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Research Article

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

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Abstract

Background: Diabetic retinopathy is a major cause of sight loss in people with diabetes. The most severe form, proliferative diabetic retinopathy, carries a high risk of vision loss, vitreous haemorrhage, macular oedema and other harms. Panretinal photocoagulation is the primary 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 diabetic retinopathy.

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

Methods: A systematic review and network meta-analysis of all published randomised controlled trials comparing anti-vascular endothelial growth factor (alone or in combination with panretinal photocoagulation) to panretinal photocoagulation in people with 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.

Results: A total of 14 trials were included: 3 of aflibercept, 5 of bevacizumab and 6 of ranibizumab. Two trials were of patients with non-proliferative diabetic retinopathy; all others were in proliferative diabetic retinopathy. Overall, anti-vascular endothelial growth factor was slightly better than panretinal photocoagulation at preventing vision loss, measured as best corrected visual acuity, at up to 2 years follow-up [mean difference in the logarithm of the minimum angle of resolution −0.089 (or 3.6 Early Treatment Diabetic Retinopathy Study letters), 95% confidence interval −0.180 to −0.019]. There was no clear evidence of any difference between the anti-vascular endothelial growth factors, but the potential for bias complicated the comparison. One trial found no benefit of anti-vascular endothelial growth factor over panretinal photocoagulation after 5 years. Anti-vascular endothelial growth factor was superior to panretinal photocoagulation at preventing macular oedema (relative risk 0.29, 95% confidence interval 0.18 to 0.49) and vitreous haemorrhage (relative risk 0.77, 95% confidence interval 0.61 to 0.99). There was no clear evidence that the effectiveness of anti-vascular endothelial growth factor varied over time.

Conclusions: Anti-vascular endothelial growth factor injections reduce vision loss when compared to panretinal photocoagulation, but the benefit is small and unlikely to be clinically meaningful. Anti-vascular endothelial growth factor may have greater benefits for preventing complications such as macular oedema. Observational studies extending follow-up beyond the 1-year duration of most trials are needed to investigate the longer-term effects of repeated anti-vascular endothelial growth factor injections.

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Background

Diabetes is a major cause of poor health that affects over 4 million people in the UK. Older people, men, people of South Asian ethnicity and more deprived populations are at higher risk.[1] Diabetic retinopathy is a 'chronic progressive, potentially sight-threatening disease of the retinal microvasculature'[2,3] that is a major complication of diabetes and a common cause of sight loss. Diabetic retinopathy impairs the sight of more than 1700 people in the UK each year.[4] The most severe form, proliferative diabetic retinopathy (PDR), places the patients at a high risk of vitreous haemorrhage, retinal detachment, neovascular glaucoma and vision loss.[5,6]

Panretinal (laser) photocoagulation (PRP) is the primary treatment for PDR, where a laser is applied to vascular abnormalities to prevent proliferation of new blood vessels or encourage regression in those with established new vessels. PRP is delivered over the entire periphery of the retina, by placing 1200–1600 laser burns per session, usually over two or three treatment sessions. It is known to be effective and long-lasting[7] but can have side effects including peripheral visual field loss, impaired night time and colour vision, and blurred vision. There is a small risk of central scotomata if laser burns are inadvertently placed at or near the foveal centre or if the laser scar extends centrally.[8]

Anti-vascular endothelial growth factor (anti-VEGF) drugs have been proposed as alternative to PRP. In the UK, the National Institute for Health and Care Excellence (NICE) has approved ranibizumab and aflibercept for the treatment of diabetic macular oedema (DMO),[9,10] and they are the standard treatment for wet age-related macular degeneration. However, whether they are beneficial for the treatment of diabetic retinopathy remains to be established. There are concerns that effects may not be long-lasting, and patients may have worse outcomes than those who had laser photocoagulation without repeated re-treatment and long-term follow-up.[11,12] They have rare but potentially serious adverse effects including: ocular hypertension, retinal detachment, endophthalmitis and other intraocular inflammation, and cataracts.[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. When this project commenced, there was no current NICE guidance for the use of anti-VEGF drugs in people with diabetic retinopathy but without macular oedema. NICE guidance is under development,[15] and this review and meta-analysis was conducted to help inform it.

Given the uncertainty around whether anti-VEGF should be used to treat diabetic retinopathy, and the need for clear guidance on this topic, a systematic assessment of the relevant evidence and appropriate synthesis were needed. In order to synthesise data from mixed comparator studies, a network meta-analysis (NMA) approach was required to assess the value, effectiveness and rank of all relevant anti-VEGF interventions.

This paper presents a systematic review and NMA of all published randomised controlled trials (RCTs) of the three main anti-VEGFs used to treat diabetic retinopathy: aflibercept, bevacizumab and ranibizumab. While all three drugs act similarly to inhibit VEGF and slow the growth of blood vessels in the eye, they are different at molecular and receptor level, and so may differ in both efficacy and safety. This is why it is important to compare the three anti-VEGFs in a NMA.

The project was funded by the National Institute for Health and Care Research (Project number NIHR132948). The main project included a systematic review and meta-analysis incorporating individual patient data (IPD) from high-quality trials. Other components of the project included a wider assessment of anti-VEGF studies, including non-randomised studies, and an economic analysis of the cost-effectiveness of using anti-VEGF to treat diabetic retinopathy. The review was registered on PROSPERO (CRD42021272642) and the full protocol is available online from the NIHR (https://fundingawards.nihr.ac.uk/award/NIHR132948).

Methods

The aim of this project was to systematically review all RCTs where anti-VEGFs were used to treat diabetic retinopathy. The review was conducted following the Centre for Reviews and Dissemination guidance on undertaking systematic reviews[16] and reported according to the principles of the overarching Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

Inclusion criteria

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, anti-VEGF combined with PRP, PRP alone and sham injection.

A full list of outcomes of interest were reported in the review protocol. This paper focuses particularly on best corrected visual acuity (BCVA), as this was the only outcome reported in all trials. The appendices to this paper report evidence on all protocol-specified outcomes reported in the trials.

Review methods

An Information Specialist (HF) designed a preliminary search strategy in Ovid MEDLINE which consisted of terms for the condition (diabetic retinopathy), that were combined with terms for the intervention (anti-VEGF, angiogenesis inhibitors, or specific drugs used for the treatment of diabetic retinopathy). A RCT study filter was applied. No date or language limits were applied. The final MEDLINE strategy was adapted for use in all resources searched. All search strategies are presented in full in *Appendix 1*.

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 [CENTRAL (Wiley)], Cochrane Database of Systematic Reviews (Wiley), Database of Abstracts of Reviews of Effects {DARE [Centre for Reviews and Dissemination (CRD)]}, PROSPERO (CRD) and Epistemonikos. The following trial registries were searched: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov and the EU Clinical Trials Registry. Search results were imported into EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA) and deduplicated.

Two researchers (RW, AL) independently screened all titles and abstracts retrieved for consideration of the full text. The reviewers then screened full texts of potentially eligible studies 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 publications. Data extraction was completed by one reviewer and checked by a second (RW, AL). Risk of bias in all included trials was assessed using the Cochrane Risk of Bias 2 tool, focusing on the BCVA outcome, given limited reporting of other outcomes.[18]

Statistical analysis

Effect estimates were pooled across trials using standard DerSimonian–Laird random-effect pairwise meta-analyses, according to the duration of follow-up. Heterogeneity was assessed in terms of I^2[19] and by inspecting the between-study heterogeneity standard deviations (SDs; τ), relative to the treatment effect size.

Network meta-analyses were performed using standard Bayesian methods of NMA in R (version 4.3.1, The R Foundation for Statistical Computing, Vienna, Austria) using the R package multinma (version 0.5.1).[11,20] This extends the standard NMA modelling approach to investigate the potential impact of patient factors (e.g. type of retinopathy) and timing of assessments on the effectiveness of anti-VEGF therapy.[20] Network consistency was checked by comparing the model fit and between-study heterogeneity from the NMA models to an unrelated mean effects model (similar to a model performing direct meta-analysis for each treatment comparison, but with a shared heterogeneity parameter).[21]

Visual acuity (BCVA) in diabetic retinopathy is commonly measured using the logarithm of the minimum angle of resolution (log-MAR) and Early Treatment Diabetic Retinopathy Study (ETDRS) scales. As both are widely used, NMAs were performed for both scales. Published data were transformed from one scale to the other, as required. This paper presents results on the log-MAR scale, with ETDRS results reported in the appendices.

The potential impact of unpublished or ongoing trials on the NMAs was investigated using threshold analysis. Threshold analysis investigates where in a NMA results might not be robust to changes in the observed evidence.[22]

All R code and data used for this paper are available on 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

General results

Key findings for BCVA, DMO, vitrectomy, vitreous haemorrhage and adverse events are presented here. A full presentation of all analyses performed for all outcomes is provided in the appendices.

Figure 1 shows the PRISMA flow chart for this review. Studies excluded from the review are listed in *Appendix 1*. Overall, 14 RCTs were included in the meta-analyses. 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 2010 (and therefore judged to be out-of-date), that used types of anti-VEGF not in widespread use, or did not include a PRP arm. Those trials therefore could not be reasonably included in the NMAs. These are summarised in *Appendix 1*.

The included RCTs are summarised in *Table 1*. Trials varied substantially in sample size from only 40 eyes up to just over 400 persons. There were six trials of ranibizumab, five of bevacizumab and three trials of aflibercept. Five trials used anti-VEGF as the intervention, while nine used anti-VEGF combined with PRP. Twelve trials were of patients with proliferative retinopathy. Two trials recruited patients with non-proliferative retinopathy; both evaluated aflibercept.[23,24] Trials of aflibercept and ranibizumab were conducted in Europe, North America or Brazil. All trials of bevacizumab were conducted in the Middle East or South Asia. BCVA was the only outcome reported consistently in all trials.

Risk of bias

For the risk-of-bias assessment of the included trials, see *Table 2* and *Appendix 1*. Overall, four trials were classed at low risk of bias, three moderate and seven at 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 patients 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. Only the larger trials of ranibizumab and aflibercept were at low risk of bias.

Impact on vision (best corrected visual acuity)

Figure 2 summarises all the data on BCVA for anti-VEGF compared to PRP, as reported across all trials. Results are shown as difference in ETDRS letters between anti-VEGF and control arms. This plot highlights significant variation in the design of the included studies, which precludes combining them all in a standard meta-analysis and demonstrates the need for NMA and meta-regression. First, some trials compare anti-VEGF to PRP directly, while others combine anti-VEGF with PRP, therefore motivating the need for NMA. Second, the time at which BCVA is measured varied enormously across trials, from 1 month to five years. Shorter trials were generally smaller in size, more likely to use bevacizumab and possibly showed larger effect sizes.

Network meta-analyses of best corrected visual acuity in proliferative retinopathy

Given the variations in timing at which BCVA results were reported, two NMAs were performed:

1. Analysis up to and including 1 year of follow-up, using the longest follow-up in each trial
2. Analysis only of trials with 1 or 2 years' follow-up

Note that trials reporting at exactly 1 year were included in both analyses. Given the clinical differences between proliferative and non-proliferative disease, the two trials of non-proliferative disease were not included in the NMA. The network diagrams for both analyses are shown in *Figure 3*. The size of the circles indicates the number of participants, and the width of the lines and the number of trials. Note that all the trials of bevacizumab combined with PRP had follow-up durations of < 1 year, so are not included in the analyses at 1–2 years. In both networks, there is only one trial of aflibercept and one of bevacizumab (without PRP).

Figure 4 shows the results of all treatment comparisons from the NMA for data up to 1 year, and *Figure 5* for data from 1 to 2 years. Full results of these NMAs are given in *Appendix 2*. In both figures, the point estimates

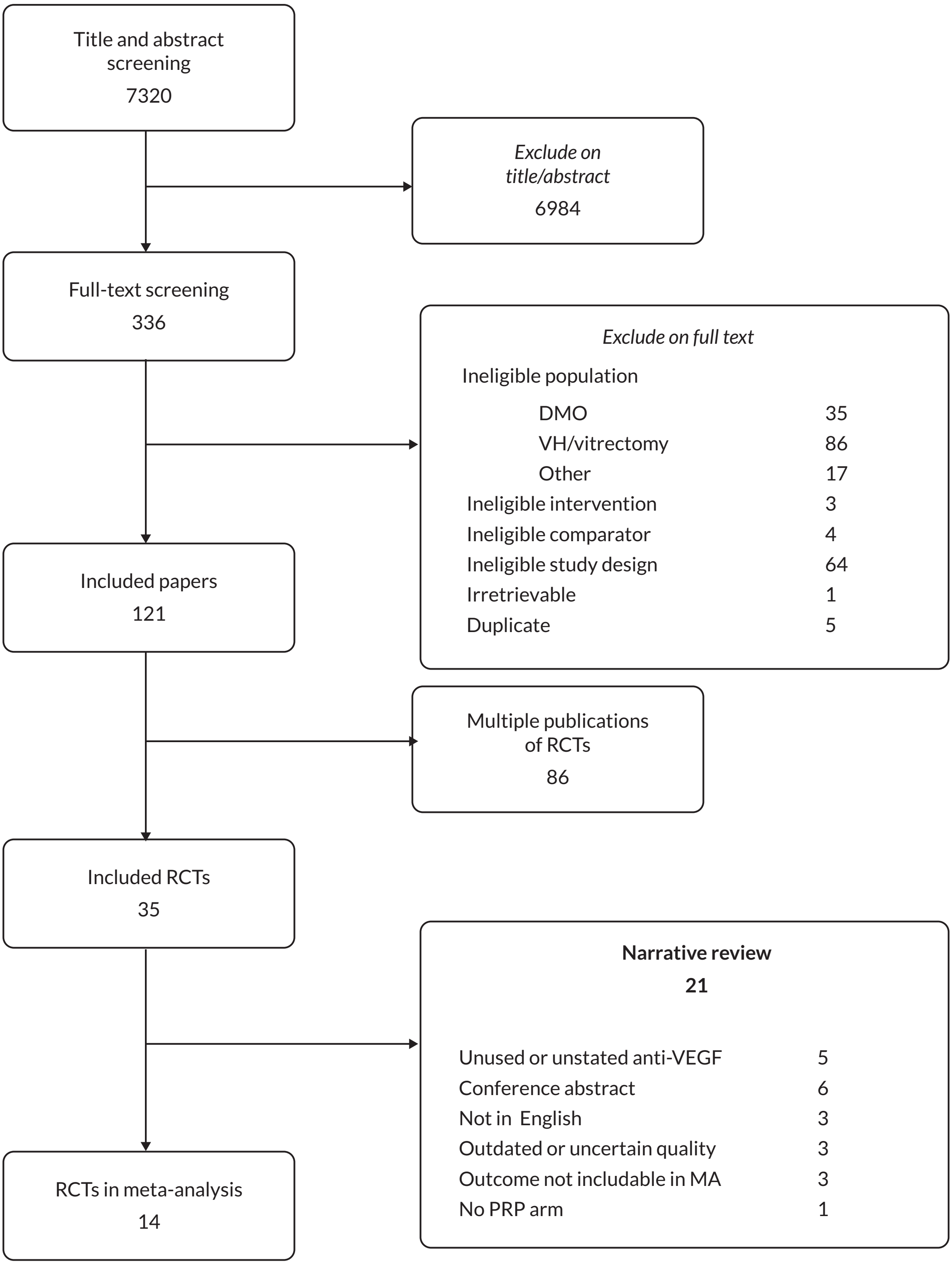

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. DMO, diabetic macular edema; VH; vitreous haemorrhage; MA, meta-analysis.

are shown by the dots, with the horizontal lines being 95% credible intervals (CrIs). Negative relative effects (to the left of the vertical line) indicate favouring the first-named intervention.

For the primary comparisons with PRP at up to 1 year, all trials favoured anti-VEGF over PRP and improved vision (reduced log-MAR scores). Changes in log-MAR scores when compared to PRP ranged from −0.078 (or 3.8 ETDRS letters) for ranibizumab with PRP to −0.198 (or 6.8 ETDRS letters) for bevacizumab. Results for aflibercept and bevacizumab (without PRP) were inconclusive because there was only one trial of each. 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,

TABLE 1 Summary of the RCTs included in the meta-analyses

Trial	Year	Anti-VEGF	Comparator	Location	Sample size	Follow-up	Population	Main outcome(s)
CLARITY[23]	2017	Aflibercept	PRP	UK	232 persons	1 year	PDR	BCVA, diabetic retinopathy severity, subsequent treatment, complications
DRCRN Protocol W[24]	2021	Aflibercept	Sham injection	USA/Canada	328 persons	2 years	Severe non-proliferative diabetic retinopathy (some DMO)	Time to proliferative diabetic retinopathy or DMO
PANORAMA[25]	2018	Aflibercept (every 16 weeks vs. 8 weeks)	Sham injection	International	402 persons	1 and 2 years	non-proliferative diabetic retinopathy	DR severity, subsequent treatment, complications
Marashi[26]	2017	Bevacizumab	PRP	Jordan/Syria	30 persons	1 year	PDR	BCVA, DR severity
Ahmad[27]	2012	Bevacizumab + PRP	PRP	Pakistan	54 eyes	3 months	PDR	BCVA
Ali[28]	2018	Bevacizumab + PRP	PRP	Pakistan	60 eyes	1 month	PDR	BCVA
Rebecca[29]	2021	Bevacizumab + PRP	PRP	Pakistan	76 eyes	6 months	PDR	BCVA
Roohipoor[30]	2016	Bevacizumab + PRP	PRP	Iran	64 eyes	10 months	PDR	BCVA
DRCRN Protocol S[31]	2018	Ranibizumab	PRP	USA	305 persons	2 and 5 years	PDR	DR severity, functional impact on vision, subsequent treatment, complications
Ferraz[32]	2015	Ranibizumab + PRP	PRP	Brazil	60 eyes	6 months	PDR	BCVA
PRIDE[33]	2019	Ranibizumab + PRP	PRP	Germany	106 persons	1 year	PDR	BCVA, DR severity, subsequent treatment
PROTEUS[34]	2018	Ranibizumab + PRP	PRP	Europe	87 persons	1 year	PDR	BCVA, subsequent treatment, complications
Sao Paulo B[35]	2011	Ranibizumab + PRP	PRP	Brazil	40 persons	1 year	PDR	BCVA, pain
Sao Paulo A[36]	2018	Ranibizumab + PRP (ETRDS)	Ranibizumab + PRP (PASCAL)	Brazil	40 eyes	1 year	PDR	BCVA

TABLE 2 Cochrane risk-of-bias assessment of outcome BCVA in the included RCTs

	Risk-of-bias domain					
Trial	Randomisation	Deviation from intended intervention	Missing outcome data	Outcome measurement	Selective reporting	Overall
Ahmad	!	!	+	–	!	High
Ali[28]	!	!	!	–	!	High
CLARITY[23]	+	+	+	!	+	Low
Ferraz[32]	!	!	+	+	!	Moderate
Marashi[26]	–	!	!	–	+	High
PANORAMA[25]	+	+	!	+	+	Low

TABLE 2 Cochrane risk-of-bias assessment of outcome BCVA in the included RCTs (*continued*)

Trial	Risk-of-bias domain					
	Randomisation	Deviation from intended intervention	Missing outcome data	Outcome measurement	Selective reporting	Overall
PRIDE[33]	!	+	!	–	+	Moderate
PROTEUS[34]	!	+	!	–	+	Moderate
Protocol S[31]	+	+	+	!	+	Low
Protocol W[24]	+	+	+	!	+	Low
Rebecca[29]	+	!	!	–	!	High
RECOVERY	!	+	+	–	+	Moderate
Roohipoor[30]	+	!	–	–	!	High
Sao Paulo A[36]	!	!	!	–	!	High
Sao Paulo B[35]	!	!	!	–	!	High
	+	Low risk				
	!	Some concerns				
	–	High risk				

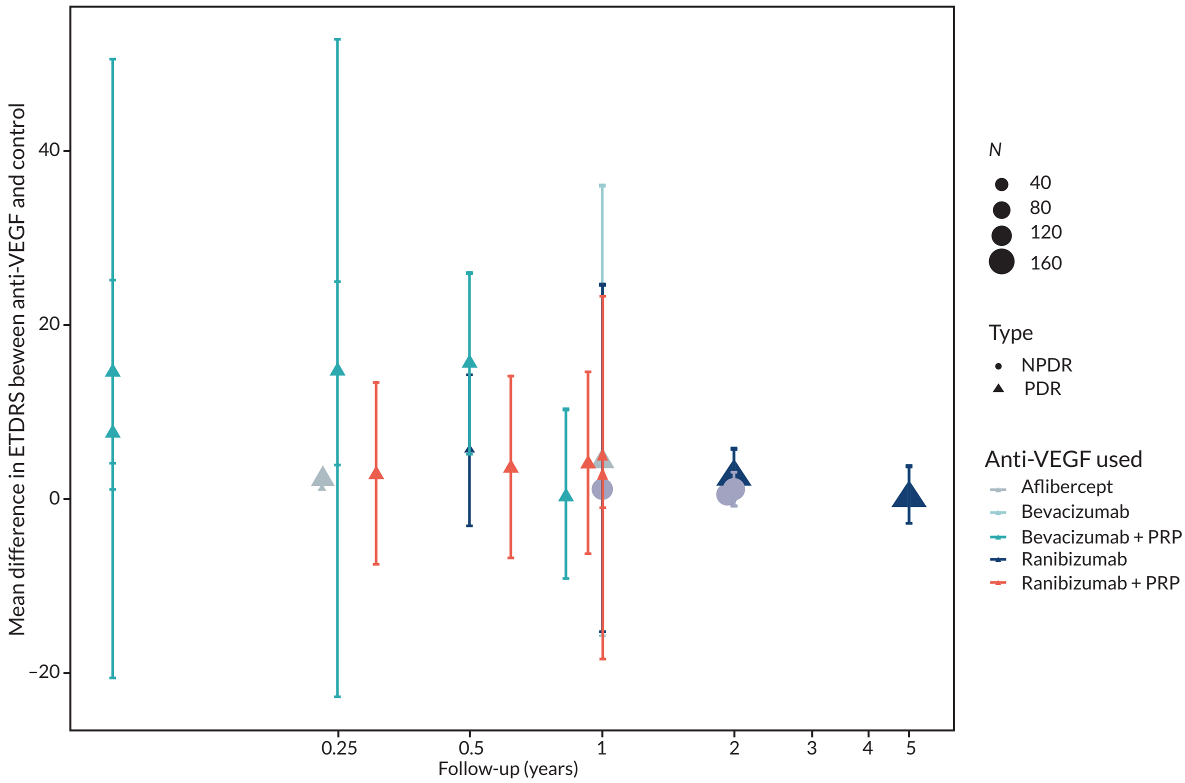

FIGURE 2 All BCVA data (ETDRS letters) from all trials of anti-VEGF.

with an estimated heterogeneity standard error (τ) of 0.04 (95% CrI 0 to 0.14). Results for trials with a follow-up duration of 1–2 years (see *Figure 5*) were similar to those at up to 1 year, suggesting no obvious trend in treatment effects at up to 2 years.

