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

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# Abstract

**Background**

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

**Objective**

To investigate the efficacy and safety of anti-VEGF therapy for the treatment of proliferative diabetic retinopathy when compared to PRP.

**Methods**

A systematic review and network meta-analysis of randomised controlled trials comparing anti-VEGF (alone or in combination) to PRP in people with PDR. Trials where the primary focus was treatment of macular oedema or vitreous haemorrhage were excluded. Key outcomes were best corrected visual acuity (BCVA), diabetic macular oedema (DMO) and vitreous haemorrhage. Individual participant data (IPD) was obtained and analysed for three large, high-quality trials in combination with published data from other trials. Network meta-analyses of BCVA and meta-analyses of other outcomes combined IPD with published data from other trials; regression analyses against patient covariates used just the IPD.

**Results**

Twelve trials were included: 1 of aflibercept, 5 of bevacizumab and 6 of ranibizumab. When considered together, anti-VEGFs produced a modest, but not clinically meaningful, benefit over PRP in BCVA, after 1 year of follow-up (mean difference in logMAR -0.116, 95% credible interval (CrI) -0.183 to -0.038). There was no clear evidence of a difference in effectiveness between the anti-VEGFs. The benefit of anti-VEGF appears to decline over time. Analysis of the IPD trials suggested that anti-VEGF therapy may be more effective in people with poorer visual acuity, in those who have vitreous haemorrhage, and possibly in people with poorer vision generally.

Anti-VEGF was superior to PRP at preventing macular oedema after 1 year (Relative risk (RR) 0.48, 95% CI 0.28 to 0.83) and possibly at preventing vitreous haemorrhage (RR 0.72, 95% CI 0.47 to 1.10). Anti-VEGF reduced the incidence of retinal detachment when compared to PRP (RR 0.41, 95% CI 0.22 to 0.77). Data on other adverse events was generally too limited to identify any differences between anti-VEGF and PRP.

**Conclusions**

Anti-VEGF has no clinically meaningful benefit over PRP for preserving visual acuity. However, anti-VEGF therapy appears to delay or prevent progression to macular oedema and vitreous haemorrhage. The possibility that anti-VEGF therapy may be more effective in patients with poorer health and poorer vision merits further clinical investigation. The long-term effectiveness and safety of anti-VEGF treatment is unclear, particularly as additional PRP and anti-VEGF treatment will be required over time.

**Registration**

This review is registered on PROSPERO (CRD42021272642)

**Funding**

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# Plain English Summary

People with diabetes are at risk of gradually losing their sight because blood vessels in the part of the eye called the retina may become damaged. This condition is called diabetic retinopathy. People with a more severe type of retinopathy, called proliferative diabetic retinopathy (PDR) are usually offered laser treatment to reduce the risk of further sight loss. Recently, drugs called anti-VEGFs (anti-vascular endothelial growth factor drugs), which are injected directly into the eye, have been used to treat other eye conditions, and might be useful to treat retinopathy.

This paper investigates whether anti-VEGF therapy is effective by identifying and re-analysing the clinical trials that used the three main anti-VEGF drugs (called aflibercept, bevacizumab and ranibizumab) to treat PDR. We identified 12 relevant clinical trials, including approximately 1,100 persons, and obtained and reanalysed the data from three of the trials.

We found that, after 1 year, people with proliferative retinopathy who received anti-VEGF injections could, on average, read 3 or 4 more letters on a standard eye test chart than people who had received laser therapy. This difference may be too small to make anti-VEGF injections worthwhile. The benefit of anti-VEGF injections may also decline over time. Anti-VEGF injections may be more beneficial in people with poorer vision when treatment starts.

We also found that people who received anti-VEGF injections were substantially less likely to experience some of the more severe consequences of vision loss, including where vision is lost in the centre of the eye (called diabetic macular oedema), and where blood leaks into the eye (called vitreous haemorrhage).

The long-term impact of using anti-VEGF injections repeatedly is still not well understood and requires further clinical research. Further trials that treat people with poorer vision or health generally would be useful.

