLODE ALL TREES = exploded indexing term (MeSH)

* = truncation

adj3 = terms within three words of each other (order specified).

:TI,KW = terms in either title or keyword fields

ClinicalTrials.gov

via https://clinicaltrials.gov/

Date searched: 26 May 2023

Records retrieved: 286

Two separate searches were used in Advanced Search, retrieving 286 records in total, which were imported into EndNote 20 and deduplicated.

1. **Condition or Disease:** (diabetic retinopathy)

Other Terms: (Aflibercept OR Eylea OR Zaltrap OR Bevacizumab OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAb VEGF OR Ranibizumab OR Lucentis OR rhuFab OR Pegaptanib OR Macugen) = **190 hits**

2. **Condition or Disease:** (diabetic retinopathy)

Other Terms: ((VEGF OR vascular endothelial growth factor OR vasculotropin OR vascular permeability factor or VPF) AND (anti OR trap or inhibitor or antagonist)) = **96 hits**

European Union Clinical Trials Register

via www.clinicaltrialsregister.eu/ctr-search/search

Date searched: 26 May 2023

Records retrieved: 163

Two separate searches were used, retrieving 163 records in total, which were imported into EndNote 20 and deduplicated.

1. (("diabetic retinopathy") AND (Aflibercept OR Eylea OR Zaltrap OR Bevacizumab OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR "rhuMAb VEGF" OR Ranibizumab OR Lucentis OR rhuFab OR Pegaptanib OR Macugen)) = **113 hits**
2. (("diabetic retinopathy") AND ((anti OR trap or inhibitor OR antagonist) AND (VEGF OR "vascular endothelial growth factor" OR vasculotropin OR "vascular permeability factor" OR VPF))) = **50 hits**

WHO International Clinical Trials Registry Platform (ICTRP)

via https://trialsearch.who.int/

Date searched: 26 May 2023

Records retrieved: 198

Two separate searches were used in Advanced Search, retrieving 198 records in total, which were imported into EndNote 20 and deduplicated.

1. Advanced Search

Condition: (diabetic retinopathy)

Intervention: (Aflibercept OR Eylea OR Zaltrap OR Bevacizumab OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAb VEGF OR Ranibizumab OR Lucentis OR rhuFab OR Pegaptanib OR Macugen)

Recruitment Status: ALL = 194 records for 180 trials

2. Advanced Search

Condition: (diabetic retinopathy)

Intervention: ((VEGF OR vascular endothelial growth factor OR vasculotropin OR vascular permeability factor or VPF) AND (anti OR trap or inhibitor or antagonist))

Recruitment Status: ALL = **23 records for 18 trials**

List of excluded studies

Randomised controlled trial of DME (35)

- Bayer AG. An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intr.

- Braimah IZ, Kenu E, Amissah-Arthur KN, Akafo S, Kwarteng KO, Amoaku WM. Safety of intravitreal ziv-aflibercept in choroido-retinal vascular diseases: a randomised double-blind intervention study. *PLOS ONE [Electronic Resource]* 2019;**14**:e0223944.
- Bressler SB, Liu D, Glassman AR, Blodi BA, Castellarin AA, Jampol LM, *et al.*; Diabetic Retinopathy Clinical Research and Network. Change in diabetic retinopathy through 2 years: Secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmol* 2017;**135**: 558–68.
- Bressler SB, Qin H, Beck RW, Chalam KV, Kim JE, Melia M, Wells JA 3rd; Diabetic Retinopathy Clinical Research and Network. Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Arch Ophthalmo* 2012;**130**:1153–61.
- Bressler SB, Qin H, Melia M, Bressler NM, Beck RW, Chan CK, *et al.*; Diabetic Retinopathy Clinical Research and Network. Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. *JAMA Ophthalmol* 2013;**131**:1033–40.
- Department of Ophthalmology and Medical University of Vienna. A randomized, double-masked study with intraocular bevacizumab (Avastin®) compared with intravitreal ranibizumab (Lucentis®) in patients with persistent diabetic macular edema or persistent active.
- Dhoot D, Hill L, Tarnowski K, Stoilov I. Baseline factors associated with >= 2-step diabetic retinopathy (DR) severity improvement with ranibizumab (RBZ). *Investig Ophthalmol Visual Sci Conf* 2018;**59**:3592.
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- Dhoot DS, Moini H, Reed K, Du W, Vitti R, Berliner AJ, Singh RP. Functional outcomes of sustained improvement on Diabetic Retinopathy Severity Scale with intravitreal aflibercept in the VISTA and VIVID trials. *Eye* 2022;**19**:19.
- Dimitriou E, Theodossiadis P, Chatzirallis A, Kazantzis D, Theodossiadis G, Chatziralli E. (2020). Intravitreal ranibizumab alone or in combination with panretinal photocoagulation for the treatment of proliferative diabetic retinopathy with coexistent macular edema: long-term outcomes in real-life data. *Investig Ophthalmol Visual Sci Conf* 2020;**61**.
- Ekinci M, Ceylan E, Cakici O, Tanyildiz B, Olcaysu O, Cagatay HH. (2014). Treatment of macular edema in diabetic retinopathy: comparison of the efficacy of intravitreal bevacizumab and ranibizumab injections. *Exp Rev Ophthalmol* 2014;**9**:139–43.
- Euctr-009909-25-De. Evaluation of the efficacy and safety of a Macugen monotherapy versus combined therapies in the treatment of diabetic retinopathy – a single centre, randomized, prospective phase II trial. 2009.
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- Gonzalez VH. Pegaptanib in diabetic retinopathy: improvements in Diabetic Macular Edema, Retinal Neovascularization, and Diabetic Retinopathy Severit. *Am Academy Ophthalmol* 2006:192.
- Gonzalez VH, Wang PW, Ruiz CQ. Panretinal photocoagulation for diabetic retinopathy in the RIDE and RISE trials: not '1 and Done'. *Ophthalmology* 2019;**21**:21.
- Gonzalez VH, Wang PW, Ruiz CQ. Panretinal photocoagulation for diabetic retinopathy in the RIDE and RISE trials: not '1 and Done'. *Ophthalmology* 2021;**128**:1448–57.
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- Irct201205029617N. Efficacy of macular laser photocoagulation with or without intravitreal injection of bevacizumab (Avastin) or triamcinolone acetonide for diffuse diabetic macular edema. 2012.
- Mehta H, Lim LL, Nguyen V, Qatarneh D, Wickremasinghe SS, Hodgson LAB, Quin GJ, *et al.* Development of new proliferative diabetic retinopathy in the BEVORDEX trial. *Ophthalmol Retina* 2019;**3**:286–7.
- Mitchell P, McAllister I, Larsen M, Staurenghi G, Korobelnik JF, Boyer DS, *et al.* Evaluating the impact of intravitreal aflibercept on diabetic retinopathy progression in the VIVID-DME and VISTA-DME studies. *Ophthalmology Retina* 2018;**2**:988–996.
- NCT. Laser-ranibizumab-triamcinolone for proliferative diabetic retinopathy. 2007.

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

- NCT. Anterior and posterior segment vascular changes following laser and anti-vascular endothelial growth factor (VEGF) treatment of diabetic retinopathy. 2009.
- NCT. Laser therapy combined with intravitreal aflibercept versus intravitreal aflibercept monotherapy (LADAMO). 2015.
- Novartis Pharma and AG. A 12-month, 2-arm, randomized, double-masked, multicenter phase III study assessing the efficacy and safety of brolucizumab every 4 weeks versus aflibercept every 4 weeks in adult patients with Vis.
- Novartis Pharma Gmb and H. A randomized, single-blinded, multicenter, phase IV study to compare systemic VEGF protein dynamics following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept until stu.
- Novartis Pharma and AG. A two-year, three-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to D.
- Novartis Pharma and AG. A two-year, two-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to Dia.
- Oxurion NV. A phase 2, randomised, single-masked, active-controlled, multicentre study to evaluate the efficacy and safety of intravitreal THR-317 administered in combination with ranibizumab, for the treatmen.
- Quark Pharmaceuticals and Inc. An Open-Label Dose Escalation Study of PF-04523655 (Stratum I) combined with a prospective, randomized, double-masked, multi-center, controlled study (stratum II) evaluating the efficacy and safety.
- Sadiq MA, Hassan M, Soliman MK, Afridi R, Do DV, Nguyen QD, Sepah YJ. Effects of two different doses of ranibizumab on diabetic retinopathy severity. *Ophthalmol Retina* 2017;**1**:566–7.
- Sameen M, Khan MS, Mukhtar A, Yaqub MA, Ishaq M. Efficacy of intravitreal bevacizumab combined with pan retinal photocoagulation versus panretinal photocoagulation alone in treatment of proliferative diabetic retinopathy. *Pakistan J Med Sci* 2017;**33**:142–5.
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Randomised controlled trial of vitreous haemorrhage or vitrectomy (86)

- Ahmadieh H, Shoeibi N, Entezari SM. Intravitreal bevacizumab for early post-vitrectomy hemorrhage in diabetics: a randomized, double masked clinical trial. *Am Acad Ophthalmol* 2008:181.
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- Albuquerque TL, Pierozzi GS, Araujo ACC, Neto NH, Carregal TB, Martins MC, Souza JC, Carlos GA, Bordon AF. Comparative, randomized, double blinded study of the use of anti-VEGF in patients with vitreous hemorrhage or tractional retinal detachment secondary to diabetic retinopathy. *Investig Ophthalmol Visual Sci* 2014;**55**:4391.
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- Bhavsar AR, Torres K, Beck RW, Friedman SM, Glassman AR, Maturi RK, *et al.*; Diabetic Retinopathy Clinical Research Network. Randomized clinical trial evaluating intravitreal ranibizumab or saline for

vitreous hemorrhage from proliferative Diabetic Retinopathy Clinical Research Network. *JAMA Ophthalmol* 2013;**131**:283–93.
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- ChiCTR. A prospective and randomized controlled clinical study for pre- and after-operative intravitreal injection of anti-VEGF combined with pars plana vitrectomy. 2020.
- ChiCTR. A prospective randomized controlled study of long-acting dexamethasone implant to improve the prognosis of PDR patients after vitrectomy. 2021.
- ChiCTR1800019455. Effects of intraocular injection of different anti-VEGF drugs on inflammatory factors in aqueous humor of patients with diabetic retinopathy. 2018.
- ChiCTR2000035032. Efficacy of different doses of anti-VEGF with vitrectomy in the treatment of proliferative diabetic retinopathy. 2020
- Comyn O, Bainbridge JWB. A pilot randomized controlled trial of ranibizumab pre-treatment for diabetic vitrectomy (the RaDiVit study). *Investig Ophthalmol Visual Sci* 2014;**55**:2302.
- Comyn O, Wickham L, Charteris DG, Sullivan PM, Ezra E, Gregor Z, Aylward GW, *et al.* Ranibizumab pretreatment in diabetic vitrectomy: a pilot randomised controlled trial (the RaDiVit study). *Eye* 2017;**31**:1253–8.
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- Diabetic Retinopathy Clinical Research and Network. Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. *JAMA Ophthalmol* 2013;**131**:283–93.
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- NCT. A multicenter, randomized study in participants with diabetic retinopathy without center-involved diabetic macular edema to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered via the port delivery system relative to the comparator arm. 2020.
- NCT. Intravitreal bevacizumab for nonproliferative diabetic retinopathy. 2020.
- NCT. Study of efficacy and safety of brolucizumab versus panretinal photocoagulation laser in patients with proliferative diabetic retinopathy. 2020.
- NCT. Intravitreal bevacizumab versus laser versus combination of bevacizumab and modified laser in PDR. 2021.
- TCTR. Change of OCT findings after intravitreal anti-VEGF injection in patients with diabetic tractional retinal detachment: a randomized controlled trial. 2021.

Irretrievable (1)

Alvarez-Villalobos N, de León-Gutiérrez H, Ruiz-Hernandez F. Safety and clinical effectiveness behavior of bevacizumab biosimilars in the intravitreal application.

Trials in narrative synthesis

TABLE 6 Trials excluded from main meta-analyses

Trial	Key paper(s)	Anti-VEGF	Comparator	Location	Sample size	Population
No PRP arm						
RECOVERY	Alagorie 2021	Aflibercept (monthly)	Aflibercept (quarterly)		40 eyes	PDR
Conference abstracts						
Garcia	Garcia-Aguirre 2008	Bevacizumab	PRP	Mexico	10 persons	NPDR, PDR
Ernst	Ernst 2012	Bevacizumab	PRP	USA	10 persons	NPDR, PDR
MEDICARE	Dufour 2017	Aflibercept	PRP	France	20 persons	PDR
Oh	Oh 2014 CA	Bevacizumab (+ PRP)	PRP	South Korea	125 persons	NPDR, PDR
Ramezani	Ramezani 2021	Bevacizumab (+ PRP)	PRP	Unknown	153 eyes	PDR
Tardieu	Tardieu 2022	Not stated	PRP	Unknown	40 persons	PDR
Papers in Chinese						
Bi	Bi 2020	Ranibizumab (+ PRP)	PRP	China	120 persons	Unclear
Meng	Meng 2019	Ranibizumab (+ PRP)	PRP	China	80 persons	PDR
Zhou	Zhou 2017	Bevacizumab (+ PRP)	PRP	China	30 persons	Unclear
Trials from before 2010						
Cho	Cho 2009–10	Bevacizumab (+ PRP)	PRP + triamcinolone	China	91 eyes	NPDR, PDR
Mirshahi	Mirshahi 2008	Bevacizumab (+ PRP)	PRP, sham injection	Iran	80 eyes	PDR
Tonello	Tonelo 2008	Bevacizumab (+ PRP)	PRP	Brazil	30 eyes	PDR
Unused or unspecified anti-VEGFs						
Chen/Zhou	Chen 2017	Unclear	PRP	China	120 persons	PDR
Gonzalez	Gonzalez 2007/2009/2014	Pegaptanib sodium	PRP	USA	20 persons	PDR
He	He 2020	Conbercept (+ PRP)	PRP	China	44 eyes	PDR
Leal	Leal 2013	Pegaptanib sodium (+ PRP)	PRP	Portugal	22 persons	PDR
Wang	Wang 2019	Conbercept (+ PRP)	PRP	China	64 persons	NPDR, PDR
No protocol-specified outcomes						
Helmy	Helmy 2023	Ranibizumab	PRP	Egypt	50 persons	PDR
Preti	Preti 2013	Bevacizumab (+ PRP)	PRP	South America	42 persons	PDR
Rentiya	Rentiya 2022	Ranibizumab (+ PRP)	PRP	Brazil	30 persons	PDR

Risk-of-bias assessment

TABLE 7 Cochrane risk-of-bias assessment for PDR trials

Trial	Risk-of-bias domain					Overall
	Randomisation	Deviation form intended intervention	Missing outcome data	Outcome measurement	Selective reporting	
Ahmad	!	!	+	–	!	High
Ali	!	!	!	–	!	High
CLARITY	+	+	+	!	+	Low
Ferraz	!	!	+	+	!	Moderate
Marashi	–	!	!	–	+	High
PRIDE	!	+	!	–	+	Moderate
PROTEUS	+	+	!	–	+	Moderate
PROTOCOL S	+	+	+	!	+	Low
Rebecca	!	!	!	–	!	High
Roohipour	!	!	–	–	!	High
Sao Paulo A	!	!	!	–	!	High
Sao Paulo B	!	!	!	–	!	High
	+	Low risk				
	!	Some concerns				
	–	High risk				

TABLE 8 Full risk-of-bias assessment – Table A

Trial	Randomisation process		Deviations from intended interventions		Missing outcome data	
	Judgement	Comments	Judgement	Comments	Judgement	Comments
Ahmad 2012	Some concerns	Randomised by 'simple lottery'. No further details. No allocation concealment method reported. No evidence of significant differences in key prognostic factors.	Some concerns	No placebo. States 'the physician did not know which eye has been injected', but the control group did not receive a placebo injection. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context. ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded.	Low	All participants completed the 90 days follow-up.
Ali 2018	Some concerns	States the study is randomised, with allocation by 'simple lottery method'. No further details. No information on whether allocation was concealed.	Some concerns	No placebo. Contralateral design. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context. ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded.	Some concerns	No information on loss to follow-up. No evidence that the result was not biased by any possible missing outcome data. Likelihood of significant missingness may be limited by relatively short follow-up duration.

continued

TABLE 8 Full risk-of-bias assessment – Table A (*continued*)

Trial	Randomisation process		Deviations from intended interventions		Missing outcome data	
	Judgement	Comments	Judgement	Comments	Judgement	Comments
CLARITY	Low	Computer generated with minimisation. Central allocation by trials unit. No significant baseline imbalances.	Low	No placebo. 'The treating ophthalmologists and participants were not masked'. CONSORT diagram reported. No evidence of deviation from intended intervention due to the trial context. Analyses conducted according to ITT principles.	Low	Available for 91% (211/232) at 52 weeks. Appropriate sensitivity analyses for missing BCVA data with prespecified alternative scenarios were conducted and showed no evidence of bias.
Ferraz 2015	Some concerns	Described as randomised. No other details. No details on allocation concealment. Contralateral design. No evidence of significant differences in key prognostic factors.	Some concerns	Placebo controlled. Contralateral design. Trial registry entry described as single masked (participants). Masking only reported for outcome assessors ('examiners' and participants), not for carers. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context. ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded.	Low	Three per cent (2/60) eyes excluded due to VH in the control arm. It appears that all other randomised eyes were analysed.
Marashi 2017	High	Described as randomised. No other details. No details on allocation concealment. Eighty per cent had DME at baseline in the IVB arm, vs. 20% in the control arm. Although the trial is small, the difference is large and considered unlikely to be due to chance alone. No adjustments for baseline imbalance were performed.	Some concerns	No placebo. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context. ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded.	Some concerns	No information on loss to follow-up. Follow-up duration means that the risk of at least some loss to follow-up is high. No evidence that the result was not biased by any possible missing outcome data.