Given the similarity in magnitude of effect for the various anti-VEGF agents compared to PRP, it is not surprising that the indirect comparisons between agents show no conclusive evidence of difference between any of them. There appears to be no difference between using ranibizumab alone versus ranibizumab combined with PRP, particularly at 2 years.

Treatment rankings are shown in *Appendix 2* (*Figures 23* and *26*). Given the similarity in effect sizes across the different types of anti-VEGF, it is difficult to draw conclusions from the ranking diagrams beyond the fact that PRP alone is likely to be the least effective treatment. The limited data on bevacizumab mean its ranking is very uncertain.

Impact of follow-up time and vision at randomisation

To further examine the impact of follow-up time on the effectiveness of anti-VEGFs, we fitted a range of NMA models including time as a covariate. This meant that all trials could be combined in a single NMA, and whether the effectiveness of anti-VEGFs varied with time could be assessed. Models were also fitted including BCVA at randomisation, to account for possible variation in the effectiveness of the anti-VEGFs with initial vision (see *Appendix 2*).

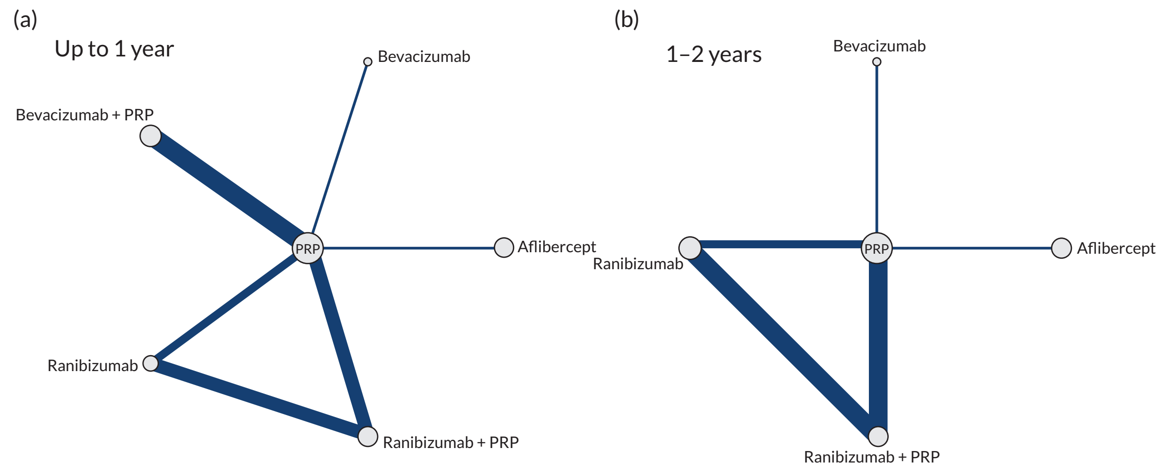

FIGURE 3 Network diagrams at (a) up to 1 year and (b) 1–2 years.

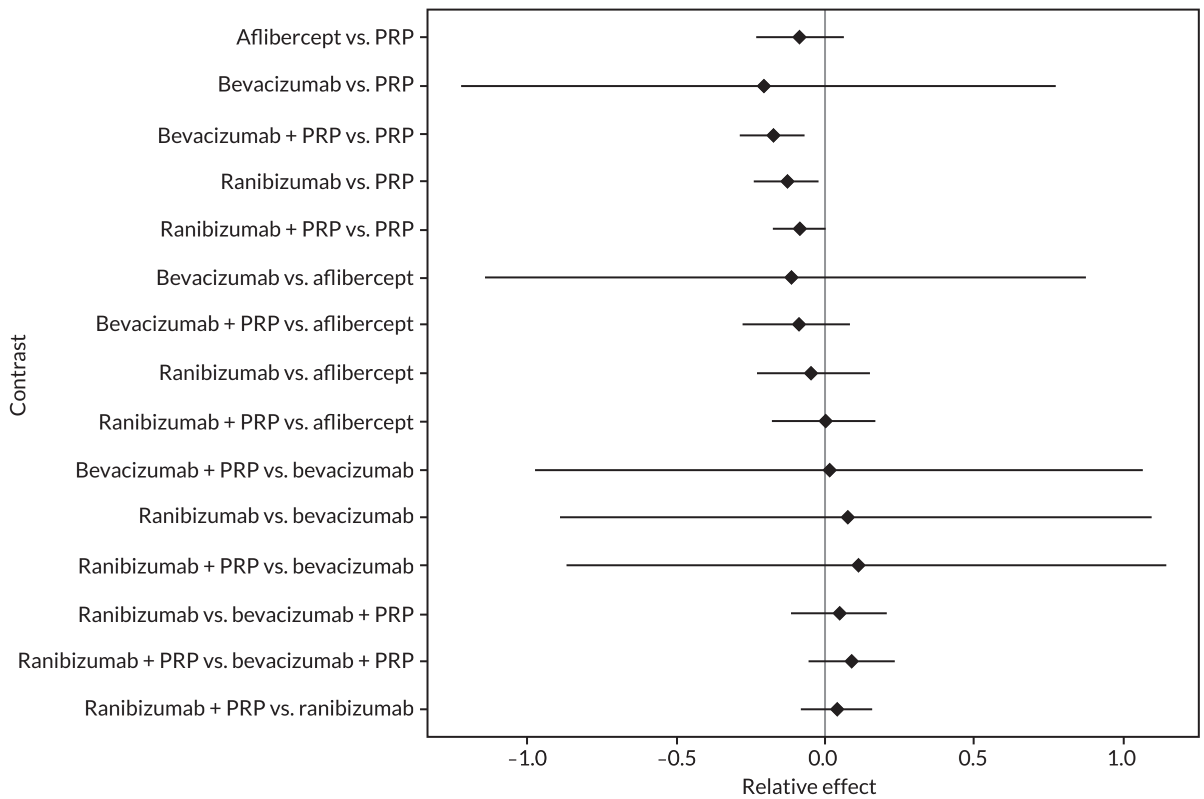

FIGURE 4 Comparison of interventions from NMA of BCVA up to 1 year.

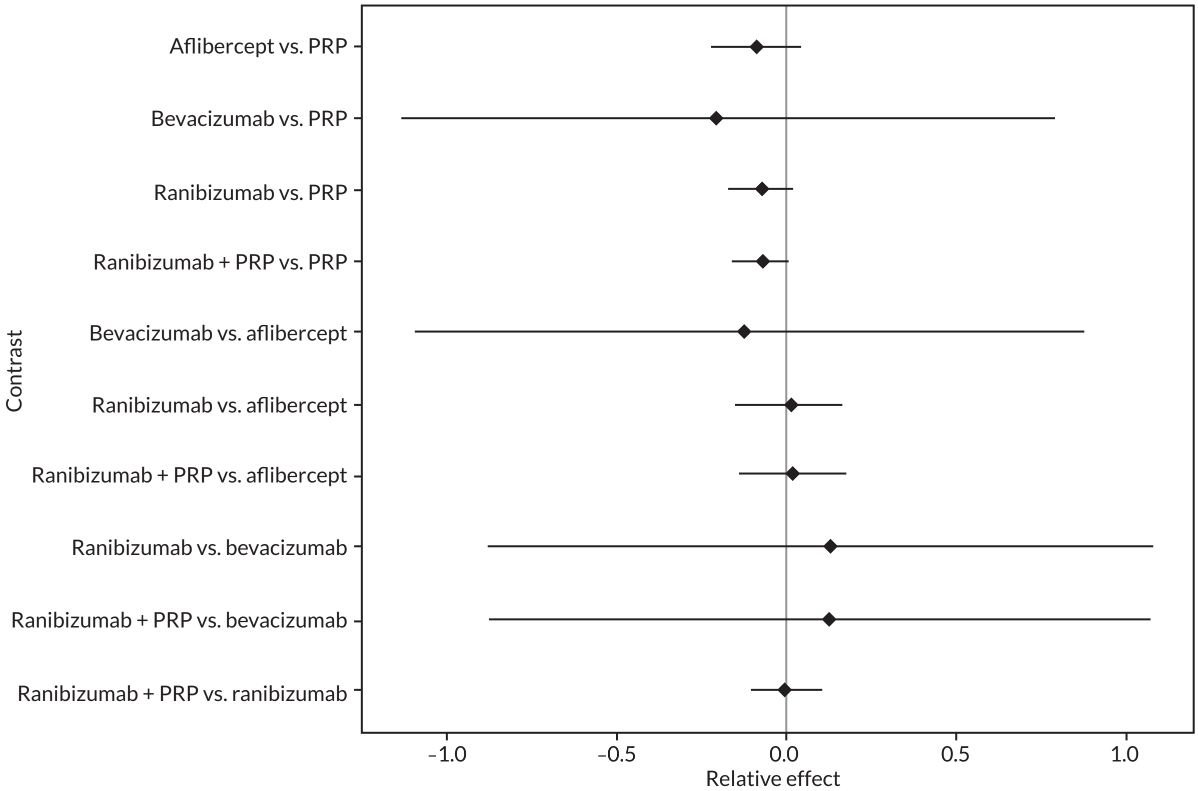

FIGURE 5 Comparison of interventions from NMA of BCVA from 1 to 2 years.

Overall, results were very similar to the NMAs at up to 1 year and 1–2 years. *Figure 6* shows the effect estimates for anti-VEGFs compared to PRP alone from a model with a linear association between anti-VEGF effect and both follow-up time and BCVA at randomisation. Estimates are presented for 1 year of follow-up and the mean BCVA

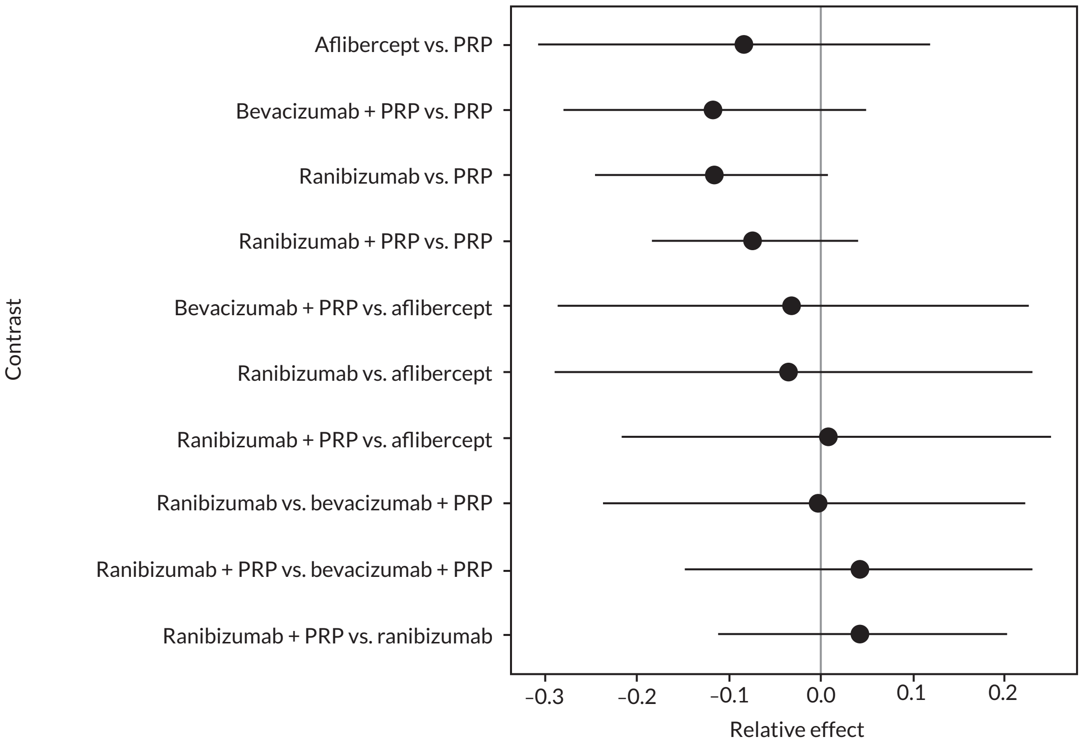

FIGURE 6 Network meta-analysis of log-MAR with adjustment for follow-up time and BCVA at baseline.

at baseline across all trials (log-MAR 0.3). The pattern of effect sizes is very similar to that seen in *Figures 4* and *5*, but CrIs are wider, suggesting that adjusting for follow-up time and baseline BCVA leads to greater uncertainty.

There was no clear evidence that the relative effectiveness of anti-VEGFs varied with time or with vision at randomisation. However, it should be noted that almost all the data were for follow-up times of 2 years or less. Only one trial followed up patients for 5 years, and that found no evidence of difference between anti-VEGF (ranibizumab) and PRP after 5 years.[31]

Further network meta-analyses

To further compare the anti-VEGFs to each other, simplified NMAs were performed by combining treatment arms. Two NMAs were performed:

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

In both cases, NMAs included adjustment for follow-up time and BCVA at randomisation. Full results for these NMAs are presented in *Appendix 2*. 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 (mean difference −0.089, 95% CrI −0.180 to −0.019), as did anti-VEGF combined with PRP compared to PRP alone (mean difference −0.108, 95% CrI −0.192 to −0.048).

When comparing the three anti-VEGFs (with or without concomitant PRP), there was no clear evidence of any difference in effectiveness between the three types of anti-VEGF; for example, there was no difference between aflibercept and ranibizumab (mean difference −0.003, 95% CI −0.166 to 0.163).

Threshold analysis

Threshold analyses of the NMAs of BCVA are reported in *Appendix 2*. These found that the evidence for anti-VEGF being superior to PRP was robust, but there was some uncertainty in the overall ranking of the various anti-VEGF treatments. This was probably because the evidence across the different anti-VEGFs showed very similar effectiveness.

Other outcomes

Results on outcomes other than BCVA were inconsistently reported, with most being reported in no more than three trials. Complete results for these outcomes are presented in *Appendix 3*. The limited data meant that NMAs were not feasible for these outcomes. A meta-analysis was performed for outcomes reported in two or more trials by assuming that the impact of anti-VEGFs is the same for all types of anti-VEGF, for anti-VEGF alone or in combination with PRP, and at all times up to 2 years. While these are strong assumptions, they may be reasonable given the results observed for BCVA, and the apparent lack of heterogeneity in the data.

Forest plots of neovascularisation of the disc (NVD) and neovascularisation elsewhere (NVE) are shown in *Appendix 3*. These suggest that neovascularisation was reduced while using anti-VEGF. The results of meta-analyses for other non-vision outcomes are shown in *Figure 7*. Although data were limited, the results suggest that anti-VEGF treatment substantially reduces the rate of macular oedema (DMO), the need for vitrectomy and reduces the rate of vitreous haemorrhage. No data on progression of diabetic retinopathy were reported.

Adverse events

As with non-BCVA outcomes, adverse events were not widely reported, with little consistency across trials as to which adverse events were reported. A meta-analysis was 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, for anti-VEGF alone or in combination with PRP, and at all times up to 2 years.

The meta-analysis results are shown in *Figure 8*. Due to the small numbers of events, and limited numbers of trials reported each adverse event, most results are inconclusive. Anti-VEGF appeared to reduce the incidence of retinal detachment. It appeared to increase the

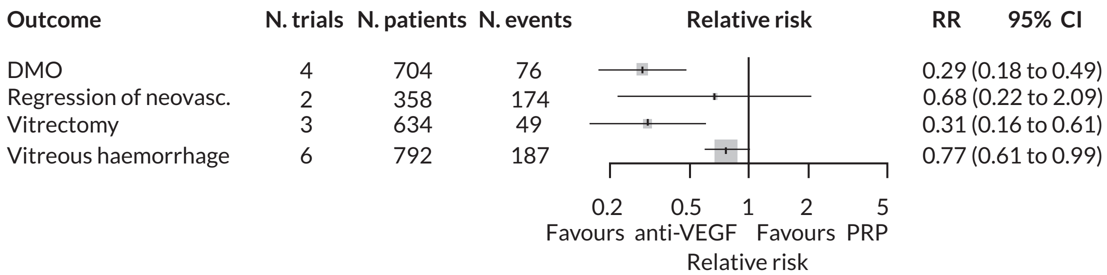

FIGURE 7 Meta-analysis of non-vision outcomes. RR, relative risk.

Outcome	N. trials	N. patients	N. events	RR	95% CI
Cardiovascular death	2	303	5	1.50	(0.25 to 9.05)
Cataracts	3	769	72	0.88	(0.58 to 1.35)
Myocardial infarct.	4	782	18	0.68	(0.25 to 1.82)
Ocular pain	2	303	15	1.93	(0.66 to 5.64)
Raised intraocular pressure	3	769	74	0.90	(0.59 to 1.36)
Retinal detachment	2	711	44	0.41	(0.22 to 0.77)
Retinal tear	2	711	2	3.09	(0.32 to 29.56)
Serious adverse event	3	550	136	0.75	(0.56 to 1.00)
Stroke	3	711	14	1.52	(0.33 to 6.95)

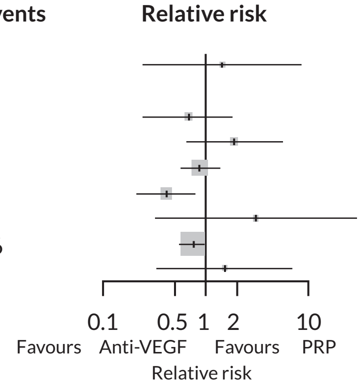

FIGURE 8 Meta-analyses of adverse event outcomes.

rate of ocular pain, but it was unclear whether this was procedure-related or post-intervention pain. Full results are presented in *Appendix 3*.

Non-proliferative retinopathy

Two trials compared aflibercept to sham injection in patients with non-proliferative retinopathy with a follow-up of 2 years (PANORAMA and Protocol W). Meta-analysis of their BCVA results found no clear evidence of any benefit of aflibercept over sham injection [mean difference (log-MAR) −0.02, 95% CI −0.05 to 0.01]. Progression to macular oedema was the only other outcome reported by both trials, with strong evidence to suggest that aflibercept reduces the risk of macular oedema [relative risk (RR) 0.283, 95% CI 0.18 to 0.44]. Protocol W reported that aflibercept reduced the rate of vitrectomy compared to sham injection (RR 0.38, 95% CI 0.24 to 0.60). Full results are presented in *Appendix 4*.

Protocol W found that aflibercept slowed the rate of progression to proliferative retinopathy when compared to sham injection (hazard ratio 0.40, 97.5% CI 0.28 to 0.57). PANORAMA found that more patients on aflibercept experienced a 2 point or more improvement in Diabetic Retinopathy Severity Scale (DRSS) (RR 4.41, 95% CI 2.81 to 6.94).

Discussion

This systematic review included 14 trials of anti-VEGFs used to treat diabetic retinopathy. For patients with PDR, the NMA found good, but not conclusive, evidence that anti-VEGF therapy is better at maintaining vision than PRP therapy, with a benefit of around −0.089 log-MAR (95% CI −0.179 to −0.019), or 3.6 ETDRS letters. This is within the region of variation that might be expected between eye tests without any intervention and is therefore unlikely to be clinically meaningful.[37] There was no compelling evidence to suggest that the three anti-VEGFs (aflibercept, ranibizumab and bevacizumab) differ in effectiveness; observed differences might be due to different trial populations or potential for bias. There was no conclusive evidence that combining anti-VEGF injection with PRP therapy is more effective at improving vision than anti-VEGF alone. Anti-VEGF appears to have no impact on BCVA in people with non-proliferative disease.

A further issue is the impact of time on the effectiveness of anti-VEGF therapy. Our meta-analysis found no evidence that the effectiveness waned over the first 2 years after initialising therapy. However, the one trial with a longer follow-up (Protocol S) found no benefit of ranibizumab over PRP after 5 years.[31] The longer-term value of anti-VEGF therapy therefore needs further investigation, particularly regarding how anti-VEGF treatment should be repeated over long time periods. There was some evidence that the benefit of anti-VEGF over PRP may be greater in people with poorer vision at time of injection. However, it was not possible to draw any firm conclusions on this from data presented in trial publications alone.

Data on outcomes other than visual acuity were limited, and not reported consistently across trials. Given the variations in follow-up and interventions used, NMAs were not feasible, and meta-analyses had to make the strong assumption of no difference in effect between the three anti-VEGFs, and no variation over time. Given these limitations, there was some evidence that anti-VEGFs are more effective than PRP at preventing the most serious consequences of diabetic retinopathy. They reduced the incidence of macular oedema (in both PDR and NPDR patients) and vitreous haemorrhage. In patients with NPDR, there was some evidence that aflibercept slows the rate of progression to PDR and improves retinopathy severity. This suggests that anti-VEGF may be valuable in preventing progression of diabetic retinopathy, even if its impact on vision directly is modest. Evidence on adverse events was limited due to inconsistent reporting, and small numbers of events. There was some evidence that anti-VEGF reduces the risk of retinal detachment.

Most trials were of short duration, with only one trial in PDR extending beyond 1 year. That trial found no vision benefit of anti-VEGF over PRP after 5 years, raising concerns as to the long-term efficacy of anti-VEGF therapy.

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.

Conclusion

Anti-VEGF injection is only marginally better than PRP at maintaining vision and the benefit is unlikely to be 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 suggest that combining anti-VEGF with PRP improves effectiveness. Anti-VEGF may prevent, or delay, progression of macular oedema and vitreous haemorrhage. Some concern over bias in the trials remains.

The benefits of anti-VEGFs appear consistent for at least 2 years after initiation of treatment, but longer-term benefits are uncertain. There is some evidence that anti-VEGFs are less effective at maintaining visual acuity in people with less severe retinopathy, but this requires further investigation. Access to original individual-level trial data might aid in resolving this. Trials or observational studies of duration substantially longer than 1 year are needed to examine whether anti-VEGF may be beneficial in the long term, particularly with the requirement for long-term repeated anti-VEGF injections.

Additional information

CRediT contribution statement

Mark Simmonds (https://orcid.org/0000-0002-1999-8515)**:** Conceptualisation (lead), Data curation (lead), Formal analysis (lead), Funding acquisition (lead), Investigation (lead), Methodology (lead), Project administration, Writing (lead).

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Ruth Walker (https://orcid.org/0000-0003-2765-7363)**:** Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Writing.

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Matthew Walton (https://orcid.org/0000-0003-1932-3689): Conceptualisation, Funding acquisition, Writing.

Rob Hodgson (https://orcid.org/0000-0001-6962-2893)**:** Conceptualisation, Funding acquisition, Writing.