# Background

Diabetes is a major public health issue, affecting over 4 million people in the UK. Diabetic retinopathy is a “chronic progressive, potentially sight-threatening disease of the retinal microvasculature”1, 2 and is a major form of diabetes-related sight loss, impairing the sight of more than 1,700 people in the UK each year.3 There are several severity stages of diabetic retinopathy with proliferative retinopathy being the most severe form. It has a high risk of retinal detachment and vitreous haemorrhage, which may result in severe vision loss.4, 5

In the UK, proliferative diabetic retinopathy (PDR) is usually treated using a form of laser therapy, called panretinal photocoagulation (PRP), where a laser is applied to the retina to prevent the proliferation of new (abnormal) blood vessels. PRP is delivered over the entire periphery of the retina, by placing 1,200-1,600 burns per session, usually over two or three treatment sessions. PRP is effective and durable6 but can have adverse effects such as macular oedema and peripheral visual field loss.7

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

International Council of Ophthalmology guidelines on diabetic eye care14 support laser photocoagulation and 'appropriate use of anti-VEGF drugs' for the management of diabetic retinopathy. NICE guidance on the treatment of diabetic retinopathy in England and Wales is in development, but may only recommend anti-VEGF if retinopathy continues to progress after PRP treatment.15

As there is now a sizeable body of evidence on the effectiveness of anti-VEGF drugs, a review and analysis of the evidence is needed. In particular, a review of raw data from key trials is important to examine key issues, such as whether the efficacy of anti-VEGF varies with patient characteristics, or changes over time. This systematic review with IPD meta-analysis aimed to address these issues and fully examine all the current clinical evidence on the use of anti-VEGFs in diabetic retinopathy. This review formed part of a larger project examining the value of anti-VEGF for treating diabetic retinopathy funded by the National Institute for Health Research (Project number NIHR132948). The review is registered on PROSPERO [CRD42021272642] and the full protocol is available online from the NIHR [https://fundingawards.nihr.ac.uk/award/NIHR132948]. The larger project also included a review of trials of anti-VEGF in non-proliferative retinopathy 16 and an economic analysis of the value of anti-VEGF in treating diabetic retinopathy.

# Methods

## Systematic review

 This review was conducted following Centre for Reviews and Dissemination guidance on undertaking systematic reviews 17 and reported according to the principles of the overarching PRISMA statement 18.

### Database searches and trial selection

An Information Specialist (HF) designed a preliminary search strategy in Ovid MEDLINE in consultation with the research team. The final MEDLINE strategy was adapted for use in all resources searched. The searches were performed on 27th August 2021 and updated were updated on 13th July 2022 and again on 26th 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 (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.

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

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

### Inclusion criteria

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

A full list of outcomes of interest are reported in the review protocol [https://fundingawards.nihr.ac.uk/award/NIHR132948]. This paper focuses on the following outcomes: best corrected visual acuity (BCVA) using a logMAR (Logarithm of the Minimum Angle of Resolution) chart, reported as either logMAR or ETDRS letter count; and the incidence of diabetic macular oedema (DMO) and vitreous haemorrhage. Other outcomes, such as adverse events, were included (see Appendix 4), but limited data were available, either in the IPD or in publications.

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

### Collection of IPD

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

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

### Statistical analysis

For BCVA, network meta-analyses (NMA) were performed using standard Bayesian methods of network meta-analysis using the R package multinma (version 0.5.1)12, 20. This extends the standard NMA modelling approach to allow joint modelling of IPD and published data, and to investigate the potential impact of patient factors and timing of assessments on the effectiveness of anti-VEGF therapy, and on the ranking of the different treatments 20.

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

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

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

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

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

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

### Patient and public involvement

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

### Equality, diversity and inclusion

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

# Results

## Included trials

Figure 1 shows the PRISMA flow chart for this review. Overall, 14 RCTs were considered. The searches also identified 21 other RCTs, which were unsuitable for meta-analyses. These included trials reported only as conference abstracts, not in English, published before 2011 (and judged to be out-of-date), or that used types of anti-VEGF not in widespread use. Those trials therefore could not be reasonably included in the NMAs. These are summarised in Appendix 1.4.