TABLE 8 Full risk-of-bias assessment – Table A (*continued*)

Trial	Randomisation process		Deviations from intended interventions		Missing outcome data	
	Judgement	Comments	Judgement	Comments	Judgement	Comments
PRIDE	Some concerns	A number of differences in baseline characteristics, including key variables, although differences do not clearly favour one arm and may have occurred by chance. Differences in mean age (IVR: 52.5, PRP: 53, IVR + PRP: 55), age distribution (< 65 years: 86%, 86%, 72%); smoker (14%, 26%, 35%); duration of diabetes (25 years, 23, 21), mean mm^2 NVD + NVE: 9.4, 5.4, 4.1; ETDRS: 83.3, 80.5, 80.0.	Low	No masking. Analyses conducted based on ITT principle, using LOCF.	Some concerns	Twenty-three per cent (25/108) of randomised participants not measured at 12 months. No significant differences in rates of missingness across groups.
PROTEUS	Low	Computer-generated block randomisation. Central allocation implemented through electronic platform. Large and statistically significant difference in mean age [IVR + PRP: 58.8 years (13.3), PRP: 52.0 (11.9)]. Non-statistically significant difference in sex (31.7% vs. 41.3% female). Difference in time since diagnosis not reported (NR). In a multivariate analysis, 'age, HbA1c, and number of PRP treatments did not show a significant association with BCVA difference from baseline to month 12'. Re-analysis with IPD provided by trialist suggested low concerns.	Low	CONSORT diagram reported. No evidence of deviation from intended intervention due to trial context. ITT-principle-based primary analysis.	Some concerns	

continued

TABLE 8 Full risk-of-bias assessment – Table A (*continued*)

Trial	Randomisation process		Deviations from intended interventions		Missing outcome data	
	Judgement	Comments	Judgement	Comments	Judgement	Comments
PROTOCOL S	Low	Permuted block randomisation. Stratification by site and presence of centrally involved DME. Central allocation concealment with web-based tool from trials unit. No evidence of baseline imbalances.	Low	No placebo. Masking only for outcome assessors. All eyes randomised received the treatment allocated. Analyses conducted according to ITT principles.	Low	Eighty-three per cent (382/394) completed 2-year follow-up. Of those, 5% (18/394) died, 12% (48/394) withdrew or missed their visit. For missing data at 2 years, SAP reports 'Markov chain Monte Carlo (MCMC) multiple imputation based on treatment group, the randomization stratification factors, and all available visual acuity data from assessment visits prior to 2 years'.
Rebecca 2021	Some concerns	Described as randomised. No other details. No details on allocation concealment. No evidence of significant differences in key prognostic factors.	Some concerns	No placebo. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context. ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded.	Some concerns	No information on loss to follow-up. Follow-up duration means that the risk of at least some loss to follow-up is high. No evidence that the result was not biased by any possible missing outcome data.
Roohipour 2019	Some concerns	Random block method, but no further details on how allocation sequence was generated. No information on allocation concealment. No evidence of significant differences in key prognostic factors.	Some concerns	No placebo. Contralateral design. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context. ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded.	High	Significant loss to follow-up. Only 59% (19 out of 32) completed 10 months follow-up. No evidence that the result was not biased by missing outcome data. Reasons for loss to follow-up were NR. The risk that at least some missingness could be due to visual acuity outcomes cannot be excluded.
Sao Paulo A	Some concerns	Randomised based on a computer-generated sequence. No further details reported. There were differences in age (mean PASCAL arm age was 7.5 years older than IVR and 2.2 years older than ETDRS), although they were not statistically significant.	Some concerns	No placebo. No evidence of deviation from the intervention due to the trial context. ITT/mITT not explicitly reported.	Some concerns	13/48 (27%) withdrew. No significant difference in withdrawal between arms. No evidence that the result was not biased by missing outcome data. Reasons for loss to follow-up were NR. The risk that at least some missingness could be due to visual acuity outcomes cannot be excluded.

TABLE 8 Full risk-of-bias assessment – Table A (*continued*)

Trial	Randomisation process		Deviations from intended interventions		Missing outcome data	
	Judgement	Comments	Judgement	Comments	Judgement	Comments
Sao Paulo B	Some concerns	Block randomisation (blocks of 2), allocation drawn randomly by technician from one of two identical opaque envelopes. No further information on randomisation and allocation concealment. No evidence of significant differences in key prognostic factors.	Some concerns	No placebo. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context. ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded.	Some concerns	Only 72.5% (29/40) participants analysed at 48 weeks. No evidence that the result was not biased by missing outcome data. Significant loss to follow-up. Reported reasons for loss to follow-up were mostly appropriate (including four deaths and two ocular events, four did not return for assessment, one not specified). No clear imbalances between arms.

CONSORT, Consolidated Standards of Reporting Trials; ITT, intention to treat; IVR, Intravitreal ranibizumab; LOCF, last observation carried forward; mITT, modified intention to treat; NVD, neovascularisation of the disc; NVE, neovascularisation elsewhere; SAP, statistical analysis plan.

TABLE 9 Full risk-of-bias assessment – Table B

Trial	Measurement of the outcome		Selection of the reported result		Overall bias
	Judgement	Comments	Judgement	Comments	Judgement
Ahmad 2012	High	Snellen chart, converted to log-MAR Participants unmasked (no placebo). No mention of blinding of outcome assessors. Participants and study personnel may have been influenced by knowledge of the intervention.	Some concerns	Insufficient information about analysis plans.	High
Ali 2018	High	Appears to be ETDRS, standard scale. No placebo	Some concerns	No protocol.	High
CLARITY	Some concerns	ETRDS, standard scale. The lack of blinding of participants means raises some concerns, although appropriate steps were taken to mask the optometrists assessing BCVA.	Low	A SAP 'was finalised before data lock and agreed with oversight committees'.	Low
Ferraz 2015	Low	ETDRS Outcome assessors masked throughout the study period.	Some concerns	Insufficient information about analysis plans. Outcome retrospectively reported in trial registry.	Some concerns
Marashi 2017	High	Snellen scale, converted to log-MAR No placebo Participants and study personnel may have been influenced by knowledge of the intervention.	Low	Protocol registered around time of study start, and prespecified outcome and time point were reported.	High
PRIDE	High	ETDRS, standard. No masking of outcome assessors.	Low	SAP not mentioned. Protocol registered before time of study start, and prespecified outcome and time point were reported.	Some concerns

continued

TABLE 9 Full risk-of-bias assessment – Table B (*continued*)

Trial	Measurement of the outcome		Selection of the reported result		Overall bias
	Judgement	Comments	Judgement	Comments	Judgement
PROTEUS	High	Standard ETDRS No placebo. Participants and outcome assessors were aware of the intervention. Participants and study personnel may have been influenced by knowledge of the intervention.	Low	No SAP. Outcome and follow-up specified in prospectively registered protocol.	Some concerns
PROTOCOL S	Some concerns	E-ETDRS Participants unmasked (no placebo), but protocol states that 'visual acuity testers [. . .] will be masked to treatment group at annual visits'.	Low	SAP v1.0 is dated March 2015. Protocol first published December 2011, primary completion dated January 2015. Outcome specified in prospectively registered protocol.	Low
Rebecca 2021	High	BCVA. Scale not reported, but standard outcome. No placebo. Participants and outcome assessors were aware of the intervention. Participants and study personnel may have been influenced by knowledge of the intervention.	Some concerns	Insufficient information about analysis plans.	High
Roohipour 2019	High	BCVA measured using standard Snellen chart. No placebo. Participants and study personnel may have been influenced by knowledge of the intervention.	Some concerns	SAP not mentioned in protocol or publication. Ten months follow-up assessment was not pre-specified (unlike 6 months).	High
Sao Paulo A	High	Standard ETDRS No placebo. Participants were aware of the intervention. No masking of outcome assessor reported.	Some concerns	No SAP. Outcome and follow-up specified in protocol, but unclear if prospectively registered.	High
Sao Paulo B	High	ETDRS, converted to log-MAR No blinding of outcome assessor, who performed the interventions. Participants and study personnel may have been influenced by knowledge of the intervention.	Some concerns	Insufficient information about analysis plans.	High

SAP, statistical analysis plan.

Appendix 2 Network meta-analyses of best corrected visual acuity (as logarithm of the minimum angle of resolution)

Note: Proliferative diabetic retinopathy

All analyses relate only to trials of proliferative retinopathy, as no IPD were available for non-proliferative retinopathy. For results from non-proliferative retinopathy trials, see the companion paper on published data meta-analyses.

TABLE 10 Schematic for dosing regimens and schedules across all trials

Trial	Arm	Randomisation	4 weeks	8 weeks	12 weeks	Later times	End point
Ahmad	Bevacizumab + PRP	1.25 mg				***Unclear***	12 weeks
	PRP	1600–2000 (300 µm spots, 2 sessions)				***Unclear***	
Ali	Bevacizumab + PRP	*Dose not stated*					1 month
	PRP	1500–2000 shots (200–500 µm spots)					
CLARITY	Aflibercept	2 mg/0.05 ml	2 mg/0.05 ml	2 mg/0.05 ml	If NV regression	If needed	52 weeks
	PRP	Week 0, 2 and 4			If needed	Assessed every 8 weeks	
Ferraz	Ranibizumab + PRP	0.5 mg	0.5 mg				
	PRP	ETDRS 3 sessions			If DME, or other need	At 6 months if DME, or other need	
Marashi	Bevacizumab	1.25 mg	1.25 mg	1.25 mg		After 18 weeks monthly if needed to stabilise PDR	
	PRP	1200–1600 burns, 1–3 sessions				Repeated if PDR worsens	
PRIDE	Ranibizumab	0.5 mg	0.5 mg	0.5 mg	Continued monthly until condition was stable	As left	1 year
	PRP	1200–1600 burns using 500 µm (monthly)				Further 500 laser spots if condition worsened	
	Ranibizumab + PRP	*As for single-treatment arms*					
PROTEUS	Ranibizumab + PRP	0.5 mg	0.5 mg	0.5 mg	If needed (e.g. NV present)	Monthly, if needed (e.g. NV present)	1 year
	PRP	Once	Two further sessions		If needed (e.g. NV present)	If needed	
PROTOCOL S	Ranibizumab	0.5 mg	0.5 mg	0.5 mg	0.5 mg	Complex, depends on NV	1 year

continued

TABLE 10 Schematic for dosing regimens and schedules across all trials (*continued*)

Trial	Arm	Randomisation	4 weeks	8 weeks	12 weeks	Later times	End point
	PRP	1200–1600 burns using 500 µm				If NV worsening, or otherwise needed	
Rebecca	Bevacizumab + PRP	1.25 mg (2 injections)				***Unclear***	
	PRP	Up to 3000 burns, 3 sessions				***Unclear***	
Roohipour	Bevacizumab (+ PRP)	1.25 mg (+ PRP as below)			If needed	At 6 months if needed	No treat after 6 months
	PRP	1200–1600 burns using 500 µm 3 sessions			If needed	At 6 months if needed	
Sao Paulo A	Ranibizumab + PRP	0.5 mg			If needed	Every 12 weeks if needed	44 weeks
	PRP–ETDRS	1600–1800 burns (2 sessions)					
	PRP PASCAL	1300–1800 burns (1 session)					
Sao Paulo B	Ranibizumab + PRP	0.5 mg				Also at week 32	Not beyond week 32
	PRP	1200–1600 burns using 500 µm (2 sessions)				Also at week 32	

Analyses at up to 1 year of follow-up

This NMA considers the maximum follow-up time from each trial, up to 1 year. As PROTOCOL S was the only trial to report data beyond 1 year, this was chosen as the cut-off point.

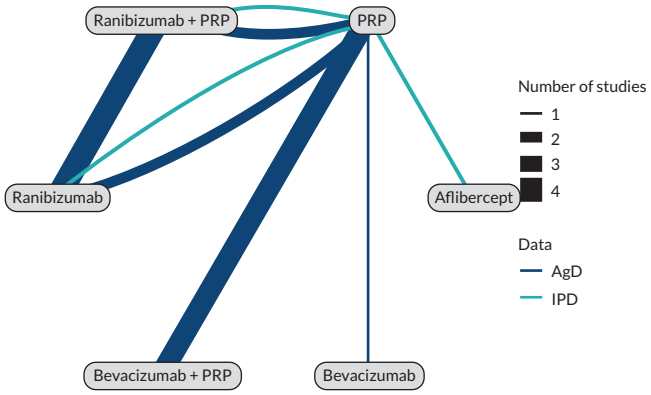

FIGURE 7 Network diagram of BCVA at up to 1 year of follow-up. AgD, Aggregate (published) data.

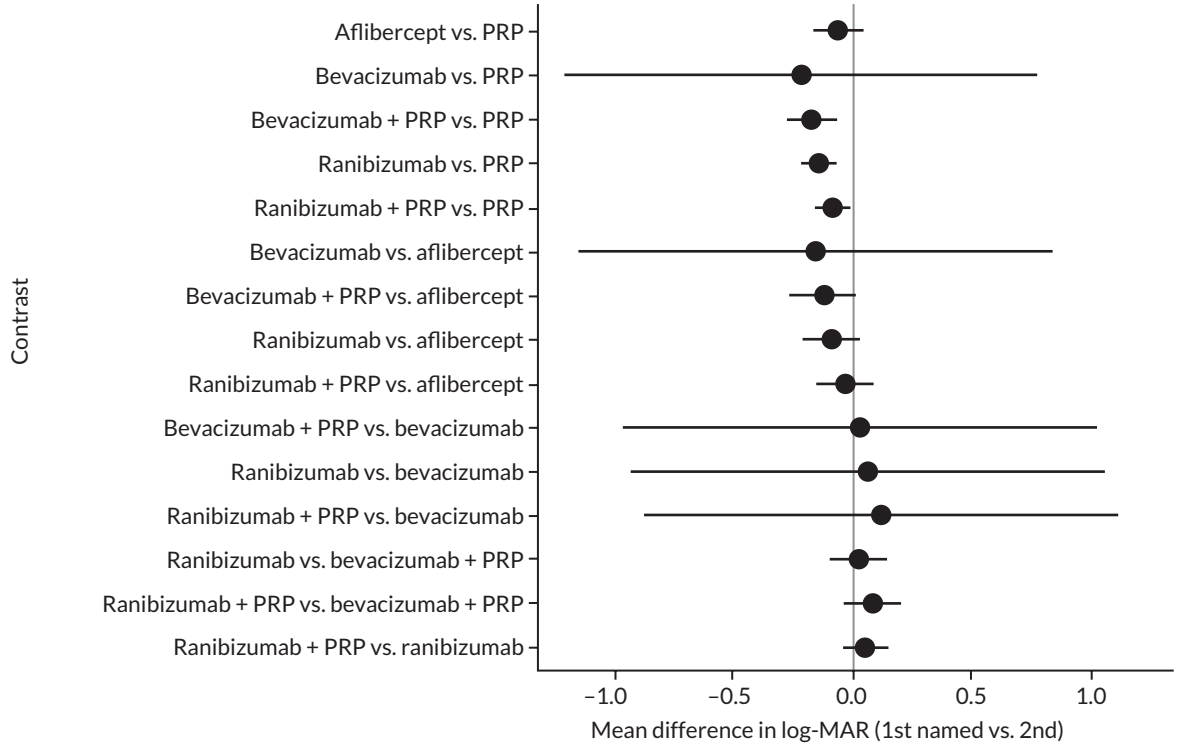

FIGURE 8 All treatment comparisons for up to 1-year random-effects NMA of log-MAR.

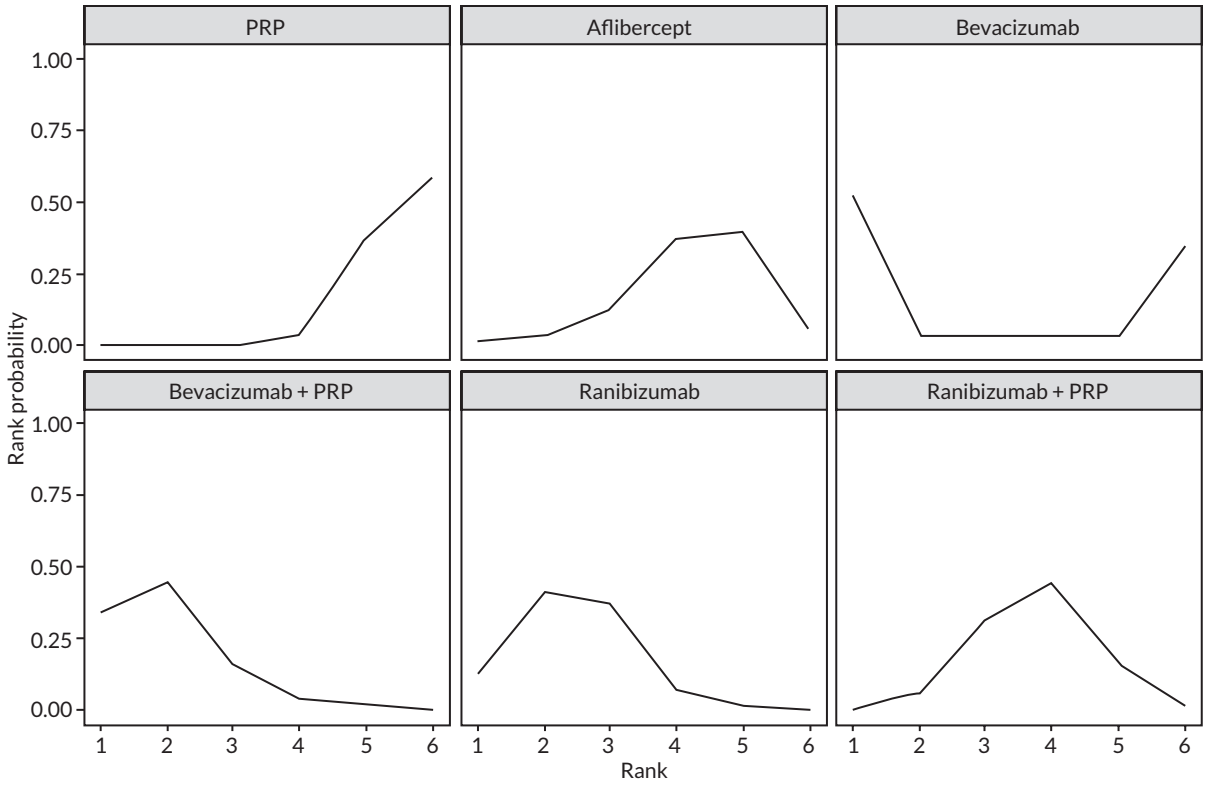

FIGURE 9 Probability of treatments for 1-year random-effects NMA of log-MAR.