Laura Bojke (https://orcid.org/0000-0001-7921-9109)**:** Conceptualisation, Funding acquisition, Writing.

Lesley Stewart (https://orcid.org/0000-0003-0287-4724)**:** Conceptualisation, Funding acquisition, Writing.

Sofia Dias (https://orcid.org/0000-0002-2172-0221)**:** Conceptualisation, Funding acquisition, Methodology, Writing.

Thomas Rush: Conceptualisation, Funding acquisition, Writing (patient and public involvement advisor).

John G Lawrenson: Conceptualisation, Funding acquisition, Writing.

Tunde Peto (https://orcid.org/0000-0001-6265-0381)**:** Conceptualisation, Funding acquisition, Writing.

David Steel (https://orcid.org/0000-0001-8734-3089)**:** Conceptualisation, Funding acquisition, Writing.

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Data-sharing statement

Data and code to reproduce the meta-analyses are available on GitHub (https://github.com/marksimmondsyork/AVID). For all other data requests please contact the corresponding author.

Ethics statement

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

Information governance statement

All data used in this paper were taken from published sources: no personal data were included.

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/PCGV5709.

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This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

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About this article

The contractual start date for this research was in August 2021. This article began editorial review in November 2023 and was accepted for publication in August 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

List of abbreviations

anti-VEGF	anti-vascular endothelial growth factor
BCVA	best corrected visual acuity
CENTRAL	Cochrane Central Register of Controlled Trials
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DMO	diabetic macular oedema
DRSS	Diabetic Retinopathy Severity Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
ICTRP	International Clinical Trials Registry Platform
IPD	individual patient data
log-MAR	logarithm of the minimum angle of resolution
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NVD	neovascularisation of the disc
NVE	neovascularisation elsewhere

PDR	proliferative diabetic retinopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	panretinal photocoagulation
RCT	randomised controlled trial
WHO	World Health Organization

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Appendix 1 Systematic review processes

Database search strategies

The aim of the literature search was to identify RCTs on anti-VEGFs, angiogenesis inhibitors and other specific drugs used for the treatment of diabetic retinopathy.

An Information Specialist (HF) designed a preliminary search strategy in Ovid MEDLINE in consultation with the research team. The strategy consisted of terms for the condition (diabetic retinopathy), which were combined with terms for the intervention (anti-VEGF, angiogenesis inhibitors, or specific drugs used for the treatment of diabetic retinopathy) using the Boolean operator AND. Text word searches for terms appearing in the title and abstracts of database records were included in the strategy alongside searches of relevant subject headings. A RCT study filter was applied using the Boolean operator AND. No date or language limits were applied. The final MEDLINE strategy was adapted for use in all resources searched.

The searches were performed on 27 August 2021. 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 (Wiley), Cochrane Database of Systematic Reviews (Wiley), DARE (CRD), PROSPERO (CRD) and Epistemonikos. The following trial registries were searched: WHO ICTRP, ClinicalTrials.gov, and the EU Clinical Trials Registry.

Search results were imported into EndNote 20 and deduplicated. All search strategies are presented in full below.

The searches were updated on 13 July 2022 and again on 26 May 2023 using all the databases and strategies as used previously, except for DARE as this database is no longer updated. For each update search, the results of the databases were deduplicated against each other in a separate EndNote 20 Library before being merged with the results of the original EndNote Library and deduplicated for a second time.

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 neovasculari?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: <1974–25 May 2023>

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. doi: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

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,kw 4547
#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,kw 1326
#5 ("new blood" NEXT vessel* and diabet*):ti,ab,kw 32
#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,kw 3457
#7 ((retinal NEXT vein* NEAR/3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*):ti,ab,kw 254
#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,kw 1610
#12 (antiVEGF*):ti,ab,kw 1523
#13 ((anti NEXT vascular or antivascular) NEAR/2 "endothelial growth" NEXT factor*):ti,ab,kw 699
#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,kw 2048
#15 ("vascular proliferation" NEAR/4 inhibit*):ti,ab,kw 1
#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,kw 2126
#20 ((antiangiogen* or anti NEXT angiogen*) NEAR/2 (agent* or drug* or effect*)):ti,ab,kw 717
#21 (angiostatic NEAR/2 (agent* or drug*)):ti,ab,kw 10
#22 ((neovasculari?ation or vasculari?ation) NEAR/2 inhibit*):ti,ab,kw 37
#23 {OR #17-#22}2691
#24 Aflibercept*:ti,ab,kw 1081
#25 (Eylea or Zaltrap or Ziv NEXT Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 252
#26 [mh ^Bevacizumab] 2633
#27 Bevacizumab*:ti,ab,kw 7386
#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,kw 941
#29 (IVB NEAR/2 inject*):ti,ab,kw 89
#30 [mh ^Ranibizumab] 1049
#31 Ranibizumab*:ti,ab,kw 2266
#32 (Lucentis or "rhuFab V2"):ti,ab,kw 451
#33 (IVR NEAR/2 inject*):ti,ab,kw 32
#34 Pegaptanib*:ti,ab,kw 166
#35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 82
#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,kw 17188
#39 #37 not #38 with Publication Year from 2000 to 2023, in Trials 1825

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 #30 2,394 Limited by 2000-01-01 to 2023-05-26
31 #29 NOT #30 2,410
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 #28 2,524
28 TS=(random* or control* or trial* or "single blind" or "double blind" or "triple blind" or placebo)8,083,064
27 #6 AND #26 6,121
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 #25 83,065

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 #5 43,073
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 degnerat* 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 #30 86 Limited by 2000-01-01 to 2023-05-26
31 #29 NOT #30 89
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 #28 92
28 TS=(random* or control* or trial* or "single blind" or "double blind" or "triple blind" or placebo) 1,616,551
27 #6 AND #26 458
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 #25 8,998
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 rhuMAbVEGF 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 #5 5,826
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 degnerat* 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

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,kw 4547
#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,kw 1326
#5 ("new blood" NEXT vessel* and diabet*):ti,ab,kw 32
#6 (((retin* or subretina* or interretina* or vitreoretin* or chorioretin* or choroid* or macula* or intraocular or intravitreal) NEAR/4 (damage* or deteriorat* or degnerat* or disease* or edema or oedema or neovasculari?ation*)) and diabet*):ti,ab,kw 3457
#7 ((retinal NEXT vein* NEAR/3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or emboli*)) and diabet*):ti,ab,kw 254
#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,kw 1610
#12 (antiVEGF*):ti,ab,kw 1523
#13 ((anti NEXT vascular or antivascular) NEAR/2 "endothelial growth" NEXT factor*):ti,ab,kw 699
#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,kw 2048
#15 ("vascular proliferation" NEAR/4 inhibit*):ti,ab,kw 1
#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,kw 2126

#20 ((antiangiogen* or anti NEXT angiogen*) NEAR/2 (agent* or drug* or effect*)):ti,ab,kw 717
#21 (angiostatic NEAR/2 (agent* or drug*)):ti,ab,kw 10
#22 ((neovasculari?ation or vasculari?ation) NEAR/2 inhibit*):ti,ab,kw 37
#23 {OR #17-#22} 2691
#24 Aflibercept*:ti,ab,kw 1081
#25 (Eylea or Zaltrap or Ziv NEXT Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 252
#26 [mh ^Bevacizumab] 2633
#27 Bevacizumab*:ti,ab,kw 7386
#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,kw 941
#29 (IVB NEAR/2 inject*):ti,ab,kw 89
#30 [mh ^Ranibizumab] 1049
#31 Ranibizumab*:ti,ab,kw 2266
#32 (Lucentis or "rhuFab V2"):ti,ab,kw 451
#33 (IVR NEAR/2 inject*):ti,ab,kw 32
#34 Pegaptanib*:ti,ab,kw 166
#35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 82
#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,kw 17188

#39 #37 not #38 with Cochrane Library publication date between January 2000 and May 2023, in Cochrane Reviews 14

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 https://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 2000–2023

Publication type: Systematic Reviews

= 1026

Key:

* = truncation

title: = searches in title field

abstract: = searches in abstract field

PROSPERO

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

Date range: Inception – 26 May 2023

Date searched: 26 May 2023

Records retrieved: 159

#1 MeSH DESCRIPTOR Diabetic Retinopathy 107
#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 intra-vitreal) adj4 (damage* or deteriorat* or degnerat* 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 #6 740
#8 MeSH DESCRIPTOR Vascular Endothelial Growth Factors EXPLODE ALL TREES WITH QUALIFIER AI 0
#9 MeSH DESCRIPTOR Receptors, Vascular Endothelial Growth Factor EXPLODE ALL TREES WITH QUALIFIER AI 0
#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 #14 412
#16 MeSH DESCRIPTOR Angiogenesis Inhibitors 40
#17 MeSH DESCRIPTOR Angiogenesis Inducing Agents EXPLODE ALL TREES WITH QUALIFIER A I0
#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 #21 224
#23 (Aflibercept*) 141
#24 (Eylea or Zaltrap or Ziv-Aflibercept or AVE 0005 or AVE0005 or AVE 005 or AVE005) 22
#25 MeSH DESCRIPTOR Bevacizumab 46
#26 (Bevacizumab*) 445
#27 (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) 59
#28 (IVB adj2 inject*) 0
#29 MeSH DESCRIPTOR Ranibizumab 7
#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 #34 500
#36 #15 OR #22 OR #35 839
#37 #7 AND #36 159

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

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.

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Trials not included in meta-analyses

TABLE 3 Trials not included in 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 2009–2010	Bevacizumab (+ PRP)	PRP + Triamcinolone	China	91 eyes	NPDR, PDR
Mirshahi	Mirshahi 2008	Bevacizumab (+ PRP)	PRP, Sham injection	Iran	80 eyes	PDR

continued

TABLE 3 Trials not included in meta-analyses (*continued*)

Trial	Key paper(s)	Anti-VEGF	Comparator	Location	Sample size	Population
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	S. America	42 persons	PDR
Rentiya	Rentiya 2022	Ranibizumab (+ PRP)	PRP	Brazil	30 persons	PDR

Risk-of-bias assessment

TABLE 4 Full risk-of-bias assessment – Table A

	Randomisation process		Deviations from intended interventions		Missing outcome data	
Trial	**Judgement**	**Comments**	**Judgement**	**Comments**	**Judgement**	**Comments**
Ahmad 2012[27]	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

TABLE 4 Full risk-of-bias assessment – Table A (*continued*)

	Randomisation process		Deviations from intended interventions		Missing outcome data	
Trial	**Judgement**	**Comments**	**Judgement**	**Comments**	**Judgement**	**Comments**
Ali 2018[28]	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
CLARITY[23]	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 *et al.* 2015[32]	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	3% (2/60) eyes excluded due to VH in the control arm. It appears that all other randomised eyes were analysed
Marashi 2017[26]	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

continued

TABLE 4 Full risk-of-bias assessment – Table A (*continued*)

Trial	Randomisation process		Deviations from intended interventions		Missing outcome data	
	Judgement	Comments	Judgement	Comments	Judgement	Comments
PANORAMA[25]	Low	Patients were randomised according to a central randomisation scheme with treatment assignments provided by an interactive voice response system/interactive web response system to the designated study pharmacist (or qualified designee) Some differences in sex at baseline: higher rate of males in 2q16 (56%) and 2q8 (60%) compared with control (52%), but no other imbalances in reported baseline characteristics	Low	Placebo controlled. Participants, outcome assessors and study personnel were masked throughout the study period, except for study drug administration which was done by an unmasked physician Rates of participants not assessed were higher in the control group (73%) at 100 weeks (and 52 weeks) compared with aflibercept arms (84% and 83%), although participants were masked throughout the study period, and there was no evidence of changes from the intended intervention that occurred because of the trial context All participants analysed. LOCF imputation method used	Low	Rates of participants not assessed were higher in the control group (73%) at 100 weeks compared with aflibercept arms (84% and 83%) Sensitivity analysis: primary efficacy analysis was also performed using all observed measurements (regardless of whether rescue treatment was given). Protocol also stated that for sensitivity analyses, only true missing values would be imputed using the LOCF procedure, and that baseline values would be carried forward if all post-baseline observations were missing or non-gradable Sensitivity analysis results showed similar results to main analyses for DRSS, although all are based on the LOCF principle, and sensitivity analyses were not performed for BCVA The risk that the higher rate of missingness in the control arm is partly due to its true value cannot be excluded However, due to the size of the difference in missingness, any possible bias arising is likely to be small

TABLE 4 Full risk-of-bias assessment – Table A (*continued*)

	Randomisation process		Deviations from intended interventions		Missing outcome data	
Trial	**Judgement**	**Comments**	**Judgement**	**Comments**	**Judgement**	**Comments**
PRIDE[33]	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 (ranibizumab: 52.5, PRP: 53, ranibizumab + PRP: 55), age distribution (< 65 years: 86%, 86%, 72%); smoker (14%, 26%, 35%); duration of diabetes (25 years, 23 years, 21 years), 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	23% (25/108) of randomised participants not measured at 12 months No significant differences in rates of missing-ness across groups
PROTEUS[34]	Low	Computer-generated block randomisation. Central allocation implemented through electronic platform Large and statistically significant difference in mean age [ranibizumab + 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 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	
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	83% (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, statistical analysis plan reports 'Markov chain Monte Carlo multiple imputation-based on treatment group, the randomisation stratification factors, and all available visual acuity data from assessment visits prior to 2 years'

continued

TABLE 4 Full risk-of-bias assessment – Table A (*continued*)

	Randomisation process		Deviations from intended interventions		Missing outcome data	
Trial	**Judgement**	**Comments**	**Judgement**	**Comments**	**Judgement**	**Comments**
Protocol W[24]	Low	Central, web-based (DRCR network) randomisation, stratified by DR severity level No evidence of baseline imbalances	Low	Placebo controlled. Participants masked. Investigators and study co-ordinators unmasked CONSORT diagram reported. No evidence of deviation from intended intervention due to trial context Analyses conducted according to ITT principles	Low	68.5% (137/200, or 74.9% excluding 17 deaths) completed their 4-year visit in intervention arm, vs. 67.3% (134/199, 73.2% excluding 16 deaths) Multiple imputation (Markov model) used for missing data (assumes data are missing at random). Model included treatment group, study eye laterality, baseline DRSS, baseline visual acuity and change in visual acuity from baseline to each protocol assessment visit up to and including 4 years. Missingness documented, balanced between arms and unlikely to depend on its true value
Rebecca 2021[29]	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

TABLE 4 Full risk-of-bias assessment – Table A (*continued*)

	Randomisation process		Deviations from intended interventions		Missing outcome data	
Trial	**Judgement**	**Comments**	**Judgement**	**Comments**	**Judgement**	**Comments**
Roohipoor 2019[30]	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	Some concerns	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 not reported. The risk that at least some missingness could be due to visual acuity outcomes cannot be excluded
Sao Paulo A[36]	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 ranibizumab 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 not reported. The risk that at least some missingness could be due to visual acuity outcomes cannot be excluded
Sao Paulo B[35]	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 generally appropriate (incl. 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; DRCR, diabetic retinopathy clinical research retina network; ITT, intention to treat; IVB, intravitreal bevacizumab; LOCF, last-observation carried forward; mITT, modified intention to treat.

TABLE 5 Full risk-of-bias assessment – Table B

	Measurement of the outcome		Selection of the reported result		Overall bias
Trial	Judgement	Comments	Judgement	Comments	Judgement
Ahmad 2012[27]	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[28]	High	Appears to be ETDRS, standard scale No placebo	Some concerns	No protocol	High
CLARITY[23]	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 Optometrists 'masked to treatment allocation throughout the study. The optometrists received the participants into the visual acuity lanes with a visual acuity-specific source data worksheet that included the PIN and details of the study eye and non-study eye to be refracted, but with no previous records or case report forms by which the patient's treatment arm could be identified'	Low	A SAP 'was finalised before data lock and agreed with oversight committees'	Low
Ferraz 2015[32]	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[26]	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
PANORAMA[25]	Low	ETRDS method Outcome assessors were masked throughout the study period	Low		Low
PRIDE[33]	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
PROTEUS[34]	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

TABLE 5 Full risk-of-bias assessment – Table B (*continued*)

	Measurement of the outcome		Selection of the reported result		Overall bias
Trial	**Judgement**	**Comments**	**Judgement**	**Comments**	**Judgement**
Protocol S[31]	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
Protocol W[24]	Low	DRSS Outcome assessors masked	Low	SAP reported and finalised before unblinded outcome data were available for analysis	Low
Rebecca 2021[29]	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
Roohipoor 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. 10 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 Proliferative diabetic retinopathy: all best corrected visual acuity analyses

All figures and tables relate to the trials of PDR, excluding the two trials (PANORAMA, Protocol W) of non-proliferative retinopathy. For their results, see *Appendix 4*.

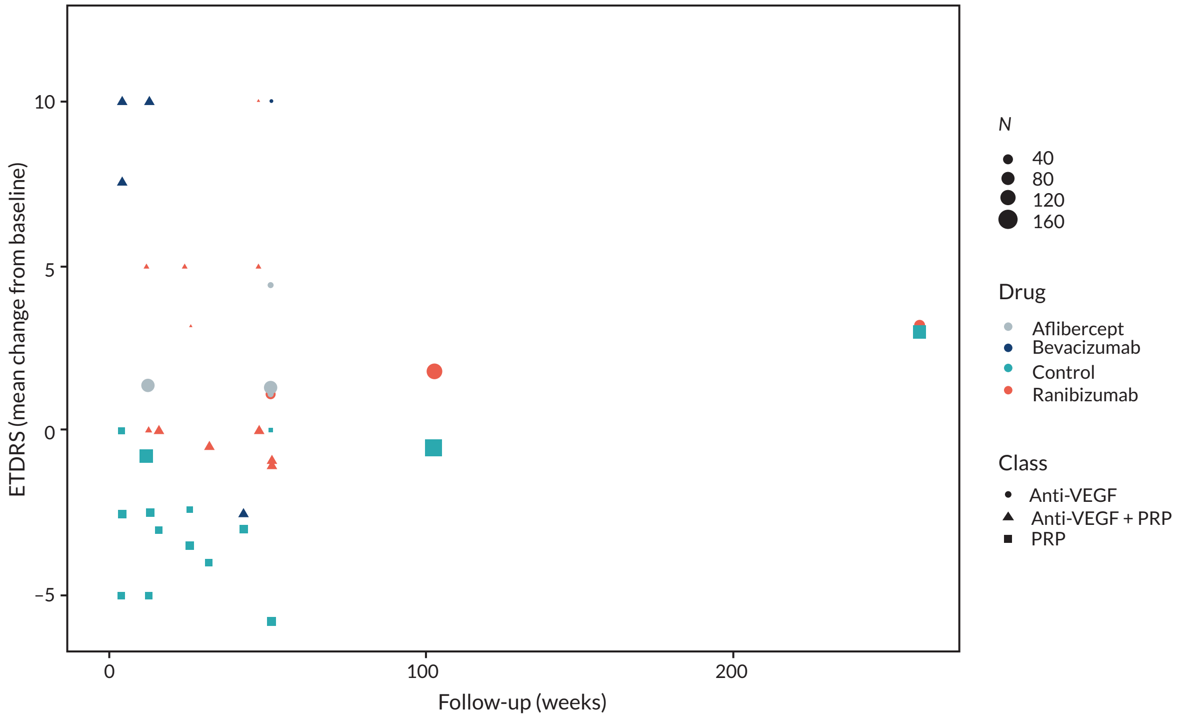


FIGURE 9 All ETDRS data (as mean change from baseline) by drug and type of intervention.

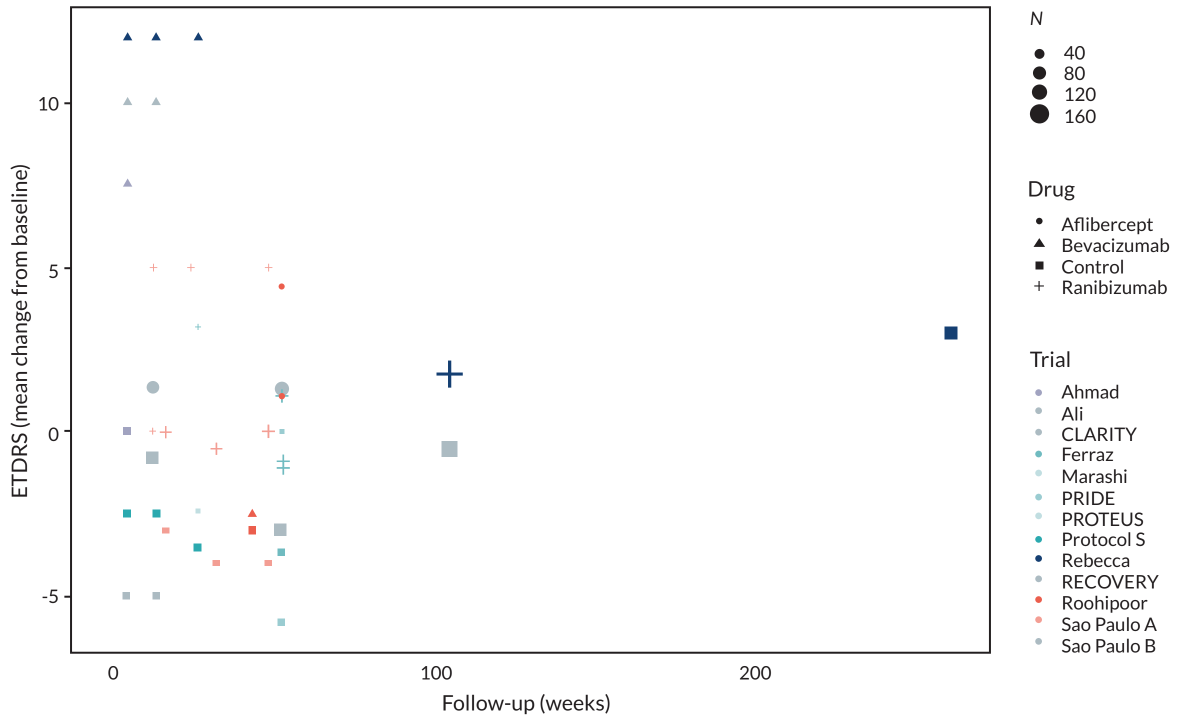


FIGURE 10 All ETDRS data (as mean change from baseline) by trial and drug type.