IPD was available for three trials (CLARITY22, PROTEUS23 and PROTOCOL S24) of the 6 contacted. One trial (PRIDE25) was unable to provide IPD at the time of the request, as analyses had not been completed. Two trials recruited patients with non-proliferative retinopathy; both evaluated aflibercept. **19,20** One (PANORAMA10) declined to provide IPD as the data holders did not wish data on NPDR to be analysed alongside data on PDR, and the other (PROTOCOL W26) stated it would make its IPD public later in 2023. As IPD were not available from either of the two trials of patients with NPDR, this paper considers only trials of patients with PDR where anti-VEGF was compared to PRP. Results of the NPDR trials have been reported elsewhere.16

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



Figure PRISMA flow diagram

Table Properties of the included trials

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Year**  | **Anti-VEGF** | **Comparator** | **Location** | **Sample size** | **Population** | **Duration** | **IPD inclusion** |
| **CLARITY23** | 2017 | Aflibercept | PRP | UK | 232 persons | PDR | 1 year | Included |
| **DRCRN Protocol S27, 28** | 2018 | Ranibizumab | PRP | USA | 305 persons | PDR | 5 years | Included |
| **Ferraz29** | 2015 | Ranibizumab +PRP | PRP | Brazil | 60 eyes | PDR | 6 months | Not sought |
| **PRIDE25** | 2019 | Ranibizumab +PRP | PRP | Germany | 106 persons | PDR | 1 year | Unavailable |
| **PROTEUS23** | 2018 | Ranibizumab +PRP | PRP | Europe | 87 persons | PDR | 1 year | Included |
| **Sao Paulo B30** | 2011 | Ranibizumab +PRP | PRP | Brazil | 40 persons | PDR | 1 year | Not sought |
| **Sao Paulo A31** | 2018 | Ranibizumab +PRP, ETRDS | Ranibizumab +PRP, PASCAL | Brazil | 40 eyes | PDR | 1 year | Not sought |
| **Marashi32** | 2017 | Bevacizumab | PRP | Jordan/Syria | 30 persons | PDR | 1 year | Not sought |
| **Ahmad33** | 2012 | Bevacizumab (+PRP) | PRP | Pakistan | 54 eyes | PDR | 3 months | Not sought |
| **Ali34** | 2018 | Bevacizumab (+PRP) | PRP | Pakistan | 60 eyes | PDR | 1 month | Not sought |
| **Rebecca35** | 2021 | Bevacizumab (+PRP) | PRP | Pakistan | 76 eyes | PDR | 6 months | Not sought |
| **Roohipour36** | 2016 | Bevacizumab (+PRP) | PRP | Iran | 64 eyes | PDR | 10 months | Not sought |

## Risk of bias

For the risk of bias assessment of the included trials, see Appendix 1.5. The trials varied in their potential risk of bias. Where possible and appropriate, IPD provided by the trialists informed the risk of bias assessment. Overall, two trials were classed at low risk of bias, three moderate, and seven at high risk of bias. Risk of bias across individual domains was predominately of 'some concerns', primarily due to poor reporting, although larger trials tended to be better reported. Concerns were most common for the outcome measurement domain, due to the lack of masking of participants and outcome assessors. Other concerns included limited description of randomisation and allocation concealment processes, and missing participants and outcome data. The direction of bias was generally unpredictable. Overall, all the trials of bevacizumab were judged to be at high risk of bias. This was a key factor in our decision to request IPD only from the aflibercept and ranibizumab trials.

## Network meta-analysis of vision (BCVA)

We first consider the analyses combining IPD with published aggregate data from trials where IPD were not available.

Two network meta-analyses of BCVA were performed: one including the longest follow-up in all trials, up to 1 year, to include all trials. The second analysis included only follow-up at exactly or almost exactly 1 year (defined as 45 to 60 weeks follow-up), to exclude trials of very short duration. As only one trial (PROTOCOL S) reported outcomes beyond 1 year, NMAs with longer follow-up times were not feasible. The network diagram for the analysis at longest follow-up up to 1 year is shown in Figure 1. The green lines show the trials where IPD were available; blue lines represent trials where published data were used. For the diagram at exactly 1 year see Appendix 2.2.