TABLE 11 Results of NMA of log-MAR up to 1 year – comparisons between treatments

Treatment	Comparator	MD	95% CrI
Aflibercept	PRP	−0.055	−0.153 to 0.049
Bevacizumab	PRP	−0.205	−1.203 to 0.776
Bevacizumab + PRP	PRP	−0.172	−0.274 to −0.071
Ranibizumab	PRP	−0.139	−0.210 to −0.062
Ranibizumab + PRP	PRP	−0.082	−0.156 to −0.008
Bevacizumab	Aflibercept	−0.150	−1.150 to 0.844
Bevacizumab + PRP	Aflibercept	−0.117	−0.262 to 0.021
Ranibizumab	Aflibercept	−0.084	−0.208 to 0.042
Ranibizumab + PRP	Aflibercept	−0.027	−0.156 to 0.096
Bevacizumab + PRP	Bevacizumab	0.033	−0.955 to 1.036
Ranibizumab	Bevacizumab	0.066	−0.923 to 1.066
Ranibizumab + PRP	Bevacizumab	0.122	−0.864 to 1.126
Ranibizumab	Bevacizumab + PRP	0.033	−0.091 to 0.158
Ranibizumab + PRP	Bevacizumab + PRP	0.090	−0.038 to 0.216
Ranibizumab + PRP	Ranibizumab	0.057	−0.037 to 0.149

TABLE 12 Results of NMA of log-MAR up to 1 year – ranking probabilities

Treatment arm	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)	Rank 4th (%)	Rank 5th (%)	Rank 6th (%)
PRP	0.00	0.00	0.12	3.39	37.77	58.73
Aflibercept	1.28	3.56	12.41	37.14	39.82	5.80
Bevacizumab	51.39	3.81	3.54	2.91	3.86	34.50
Bevacizumab + PRP	33.57	45.08	15.65	4.47	1.15	0.10
Ranibizumab	12.89	41.38	37.45	6.99	1.28	0.03
Ranibizumab + PRP	0.89	6.18	30.84	45.13	16.12	0.86

Analyses at exactly 1 year follow-up

This analysis removes trials with short follow-up times and includes only results at exactly or nearly 1 year of follow-up, defined as between 48 and 60 weeks of follow-up.

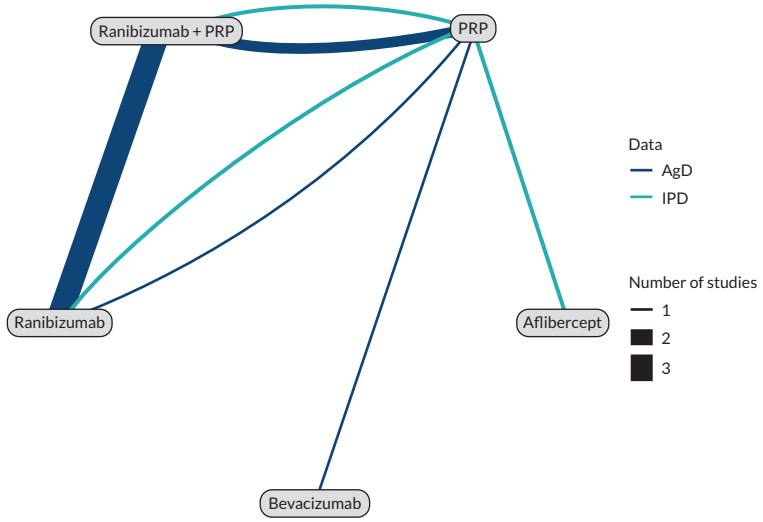

FIGURE 10 Network diagram of BCVA at exactly 1 year of follow-up. Note that all bevacizumab with PRP trials are now excluded from the analysis.

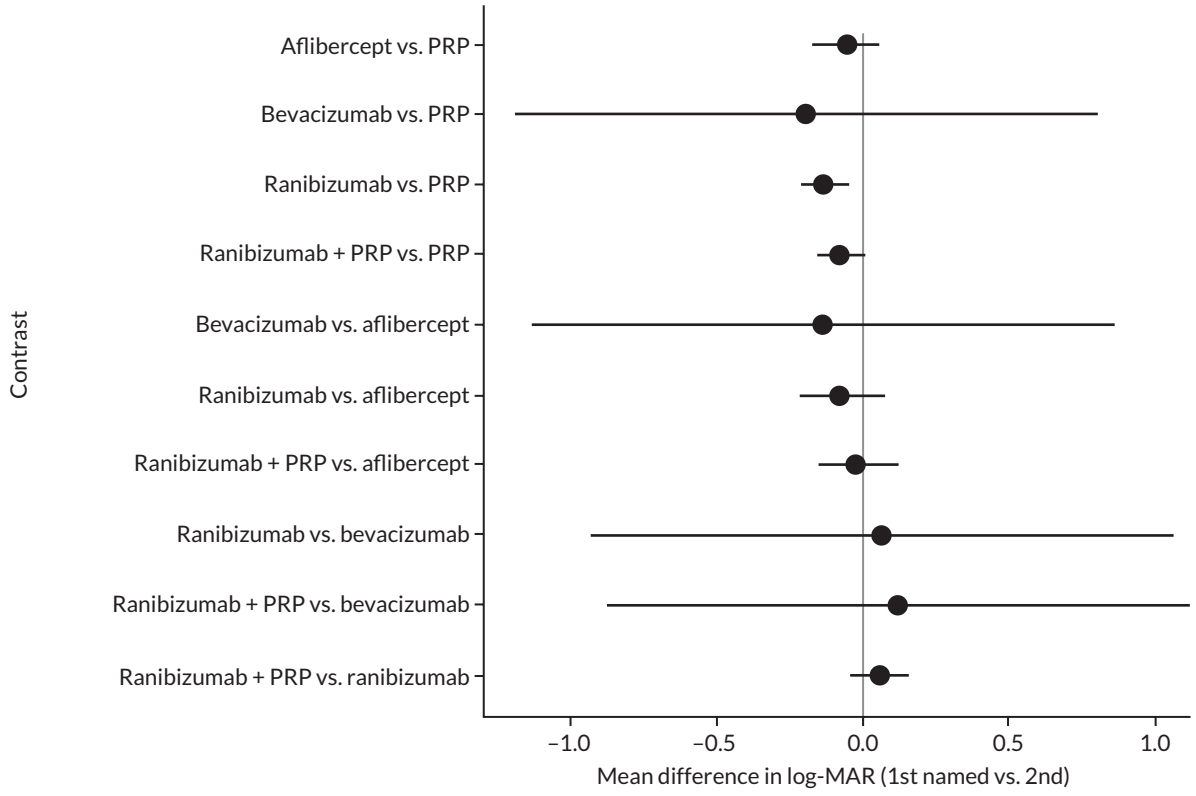

FIGURE 11 All treatment comparisons for random-effects NMA of log-MAR at exactly 1 year.

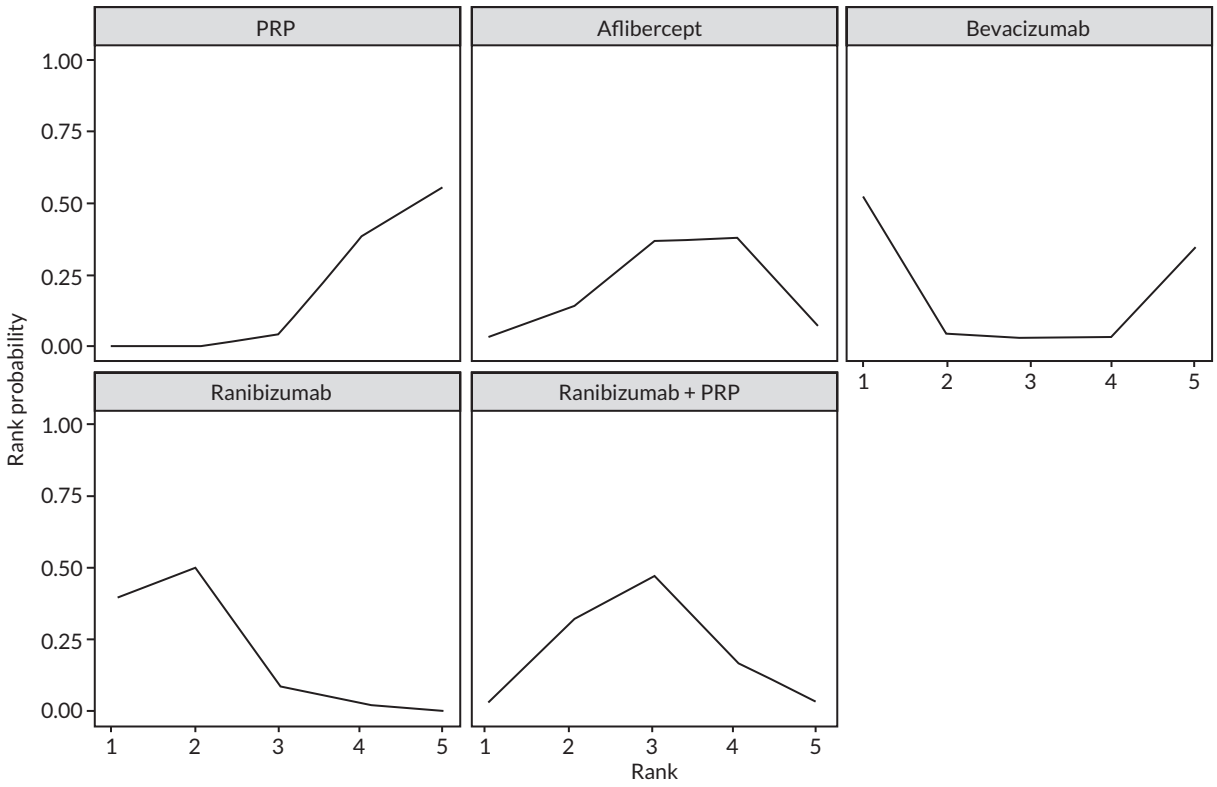

FIGURE 12 Probability of treatments for random-effects NMA of log-MAR at exactly 1 year.

TABLE 13 Results of NMA of log-MAR at exactly 1 year – comparisons between treatments

Treatment	Comparator	MD	95% CrI
Aflibercept	PRP	−0.057	−0.178 to 0.059
Bevacizumab	PRP	−0.199	−1.191 to 0.805
Ranibizumab	PRP	−0.137	−0.221 to −0.045
Ranibizumab + PRP	PRP	−0.082	−0.162 to −0.001
Bevacizumab	Aflibercept	−0.142	−1.135 to 0.867
Ranibizumab	Aflibercept	−0.080	−0.220 to 0.075
Ranibizumab + PRP	Aflibercept	−0.025	−0.157 to 0.121
Ranibizumab	Bevacizumab	0.062	−0.942 to 1.061
Ranibizumab + PRP	Bevacizumab	0.118	−0.886 to 1.111
Ranibizumab + PRP	Ranibizumab	0.055	−0.044 to 0.156

TABLE 14 Results of NMA of log-MAR at exactly 1 year – ranking probabilities

Treatment	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)	Rank 4th (%)	Rank 5th (%)
PRP	0.01	0.23	4.38	38.81	56.58
Aflibercept	3.52	14.10	36.90	38.47	7.02
Bevacizumab	53.46	4.82	3.21	3.74	34.78
Ranibizumab	39.31	50.31	8.30	1.88	0.21
Ranibizumab + PRP	3.71	30.55	47.22	17.11	1.42

Network meta-analyses allowing for follow-up time and best corrected visual acuity at baseline

Network meta-analyses incorporating variation in effect of anti-VEGF by follow-up duration and varying effect by log-MAR at randomisation. Time and log-MAR variation are assumed to be the same for all types of anti-VEGF. Results are presented for the predicted effects after 1 year of follow-up and at mean baseline BCVA across the available IPD (log-MAR 0.17, ETDRS 76.5).

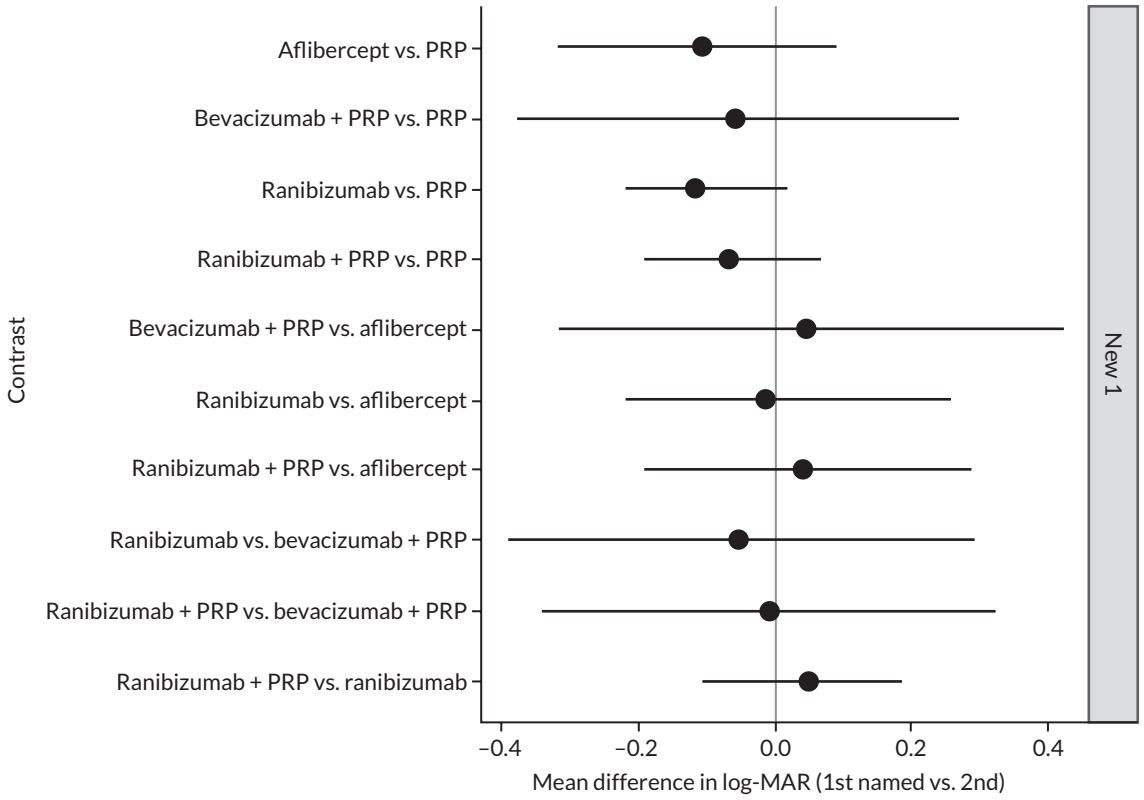

FIGURE 13 All treatment comparisons for time-adjusted and baseline BCVA-adjusted random-effects NMA of log-MAR.

TABLE 15 Results of NMA of log-MAR adjusting for time and baseline BCVA – comparisons between treatments

Comparison	MD	95% CrI
Aflibercept vs. PRP	−0.109	0.095 to −0.319
Bevacizumab + PRP vs. PRP	−0.060	0.161 to −0.377
Ranibizumab vs. PRP	−0.112	0.058 to −0.220
Ranibizumab + PRP vs. PRP	−0.067	0.061 to −0.192
Bevacizumab + PRP vs. aflibercept	0.049	0.186 to −0.319
Ranibizumab vs. aflibercept	−0.004	0.112 to −0.225
Ranibizumab + PRP vs. aflibercept	0.042	0.113 to −0.194
Ranibizumab vs. bevacizumab + PRP	−0.053	0.169 to −0.391
Ranibizumab + PRP vs. bevacizumab + PRP	−0.007	0.163 to −0.343
Ranibizumab + PRP vs. ranibizumab	0.046	0.073 to −0.111

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

TABLE 16 Results of NMA of log-MAR adjusting for time and baseline BCVA – ranking probabilities

Treatment	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)	Rank 4th (%)	Rank 5th (%)
PRP	0	1	9	36	54
Aflibercept	30	30	21	13	6
Bevacizumab + PRP	28	13	13	15	32
Ranibizumab	35	35	20	8	2
Ranibizumab + PRP	7	21	38	28	6

Excluding bevacizumab

TABLE 17 Results of NMA of log-MAR adjusting for time and baseline BCVA – excluding bevacizumab

Comparison	MD	95% CrI
Aflibercept vs. PRP	−0.105	−0.319 to 0.124
Ranibizumab vs. PRP	−0.112	−0.228 to 0.043
Ranibizumab + PRP vs. PRP	−0.073	−0.216 to 0.079
Ranibizumab vs. aflibercept	−0.007	−0.250 to 0.269
Ranibizumab + PRP vs. aflibercept	0.032	−0.243 to 0.301
Ranibizumab + PRP vs. ranibizumab	0.039	−0.147 to 0.192

Network meta-analyses of reduced networks

Assuming anti-vascular endothelial growth factor and anti-vascular endothelial growth factor + panretinal photocoagulation are equivalent

This analysis assumes that anti-VEGF only arms and anti-VEGF + PRP arms have equal effect. To be used to assess differences between anti-VEGF types. A model allowing effect to vary with time and baseline log-MAR was used. Results are presented for the predicted effects after 1 year of follow-up and at mean baseline BCVA across the IPD.

