# 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 (PDR), carries a high risk of vision loss, vitreous haemorrhage, macular oedema and other harms. Panretinal photocoagulation (PRP) is the primary 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 diabetic retinopathy.

**Objective**

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

**Methods**

A systematic review and network meta-analysis of all published randomised controlled trials comparing anti-VEGF (alone or in combination with PRP) to PRP in people with diabetic retinopathy. 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 PDR. Overall anti-VEGF was slightly better than PRP at preventing vison loss, measured as best corrected visual acuity (BCVA), at up to two years follow-up (mean difference in logMAR -0.089 (or 3.6 ETDRS letters), 95% confidence interval (CI) -0.180 to -0.019). There was no clear evidence of any difference between the anti-VEGFs, but potential for bias complicated the comparison. Anti-VEGF was superior to PRP at preventing macular oedema (Relative risk 0.29, 95% CI 0.18 to 0.49) and vitreous haemorrhage (Relative risk 0.77, 95% CI 0.61 to 0.99). There was no clear evidence that the effectiveness of anti-VEGF varied over time. One trial found no benefit of anti-VEGF over PRP after 5 years.

**Conclusions**

Anti-VEGF injections reduce vision loss when compared to PRP, but the benefit is small and unlikely to be clinically meaningful. Anti-VEGF may have greater benefit for preventing complications such as macular oedema. Observational studies extending follow-up beyond the one-year duration of most trials are needed to investigate the longer-term effects of repeated anti-VEGF injections.

**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. This is because blood vessels in the part of the eye called the retina may become damaged, leading to sight loss. 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 project investigated whether anti-VEGF therapy is effective by identifying and re-analysing all the clinical trials that used the three main anti-VEGF drugs (called aflibercept, bevacizumab and ranibizumab) to treat diabetic retinopathy. We identified 14 relevant clinical trials, including approximately 1,800 persons.

Our analyses found that anti-VEGF injections were slightly better than laser therapy at maintaining vision. 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. People with less severe forms of retinopathy saw no benefit in vison after receiving anti-VEGF therapy.

We did find 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).

Most of the trials lasted for one year or less, so the long-term impact of using anti-VEGF injections is still not well understood. This long-term impact of anti-VEGF use requires further clinical research.

# 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 1,700 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 1,200-1,600 laser burns per session, usually over two or three treatment sessions. It is known to be effective and long-lasting7 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 there laser scar extension 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 care14 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 was 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.

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 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 reviews16 and reported according to the principles of the overarching 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-vascular endothelial growth factor, angiogenesis inhibitors, or specific drugs used for the treatment of diabetic retinopathy). An 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 1.1.

The searches were performed on 27th August 2021 and 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. Search results were imported into EndNote 20 (Clarivate Analytics, US) 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, focussing 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 duration of follow-up. Heterogeneity was assessed in terms of I2 19 and by inspecting the between-study heterogeneity standard deviations (τ), relative to the treatment effect size.

Network meta-analyses were performed using standard Bayesian methods of network meta-analysis in R (version 4.3.1) 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 (logMAR) and Early Treatment Diabetic Retinopathy Study (ETDRS) scales. As both are widely used, network meta-analyses were performed for both scales. Published data was transformed for one scale to the other, as required. This paper presents results on the logMAR scale; with ETDRS results reported in the supplementary material.

The potential impact of unpublished or ongoing trials on the NMAs was investigated using threshold analysis. Threshold analysis investigates where in an 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]

# 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. 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 1.4.

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.



Figure 1 PRISMA flow diagram

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)** |
| **CLARITY23** | 2017 | Aflibercept | PRP | UK | 232 persons | 1 year | PDR | BCVA, DR severity, subsequent treatment, complications |
| **DRCRN**  **Protocol W24** | 2021 | Aflibercept | Sham injection | USA/Canada | 328 persons | 2 years | Severe NPDR (some DMO) | Time to PDR or DMO |
| **PANORAMA 25** | 2018 | Aflibercept (every 16 weeks vs. 8 weeks) | Sham injection | International | 402 persons | 1 & 2 years | NPDR | DR severity, subsequent treatment, complications |
| **Mirshahi26** | 2017 | Bevacizumab | PRP | Jordan/Syria | 30 persons | 1 year | PDR | BCVA, DR severity |
| **Ahmad27** | 2012 | Bevacizumab +PRP | PRP | Pakistan | 54 eyes | 3 months | PDR | BCVA |
| **Ali28** | 2018 | Bevacizumab +PRP | PRP | Pakistan | 60 eyes | 1 month | PDR | BCVA |
| **Rebecca29** | 2021 | Bevacizumab +PRP | PRP | Pakistan | 76 eyes | 6 months | PDR | BCVA |
| **Roohipour30** | 2016 | Bevacizumab +PRP | PRP | Iran | 64 eyes | 10 months | PDR | BCVA |
| **DRCRN Protocol S31, 32** | 2018 | Ranibizumab | PRP | USA | 305 persons | 2 & 5 years | PDR | DR severity, functional impact on vision, subsequent treatment, complications |
| **Ferraz33** | 2015 | Ranibizumab +PRP | PRP | Brazil | 60 eyes | 6 months | PDR | BCVA |
| **PRIDE34** | 2019 | Ranibizumab +PRP | PRP | Germany | 106 persons | 1 year | PDR | BCVA, DR severity, subsequent treatment |
| **PROTEUS35** | 2018 | Ranibizumab +PRP | PRP | Europe | 87 persons | 1 year | PDR | BCVA, subsequent treatment, complications |
| **Sao Paulo B36** | 2011 | Ranibizumab +PRP | PRP | Brazil | 40 persons | 1 year | PDR | BCVA, pain |
| **Sao Paulo A37** | 2018 | Ranibizumab +PRP( ETRDS) | Ranibizumab +PRP (PASCAL) | Brazil | 40 eyes | 1 year | PDR | BCVA |