Figure Network diagram at up to 1 year of follow-up

Figure 2 shows the results of all treatment comparisons from the NMA for data up to 1 year, and Figure 3 for data at exactly 1 year. In both figures negative relative effects (to the left of the vertical line) indicate favouring the first-named intervention. For the primary comparisons with PRP all anti-VEGF agents favour anti-VEGF over PRP and improved vision. Reductions in logMAR when compared to PRP ranged from -0.055 (or 2.6 ETDRS letters) for aflibercept to -0.172 (or 6.8 ETDRS letters) for bevacizumab with PRP. However, for aflibercept no difference between aflibercept and PRP remains within the credible interval. Results are broadly similar across anti-VEGF agents in both analyses. Results for bevacizumab (without PRP) are inconclusive because of the very limited data on this treatment group. Indirect comparisons between anti-VEGFs found no conclusive evidence that any one anti-VEGF was superior to the others. Heterogeneity across the network appeared to be modest, with an estimated heterogeneity standard error (τ) of 0.04 (95% CrI 0 to 0.12). For full results of both analyses see Appendices 2.1 and 2.2.

Figure Comparison of interventions from NMA of BCVA up to 1 year



*\* Points on left-hand side of the plot favour the first-named treatment.*

Figure Comparison of interventions from NMA of BCVA at exactly 1 year



*\* Points on left-hand side of the plot favour the first-named treatment.*

### Impact of follow-up time and vision at randomisation

An NMA was fitted to allow the effectiveness of anti-VEGFs to vary with follow-up time in each trial and with BCVA at randomisation, using the individual baseline BCVA scores for the IPD alongside the trial-level averages from published data where IPD were unavailable. The results of this analysis are shown in Figure 5 at 1 year of follow-up and the average baseline BCVA across IPD trials (which was 75 ETDRS letters). Effect estimates are broadly similar for this analysis as for the unadjusted analyses in Figure 3. Improvements in logMAR scores when compared to PRP ranged from -0.067 for bevacizumab with PRP to -0.112 for ranibizumab. However, confidence intervals are wider, generating uncertainty as to the effectiveness of anti-VEGFs. We note that the relative effect of aflibercept compared to PRP is larger than in previous analyses (e.g. Figure 2), and for bevacizumab it is smaller, perhaps because most bevacizumab trials were of short duration and mostly recruited patients with poorer vison, while the CLARITY trial of aflibercept included patients with generally good vison at randomisation.

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

Figure NMA of logMAR with adjustment for follow-up time and BCVA at baseline

*\* Points on left-hand side of the plot favour the first-named treatment.*

### Further network meta-analyses of BCVA

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

1. Comparing anti-VEGF (of any type), anti-VEGF (any type) combined with PRP, and PRP alone.

2 Comparing aflibercept, ranibizumab (with or without PRP), bevacizumab (with or without PRP), and PRP alone.

Results for these NMAs are presented in Table 2 and given in full in Appendix 2.4. In summary, there was good evidence that, when all types of anti-VEGF were combined, anti-VEGF in general improved BCVA when compared to PRP at one year (Mean difference (MD) in logMAR -0.116 [or 4.46 ETDRS letters], 95% CrI -0.183 to -0.038). When comparing anti-VEGF combined with PRP to Anti-VEGF alone there was no evidence of any difference (MD in logMAR 0.042 [or -1.47 ETDRS letters], 95% CrI -0.057 to 0.127). Removing the trials of bevacizumab, which were generally at higher risk of bias, had no substantial impact on the results. When comparing the three anti-VEGFs (with or without concomitant PRP) there was no conclusive evidence of any difference between the three anti-VEGFs.

Table Results of NMAs of reduced networks (logMAR BCVA at 1 year follow-up)

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

*\* Negative mean differences favour the treatment over comparator*

### Threshold analyses

Results of the threshold analyses to test the robustness of the NMAs are presented in Appendix 2.5. In general, the threshold analyses found that the ordering of effectiveness of the anti-VEGFs is not robust, given the small differences in effect between the anti-VEGFs and the wide credible intervals. This suggests that there is not currently enough robust evidence to conclude if any one of the three anti-VEGFs is superior to the others.