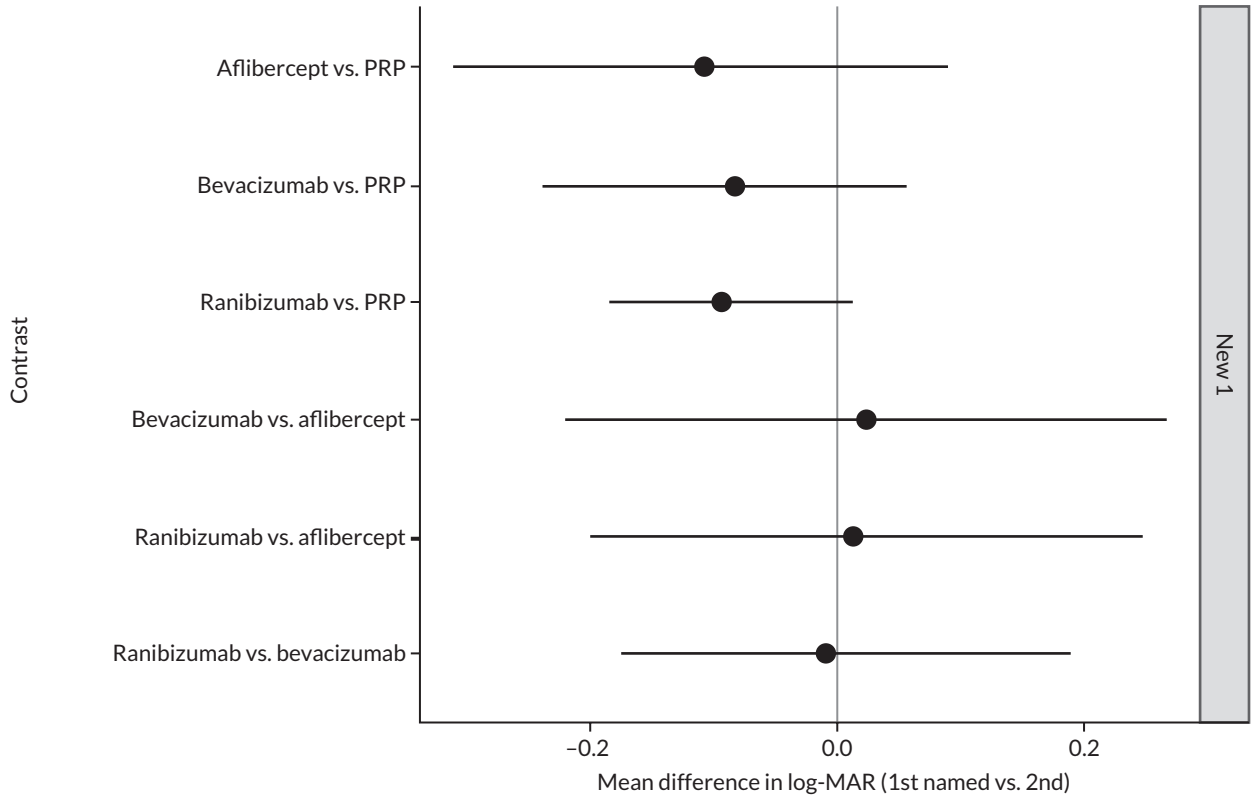

FIGURE 14 Results from a reduced network to compare anti-VEGFs.

TABLE 18 Results of reduced network to compare anti-VEGFs – comparisons between treatments

Treatment	Comparator	MD	95% CrI
Aflibercept	PRP	−0.108	−0.310 to 0.090
Bevacizumab	PRP	−0.086	−0.239 to 0.058
Ranibizumab	PRP	−0.091	−0.184 to 0.012
Bevacizumab	Aflibercept	0.023	−0.224 to 0.265
Ranibizumab	Aflibercept	0.017	−0.197 to 0.250
Ranibizumab	Bevacizumab	−0.005	−0.174 to 0.183

TABLE 19 Results of reduced network to compare anti-VEGFs – ranking probabilities

Treatment	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)	Rank 4th (%)
PRP	0	2	21	77
Aflibercept	44	27	20	9
Bevacizumab	29	28	32	11
Ranibizumab	26	43	27	3

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

Assuming all types of anti-vascular endothelial growth factor are equivalent

This analysis assumes that all three anti-VEGF drugs have equal effect. To be used to assess the overall effect of anti-VEGF. A model allowing effect to vary with time and baseline log-MAR was used.

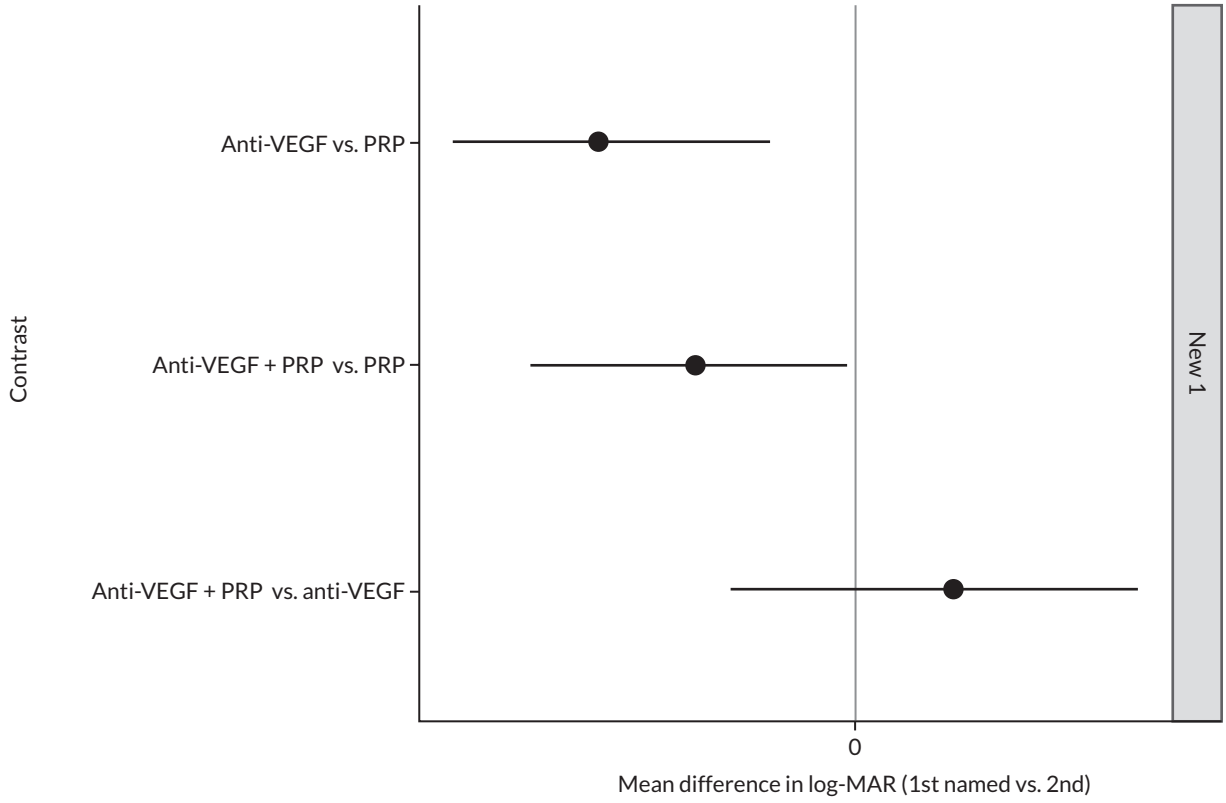

FIGURE 15 Results from a reduced network to compare treatment classes.

TABLE 20 Results of reduced network to compare treatment classes – comparisons between treatments

Treatment	Comparator	MD	95% CI
Anti-VEGF	PRP	−0.116	−0.183 to −0.038
Anti-VEGF + PRP	PRP	−0.074	−0.149 to −0.004
Anti-VEGF + PRP	Anti-VEGF	0.042	−0.057 to 0.127

TABLE 21 Results of reduced network to compare treatment classes – ranking probabilities

Treatment	*p*_rank[1] (%)	*p*_rank[2] (%)	*p*_rank[3] (%)
PRP	0	2	98
Anti-VEGF	84	15	0
Anti-VEGF + PRP	16	82	2

Excluding bevacizumab

TABLE 22 Results of reduced network to compare treatment classes – excluding bevacizumab

Treatment	Comparator	MD	95% CI
Anti-VEGF	PRP	−0.117	−0.175 to −0.044
Anti-VEGF + PRP	PRP	−0.068	−0.147 to 0.007
Anti-VEGF + PRP	Anti-VEGF	0.048	−0.049 to 0.132

Threshold analyses

Contrast	log-MAR	95% CrI	Invariant interval		
Bevacizumab + PRP vs. PRP	−0.17	(−0.28 to −0.06)	–	(NT to −0.14)	Ranibizumab
Ranibizumab + PRP vs. PRP	−0.08	(−0.17 to 0.02)	Ranibizumab + PRP	(−0.20 to NT)	–
Ranibizumab vs. PRP	−0.14	(−0.22 to −0.05)	Ranibizumab	(−0.18 to NT)	–
Bevacizumab vs. PRP	−0.10	(−0.27 to 0.07)	Bevacizumab	(−0.17 to 0.73)	Ranibizumab
Aflibercept vs. PRP	−0.04	(−0.16 to 0.09)	Aflibercept	(−0.17 to 0.70)	Ranibizumab
Ranibizumab vs. ranibizumab + PRP	−0.06	(−0.17 to 0.05)	Ranibizumab	(−0.25 to 0.33)	Ranibizumab + PRP

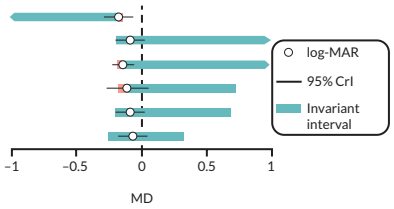

FIGURE 16 Threshold analysis of NMA at up to 1 year of follow-up.

Contrast	log-MAR	95% CrI	Invariant interval		
Bevacizumab + PRP vs. PRP	−0.05	(−0.41 to 0.33)	Bevacizumab vs. PRP	(−0.10 to NT)	–
Ranibizumab + PRP vs. PRP	−0.06	(−0.25 to 0.13)	Ranibizumab + PRP	(−0.14 to −0.03)	Bevacizumab
Ranibizumab vs. PRP	−0.10	(−0.25 to 0.07)	–	(NT to −0.10)	Bevacizumab
Bevacizumab vs. PRP	−0.10	(−0.39 to 0.19)	Bevacizumab	(−0.10 to 2.69)	Bevacizumab + PRP
Aflibercept vs. PRP	−0.09	(−0.35 to 0.18)	Aflibercept	(−0.10 to NT)	–
Ranibizumab vs. ranibizumab + PRP	−0.05	(−0.23 to 0.17)	–	(NT to −0.03)	Bevacizumab

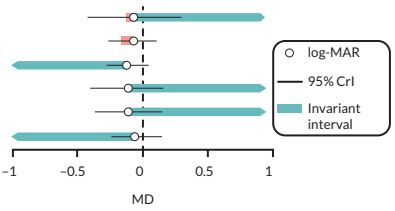

FIGURE 17 Threshold analysis of NMA adjusted for follow-up time and baseline BCVA.

Contrast	log-MAR	95% CrI	Invariant interval		
Ranibizumab vs. PRP	−0.07	(−0.18 to 0.20)	Aflibercept	(−0.08 to NT)	–
Bevacizumab vs. PRP	−0.10	(−0.36 to 0.05)	–	(NT to −0.09)	Aflibercept
Aflibercept vs. PRP	−0.08	(−0.30 to 0.11)	Aflibercept	(−0.09 to NT)	–

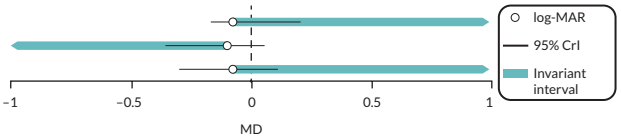

FIGURE 18 Threshold analysis for NMA assuming anti-VEGF and anti-VEGF + PRP are equivalent.

Contrast	log-MAR	95% CrI	Invariant interval		
Anti-VEGF vs. PRP	−0.10	(−0.18 to 0.01)	–	(NT to -0.03)	**Anti-VEGF + PRP**
Anti-VEGF + PRP vs. PRP	−0.07	(−0.15 to 0.01)	**Anti-VEGF + PRP**	(-0.14 to 0.23)	**PRP**
Anti-VEGF + PRP vs. anti-VEGF	0.03	(−0.09 to 0.13)	**Anti-VEGF + PRP**	(-0.03 to NT)	–

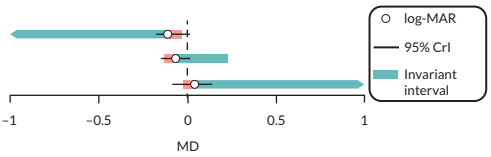

FIGURE 19 Threshold analysis for NMA assuming all types of anti-VEGF are equivalent.

Appendix 3 Network meta-analyses of best corrected visual acuity (as ETDRS)

Analyses at up to 1 year of follow-up

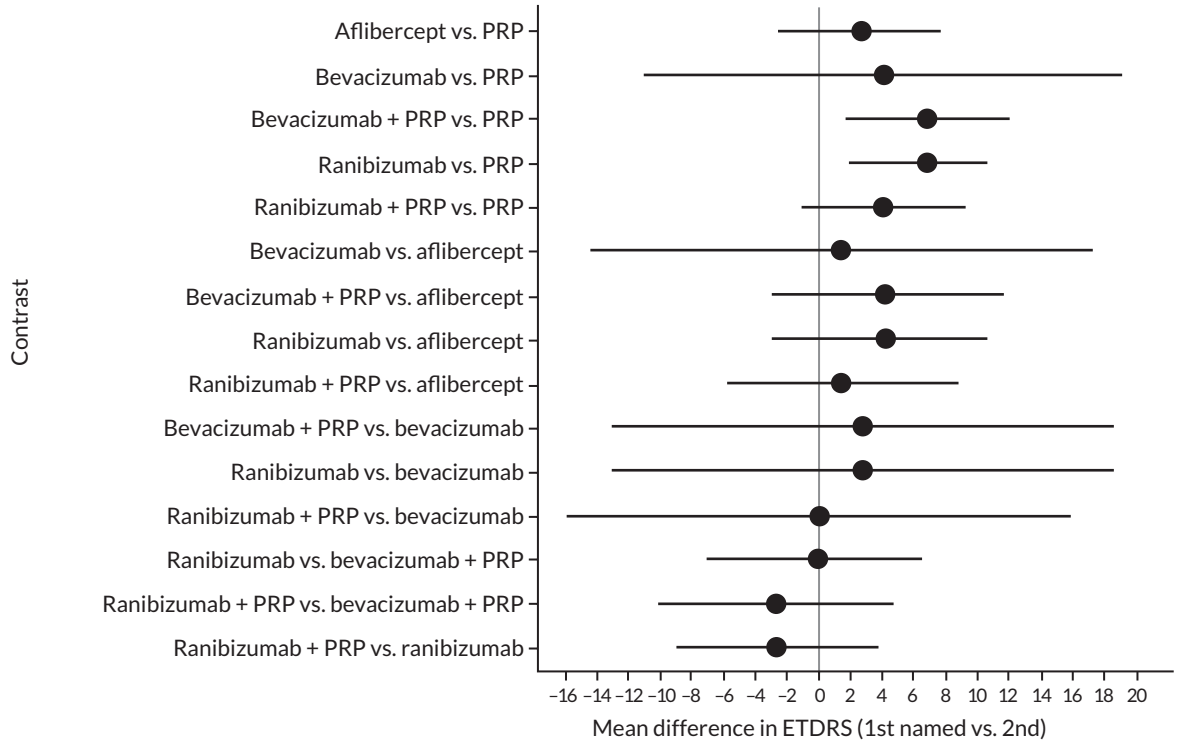

FIGURE 20 All treatment comparisons for up to 1-year random-effects NMA of ETDRS.