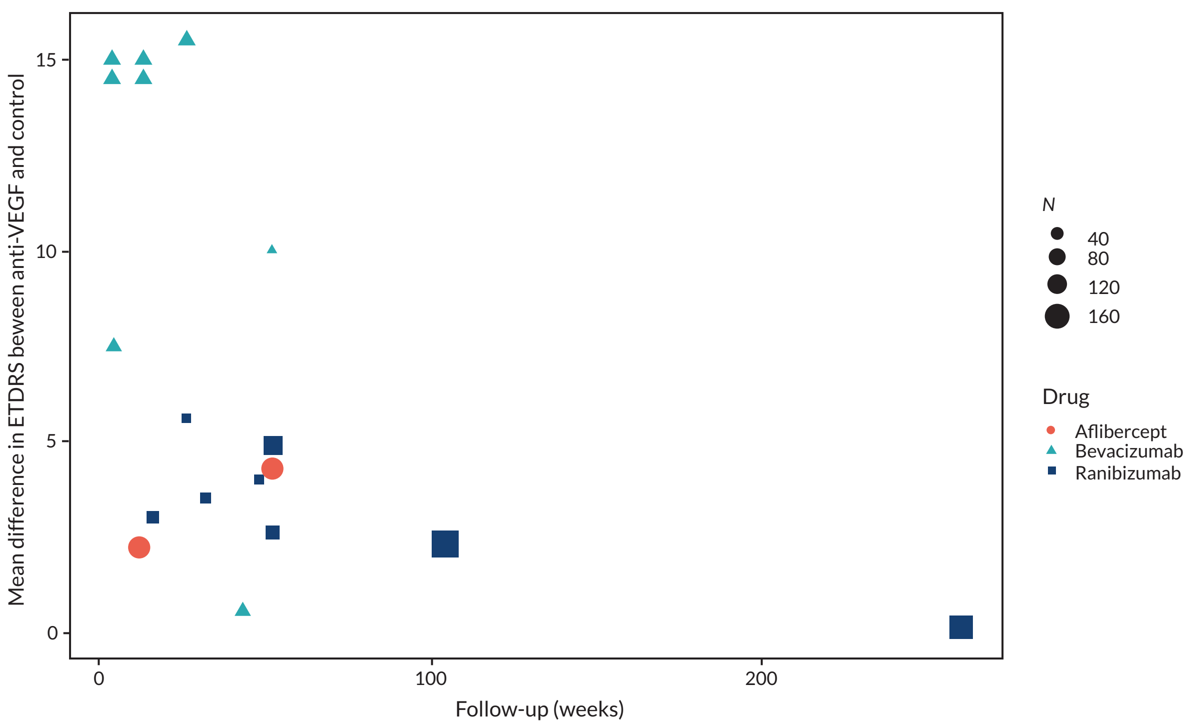


FIGURE 11 Mean difference in ETDRS between anti-VEGF and control arms over time.

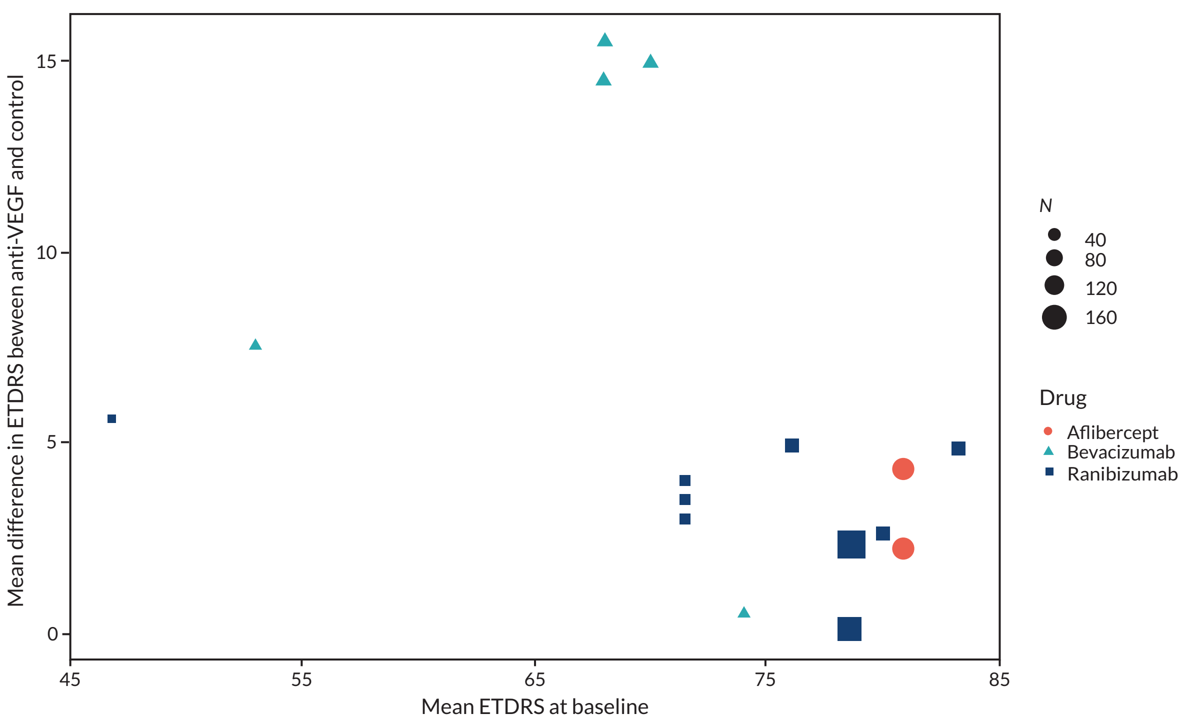


FIGURE 12 Mean difference between anti-VEGF and control arms by ETDRS at randomisation.

Figures and forest plots summarising best corrected visual acuity data

Note from these figures that there appears to be a possible decline in benefit to vison over time, and that the benefit of ant-VEGF may be greater in people with poorer initial vision, but these differences may be confounded by differences between types of anti-VEGF.

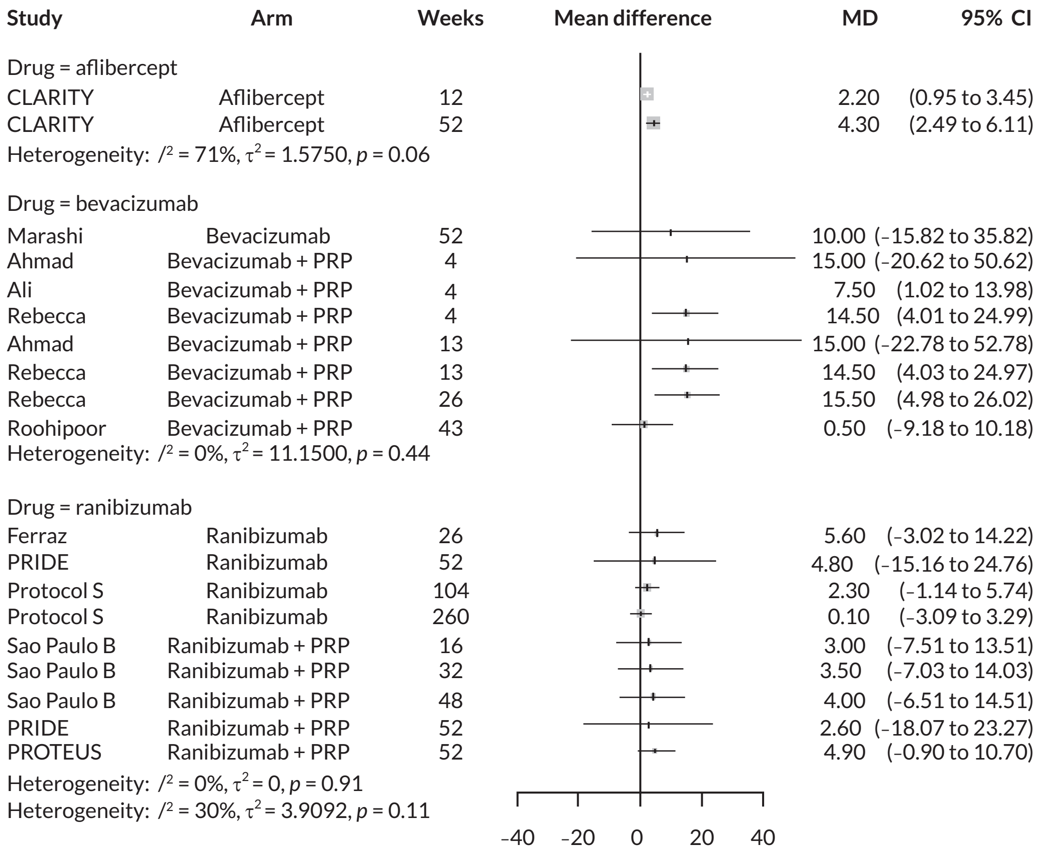


FIGURE 13 Forest plot of all mean differences in ETDRS between anti-VEGF and control (right side favours anti-VEGF).

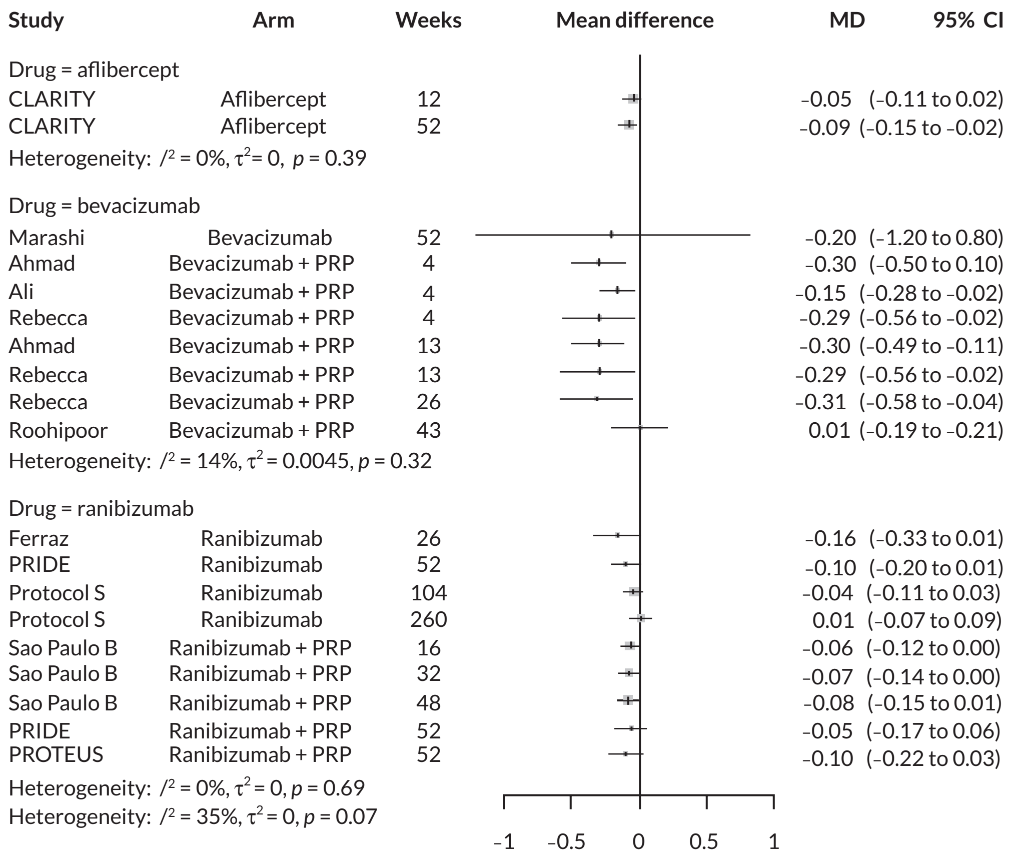


FIGURE 14 Forest plot of all mean differences in log-MAR between anti-VEGF and control (left side favours anti-VEGF).

Forest plots of meta-analyses of best corrected visual acuity

Up to 1 year

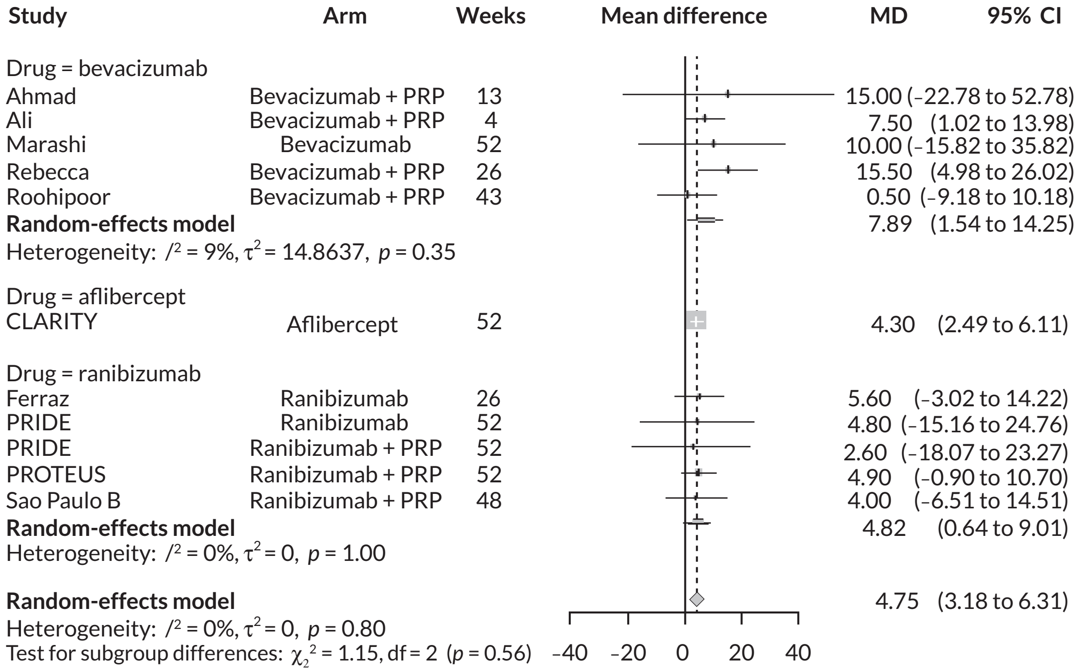


FIGURE 15 Meta-analysis of mean differences in ETDRS between anti-VEGF and control up to 1 year of follow-up (right side favours anti-VEGF).

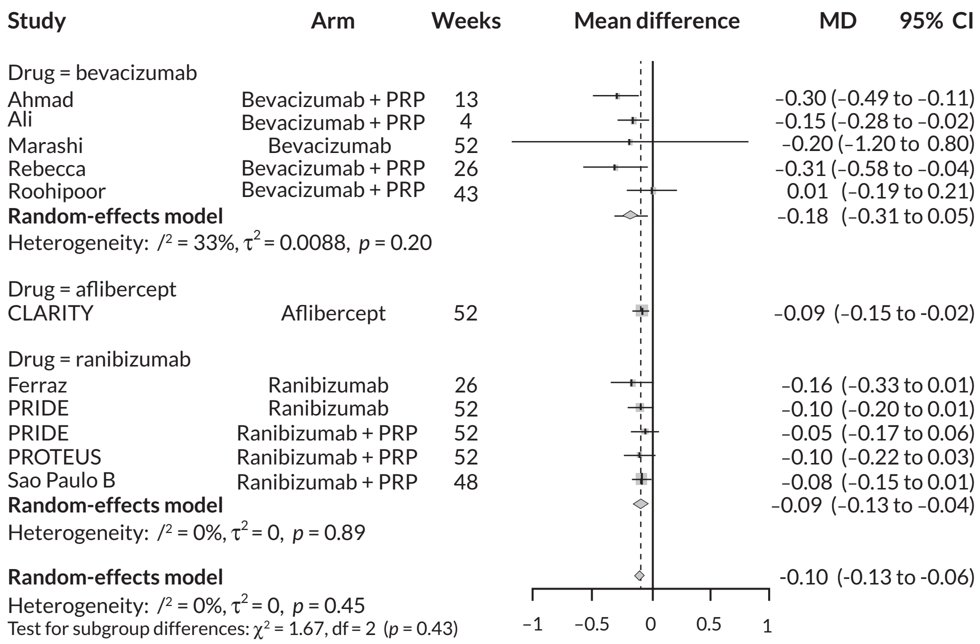


FIGURE 16 Meta-analysis of mean differences in log-MAR between anti-VEGF and control up to 1 year of follow-up (left side favours anti-VEGF).

One to 2 years' follow-up

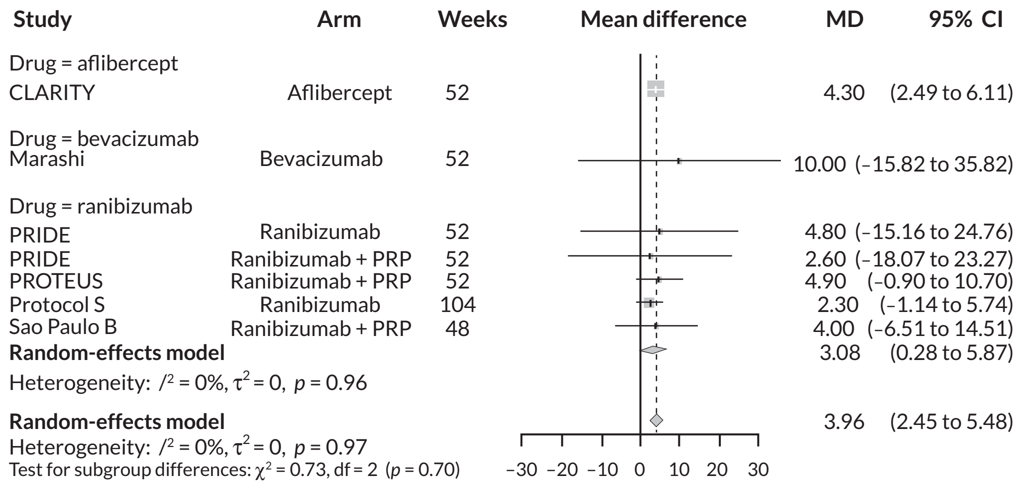


FIGURE 17 Meta-analysis of mean differences in ETDRS between anti-VEGF and control with 1–2 years' of follow-up (right side favours anti-VEGF).

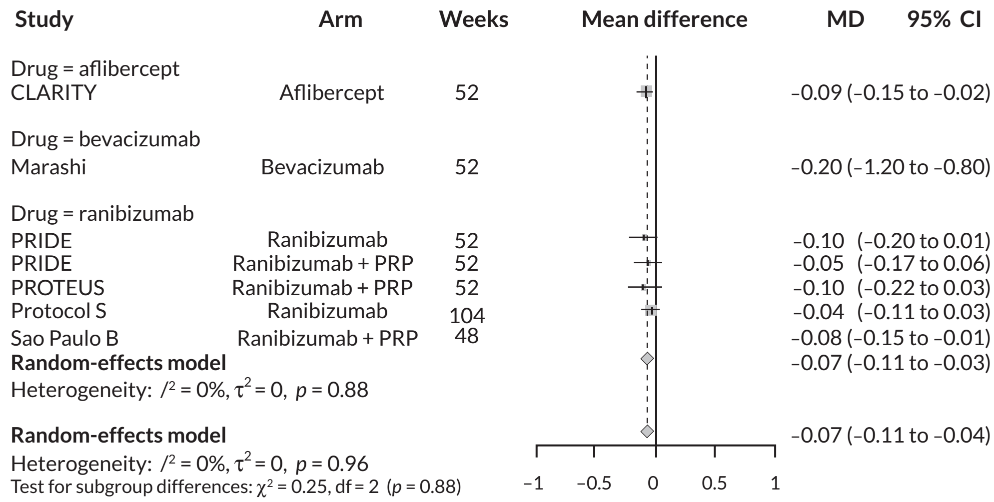


FIGURE 18 Meta-analysis of mean differences in log-MAR between anti-VEGF and control with 1–2 years' of follow-up (left side favours anti-VEGF).

Maximum follow-up in trial (up to 2 years)

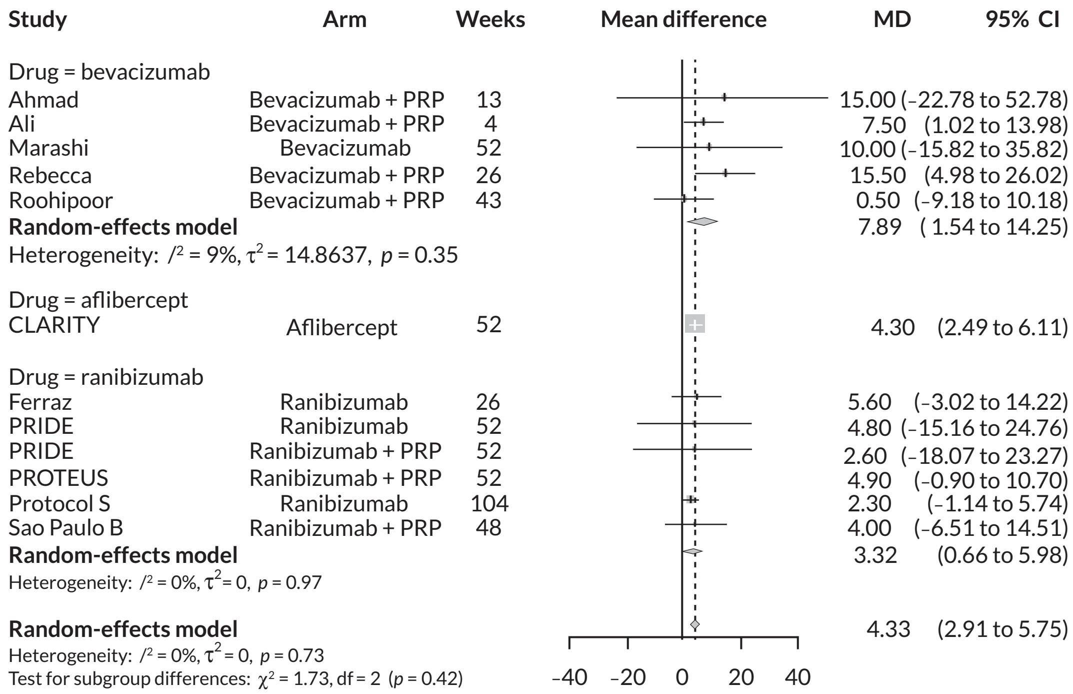


FIGURE 19 Meta-analysis of mean differences in ETDRS between anti-VEGF and control at end of trial (right side favours anti-VEGF).