## Other outcomes

Results on outcomes other than BCVA were inconsistently reported, with most being reported in no more than three trials. Given limited reporting both in publications and IPD, network meta-analyses were not feasible for these outcomes. Forest plots for all outcomes are given in Appendix 4.1. Analyses were based on number of events reported at exactly 1 year of follow-up, excluding patients with the outcome at randomisation for the IPD trials, so numbers may not exactly match publications of those trials. Meta-analyses could be performed for DMO, vitreous haemorrhage and use of vitrectomy by assuming that all three types of anti-VEGF are equally effective. Table 3 summarises the results of random effects meta-analyses of those outcomes. Some data were available for neovascularisation, but mostly from trials where we did not have IPD.

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

Table Random effects meta-analyses of non-BCVA outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **N. trials** | **N. events** | **Relative risk** **(anti-VEGF vs PRP)** | **95% CI** | **I2** |
| **DMO** | 4 | 120 | 0.48 | 0.28 | 0.83 | 29% |
| **Vitreous haemorrhage** | 6 | 77 | 0.72 | 0.47 | 1.10 | 0 |
| **Vitrectomy** | 4 | 18 | 0.63 | 0.16 | 2.42 | 31% |

## Adverse events

As with other non-BCVA outcomes, adverse events were not widely reported, with little consistency across trials as to which adverse events were reported. Full data for all reported adverse events are given in Appendix 4.2. Meta-analyses were performed for adverse event types reported in two or more trials by assuming that the impact of anti-VEGFs is the same for all types of anti-VEGF.

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

Figure Meta-analysis summary for adverse events



## Analysis of IPD trials

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

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

### BCVA

The potential impact of follow-up duration on the effectiveness of anti-VEGF was investigated by fitting a repeated measures model with a linear interaction between anti-VEGF effect and follow-up time. Results of these repeated measures analyses are shown in Table 5. All three analyses show that anti-VEGF improves vision when compared to PRP by 0.062 to 0.074 logMAR after one year, which is equivalent to 3.1 to 3.7 ETDRS letters. Heterogeneity was modest (τ = 0.03), and similar to heterogeneity observed in the NMAs.

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

Table IPD repeated measures analysis of effectiveness of anti-VEGF over time

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

Further analyses were conducted to investigate the impact of protocol-specified patient characteristics on the effectiveness of anti-VEGF. A repeated measures analysis was performed on all data up to 1 year of follow-up, including an interaction between anti-VEGF and the protocol-specified patient covariate. Results are summarised in Table 6 for the analysis at 1 year of follow-up.

The overall effect of anti-VEGF on BCVA was consistent across analyses, with an improvement in BCVA for anti-VEGF vs PRP or around -0.08 logMAR (or 4 ETDRS letters). Statistically significant interactions between anti-VEGF and patient characteristics were identified for:

Sex, where men benefit more than women by 0.07 logMAR (95% CI 0.014 to 0.127, or 3.5 ETDRS letters). Vision at randomisation, where people with poorer vision before treatment have greater benefits from anti-VEGF (by 0.137 logMAR per whole logMAR unit at baseline; or 0.14 ETDRS letters per letter poorer at baseline). Vitreous haemorrhage at baseline, where people with haemorrhage benefit more from anti-VEGF (by 0.127 logMAR, 95% CI 0.058 to 0.197, or 6.4 ETDRS letters). HbA1c, where people with higher HbA1c benefit more from anti-VEGF (by 0.002 logMAR per unit HbA1c, or 0.1 ETDRS letters).

Some caution is required in interpreting these results, given the number of analyses performed and associated risk of finding false positive results. Also, when analyses were performed at a follow-up of exactly one year, excluding earlier reported times, these treatment-covariate interactions were not statistically significant (see Appendix 5.1).