TABLE 23 Results of NMA of ETDRS up to 1 year – comparisons between treatments

Treatment	Comparator	MD	95% CrI
Aflibercept	PRP	2.642	−2.667 to 7.785
Bevacizumab	PRP	4.102	−10.991 to 19.142
Bevacizumab + PRP	PRP	6.846	1.582 to 12.129
Ranibizumab	PRP	6.751	1.950 to 10.765
Ranibizumab + PRP	PRP	4.065	−1.169 to 9.130
Bevacizumab	Aflibercept	1.460	−14.367 to 17.366
Bevacizumab + PRP	Aflibercept	4.204	−3.072 to 11.491
Ranibizumab	Aflibercept	4.109	−3.037 to 10.653
Ranibizumab + PRP	Aflibercept	1.422	−5.741 to 8.707
Bevacizumab + PRP	Bevacizumab	2.744	−13.158 to 18.683
Ranibizumab	Bevacizumab	2.649	−13.033 to 18.271
Ranibizumab + PRP	Bevacizumab	−0.037	−16.041 to 15.901
Ranibizumab	Bevacizumab + PRP	−0.095	−7.158 to 6.462
Ranibizumab + PRP	Bevacizumab + PRP	−2.781	−10.244 to 4.509
Ranibizumab + PRP	Ranibizumab	−2.687	−8.827 to 3.693

TABLE 24 Results of NMA of log-MAR up to 1 year – ranking probabilities

Treatment arm	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)	Rank 4th (%)	Rank 5th (%)	Rank 6th (%)
PRP	0.00	0.67	7.54	37.03	54.77	0.00
Aflibercept	3.21	10.82	32.80	38.58	13.39	3.21
Bevacizumab	10.85	11.59	12.31	8.55	27.47	10.85
Bevacizumab + PRP	32.79	22.20	9.26	2.22	0.35	32.79
Ranibizumab	38.34	22.76	7.03	1.44	0.25	38.34
Ranibizumab + PRP	14.82	31.97	31.07	12.19	3.78	14.82

Network meta-analyses allowing for follow-up time and best corrected visual acuity at baseline

Network meta-analyses incorporating variation in effect of anti-VEGF by follow-up duration and varying effect by ETDRS at randomisation. Time and ETDRS variation are assumed to be the same for all types of anti-VEGF. Results are presented for the predicted effects after 1 year of follow-up and at mean baseline BCVA across the available IPD (log-MAR 0.17, ETDRS 76.5).

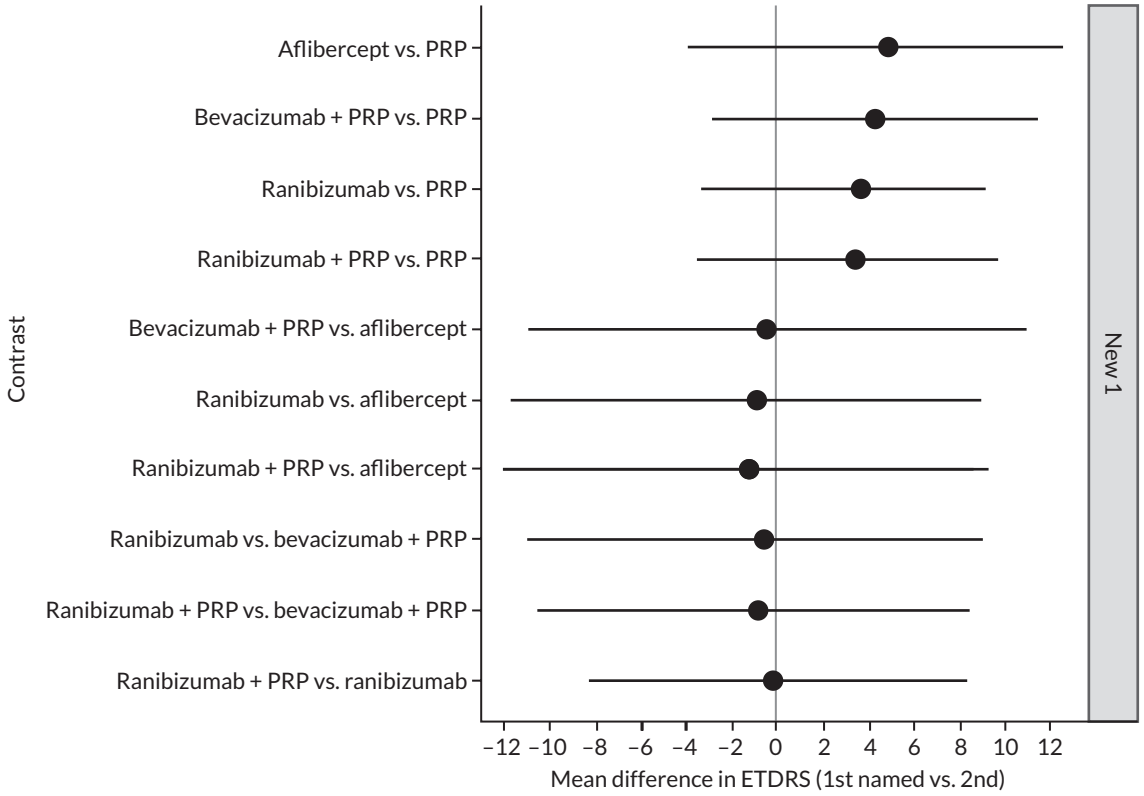

FIGURE 21 All treatment comparisons for time-adjusted and baseline BCVA-adjusted random-effects NMA of ETDRS.

TABLE 25 Results of NMA of ETDRS adjusting for time and baseline BCVA – comparisons between treatments

Comparison	MD	95% CrI
Aflibercept vs. PRP	4.563	−4.088 to 12.442
Bevacizumab + PRP vs. PRP	4.200	−2.889 to 11.374
Ranibizumab vs. PRP	3.417	−3.345 to 9.159
Ranibizumab + PRP vs. PRP	3.314	−3.491 to 9.613
Bevacizumab + PRP vs. aflibercept	−0.363	−10.866 to 10.945
Ranibizumab vs. aflibercept	−1.146	−11.808 to 8.891
Ranibizumab + PRP vs. aflibercept	−1.249	−11.555 to 9.276
Ranibizumab vs. bevacizumab + PRP	−0.784	−10.922 to 8.506
Ranibizumab + PRP vs. bevacizumab + PRP	−0.886	−10.572 to 8.332
Ranibizumab + PRP vs. ranibizumab	−0.102	−8.265 to 8.301

TABLE 26 Results of NMA of ETDRS adjusting for time and baseline BCVA – ranking probabilities

Treatment	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)	Rank 4th (%)	Rank 5th (%)
PRP	0	2	9	30	59
Aflibercept	34	25	19	13	10
Bevacizumab + PRP	29	24	19	17	10
Ranibizumab	20	25	26	19	11
Ranibizumab + PRP	17	24	26	21	11

Excluding bevacizumab

TABLE 27 Results of NMA of ETDRS adjusting for time and baseline BCVA – excluding bevacizumab

Comparison	MD	95% CrI
Aflibercept vs. PRP	2.625	−2.721 to 7.353
Ranibizumab vs. PRP	6.825	2.250 to 10.630
Ranibizumab + PRP vs. PRP	4.039	−1.154 to 9.143
Ranibizumab vs. aflibercept	4.199	−2.543 to 10.475
Ranibizumab + PRP vs. aflibercept	1.413	−5.626 to 8.537
Ranibizumab + PRP vs. ranibizumab	−2.786	−8.965 to 3.588

Network meta-analyses of reduced networks

Assuming anti-vascular endothelial growth factor and anti-vascular endothelial growth factor + panretinal photocoagulation are equivalent

This analysis assumes that anti-VEGF only arms and anti-VEGF + PRP arms have equal effect. To be used to assess differences between anti-VEGF types. A model allowing effect to vary with time and baseline ETDRS was used. Results are presented for the predicted effects after 1 year of follow-up and at mean baseline BCVA across the IPD.

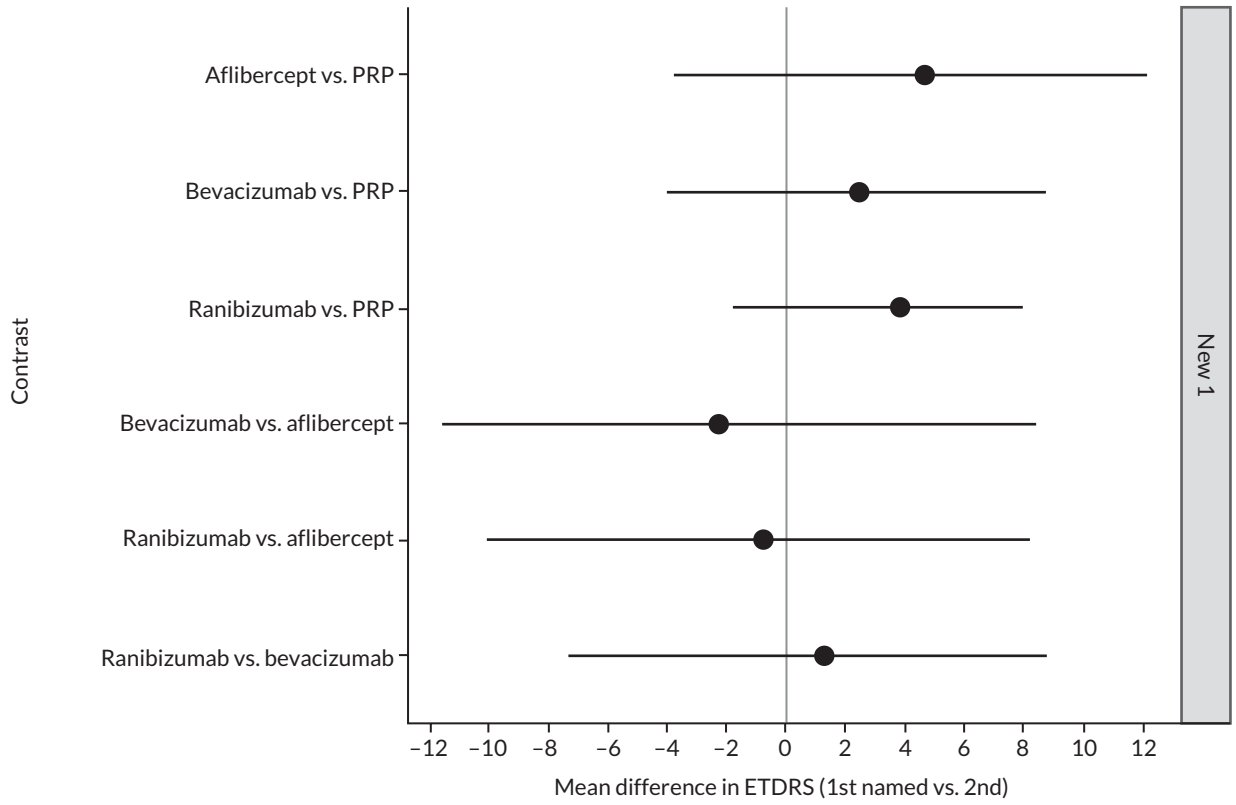

FIGURE 22 Results from a reduced network to compare anti-VEGFs.

TABLE 28 Results of reduced network to compare anti-VEGFs – comparisons between treatments

Treatment	Comparator	MD	95% CrI
Aflibercept	PRP	4.465	−3.862 to 12.137
Bevacizumab	PRP	2.431	−3.985 to 8.820
Ranibizumab	PRP	3.605	−1.718 to 8.050
Bevacizumab	Aflibercept	−2.035	−11.576 to 8.432
Ranibizumab	Aflibercept	−0.860	−10.184 to 8.228
Ranibizumab	Bevacizumab	1.175	−7.324 to 8.865

TABLE 29 Results of reduced network to compare anti-VEGFs – ranking probabilities

Treatment	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)	Rank 4th (%)
PRP	0	5	30	64
Aflibercept	48	27	15	10
Bevacizumab	20	26	34	20
Ranibizumab	31	42	21	6

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

Assuming all types of anti-vascular endothelial growth factor are equivalent

This analysis assumes that all three anti-VEGF drugs have equal effect. To be used to assess the overall effect of anti-VEGF. A model allowing effect to vary with time and baseline ETDRS was used.

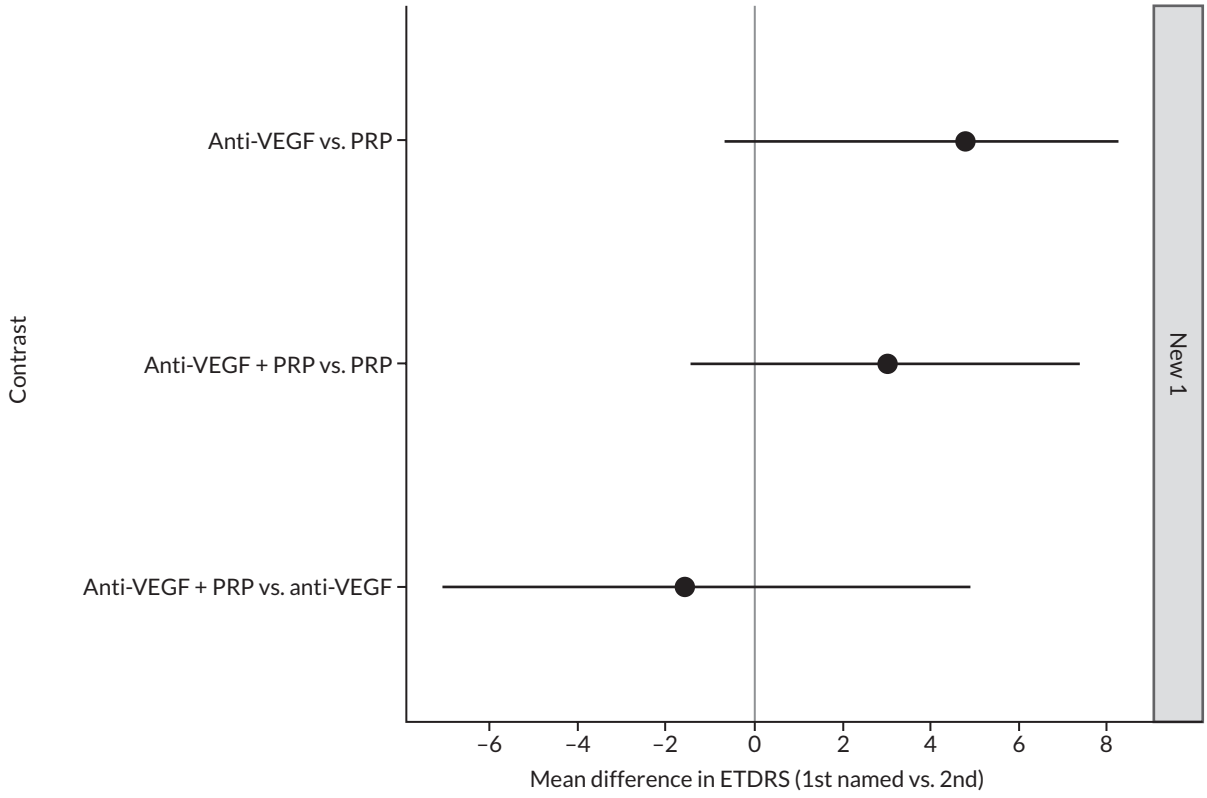

FIGURE 23 Results from a reduced network to compare treatment classes.

TABLE 30 Results of reduced network to compare treatment classes – comparisons between treatments

Treatment	Comparator	MD	95% CI
Anti-VEGF	PRP	4.464	−0.724 to 8.262
Anti-VEGF + PRP	PRP	2.993	−1.489 to 7.387
Anti-VEGF + PRP	Anti-VEGF	−1.471	−7.160 to 4.945

TABLE 31 Results of reduced network to compare treatment classes – ranking probabilities

Treatment	Rank 1st (%)	Rank 2nd (%)	Rank 3rd (%)
PRP	1	11	88
Anti-VEGF	71	26	4
Anti-VEGF + PRP	29	63	8

Excluding bevacizumab

TABLE 32 Results of reduced network to compare treatment classes – excluding bevacizumab

Treatment	Comparator	MD	95% CI
Anti-VEGF	PRP	4.565	−0.952 to 8.474
Anti-VEGF + PRP	PRP	3.345	−2.908 to 9.073
Anti-VEGF + PRP	Anti-VEGF	−1.220	−7.977 to 6.119

Appendix 4 Results and meta-analyses of other outcomes

This appendix presents tables and figures for all analyses, using IPD and data from where IPD were not collected for outcomes other than BCVA. These mostly consist of forest plots without meta-analysis, because the evidence was generally too limited in extent, and too diverse in intervention and follow-up times, to justify a full meta-analysis.

Forest plots of outcomes

These forest plots show results for all anti-VEGF types, at 1 year of follow-up (or less if trial had shorter follow-up). Meta-analyses assume the same effect for all types of anti-VEGF, and at all trial durations (but allowing for heterogeneity).

Diabetic macular oedema

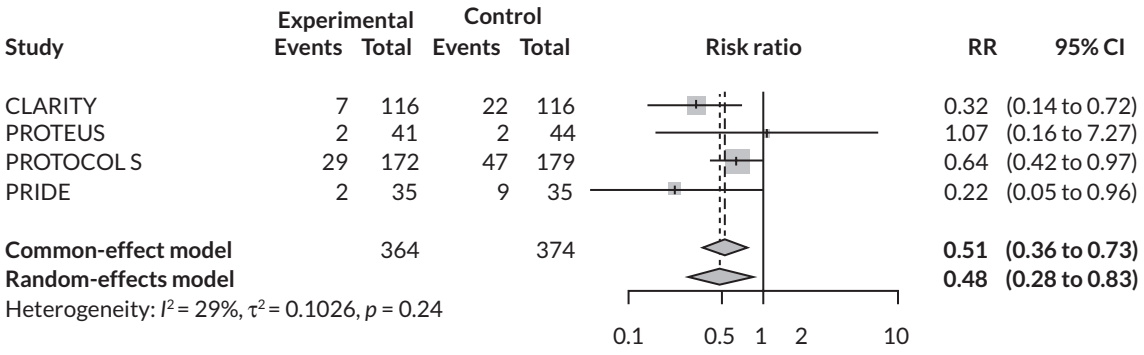

FIGURE 24 Forest plot of DMO incidence (left side favours anti-VEGF).