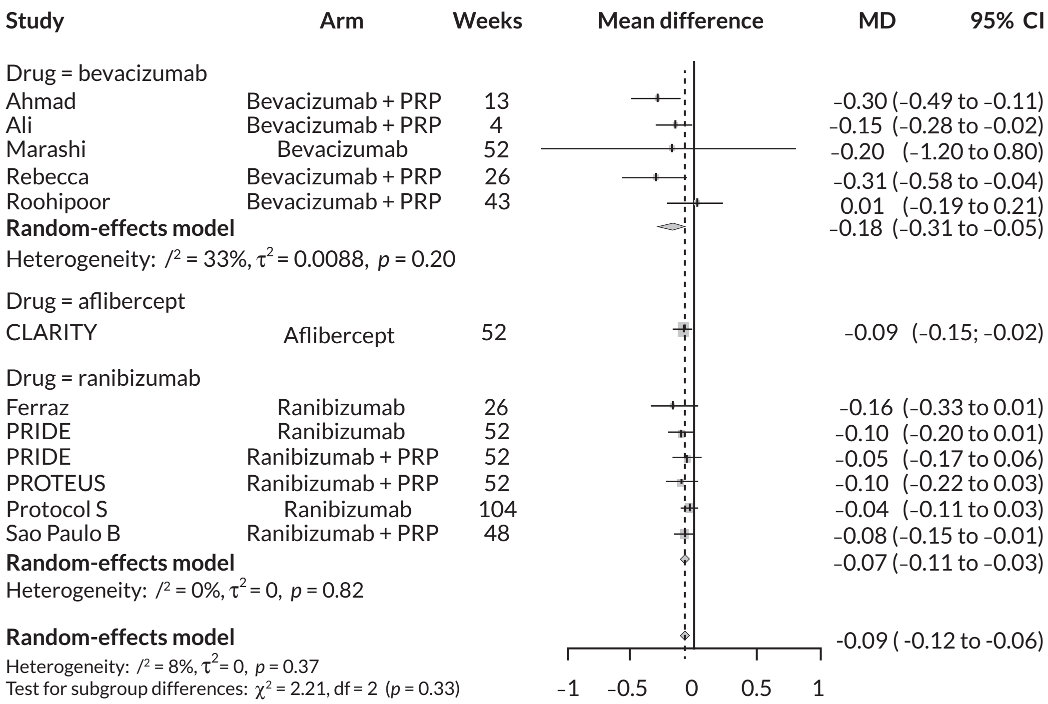


FIGURE 20 Meta-analysis of mean differences in log-MAR between anti-VEGF and control at end of trial (left side favours anti-VEGF).

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

Note: From this point forward on, meta-analyses of BCVA measured using log-MAR are presented. Some analyses using ETDRS were performed but are not included here. Similarly, only random-effects analyses are presented for simplicity, as differences between random- and fixed-effect analyses were minimal.

Analyses at up to 1 year of follow-up

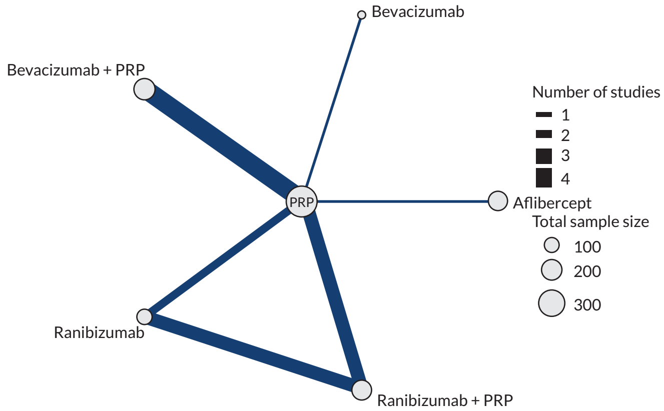


FIGURE 21 Network diagram of BCVA at up to 1 year of follow-up.

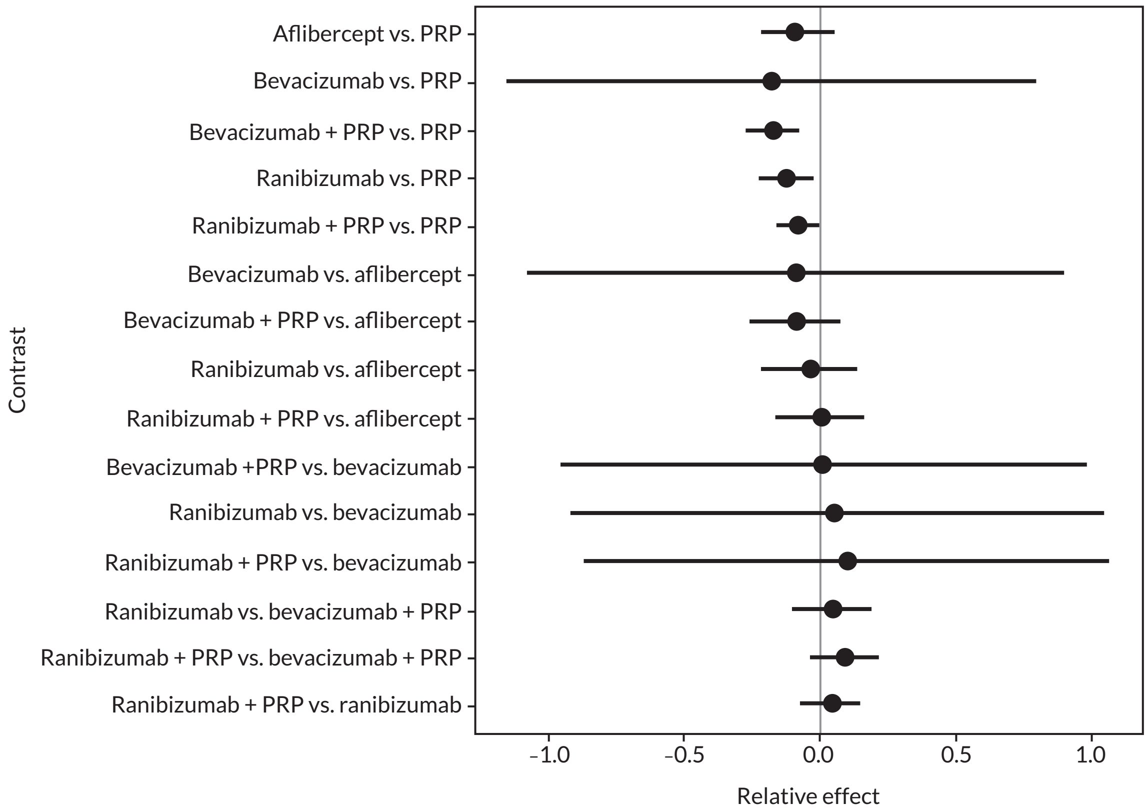


FIGURE 22 All treatment comparisons for 1-year random-effects NMA of log-MAR.

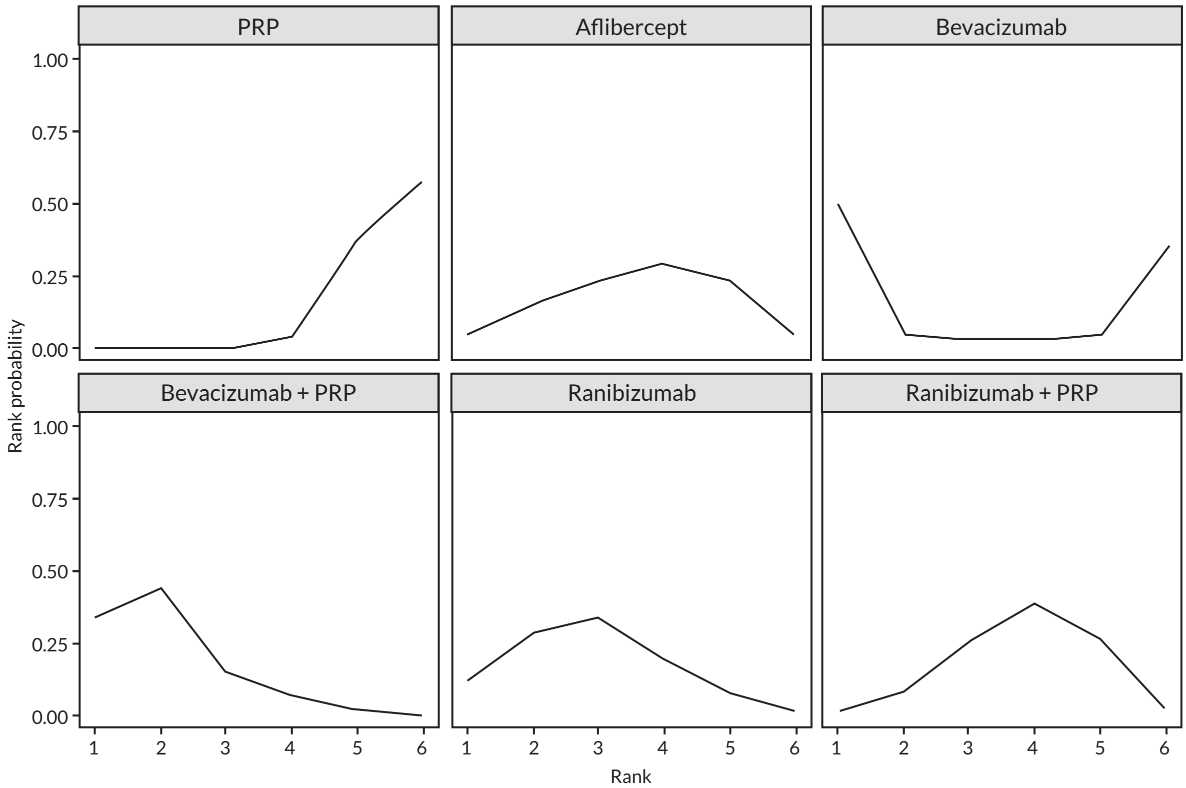


FIGURE 23 Probability of treatments for 1-year random-effects NMA of log-MAR.

TABLE 6 Results of NMA of log-MAR up to 1 year – comparisons between treatments

Intervention	Comparator	Mean difference	95% CI	
Aflibercept	PRP	−0.084	−0.222	0.056
Bevacizumab	PRP	−0.198	−1.213	0.785
Bevacizumab + PRP	PRP	−0.172	−0.279	−0.069
Ranibizumab	PRP	−0.121	−0.233	−0.006
Ranibizumab + PRP	PRP	−0.078	−0.165	0.013
Bevacizumab	Aflibercept	−0.115	−1.142	0.853
Bevacizumab + PRP	Aflibercept	−0.088	−0.273	0.082
Ranibizumab	Aflibercept	−0.037	−0.213	0.130
Ranibizumab + PRP	Aflibercept	0.006	−0.151	0.173
Bevacizumab + PRP	Bevacizumab	0.026	−0.947	1.027
Ranibizumab	Bevacizumab	0.077	-0.913	1.098
Ranibizumab + PRP	Bevacizumab	0.121	−0.867	1.151
Ranibizumab	Bevacizumab + PRP	0.051	−0.095	0.208
Ranibizumab + PRP	Bevacizumab + PRP	0.094	−0.040	0.236
Ranibizumab + PRP	Ranibizumab	0.043	−0.067	0.160

TABLE 7 Results of NMA of log-MAR up to 1 year – ranking probabilities

	Probability of ranking					
Treatment arm	1st (%)	2nd (%)	3rd (%)	4th (%)	5th (%)	6th (%)
PRP	0.00	0.13	0.65	4.93	37.65	56.65
Aflibercept	4.33	12.65	24.65	30.48	23.10	4.80
Bevacizumab	50.73	5.05	2.38	2.63	3.83	35.40
Bevacizumab + PRP	33.60	44.23	14.73	5.68	1.73	0.05
Ranibizumab	10.25	30.30	33.60	17.40	7.25	1.20
Ranibizumab + PRP	1.10	7.65	24.00	38.90	26.45	1.90

Analyses at 1–2 years' follow-up

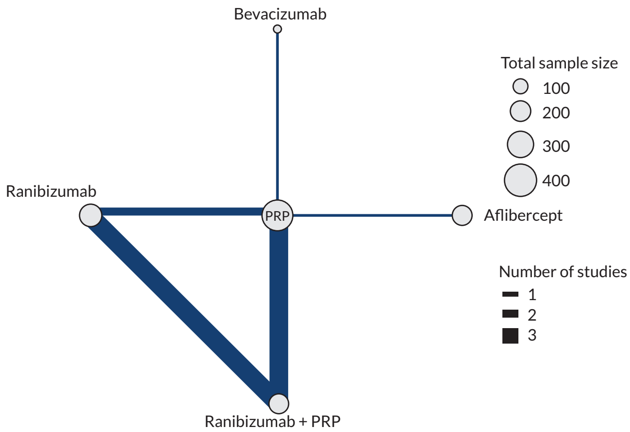


FIGURE 24 Network diagram of BCVA at up to 1–2 years of follow-up.

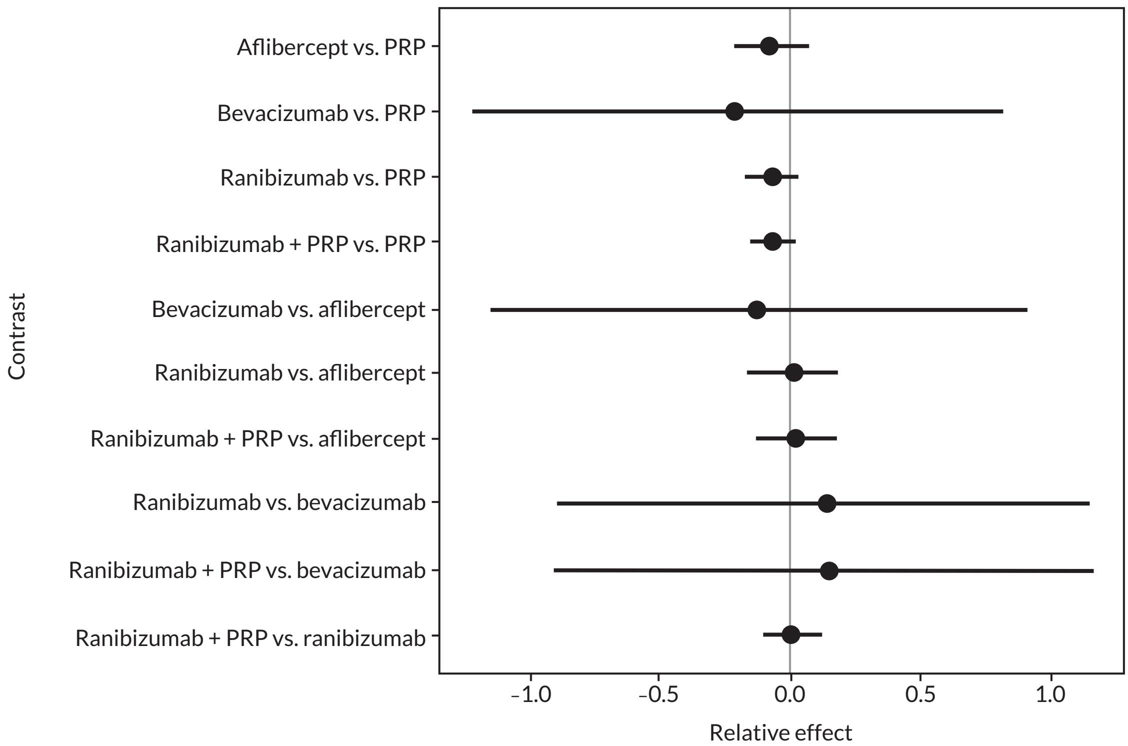


FIGURE 25 All treatment comparisons for 1–2 year random-effects NMA of log-MAR.

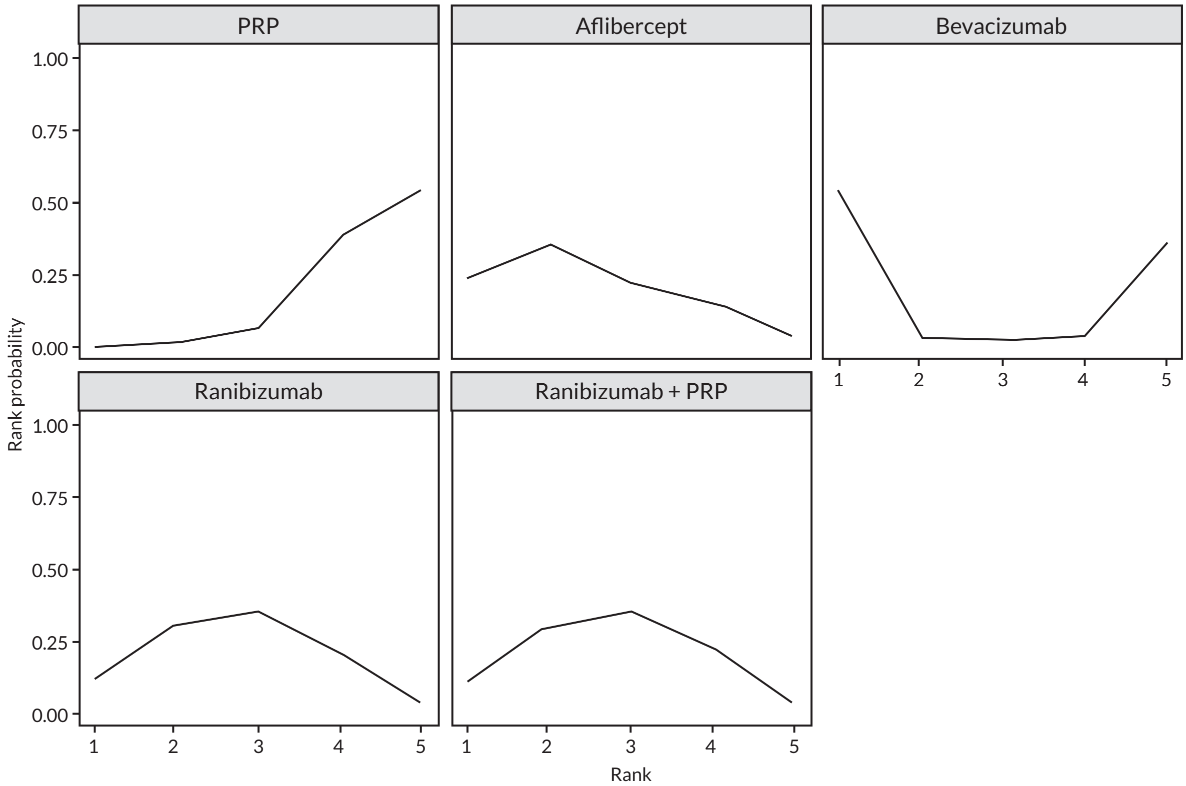


FIGURE 26 Probability of treatments for 1–2-year random-effects NMA of log-MAR.

TABLE 8 Results of NMA of log-MAR 1–2 years – comparisons between treatments

Intervention	Comparator	Mean difference	95% CI	
Aflibercept	PRP	−0.080	−0.225	0.100
Bevacizumab	PRP	−0.182	−1.181	0.816
Ranibizumab	PRP	−0.072	−0.171	0.017
Ranibizumab + PRP	PRP	−0.068	−0.152	0.020
Bevacizumab	Aflibercept	−0.102	−1.095	0.899
Ranibizumab	Aflibercept	0.008	−0.200	0.187
Ranibizumab + PRP	Aflibercept	0.012	−0.174	0.189
Ranibizumab	Bevacizumab	0.110	−0.887	1.104
Ranibizumab + PRP	Bevacizumab	0.114	−0.885	1.112
Ranibizumab + PRP	Ranibizumab	0.004	−0.100	0.114

TABLE 9 Results of NMA of log-MAR 1–2 years – ranking probabilities

	Probability of ranking				
Treatment arm	**1st (%)**	**2nd (%)**	**3rd (%)**	**4th (%)**	**5th (%)**
PRP	0.05	1.20	6.25	37.93	54.58
Aflibercept	21.38	34.58	20.98	17.00	6.08
Bevacizumab	56.20	3.15	2.88	3.35	34.43
Ranibizumab	13.13	30.28	34.13	20.15	2.33
Ranibizumab + PRP	9.25	30.80	35.78	21.58	2.60

Analysis at maximum follow-up time (up to 2 years)

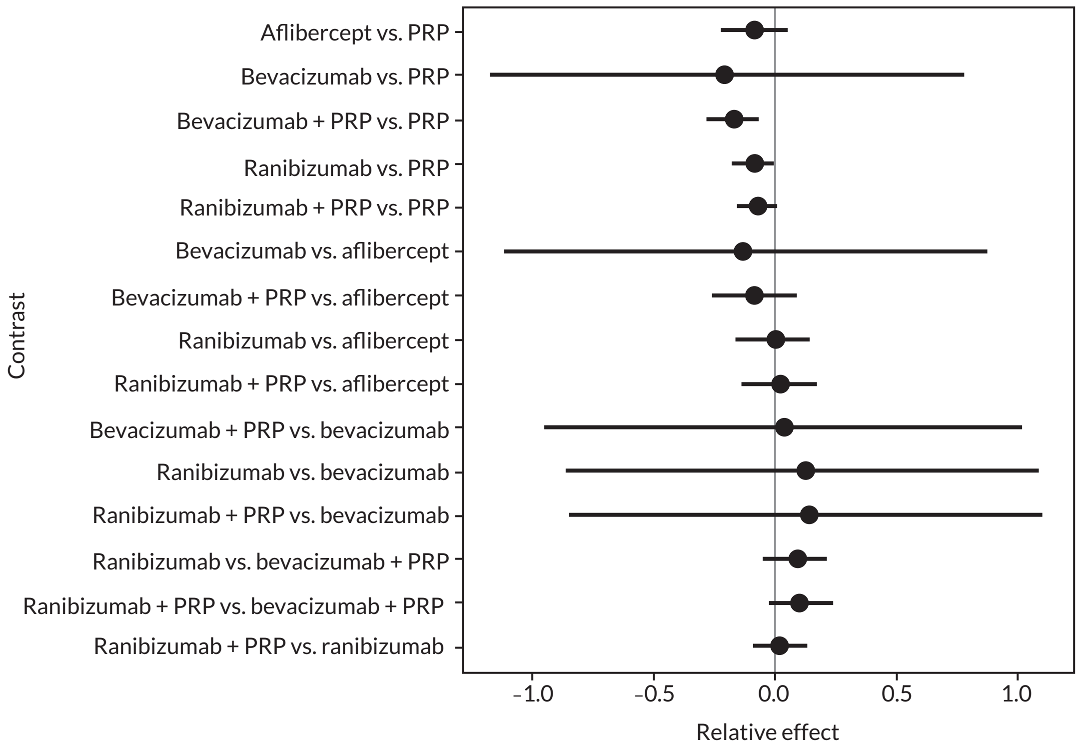


FIGURE 27 All treatment comparisons for end-of-trial random-effects NMA of log-MAR.