Table IPD meta-regression of anti-VEGF interacting with patient characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Parameter** | **Mean difference (logMAR)** | **95% CI** |
| **Age** | Anti-VEGF vs PRP | -0.076 | -0.13 | -0.022 |
|  | **Anti-VEGF x Covariate interaction** | 0.002 | -0.001 | 0.004 |
| **Sex (Male)** | Anti-VEGF vs PRP | -0.073 | -0.132 | -0.014 |
|  | **Anti-VEGF x Covariate interaction** | -0.07 | -0.127 | -0.014 |
| **BCVA at randomisation** | Anti-VEGF vs PRP | -0.076 | -0.124 | -0.028 |
|  | **Anti-VEGF x Covariate interaction** | -0.137 | -0.246 | -0.028 |
| **Diabetes (Type II)** | Anti-VEGF vs PRP | -0.077 | -0.158 | 0.004 |
|  | **Anti-VEGF x Covariate interaction** | -0.023 | -0.089 | 0.042 |
| **Prior AVEGF use** | Anti-VEGF vs PRP | -0.052 | -0.123 | 0.02 |
|  | **Anti-VEGF x Covariate interaction** | -0.027 | -0.14 | 0.087 |
| **Prior PRP use** | Anti-VEGF vs PRP | -0.094 | -0.148 | -0.04 |
|  | **Anti-VEGF x Covariate interaction** | 0.065 | -0.001 | 0.13 |
| **Vitreous haem. at randomisation** | Anti-VEGF vs PRP | -0.064 | -0.1 | -0.028 |
|  | **Anti-VEGF x Covariate interaction** | -0.127 | -0.197 | -0.058 |
| **DMO at randomisation** | Anti-VEGF vs PRP | -0.094 | -0.17 | -0.018 |
|  | **Anti-VEGF x Covariate interaction** | 0.04 | -0.02 | 0.1 |
| **HbA1c** | Anti-VEGF vs PRP | -0.078 | -0.124 | -0.031 |
|  | **Anti-VEGF x Covariate interaction** | -0.002 | -0.003 | -0.001 |
| **CST at randomisation** | Anti-VEGF vs PRP | -0.073 | -0.129 | -0.018 |
|  | **Anti-VEGF x Covariate interaction** | 0 | 0 | 0.001 |

### Other outcomes

The IPD were analysed to investigate the effectiveness of anti-VEGF on DMO and vitreous haemorrhage (see Appendix 5.2). There was insufficient data to perform meta-regressions for any other outcomes. Results were consistent with those from the full data analysis. At one year, anti-VEGF reduced DMO incidence when compared to PRP (OR 0.471, 95% CI 0.254 to 0.874) and was in the direction of reduced incidence of vitreous haemorrhage (OR 0.700, 95% CI 0.408 to 1.199).

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

The impact of patient characteristics on the effectiveness of anti-VEGF was investigated using meta-regression, but models were unreliable, and some did not converge, due to the limited data. Few statistically significant interactions between patient characteristics and anti-VEGF were found for either DMO incidence or vitreous haemorrhage incidence. There was statistically significant evidence that anti-VEGF produced a greater reduction in vitreous haemorrhage incidence in men (OR 0.161, 95% CI 0.038 to 0.681).

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

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

### Additional treatment

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

## Discussion

This meta-analysis included 12 trials of anti-VEGFs used to treat proliferative diabetic retinopathy, with a total of 1145 participants. IPD were available from 3 trials (624 participants). The network meta-analyses found evidence that all anti-VEGF therapies are better at maintaining vision than PRP therapy at up to one year of follow-up. However, this benefit appears to be small. On average across the three types of anti-VEGF, it was -0.116 logMAR (95% CI -0.183 to -0.038) or, equivalently, around 4.5 ETDRS letters. This is within the region of variation that might be expected between visual acuity measurements without any intervention.37 Evidence from the PROTOCOL S trial suggests that even this benefit may disappear within 5 years.24 There was no evidence to suggest that the three anti-VEGFs (aflibercept, ranibizumab and bevacizumab) differ in effectiveness; in particular, aflibercept and ranibizumab appear to have very similar effectiveness. There was also no evidence that combining anti-VEGF injection with PRP therapy is more effective at improving vision than anti-VEGF alone.

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

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

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

# Conclusion

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

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

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

**Disclosure of interest**

XX declares…. All other authors have no conflicts of interest to declare.

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**Data-sharing statement**

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

**Ethics statement**

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

**Information Governance statement**

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

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