Vitrectomy

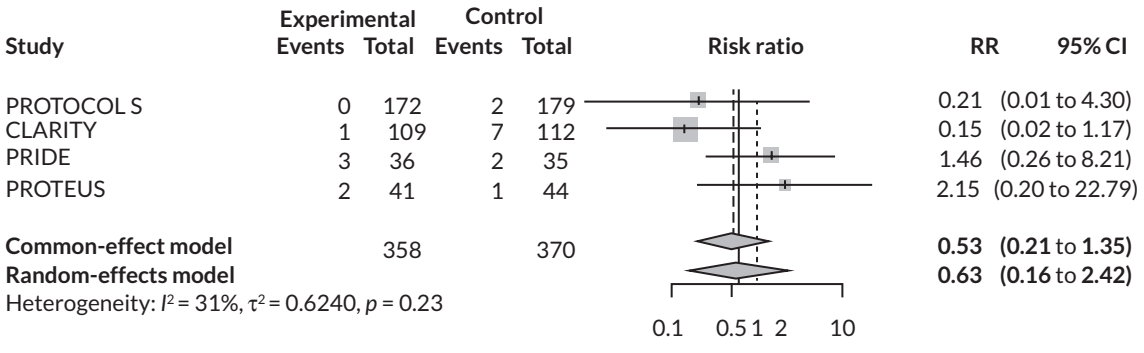

FIGURE 25 Forest plot of vitrectomy incidence (left side favours anti-VEGF).

Vitreous haemorrhage

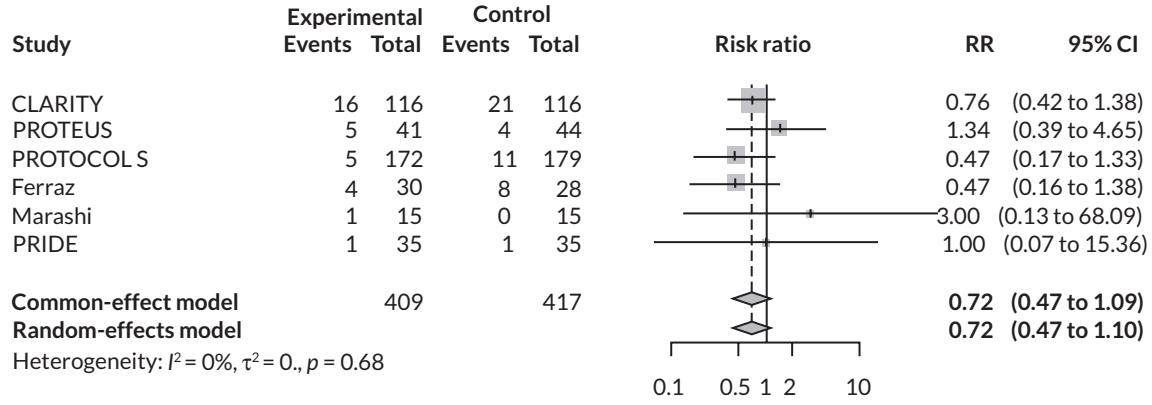

FIGURE 26 Forest plot of vitreous haemorrhage incidence (left side favours anti-VEGF).

Neovascularisation of the disc

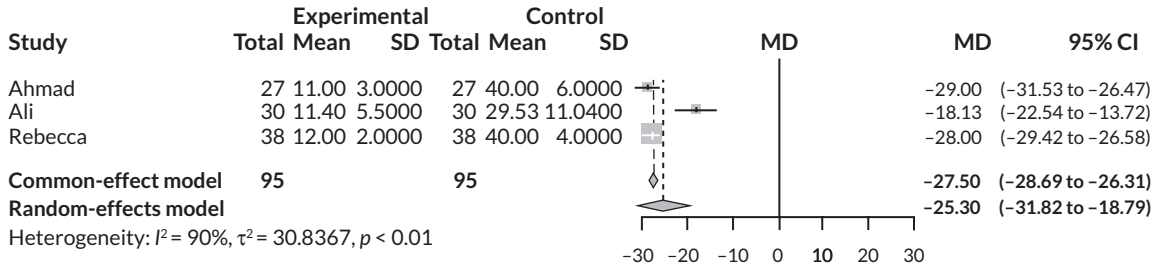

FIGURE 27 Forest plot of all neovascularisation of the disc data (left side favours anti-VEGF).

Neovascularisation elsewhere

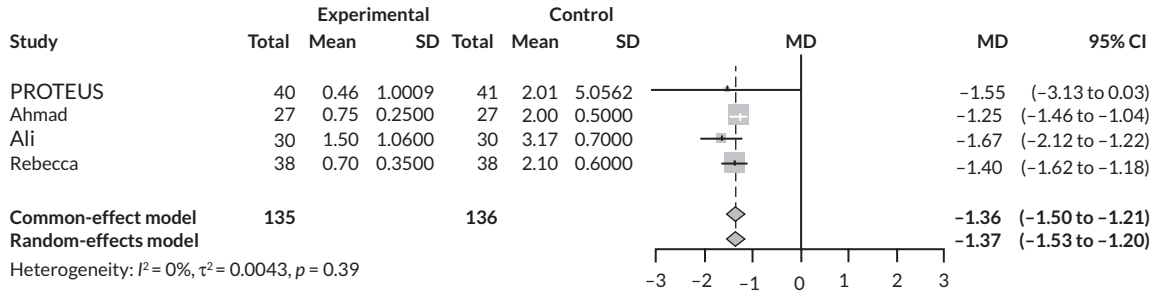

FIGURE 28 Forest plot of all neovascularisation elsewhere data (left side favours anti-VEGF).

Use of other treatments

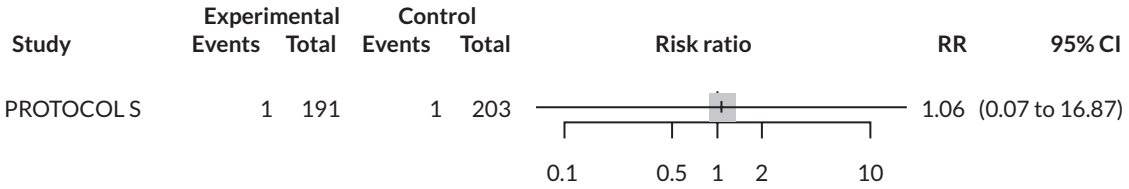

FIGURE 29 Forest plot of use of other treatments (left side favours anti-VEGF).

Adverse event outcomes

These forest plots show results for all anti-VEGF types, and at all follow-up times. As reporting of adverse events was limited, forest plots for each adverse event type are presented without meta-analysis. Trials where no events were reported are excluded from p lots.

Cataracts

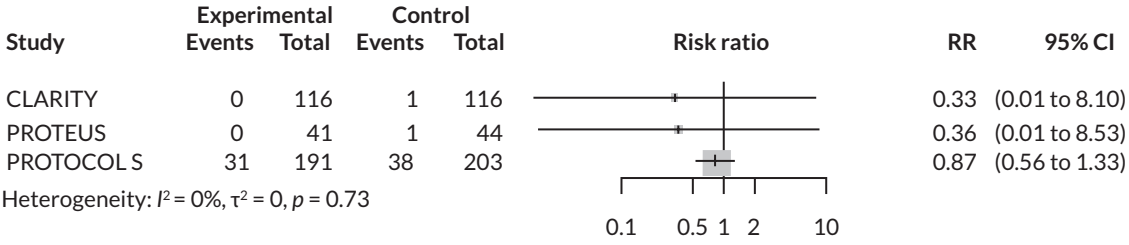

FIGURE 30 Forest plot of cataracts data (left side favours anti-VEGF).

Conjunctival haemorrhage

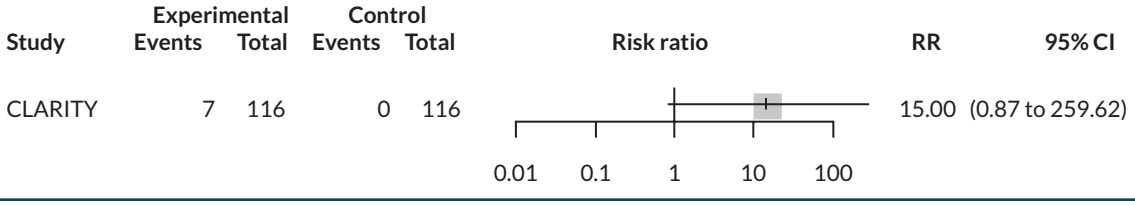

FIGURE 31 Forest plot of conjunctival haemorrhage data (left side favours anti-VEGF).

Cardiovascular mortality

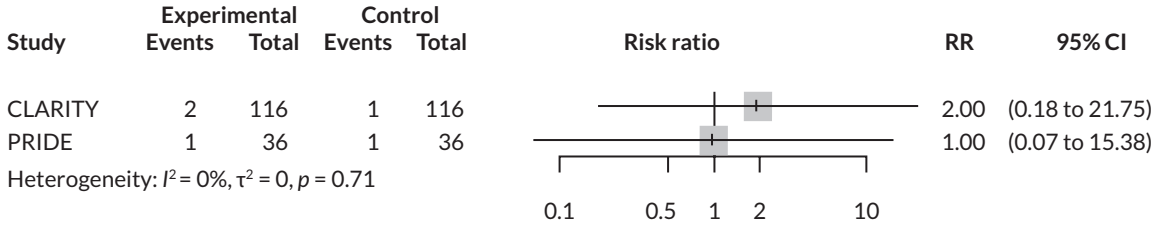

FIGURE 32 Forest plot of cardiovascular mortality data (left side favours anti-VEGF).

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

Death (all-cause mortality)

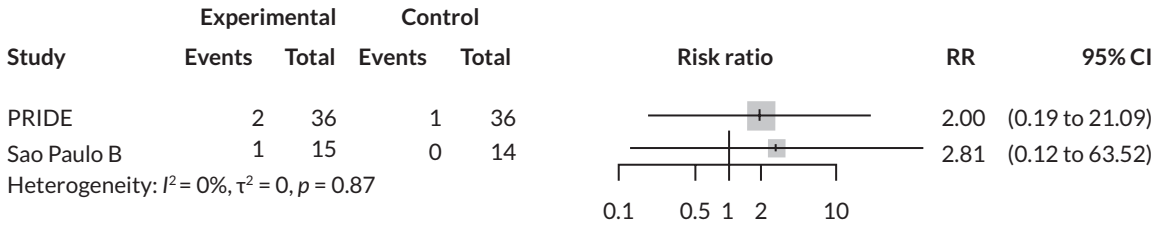

FIGURE 33 Forest plot of death data (left side favours anti-VEGF).

Macular fibrosis

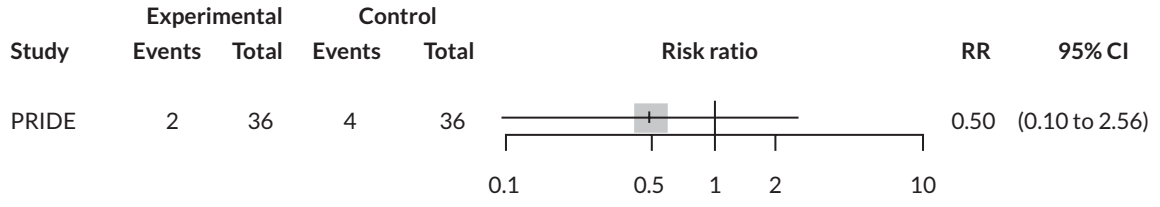

FIGURE 34 Forest plot of macular fibrosis data (left side favours anti-VEGF).

Myocardial infarction

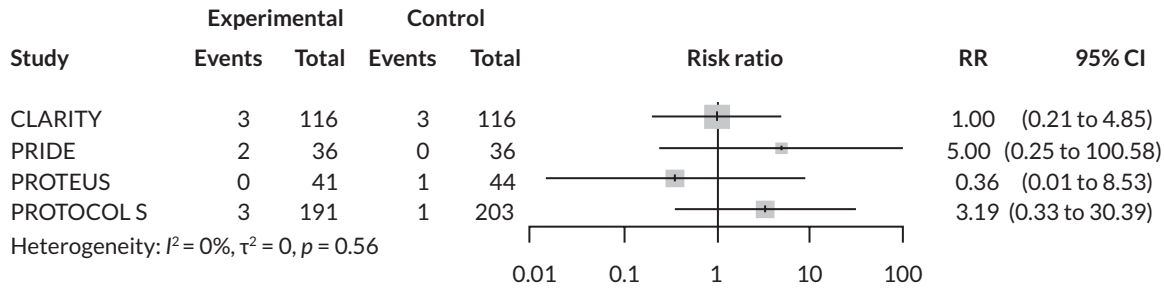

FIGURE 35 Forest plot of myocardial infarction data (left side favours anti-VEGF).

Ocular pain

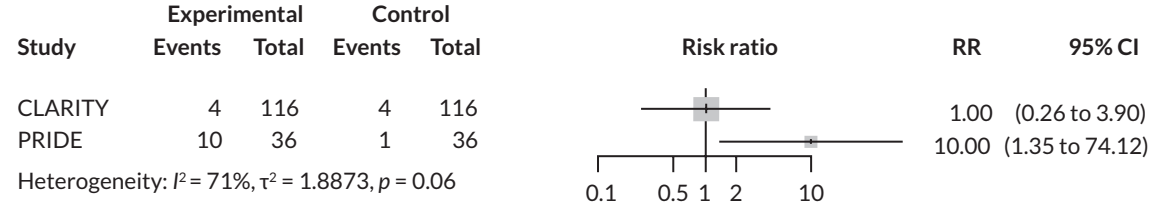

FIGURE 36 Forest plot of ocular pain data (left side favours anti-VEGF).

Raised intraocular pressure

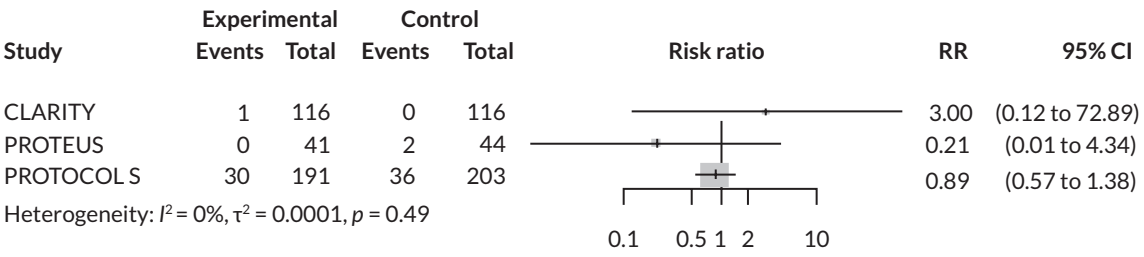

FIGURE 37 Forest plot of raised intraocular pressure data (left side favours anti-VEGF).

Retinal detachment

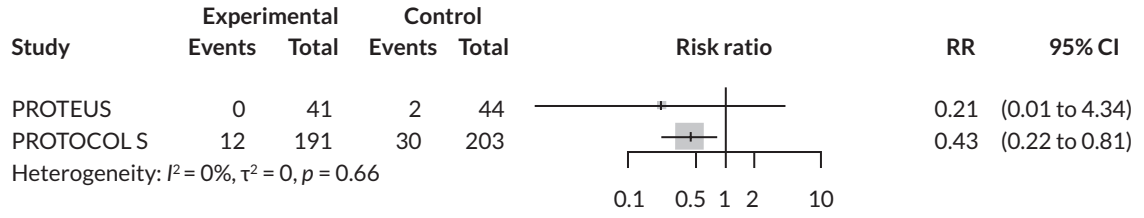

FIGURE 38 Forest plot of retinal detachment data (left side favours anti-VEGF).

Retinal neovascularisation

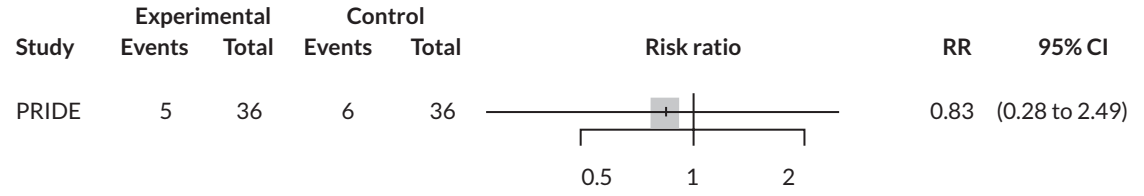

FIGURE 39 Forest plot of regressive neovascularisation (left side favours anti-VEGF).

Retinal tear

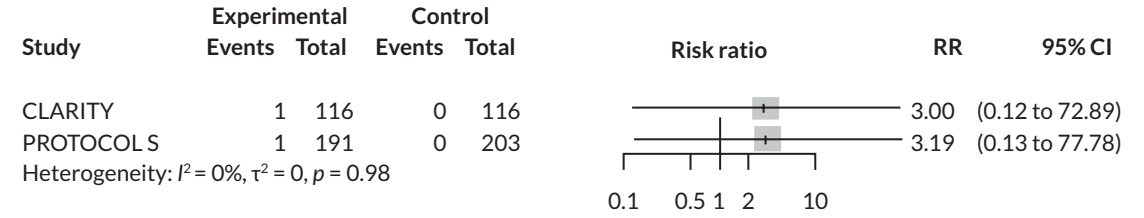

FIGURE 40 Forest plot of retinal data (left side favours anti-VEGF).

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

Serious adverse event (however defined)

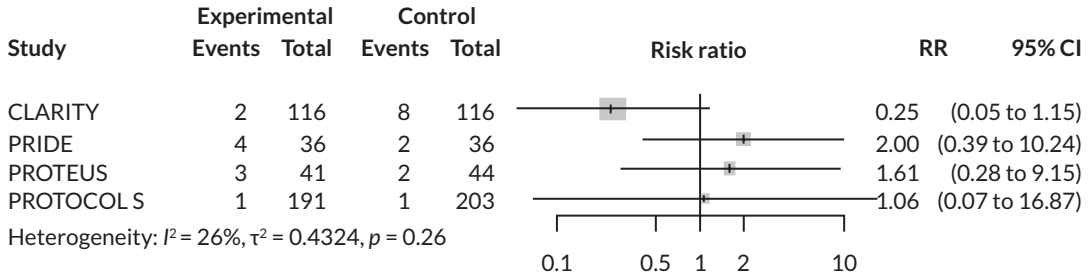

FIGURE 41 Forest plot of SAE data (left side favours anti-VEGF).