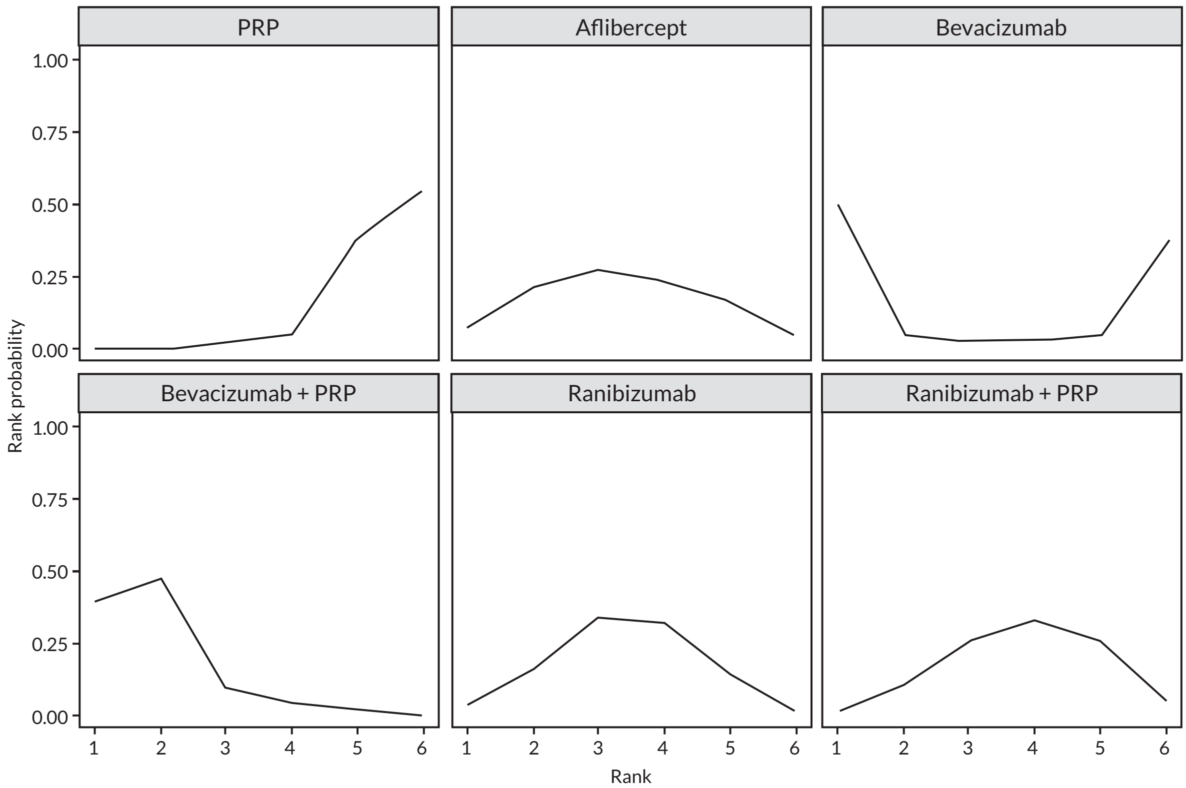


FIGURE 28 Probability of treatments for end-of-trial random-effects NMA of log-MAR.

TABLE 10 Results of NMA of log-MAR at end of trial – comparisons between treatments

Intervention	Comparator	Mean difference	95% CI	
Aflibercept	PRP	−0.087	−0.228	0.049
Bevacizumab	PRP	−0.209	−1.176	0.782
Bevacizumab + PRP	PRP	−0.171	−0.284	−0.064
Ranibizumab	PRP	−0.085	−0.177	−0.004
Ranibizumab + PRP	PRP	−0.069	−0.151	0.016
Bevacizumab	Aflibercept	−0.122	−1.117	0.881
Bevacizumab + PRP	Aflibercept	−0.085	−0.265	0.093
Ranibizumab	Aflibercept	0.002	−0.167	0.151
Ranibizumab + PRP	Aflibercept	0.017	−0.139	0.180
Bevacizumab + PRP	Bevacizumab	0.038	−0.956	1.030
Ranibizumab	Bevacizumab	0.124	−0.868	1.100
Ranibizumab + PRP	Bevacizumab	0.140	−0.830	1.116
Ranibizumab	Bevacizumab + PRP	0.087	−0.054	0.225
Ranibizumab + PRP	Bevacizumab + PRP	0.102	−0.032	0.243
Ranibizumab + PRP	Ranibizumab	0.015	−0.086	0.128

TABLE 11 Results of NMA of log-MAR at end of trial – ranking probabilities

	Probability of ranking					
Treatment arm	1st (%)	2nd (%)	3rd (%)	4th (%)	5th (%)	6th (%)
PRP	0.00	0.63	4.80	35.88	58.70	0.00
Aflibercept	20.58	29.20	23.05	17.80	4.35	20.58
Bevacizumab	5.90	2.70	1.85	3.65	33.43	5.90
Bevacizumab + PRP	46.80	9.78	3.88	1.23	0.10	46.80
Ranibizumab	17.03	31.83	31.10	16.20	0.93	17.03
Ranibizumab + PRP	9.70	25.88	35.33	25.25	2.50	9.70

Network meta-analyses allowing for interaction with follow-up time and best corrected visual acuity at randomisation

Allowing for variation with follow-up time

Network meta-analyses incorporating all follow-up times (longest in each trial), allowing varying effect of anti-VEGF with follow-up time. Time variation is assumed to be the same for all types of anti-VEGF. A selection of output plots is presented. Results are presented for the predicted effects after 1 year of follow-up.

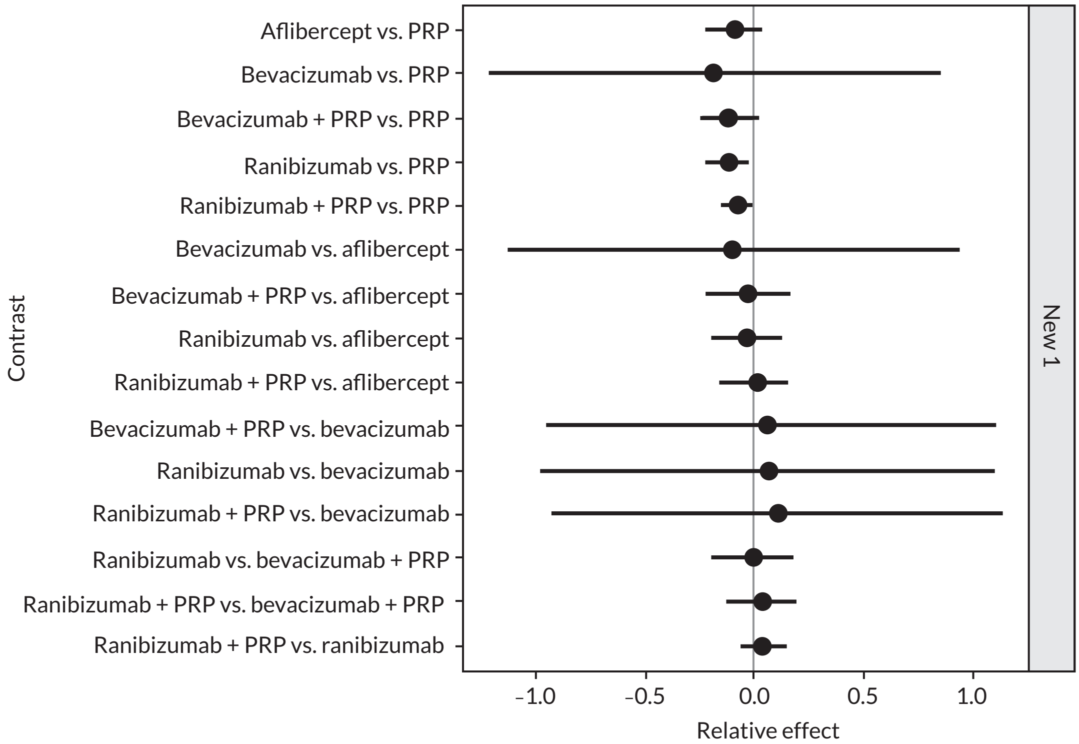


FIGURE 29 All treatment comparisons for time-adjusted random-effects NMA of log-MAR.

TABLE 12 Results of NMA of log-MAR adjusting for time – comparisons between treatments

Intervention	Comparator	Mean difference	95% CI	
Aflibercept	PRP	−0.086	−0.221	0.045
Bevacizumab	PRP	−0.199	−1.218	0.858
Bevacizumab + PRP	PRP	−0.112	−0.245	0.027
Ranibizumab	PRP	−0.119	−0.214	−0.023
Ranibizumab + PRP	PRP	−0.075	−0.153	0.001
Bevacizumab	Aflibercept	−0.112	−1.135	0.945
Bevacizumab + PRP	Aflibercept	−0.026	−0.216	0.163
Ranibizumab	Aflibercept	−0.033	−0.200	0.130
Ranibizumab + PRP	Aflibercept	0.011	−0.138	0.163
Bevacizumab + PRP	Bevacizumab	0.086	−0.957	1.127
Ranibizumab	Bevacizumab	0.080	−0.973	1.105
Ranibizumab + PRP	Bevacizumab	0.123	−0.919	1.138
Ranibizumab	Bevacizumab + PRP	−0.007	−0.197	0.184
Ranibizumab + PRP	Bevacizumab + PRP	0.037	−0.123	0.195
Ranibizumab + PRP	Ranibizumab	0.044	−0.064	0.155

TABLE 13 Results of NMA of log-MAR adjusting for time – ranking probabilities

	Probability of ranking					
Treatment arm	**1st (%)**	**2nd (%)**	**3rd (%)**	**4th (%)**	**5th (%)**	**6th (%)**
PRP	0.00	0.05	0.65	5.13	38.10	56.08
Aflibercept	7.60	19.98	25.30	25.10	17.48	4.55
Bevacizumab	51.98	3.88	2.58	2.78	4.35	34.45
Bevacizumab + PRP	18.73	30.70	17.90	17.35	12.35	2.98
Ranibizumab	19.40	34.13	25.88	14.88	5.25	0.48
Ranibizumab + PRP	2.30	11.28	27.70	34.78	22.48	1.48

Allowing for variation over time and by logarithm of the minimum angle of resolution at randomisation

Network meta-analyses incorporating all follow-up times (longest in each trial), allowing for varying effect of anti-VEGF by follow-up duration and varying effect by trial mean log-MAR at randomisation. Time and log-MAR variation are assumed to be the same for all types of anti-VEGF. A selection of output plots is presented. Results are presented for the predicted effects after 1 year of follow-up and at mean baseline BCVA across trials.

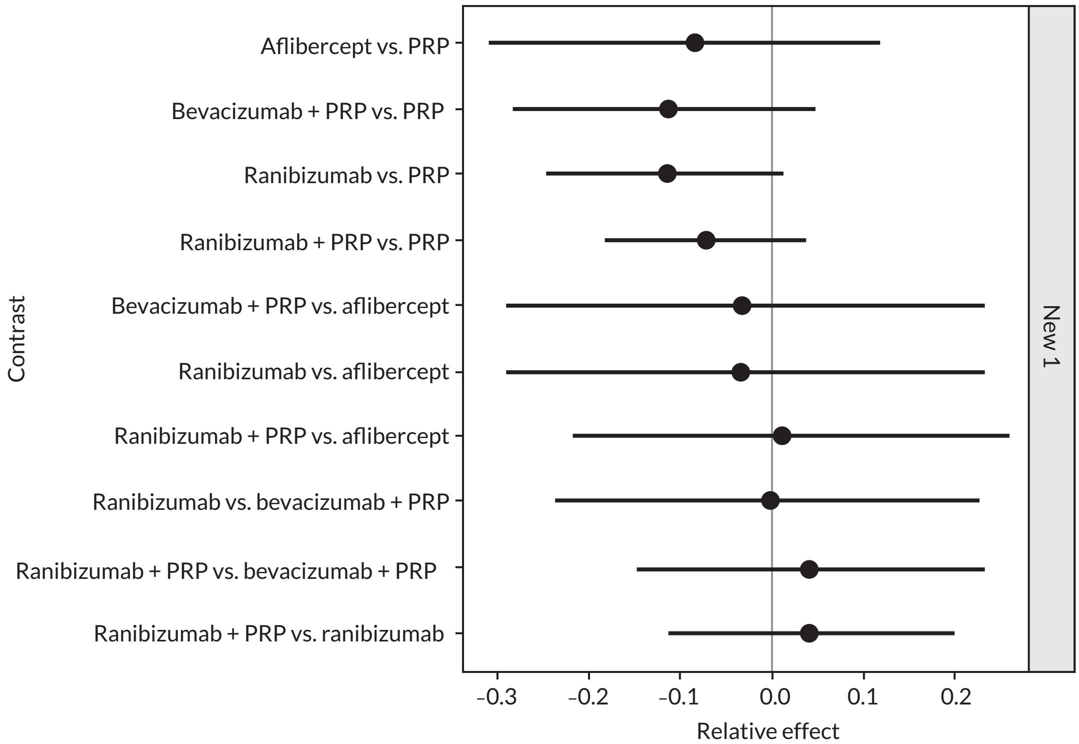


FIGURE 30 All treatment comparisons for time-adjusted and baseline BCVA adjusted random-effects NMA of log-MAR.

TABLE 14 Results of NMA of log-MAR adjusting for time and baseline BCVA – comparisons between treatments

Intervention	Comparator	Mean difference	95% CI	
Aflibercept	PRP	−0.085	−0.310	0.119
Bevacizumab + PRP	PRP	−0.116	−0.281	0.050
Ranibizumab	PRP	−0.117	−0.247	0.011
Ranibizumab + PRP	PRP	−0.073	−0.187	0.041
Bevacizumab + PRP	Aflibercept	−0.031	−0.287	0.228
Ranibizumab	Aflibercept	−0.032	−0.288	0.233
Ranibizumab + PRP	Aflibercept	0.012	−0.218	0.251
Ranibizumab	Bevacizumab + PRP	−0.001	−0.239	0.225
Ranibizumab + PRP	Bevacizumab + PRP	0.043	−0.151	0.234
Ranibizumab + PRP	Ranibizumab	0.044	−0.112	0.203

TABLE 15 Results of NMA of log-MAR adjusting for time and baseline BCVA – ranking probabilities

	Probability of ranking				
Treatment arm	1st (%)	2nd (%)	3rd (%)	4th (%)	5th (%)
PRP	0.08	0.70	4.23	19.50	75.50
Aflibercept	19.25	23.45	21.43	22.70	13.18
Bevacizumab + PRP	38.40	23.30	18.10	15.68	4.53
Ranibizumab	36.93	30.48	19.63	10.75	2.23
Ranibizumab + PRP	5.35	22.08	36.63	31.38	4.58

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 trials.

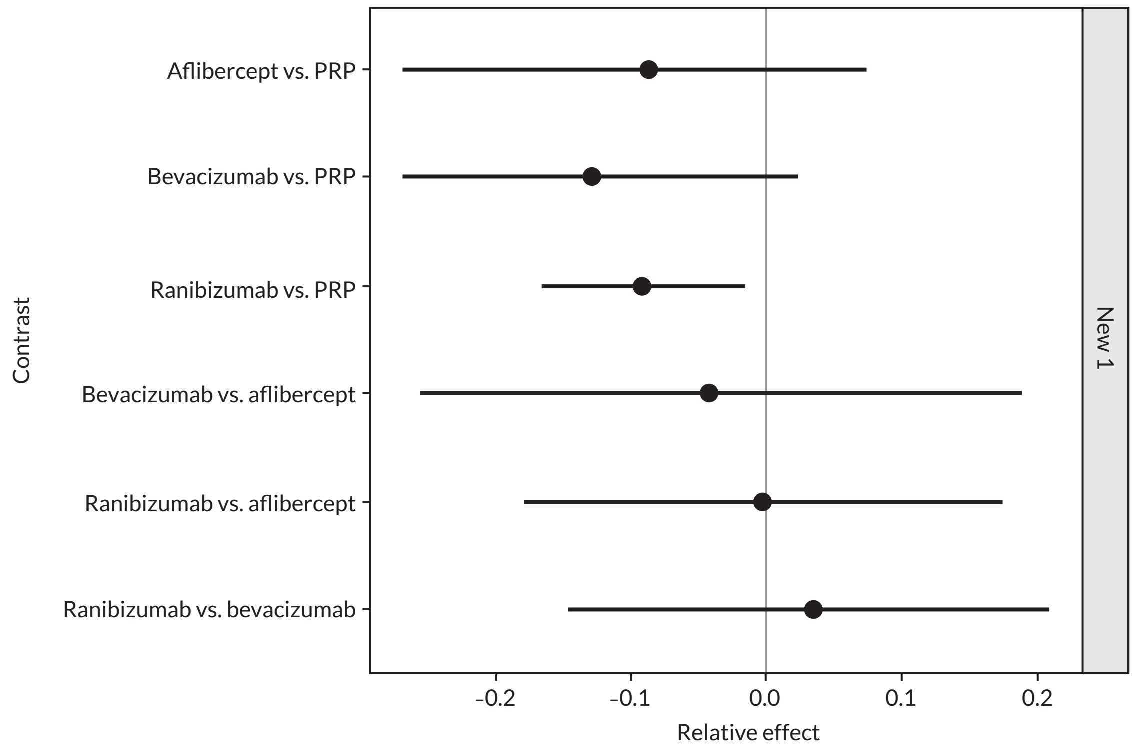


FIGURE 31 Results from a reduced network to compare anti-VEGFs.

TABLE 16 Results of reduced network to compare anti-VEGFs – comparisons between treatments

Intervention	Comparator	Mean difference	95% CI	
Aflibercept	PRP	−0.091	−0.245	0.063
Bevacizumab	PRP	−0.126	−0.261	0.007
Ranibizumab	PRP	−0.094	−0.173	−0.023
Bevacizumab	Aflibercept	−0.035	−0.238	0.174
Ranibizumab	Aflibercept	−0.003	−0.166	0.163
Ranibizumab	Bevacizumab	0.032	−0.142	0.200

TABLE 17 Results of reduced network to compare anti-VEGFs – ranking probabilities

	Probability of ranking			
Treatment	1st (%)	2nd (%)	3rd (%)	4th (%)
PRP	0.00	0.80	11.48	87.73
Aflibercept	25.08	32.93	33.35	8.65
Bevacizumab	53.60	23.33	20.18	2.90
Ranibizumab	21.33	42.95	35.00	0.73

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.

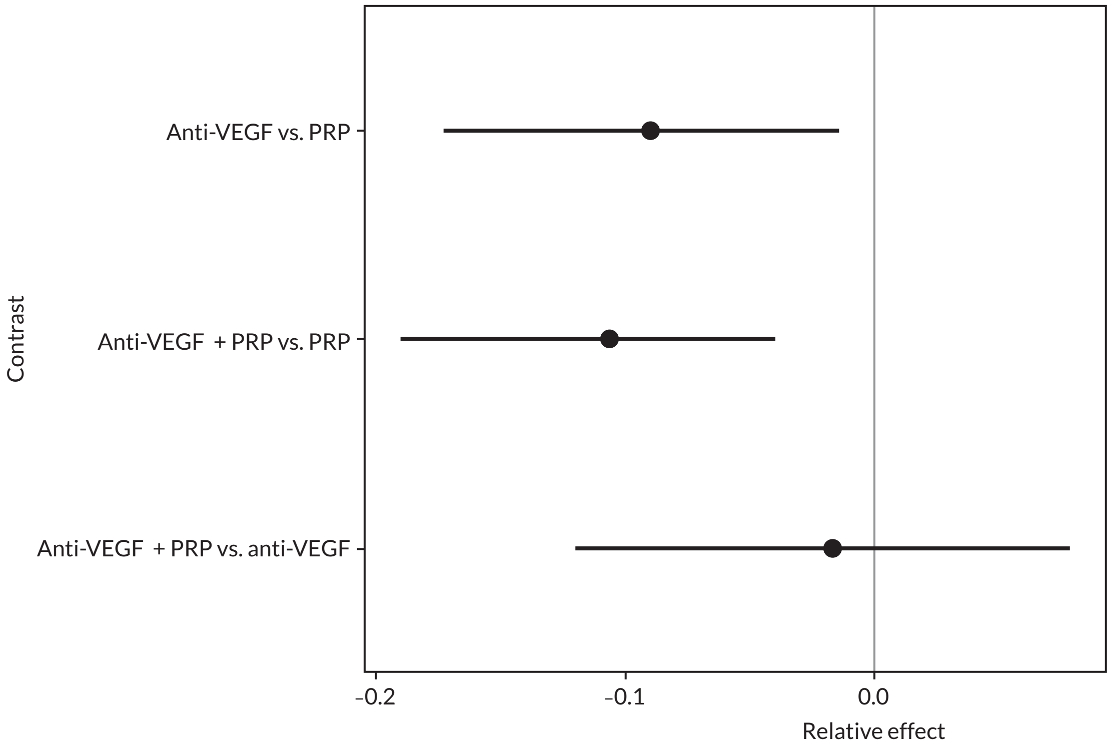


FIGURE 32 Results from a reduced network to compare treatment classes.

TABLE 18 Results of reduced network to compare treatment classes – comparisons between treatments

Intervention	Comparator	Mean difference	95% CI	
Anti-VEGF	PRP	−0.089	−0.180	−0.019
Anti-VEGF + PRP	PRP	−0.108	−0.192	−0.039
Anti-VEGF + PRP	Anti-VEGF	−0.019	−0.126	0.083

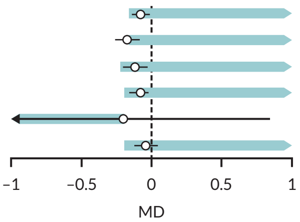
TABLE 19 Results of reduced network to compare treatment classes – ranking probabilities

	Probability of ranking		
Treatment	1st (%)	2nd (%)	3rd (%)
PRP	0.03	1.20	98.78
Anti-VEGF	33.05	65.88	1.08
Anti-VEGF + PRP	66.93	32.93	0.15

Threshold analyses

Up to 1 year

Contrast	log-MAR	95% CrI	Invariant interval		
Ranibizumab + PRP vs. PRP	−0.08	(−0.13 to −0.02)	Bevacizumab + PRP	(−0.16 to NT)	–
Bevacizumab + PRP vs. PRP	−0.17	(−0.26 to −0.08)	Bevacizumab + PRP	(−0.19 to NT)	–
Ranibizumab vs. PRP	−0.12	(−0.20 to −0.04)	Ranibizumab	(−0.22 to NT)	–
Aflibercept vs. PRP	−0.09	(−0.15 to −0.02)	Aflibercept	(−0.19 to 7.11)	Ranibizumab + PRP
Bevacizumab vs. PRP	−0.19	(−1.20 to 0.83)	–	(NT to −0.17)	Bevacizumab + PRP
Ranibizumab vs. ranibizumab + PRP	−0.04	(−0.12 to 0.05)	Ranibizumab	(−0.19 to 1.96)	Ranibizumab + PRP

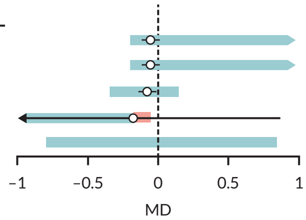


○ logMAR —95% CrI Invariant interval

FIGURE 33 Threshold analyses of data up to 1 year of follow-up.