Stroke

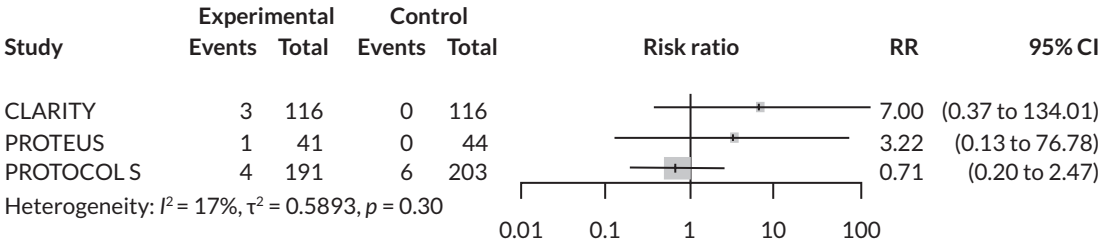

FIGURE 42 Forest plot of stroke data (left side favours anti-VEGF).

Visual disturbances

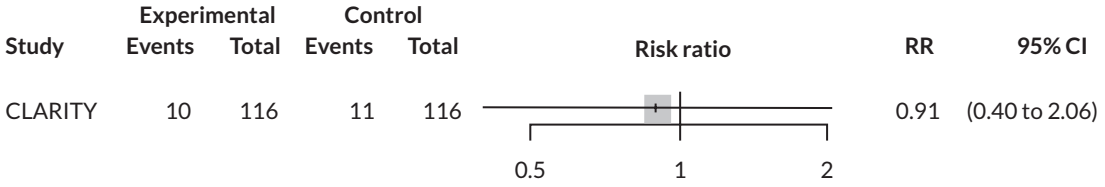

FIGURE 43 Forest plot of visual disturbances data (left side favours anti-VEGF).

Meta-analysis of adverse events

This forest plot shows the summary results of each meta-analysis (each bar is a meta-analysis result). Results are presented only for adverse events reported in two or more trials.

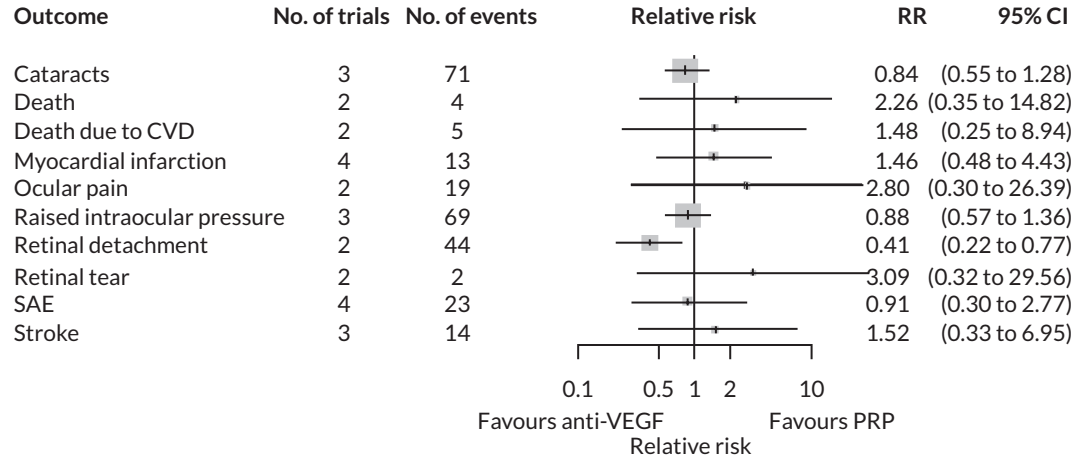

FIGURE 44 Meta-analysis summary for adverse events (left side favours anti-VEGF). CVD, cardiovascular disease.

Appendix 5 Complete results of all analyses of individual participant data trials

This document presents tables and figures for all analyses, including meta-analyses, using data from the three trials (CLARITY, PROTEUS, PROTOCOL S) for which IPD were available.

All analyses were performed using linear mixed-effect models (for BCVA and CST) or logistic mixed-effect models (for all other, binary, outcomes). Random effects were applied to the trial intercept parameters and to the treatment parameters. All other parameters were assumed common to all trials. As only three trials were included, it was not possible to compare anti-VEGFs, so all anti-VEGFs in these trials (aflibercept, ranibizumab and ranibizumab with PRP) are assumed to have the same overall effectiveness for all outcomes (but with random effects across the trials).

Analyses were performed as follows:

1. Repeated-measures analyses of the overall effect of anti-VEGF treatment, at 1, 2 and 5 years follow-up.
2. Meta-regression models at 1 year of follow-up to investigate any interaction between anti-VEGFs and key patient characteristics.

For BCVA, analyses were performed using both ETDRS and log-MAR as outcomes.

Analyses of best corrected visual acuity

Analyses of anti-vascular endothelial growth factor versus panretinal photocoagulation at 1, 2 and 5 years

TABLE 33 Analyses of BCVA

		Log-MAR		ETDRS	
Time	**Parameter**	**MD**	**95% CI**	**MD**	**95% CI**
1 year	Anti-VEGF vs. PRP	−0.071	−0.119 to −0.023	3.548	1.16 to 5.937
2 years (PROTOCOL S only)	Anti-VEGF vs. PRP	−0.07	−0.137 to −0.004	3.519	0.207 to 6.831
5 years (PROTOCOL S only)	Anti-VEGF vs. PRP	0.02	−0.059 to 0.098	−0.987	−4.908 to 2.934

Repeated-measures analyses of anti-vascular endothelial growth factor versus panretinal photocoagulation

TABLE 34 Repeated-measures analysis of BCVA

		Log-MAR		ETDRS	
Time	**Parameter**	**MD**	**95% CI**	**MD**	**95% CI**
1 year	Anti-VEGF vs. PRP	−0.074	−0.13 to −0.018	3.724	0.925 to 6.524
	Time (PRP arm)	−0.005	−0.039 to 0.029	0.247	−1.449 to 1.943
	Time × anti-VEGF interaction	0.007	−0.041 to 0.054	−0.339	−2.709 to 2.031
2 years	Anti-VEGF vs. PRP	−0.073	−0.128 to −0.017	3.647	0.875 to 6.419
	Time (PRP arm)	−0.003	−0.023 to 0.018	0.138	−0.888 to 1.164
	Time × anti-VEGF interaction	0.014	−0.015 to 0.042	−0.685	−2.101 to 0.731
5 years	Anti-VEGF vs. PRP	−0.062	−0.115 to −0.01	3.122	0.502 to 5.742
	Time (PRP arm)	−0.013	−0.022 to −0.004	0.637	0.188 to 1.085
	Time × anti-VEGF interaction	0.037	0.025 to 0.05	−1.862	−2.489 to −1.235

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

Meta-regression analyses

TABLE 35 Baseline properties in the IPD trials – dichotomous variables

Trial	Arm	Percentage at baseline					
		Women	Type 2 diabetes	DMO	VH	Prior anti-VEGF use	Prior PRP use
CLARITY	Aflibercept	28.4	46.6	24.1		5.2	48.3
	PRP	37.9	44.0	25.0		4.3	45.7
PROTEUS	Ranibizumab + PRP	31.7			2.4		65.9
	PRP	41.3			8.7		76.1
PROTOCOL S	Ranibizumab	43.5	22.5	49.2	31.4	11.0	
	PRP	45.3	20.2	46.3	34.5	6.4	

TABLE 36 Baseline properties in the IPD trials – continuous variables

Trial	Arm	Age		ETDRS		HbA1c		CST	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
CLARITY	Aflibercept	51.1	14.6	81.3	8.0	72.2	17.0	336.3	697.4
	PRP	50.8	13.2	82.0	8.0	72.2	16.5	275.3	30.9
PROTEUS	Ranibizumab + PRP	59.4	13.3	76.1	10.4	65.6	14.5	290.8	36.9
	PRP	52.6	11.8	75.3	10.6	69.0	17.1	298.8	37.0
PROTOCOL S	Ranibizumab	50.4	11.5	74.9	12.8	75.9	26.2	295.9	98.0
	PRP	50.5	11.7	75.3	12.5	77.7	25.0	291.7	77.4

TABLE 37 Meta-regression of effect of anti-VEGF and its interaction with patient characteristics at 1 year with repeated measures

Covariate	Parameter	Log-MAR		ETDRS	
		MD	95% CI	MD	95% CI
Age	Anti-VEGF vs. PRP	−0.076	−0.13 to −0.022	3.796	1.112 to 6.481
	Anti-VEGF × covariate interaction	0.002	−0.001 to 0.004	−0.081	−0.193 to 0.032
Sex	Anti-VEGF vs. PRP	−0.073	−0.132 to −0.014	3.664	0.708 to 6.62
	Anti-VEGF × covariate interaction	−0.07	−0.127 to −0.014	3.51	0.677 to 6.342
BCVA at baseline	Anti-VEGF vs. PRP	−0.076	−0.124 to −0.028	3.809	1.395 to 6.222
	Anti-VEGF × covariate interaction	−0.137	−0.246 to −0.028	−0.138	−0.247 to −0.029
Type 2 diabetes	Anti-VEGF vs. PRP	−0.077	−0.158 to 0.004	3.839	−0.216 to 7.895
	Anti-VEGF × covariate interaction	−0.023	−0.089 to 0.042	1.171	−2.107 to 4.449
Prior anti-VEGF use	Anti-VEGF vs. PRP	−0.052	−0.123 to 0.02	2.586	−0.976 to 6.148
	Anti-VEGF × covariate interaction	−0.027	−0.14 to 0.087	1.336	−4.324 to 6.995
Prior PRP use	Anti-VEGF vs. PRP	−0.094	−0.148 to −0.04	4.688	1.978 to 7.399
	Anti-VEGF × covariate interaction	0.065	−0.001 to 0.13	−3.234	−6.502 to 0.034
Vitreous haemorrhage at baseline	Anti-VEGF vs. PRP	−0.064	−0.1 to −0.028	3.217	1.417 to 5.017

TABLE 37 Meta-regression of effect of anti-VEGF and its interaction with patient characteristics at 1 year with repeated measures (*continued*)

Covariate	Parameter	Log-MAR		ETDRS	
		MD	95% CI	MD	95% CI
	Anti-VEGF × covariate interaction	−0.127	−0.197 to −0.058	6.37	2.897 to 9.843
DME at baseline	Anti-VEGF vs. PRP	−0.094	−0.17 to −0.018	4.683	0.881 to 8.484
	Anti-VEGF × covariate interaction	0.04	−0.02 to 0.1	−2.017	−5.015 to 0.982
HbA1c	Anti-VEGF vs. PRP	−0.078	−0.124 to −0.031	3.893	1.571 to 6.216
	Anti-VEGF × covariate interaction	−0.002	−0.003 to −0.001	0.103	0.033 to 0.172
CST at baseline	Anti-VEGF vs. PRP	−0.073	−0.129 to −0.018	3.671	0.911 to 6.431
	Anti-VEGF × covariate interaction	0	0 to 0.001	−0.011	−0.03 to 0.009

Note
Yellow highlights indicate where results for treatment–covariate interactions were statistically significant.

TABLE 38 Meta-regression of effect of anti-VEGF and its interaction with patient characteristics at exactly 1 year without repeated measures

Covariate	Parameter	Log-MAR		ETDRS	
		MD	95% CI	MD	95% CI
Age	Anti-VEGF vs. PRP	−0.072	−0.117 to −0.026	3.587	1.302 to 5.873
	Anti-VEGF × covariate interaction	0.002	0 to 0.005	−0.114	−0.249 to 0.021
Sex	Anti-VEGF vs. PRP	−0.07	−0.119 to −0.022	3.512	1.076 to 5.947
	Anti-VEGF × covariate interaction	−0.011	−0.08 to 0.058	0.556	−2.885 to 3.998
BCVA at baseline	Anti-VEGF vs. PRP	−0.079	−0.126 to −0.032	3.941	1.594 to 6.289
	Anti-VEGF × covariate interaction	−0.069	−0.218 to 0.081	−0.069	−0.218 to 0.081
Type 2 diabetes	Anti-VEGF vs. PRP	−0.078	−0.169 to 0.013	3.904	−0.627 to 8.434
	Anti-VEGF × covariate interaction	−0.033	−0.107 to 0.041	1.642	−2.052 to 5.337
Prior anti-VEGF use	Anti-VEGF vs. PRP	−0.016	−0.075 to 0.043	0.801	−2.125 to 3.727
	Anti-VEGF × covariate interaction	0.02	−0.092 to 0.132	−1.011	−6.619 to 4.597
Prior PRP use	Anti-VEGF vs. PRP	−0.071	−0.158 to 0.017	3.528	−0.861 to 7.918
	Anti-VEGF × covariate interaction	0.115	0.033 to 0.197	−5.735	−9.833 to −1.637
Vitreous haemorrhage at baseline	Anti-VEGF vs. PRP	−0.076	−0.113 to −0.039	3.791	1.933 to 5.65
	Anti-VEGF × covariate interaction	−0.085	−0.177 to 0.008	4.234	−0.395 to 8.863
DME at baseline	Anti-VEGF vs. PRP	−0.072	−0.144 to 0.001	3.575	−0.056 to 7.206
	Anti-VEGF × covariate interaction	−0.014	−0.085 to 0.058	0.678	−2.888 to 4.243
HbA1c	Anti-VEGF vs. PRP	−0.078	−0.128 to −0.027	3.88	1.368 to 6.392
	Anti-VEGF × covariate interaction	−0.002	−0.004 to 0	0.09	0.004 to 0.176
CST at baseline	Anti-VEGF vs. PRP	−0.076	−0.125 to −0.026	3.779	1.314 to 6.245
	Anti-VEGF × covariate interaction	0	0 to 0.001	−0.003	−0.028 to 0.022

Note
Yellow highlights indicate where results for treatment–covariate interactions were statistically significant.

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

Analyses of other outcomes

DME and vitreous haemorrhage

TABLE 39 Analyses of impact of anti-VEGF on binary outcomes at 1 year

Outcome	OR vs. PRP	95% CI
DME	0.471	0.254 to 0.874
Vitreous haemorrhage	0.700	0.408 to 1.199

TABLE 40 Meta-regressions analyses for DME

Covariate	Parameter	OR vs. PRP	95% CI
Age	Anti-VEGF	0.281	0.13 to 0.604
	Anti-VEGF × covariate interaction	1.009	0.953 to 1.068
Sex	Anti-VEGF	0.286	0.137 to 0.595
	Anti-VEGF × covariate interaction	0.411	0.097 to 1.74
BCVA at baseline	Anti-VEGF	0.315	0.142 to 0.698
	Anti-VEGF × covariate interaction	0.615	0.024 to 15.916
Type 2 diabetes	Anti-VEGF	0.273	0.13 to 0.574
	Anti-VEGF × covariate interaction	0.992	0.219 to 4.495
Prior anti-VEGF use	Anti-VEGF	0.285	0.118 to 0.693
	Anti-VEGF × covariate interaction	1.128	0.129 to 9.861
Prior PRP use	Anti-VEGF	Did not converge	
	Anti-VEGF × covariate interaction		
Vitreous haemorrhage at baseline	Anti-VEGF	0.308	0.148 to 0.64
	Anti-VEGF × covariate interaction	2.339	0.18 to 30.416
HbA1c	Anti-VEGF	0.297	0.14 to 0.628
	Anti-VEGF × covariate interaction	1.01	0.972 to 1.05
CST at baseline	Anti-VEGF	0.316	0.153 to 0.652
	Anti-VEGF × covariate interaction	0.991	0.97 to 1.013

TABLE 41 Meta-regressions analyses for vitreous haemorrhage

Covariate	Parameter	OR vs. PRP	95% CI
Age	Anti-VEGF	0.631	0.197 to 2.027
	Anti-VEGF × covariate interaction	0.963	0.916 to 1.012
Sex	Anti-VEGF	0.584	0.168 to 2.03
	Anti-VEGF × covariate interaction	0.161	0.038 to 0.681
BCVA at baseline	Anti-VEGF	0.661	0.205 to 2.132
	Anti-VEGF × covariate interaction	7.561	0.105 to 543.94
Type 2 diabetes	Anti-VEGF	0.658	0.209 to 2.073
	Anti-VEGF × covariate interaction	1.266	0.322 to 4.98

TABLE 41 Meta-regressions analyses for vitreous haemorrhage (*continued*)

Covariate	Parameter	OR vs. PRP	95% CI
Prior anti-VEGF use	Anti-VEGF	Did not converge	
	Anti-VEGF × covariate interaction		
Prior PRP use	Anti-VEGF	Did not converge	
	Anti-VEGF × covariate interaction		
DME at baseline	Anti-VEGF	0.623	0.352 to 1.103
	Anti-VEGF × covariate interaction	3.389	0.753 to 15.253
HbA1c	Anti-VEGF	0.29	0.015 to 5.683
	Anti-VEGF × covariate interaction	1.025	0.984 to 1.068
CST at baseline	Anti-VEGF	0.694	0.215 to 2.238
	Anti-VEGF × covariate interaction	0.993	0.97 to 1.016

Note
Yellow highlights indicate where results for treatment–covariate interactions were statistically significant.

Central subfield thickness

TABLE 42 Analyses of central subfield thickness at 1 year

Parameter	MD	95% CI
Anti-VEGF vs. PRP	−5.145	−112.34 to 102.05

Diabetic retinopathy severity score (PROTOCOL S only)

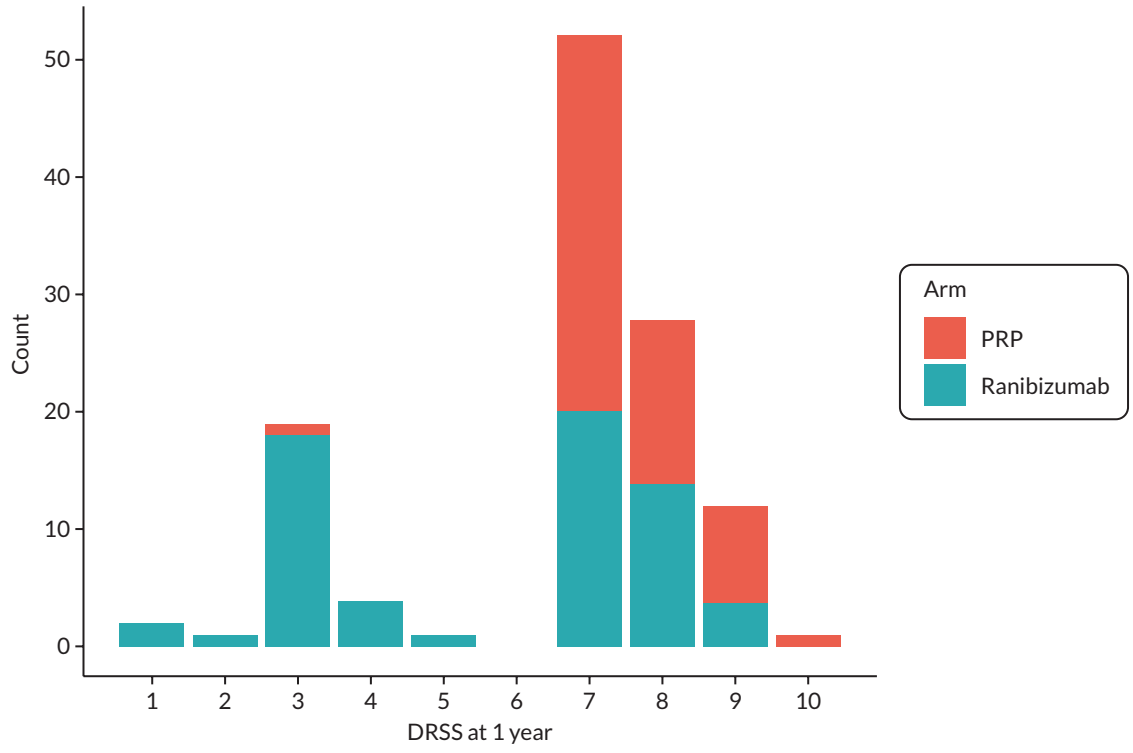

FIGURE 45 Diabetic retinopathy severity score after 1 year in PROTOCOL S.

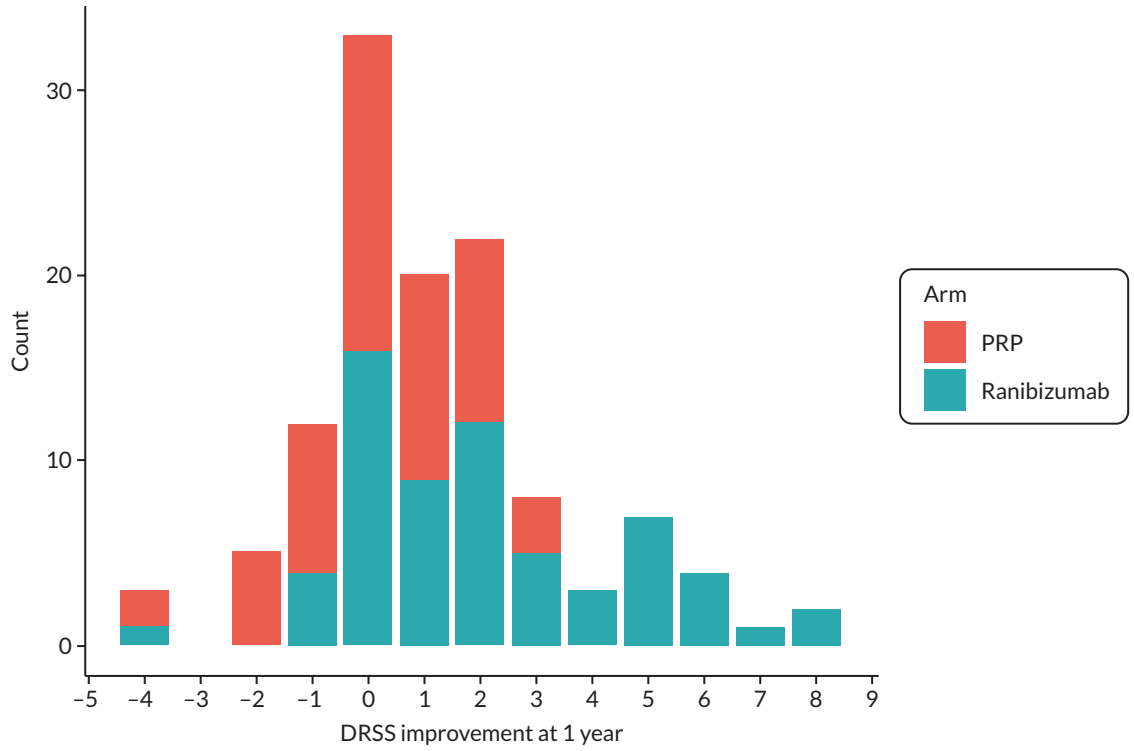

FIGURE 46 Improvement in DRSS after 1 year in PROTOCOL S.

Reading, driving and employment (PROTOCOL S only)

TABLE 43 Reading, driving and employment in PROTOCOL S after 1 year

Outcome	Arm	Improved	No change	Worsened
Reading ability	Ranibizumab	5	71	2
	PRP	2	53	4
Ability to drive	Ranibizumab	2	63	3
	PRP	4	44	3
Employment status	Ranibizumab	11	49	9
	PRP	8	44	3

Quality of life (EuroQol-5 Dimensions and NEI, CLARITY only)

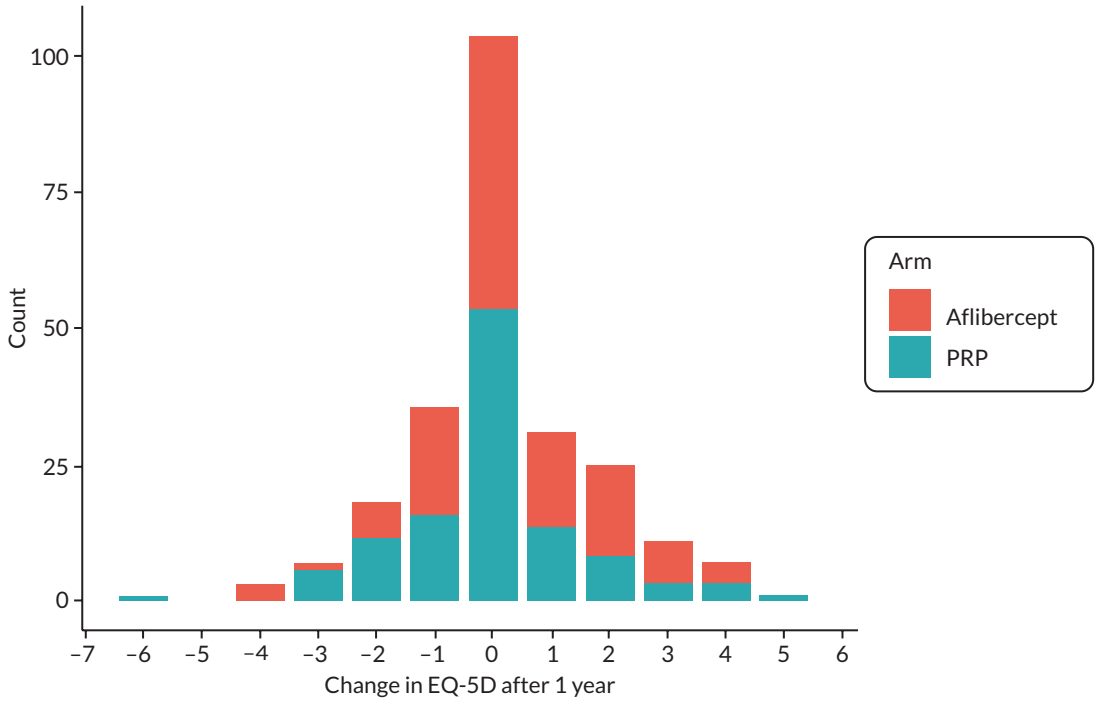

FIGURE 47 Change in EQ-5D after 1 year in CLARITY. Mann–Whitney U-test *p*-value for difference in arms ($p = 0.135$).

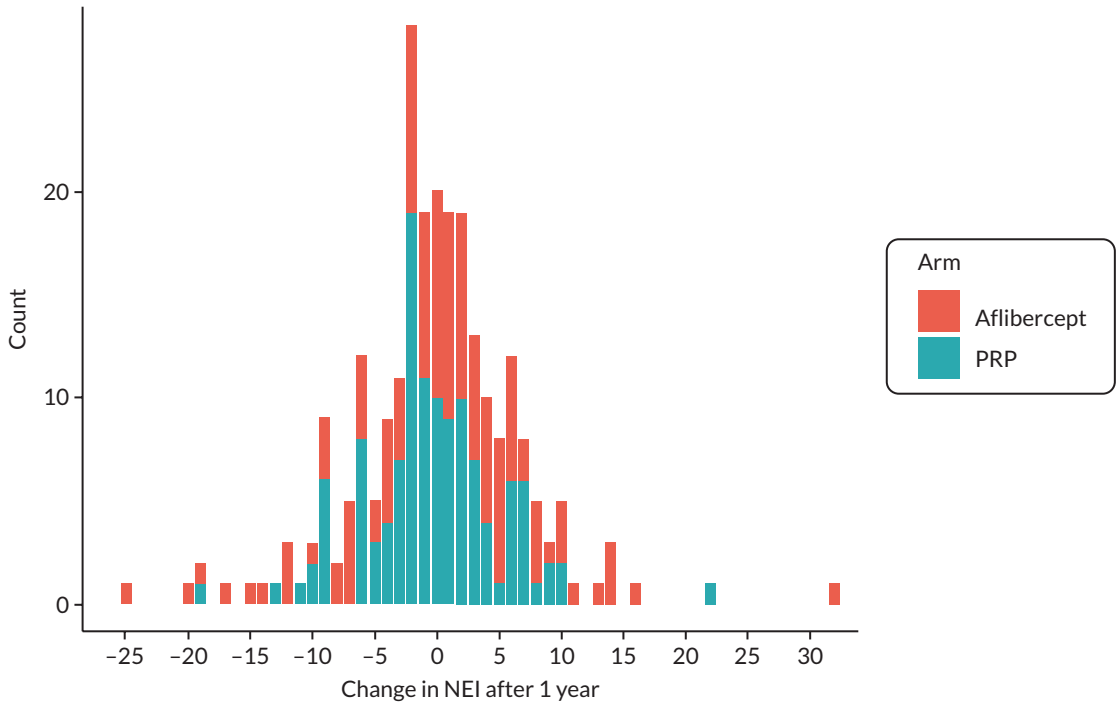

FIGURE 48 Change in NEI after 1 year in CLARITY. Mann–Whitney U-test *p*-value for difference in arms ($p = 0.282$).

This article should be referenced as follows:
Simmonds M, Llewellyn A, Walker R, Fulbright H, Walton M, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and individual participant data meta-analysis [published online ahead of print April 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/MJYP6578

Additional panretinal photocoagulation and anti-vascular endothelial growth factor treatment

TABLE 44 Number of patients receiving further anti-VEGF or PRP treatment

		Patients/eyes with additional treatment			
Trial	**Arm**	**No treatment**	**PRP/laser only**	**Anti-VEGF only**	**Anti-VEGF and PRP**
CLARITY	Aflibercept	41	75	0	0
	PRP	36	1	77	2
PROTEUS	Ranibizumab + PRP	5	3	0	32
	PRP	7	39	0	0
PROTOCOL S	Ranibizumab	14	0	142	35
	PRP	41	44	47	71

Appendix 6 Statistical methods

General notes

All data management and statistical analyses for the AVID project were conducted in R version 4.3. Data management was performed with the aid of the tidyverse package system. Plots other than forest and network plots were produced using the ggplot2 package. All codes can be viewed on the project GitHub site (https://github.com/marksimmondsyork/avid).

Network meta-analyses

All NMAs were conducted using the multinma package in R. This fits Bayesian NMAs using STAN to perform the Markov chain Monte Carlo sampling. NMAs were fitted by combining IPD with published data where IPD were not requested.

For all NMAs, 'vague' prior distributions were used, generally the default priors for multinma.

Typical R code is presented below for the NMA of BCVA at any time up to 1 year:

```
# set up published data network
AD.setup <- set_agd_arm(ad.bcva,
                        study=Trial,
                        trt=Arm,
                        y=logMAR.mcfb,
                        se=logMAR.mcfb.sem,
                        sample_size=N,
                        trt_ref="PRP")

# set up IPD network
IPD.setup <- set_ipd(ipd.bcva,
                     study=Trial,
                     trt=Arm,
                     y=logMAR.cfb,
                     trt_ref="PRP")

# combine both networks
NMA.1yr <- combine_network(AD.setup, IPD.setup,trt_ref="PRP")

# network diagram
plot(NMA.1yr,weight_edges=T,weight_nodes=T,layout="star")

# run NMA (using vague priors)
NMA.1yr.run <- nma(NMA.1yr,
              trt_effects="random",
              prior_intercept=normal(scale=10),
              prior_trt=normal(scale=10),
              prior_het=half_normal(scale=5),
              chains=4,iter=10000)

# results (ORs)
relative_effects(NMA.1yr.run,all_contrasts=TRUE)$summary

# prob. rankings
posterior_rank_probs(NMA.1yr.run)
posterior_ranks(NMA.1yr.run)

# forest plot
plot(relative_effects(NMA.1yr.run,all_contrasts=TRUE),
ref_line=0, .width=c(0,0.95))
```

For the model with adjustment for follow-up time and BCVA at randomisation, the code was:

```
NMA.adj.run <- nma(NMA.adj,
                   trt_effects="random",
                   regression= ~(logMAR.base + Year):.trtclass,
                   prior_intercept=normal(scale=10),
                   prior_trt=normal(scale=10),
                   prior_reg=normal(scale=2),
                   prior_het=half_normal(scale=5),
                   prior_aux=half_normal(scale=5),
                   center=T,
                   iter=5000)
```

Other outcomes

Other outcomes (DMO, vitreous haemorrhage, adverse events) were analysed by summarising data from the IPD (e.g. numbers of events and patients by treatment arm) and pooling this with equivalent summary data extracted from publications for other trials. DerSimonian–Laird random-effects meta-analyses based on relative risks were performed for each outcome. The R package meta was used to conduct these meta-analyses and to produce forest plots.

Regression models of individual participant data

The IPD trials were analysed using a 'one-stage' mixed-effect regression modelling approach, where outcome (e.g. change in BCVA from baseline) was regressed against treatment arm, patient characteristics, time, with appropriate interaction terms. The lme4 package in R was used for these analyses: using the lmer command for BCVA and glmer for DMO and vitreous haemorrhage.

The general model structure used correlated random effects for intercept and treatment effect terms, and fixed effects for all other parameters.

For example, modelling treatment effect for BCVA at 1 year, with a treatment–age interaction used the model:

$$y_{ij} = \alpha_i + \beta_i x_{ij} + \mu z_{ij} + \gamma x_{ij} z_{ij} + \epsilon_{ij}$$

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim N\left(\begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \begin{pmatrix} \tau_\alpha^2 \lambda \\ \lambda \ \tau_\beta^2 \end{pmatrix} \right)$$

where y is the change in BCVA over 1 year in patient j in trial i; x is the treatment coding (1 = anti-VEGF, 0 = PRP) and z is the age at randomisation.

All continuous covariates were centred at their average values across all trials.

Typical lme4 code is:

```
lmer(BCVA.change ~ factor(Treatment)*Age + (1+Treatment|Trial),
data=IPD.1yr)
```

For repeated-measures analyses to examine how treatment effect varies over time, the model also included a random effect by patient to account for repeated measures, such as:

$$y_{ijk} = \alpha_i + \beta_i x_{ij} + \nu t_{ijk} + \gamma x_{ij} t_{ijk} + \xi_{ijk} + \epsilon_{ijk}$$

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim N\left(\begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \begin{pmatrix} \tau_\alpha^2 \lambda \\ \lambda \ \tau_\beta^2 \end{pmatrix} \right) , \quad \xi_{ijk} \sim N\left(\xi_{ij}, \tau_\xi^2\right)$$

where t indicates the time of observation k in patient j in trial i. In all analyses, time was centred at 1 year, so the main treatment effect is that at 1 year of follow-up.

Typical lme4 code is:

```
lmer(BCVA.change ~ factor(Treatment)*Year + (1+Treatment|Trial) +
(1|PatientID/Trial), data=IPD.alltimes)
```

For models with both repeated measures and treatment–covariate interactions, the typical R code was, for example:

```
lmer(BCVA.change ~ factor(Treatment)*(Year+Age) + (1+Treatment|Trial) +
(1|PatientID/Trial), data=IPD.alltimes)
```

So only one-way interactions with treatment were included. Models with higher-level interactions were considered but were found to be unstable and generally they did not converge.

We note that models separating within-trial and across-trial information were not used. As there were only three IPD trials, with broadly similar patient characteristics, these were judged unlikely to give meaningful results.

For vitreous haemorrhage and DMO analyses, the general model structure was unchanged, but mixed-effect logistic regression (with the R command 'glmer') was used in place of linear regression and lmer.