One to 2 years

Contrast	log-MAR	95% CrI	Invariant interval		
Ranibizumab + PRP vs. PRP	−0.07	(−0.12 to −0.02)	Ranibizumab + PRP	(−0.20 to NT)	–
Ranibizumab vs. PRP	−0.07	(−0.12 to −0.01)	Ranibizumab	(−0.21 to NT)	–
Aflibercept vs. PRP	−0.09	(−0.15 to −0.02)	Aflibercept	(−0.35 to 0.15)	Ranibizumab
Bevacizumab vs. PRP	−0.20	(−1.20 to 0.80)	–	(NT to −0.09)	Aflibercept
Ranibizumab vs. ranibizumab + PRP	−0.00	(−0.07 to 0.07)	Ranibizumab	(−0.81 to 0.85)	Ranibizumab + PRP

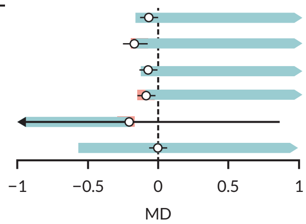


○ logMAR —95% CrI Invariant interval

FIGURE 34 Threshold analyses of data with 1–2 years of follow-up.

Maximum follow-up (up to 2 years)

Contrast	log-MAR	95% CrI	Invariant interval		
Ranibizumab + PRP vs. PRP	−0.07	(−0.12 to −0.02)	Bevacizumab + PRP	(−0.17 to NT)	–
Bevacizumab + PRP vs. PRP	−0.17	(−0.26 to −0.08)	Bevacizumab + PRP	(−0.20 to NT)	–
Ranibizumab vs. PRP	−0.08	(−0.13 to −0.02)	Bevacizumab + PRP	(−0.13 to NT)	–
Aflibercept vs. PRP	−0.09	(−0.16 to −0.02)	Bevacizumab + PRP	(−0.14 to NT)	–
Bevacizumab vs. PRP	−0.21	(−1.21 to 0.75)	–	(NT to −0.17)	Bevacizumab + PRP
Ranibizumab vs. ranibizumab + PRP	−0.00	(−0.07 to 0.07)	Ranibizumab	(−0.58 to 1.09)	Ranibizumab + PRP

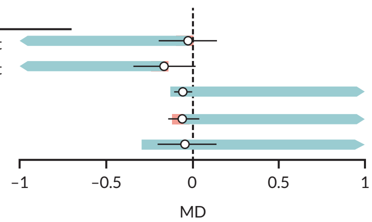


○ logMAR —95% CrI Invariant interval

FIGURE 35 Threshold analyses of data at end of trial (up to 2 years).

Allowing for effect variation with time and baseline logarithm of the minimum angle of resolution

Contrast	log-MAR	95% CrI	Invariant interval		
Bevacizumab + PRP vs. PRP	−0.02	(−0.19 to 0.14)	Bevacizumab + PRP	(−4.51 to 0.01)	Aflibercept
Ranibizumab + PRP vs. PRP	−0.16	(−0.34 to 0.02)	–	(NT to −0.13)	Aflibercept
Ranibizumab vs. PRP	−0.06	(−0.11 to 0.00)	Ranibizumab	(−0.13 to NT)	–
Aflibercept vs. PRP	−0.05	(−0.14 to 0.03)	Aflibercept	(−0.12 to NT)	–
Ranibizumab vs. bevacizumab + PRP	−0.04	(−0.20 to 0.14)	Ranibizumab	(−0.29 to NT)	–



○ logMAR —95% CrI Invariant interval

FIGURE 36 Threshold analyses of model adjusting for effect of time and baseline log-MAR.

Reduced network (for comparing anti-vascular endothelial growth factors)

Adjusted for follow-up time and BCVA at baseline.

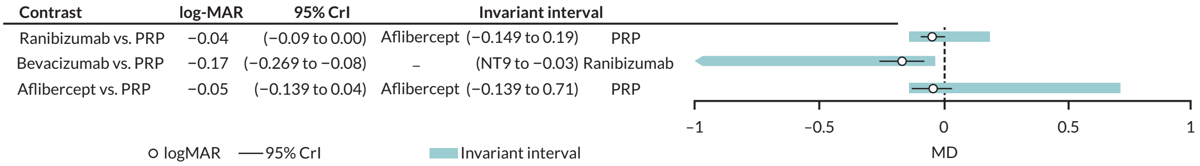


FIGURE 37 Threshold analysis of simplified network to compare anti-VEGF types, with time and baseline BCVA adjustment.

Reduced network (comparing anti-vascular endothelial growth factor to panretinal photocoagulation)

Adjusted for follow-up time and BCVA at baseline.

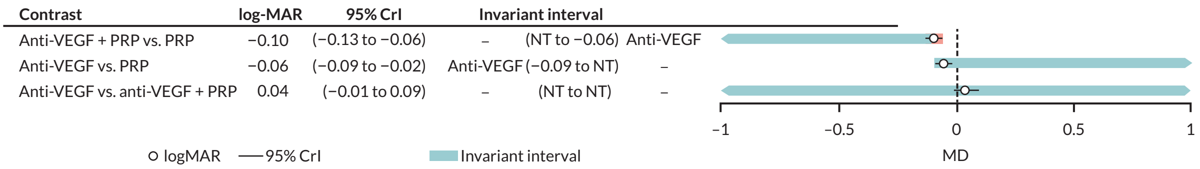


FIGURE 38 Threshold analyses of simplified network to compare anti-VEGF to PRP, adjusted for follow-up time and baseline BCVA.

Appendix 3 Other outcomes

This appendix presents tables and figures for all analyses, using data from publications of included RCTs 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.

As meta-analysis was not possible for most outcomes, the forest plots without meta-analysis include trials of proliferative and non-proliferative retinopathy, to aid comparison.

Forest plots of outcomes without meta-analysis

These forest plots show results for all anti-VEGF types, and at all follow-up times. Note that this means some trials appear more than once in a forest plot.

Neovascularisation of the disc

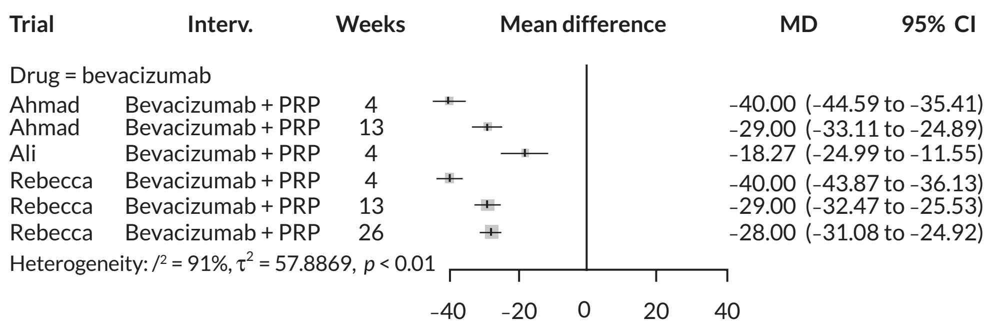


FIGURE 39 Forest plot of all NVD data (left side favours anti-VEGF).

Neovascularisation elsewhere

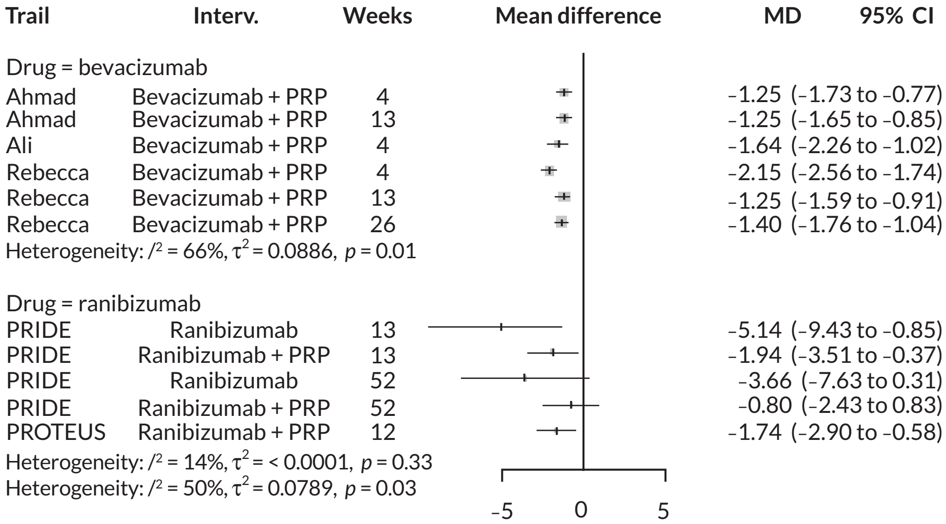


FIGURE 40 Forest plot of all NVE data (left side favours anti-VEGF).

Diabetic macular oedema

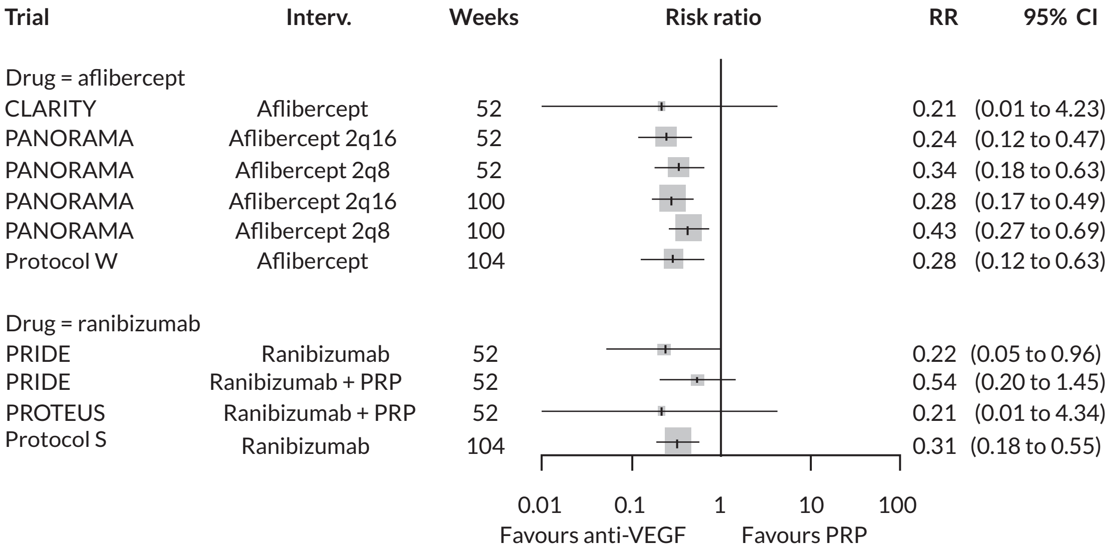


FIGURE 41 Forest plot of DME incidence (left side favours anti-VEGF).

Improvement in diabetic retinopathy severity score (Diabetic Retinopathy Severity Scale)

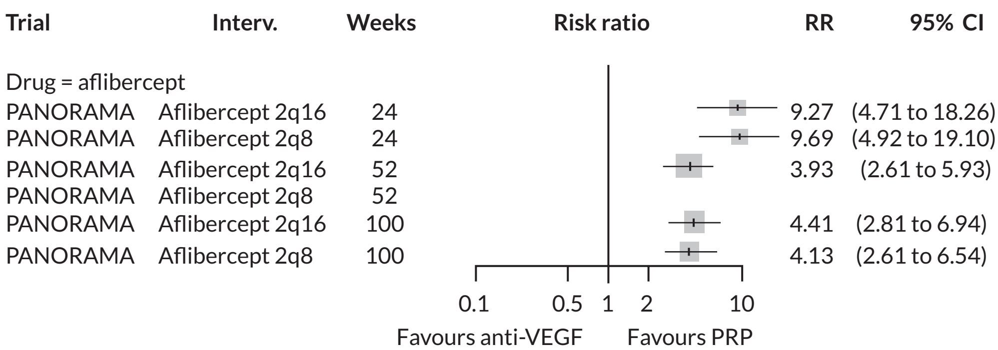


FIGURE 42 Forest plot of improvement in DRSS severity (right side favours anti-VEGF).

Proliferative retinopathy incidence

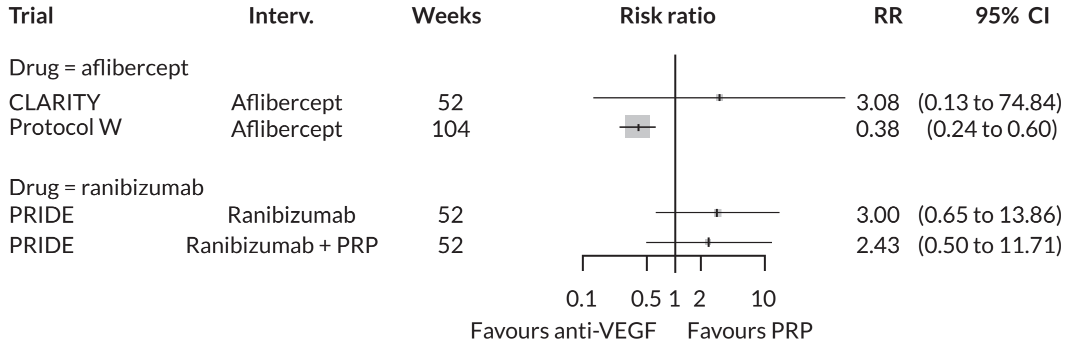


FIGURE 43 Forest plot of proliferative DR (left side favours anti-VEGF).

Regression of neovascularisation

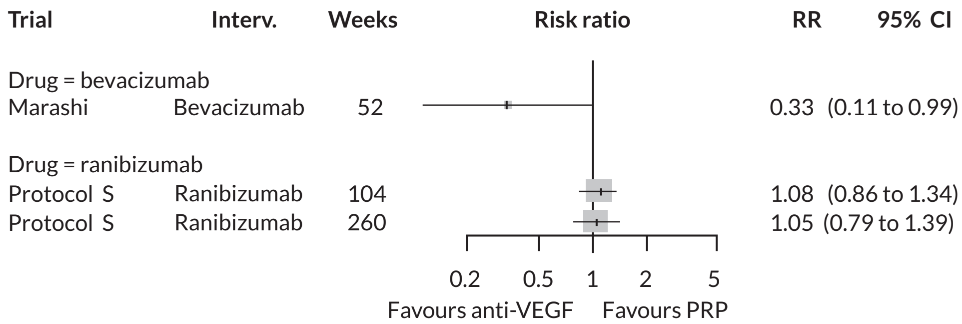


FIGURE 44 Forest plot of regressive neovascularisation (left side favours anti-VEGF).

Use of other treatments

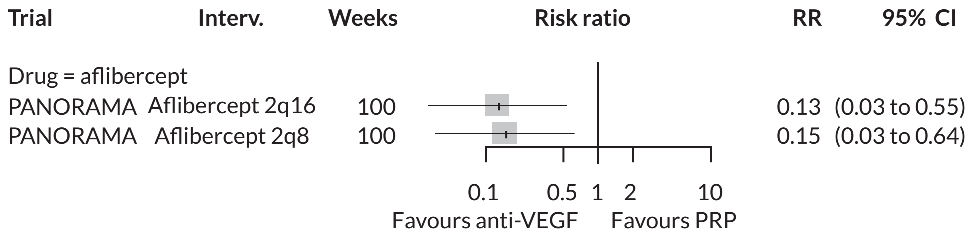


FIGURE 45 Forest plot of use of other treatments (left side favours anti-VEGF).

Vitrectomy

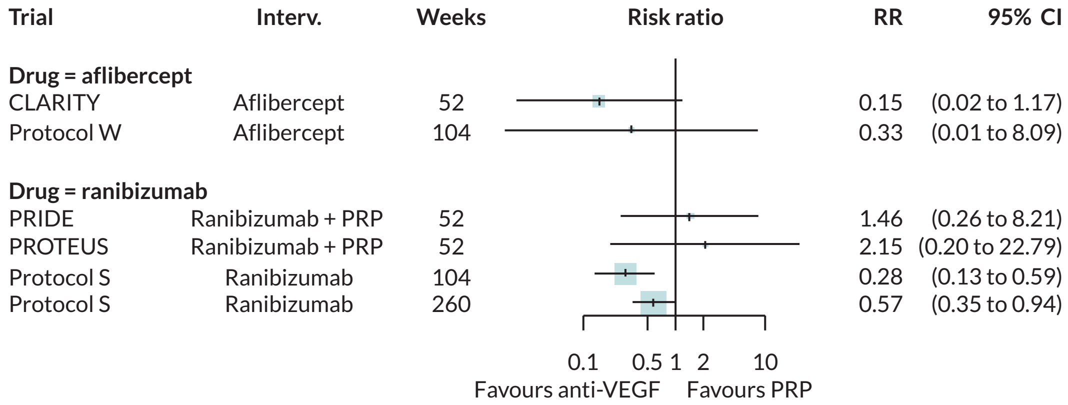


FIGURE 46 Forest plot of vitrectomy incidence (left side favours anti-VEGF).

Vitreous haemorrhage

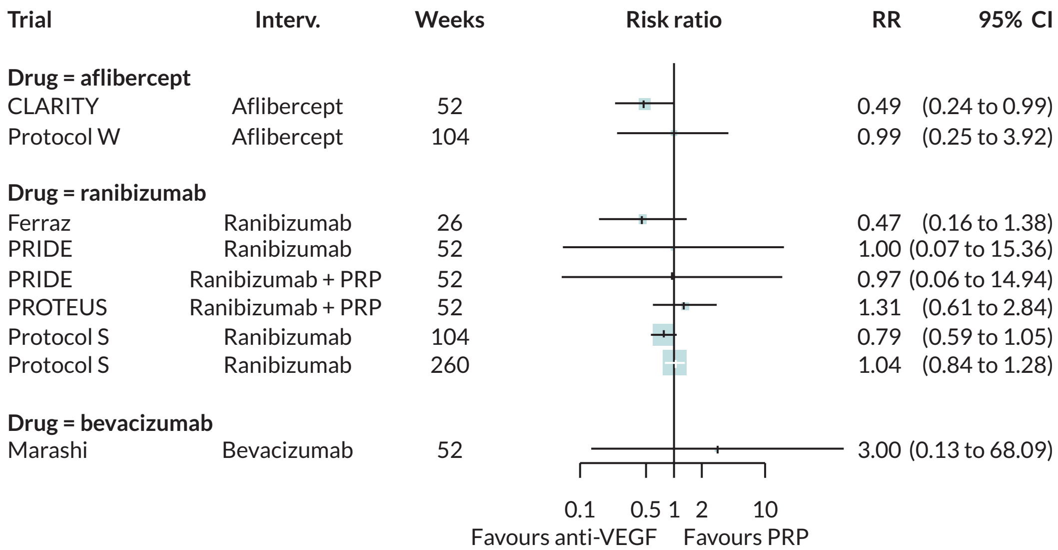


FIGURE 47 Forest plot of vitreous haemorrhage incidence (left side favours anti-VEGF).

Adverse event outcomes

These forest plots show results for all anti-VEGF types, and at all follow-up times. Note that this means some trials appear more than once in a forest plot. For simplicity, only adverse event outcomes reported in two or more studies are presented.

Cataracts

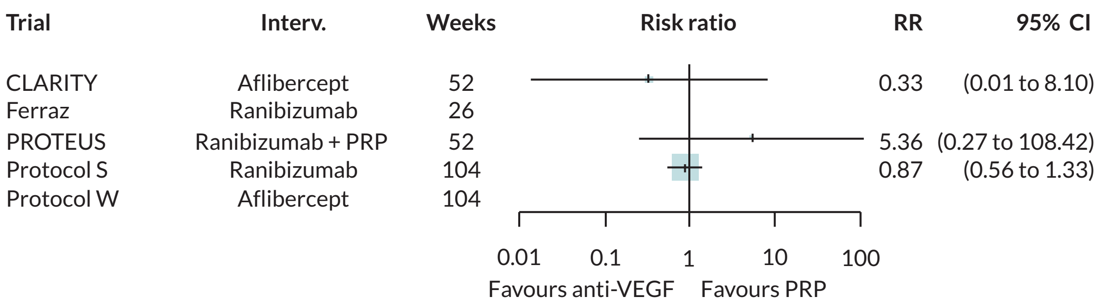


FIGURE 48 Forest plot of cataracts data (left side favours anti-VEGF).

Conjunctival haemorrhage

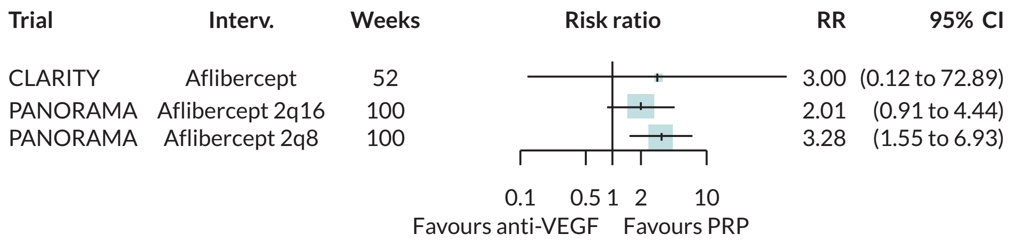


FIGURE 49 Forest plot of conjunctival haemorrhage data (left side favours anti-VEGF).

Cardiovascular mortality

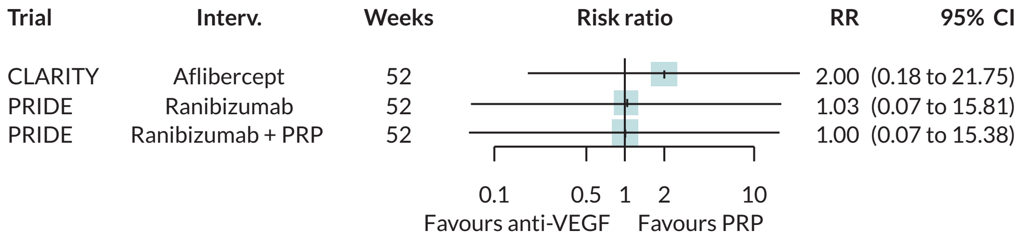


FIGURE 50 Forest plot of cardiovascular mortality data (left side favours anti-VEGF).

Death (all-cause mortality)

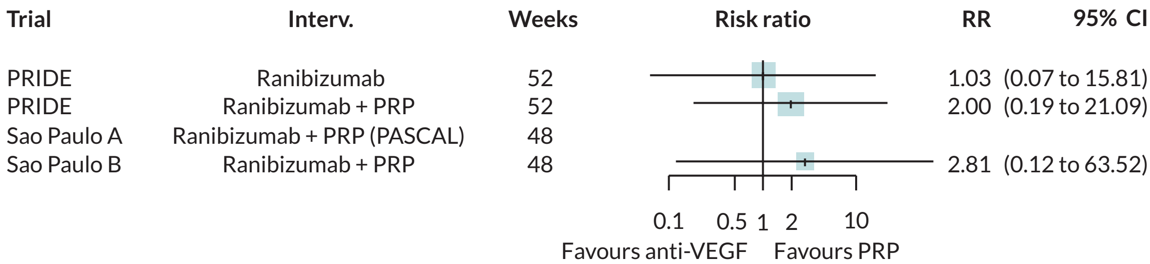


FIGURE 51 Forest plot of death data (left side favours anti-VEGF).

Myocardial infarction

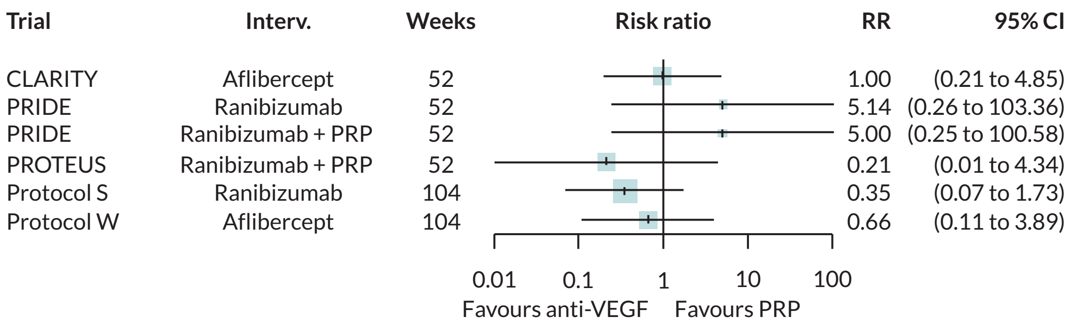


FIGURE 52 Forest plot of myocardial infarction data (left side favours anti-VEGF).

Ocular pain

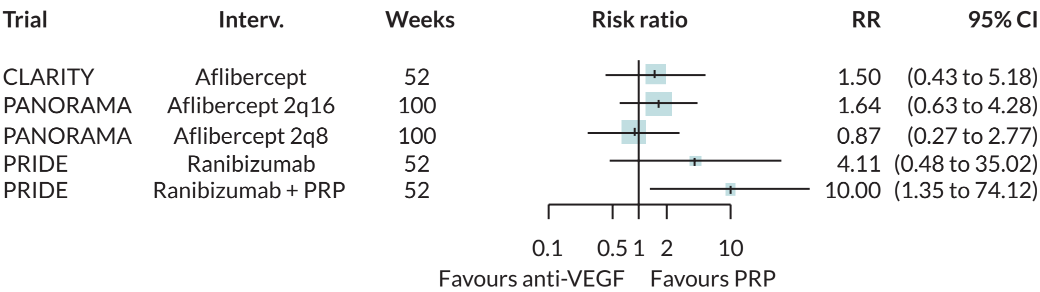


FIGURE 53 Forest plot of ocular pain data (left side favours anti-VEGF).

Raised intraocular pressure

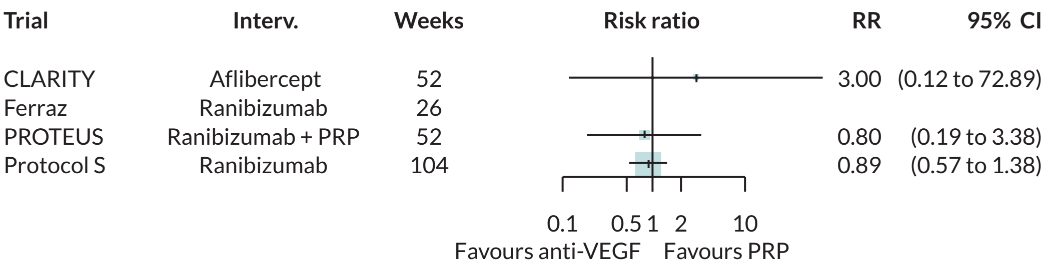


FIGURE 54 Forest plot of raised intraocular pressure data (left side favours anti-VEGF).

Retinal detachment

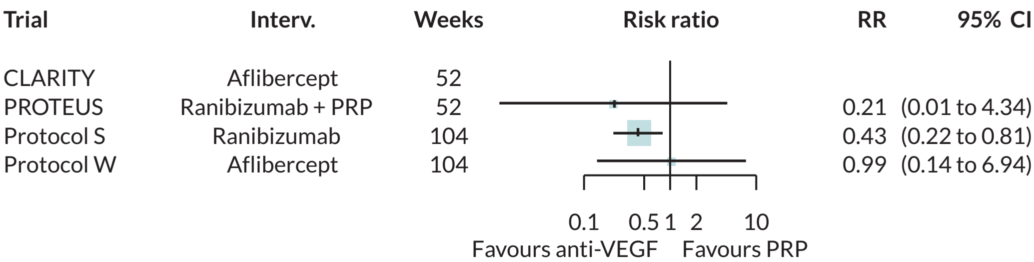


FIGURE 55 Forest plot of retinal detachment data (left side favours anti-VEGF).

Retinal tear

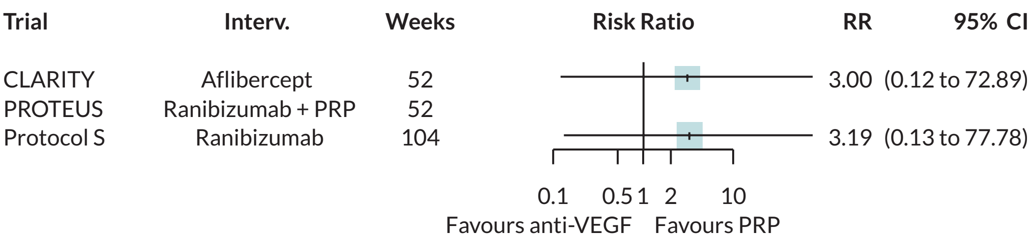


FIGURE 56 Forest plot of retinal data (left side favours anti-VEGF).

Serious adverse event (however defined)

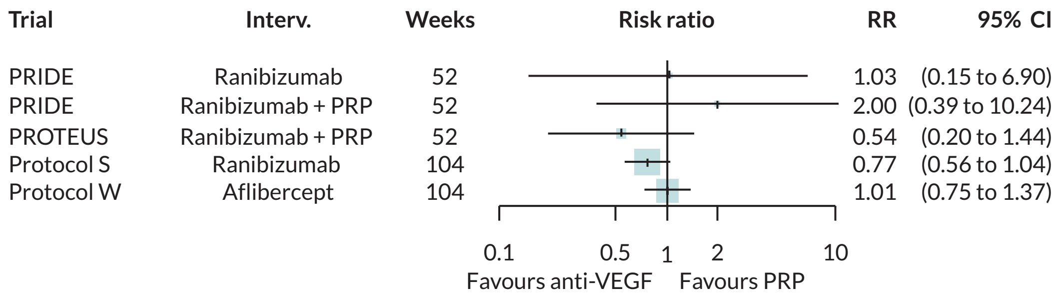


FIGURE 57 Forest plot of serious adverse event data (left side favours anti-VEGF).

Stroke

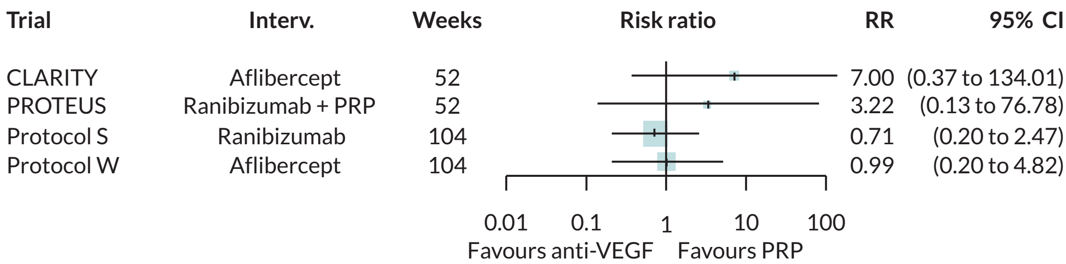


FIGURE 58 Forest plot of stroke data (left side favours anti-VEGF).

Meta-analyses of other outcomes and adverse events

All meta-analyses presented assumed that the impact of anti-VEGF on outcome (or adverse event) is the same for all types of anti-VEGF (in isolation or combined with PRP), and at all follow-up times. For trials with multiple time points, the longest follow-up was used. For trial with multiple arms, only one anti-VEGF arm was used; arms using anti-VEGF alone were preferred.

Neovascularisation elsewhere

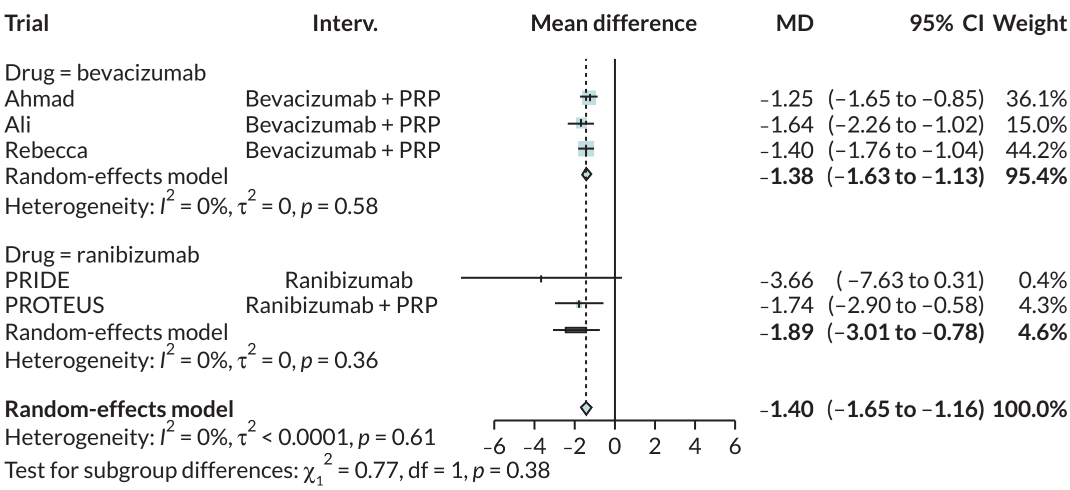


FIGURE 59 Meta-analysis of NVE (left side favours anti-VEGF).

Neovascularisation of the disc

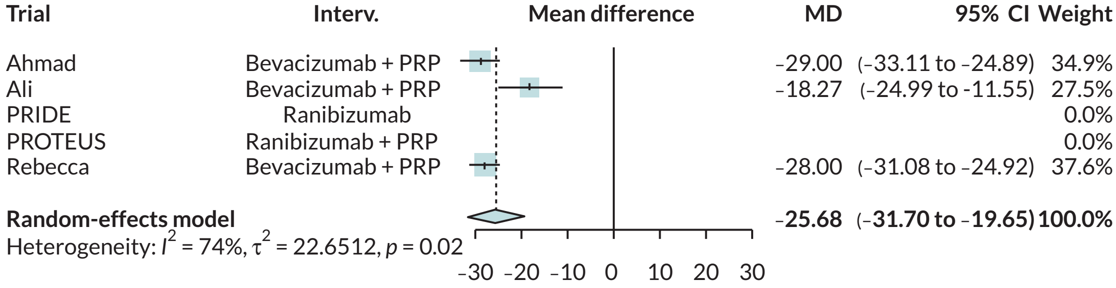


FIGURE 60 Meta-analysis of NVD (left side favours anti-VEGF).

Other non-vison outcomes

This forest plot shows the summary results of each meta-analysis (each bar is a meta-analysis result). Meta-analyses are restricted to trials of proliferative retinopathy. Full forest plots for each outcome are not presented.

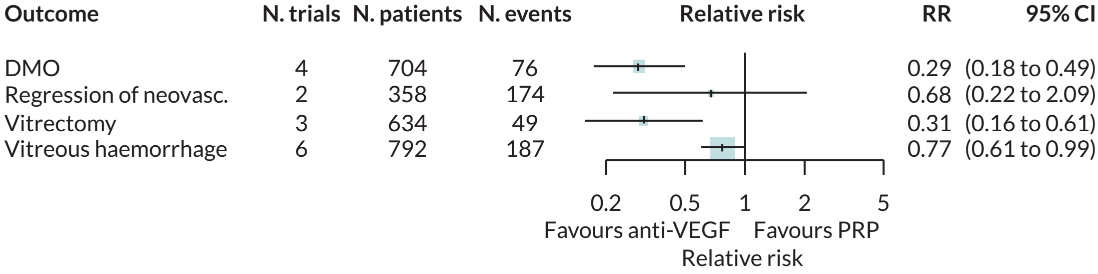


FIGURE 61 Meta-analysis summary for non-vision outcomes in PDR trials (left side favours anti-VEGF).

Adverse events

This forest plot shows the summary results of each meta-analysis (each bar is a meta-analysis result). Meta-analyses are restricted to trials of proliferative retinopathy. Full forest plots for each outcome are not presented.

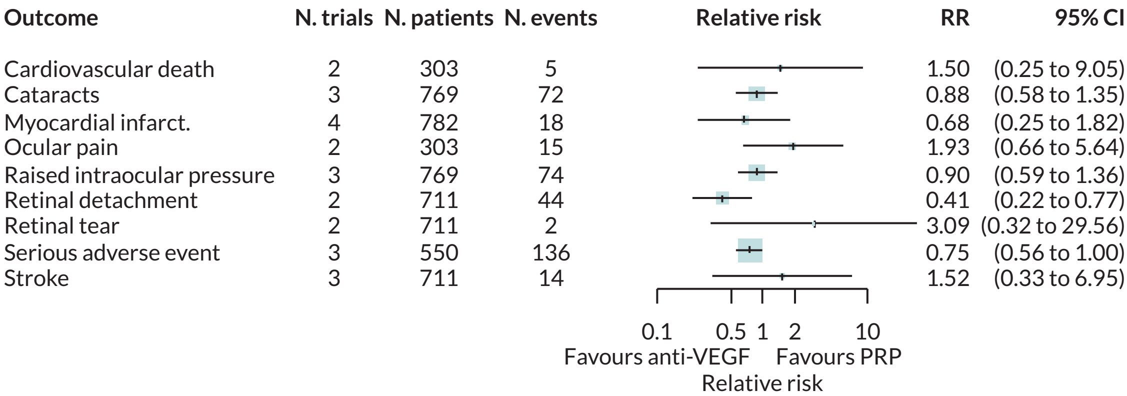


FIGURE 62 Meta-analysis summary for adverse events (left side favours anti-VEGF).

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 diabetic retinopathy: a systematic review and meta-analysis. [published online ahead of print December 11 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/PCGV5709

Appendix 4 Non-proliferative diabetic retinopathy

This section reports the findings of the two trials in non-proliferative retinopathy. As both trials compared aflibercept to sham injection, no NMAs were performed.

PANORAMA had two aflibercept arms: injections every 8 weeks or every 16 weeks. Only the 16-week arm is analysed here, as that was the schedule used in Protocol W.

Best corrected visual acuity

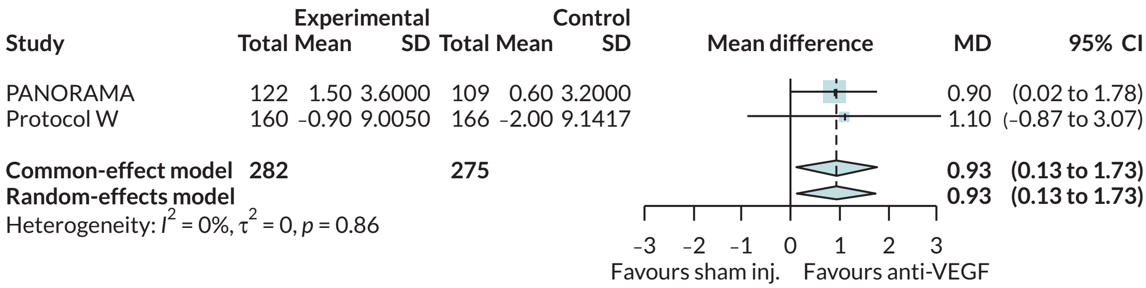


FIGURE 63 Mean difference in ETDRS after 2 years in NPDR trials.

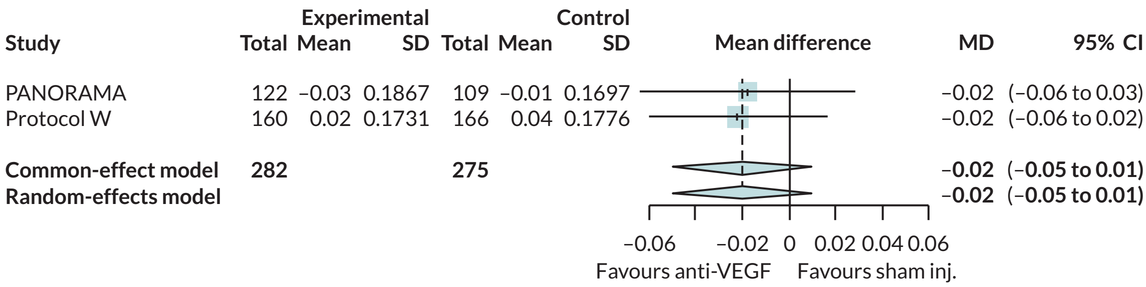


FIGURE 64 Mean difference in log-MAR after 2 years in NPDR trials.

Diabetic macular oedema in non-proliferative retinopathy

Diabetic macular oedema was the only outcome other than BCVA reported in both trials of NPDR.

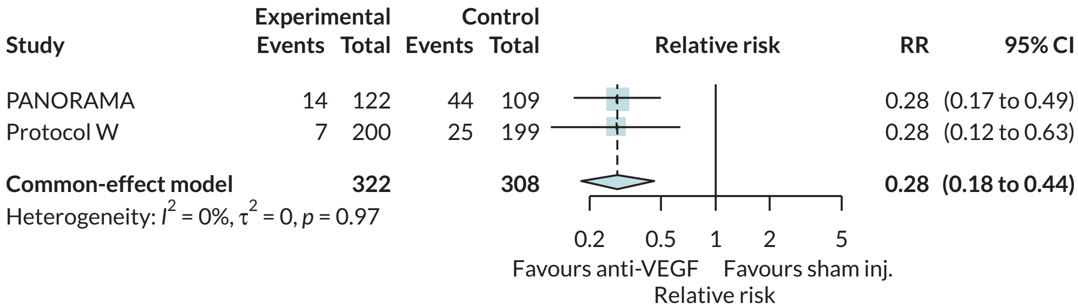


FIGURE 65 Diabetic macular oedema incidence in NPDR trials.

Other outcomes

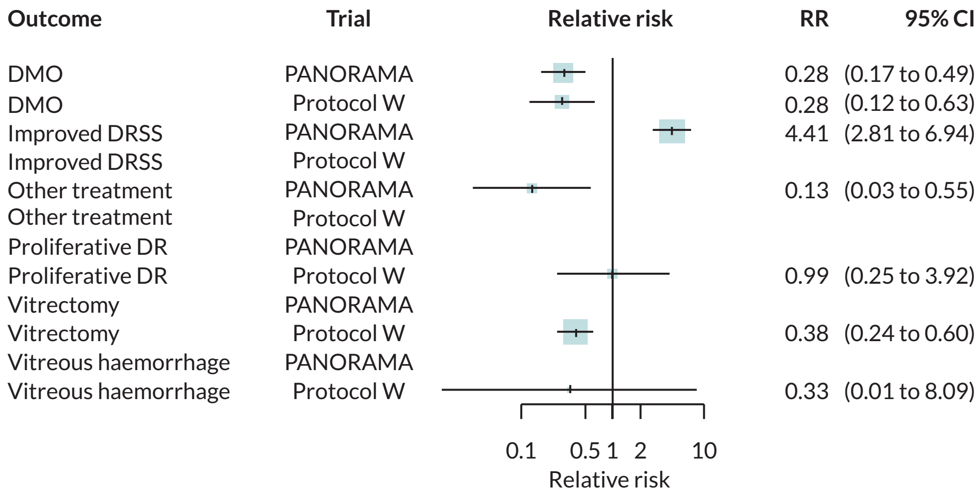


FIGURE 66 Non-BCVA outcomes in NPDR trials.

Adverse events

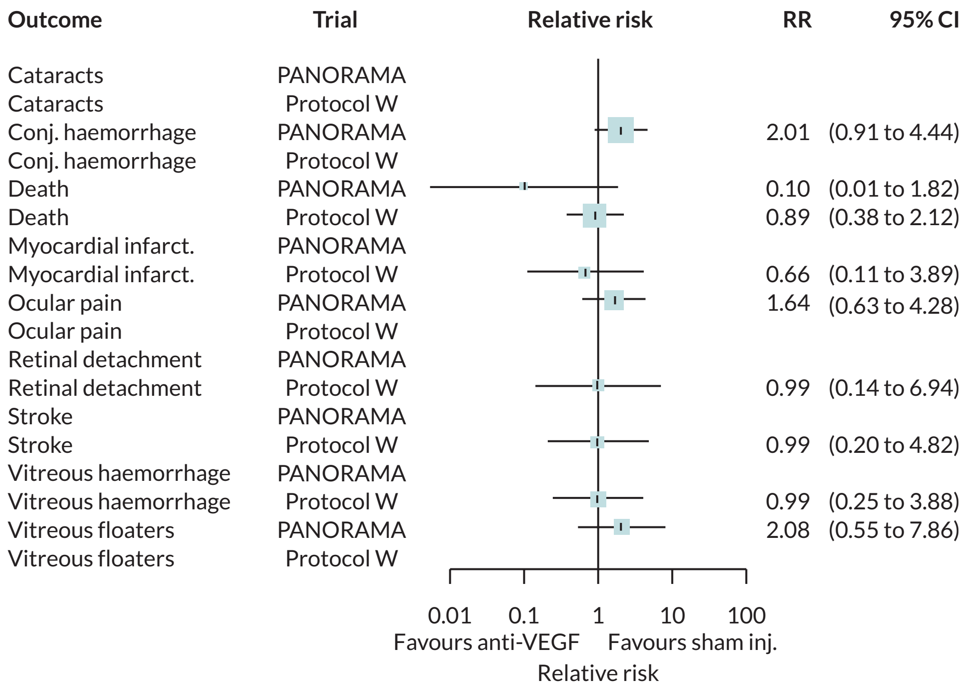


FIGURE 67 Adverse event outcomes in NPDR trials.