## Risk of bias

For the risk of bias assessment of the included trials see Table 2 and Appendix 1.5. 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.

Table 2 Cochrane Risk of bias assessment of outcome BCVA in the included RCTs

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

## Impact on vision (BCVA)

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 network-meta-analysis and meta-regression. First, that some trials compare anti-VEGF to PRP directly, while others combine anti-VEGF with PRP, therefore motivating the need for NMA. Second, that the time at which BCVA is measured varied enormously across trials, from one month to 5 years. Shorter trials were generally smaller in size, more likely to use bevacizumab and possibly showed larger effect sizes.



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

## Network meta-analyses of BCVA 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 network meta-analysis. 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 the number of trials. Note that all the trials of bevacizumab combined with PRP had follow-up durations of less than one year so are not included in the analyses at 1 to 2 years. In both networks there is only one trial of aflibercept and one of bevacizumab (without PRP).

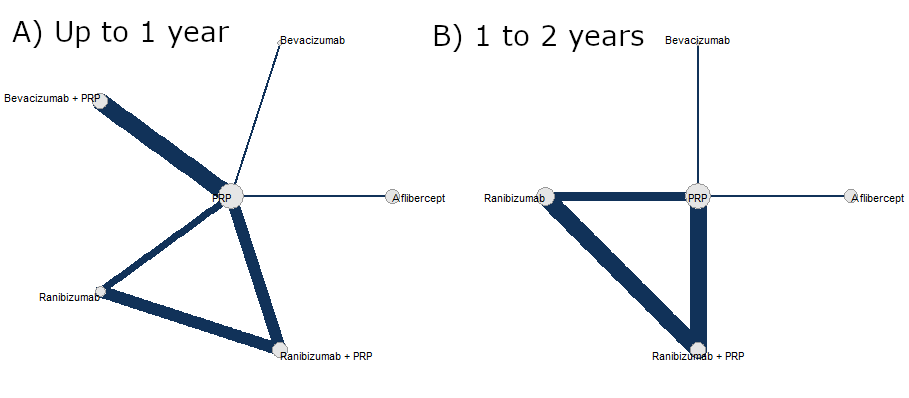


Figure 3 Network diagrams at A) Up to 1 year and B) 1 to 2 years

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 2.3. In both figures the point estimates are shown by the dots, with the horizontal lines being 95% credible intervals. 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 logMAR scores). Changes in logMAR 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, 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 to 2 years (Figure 5) were similar to those at up to one 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 vs ranibizumab combined with PRP, particularly at 2 years.

Treatment rankings are shown in Appendix 2.3 (Figures 16 and 19). 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 means its ranking is very uncertain.

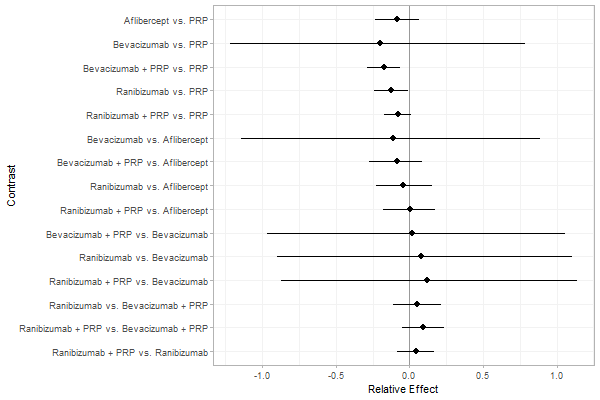


Figure 4 Comparison of interventions from NMA of BCVA up to 1 year

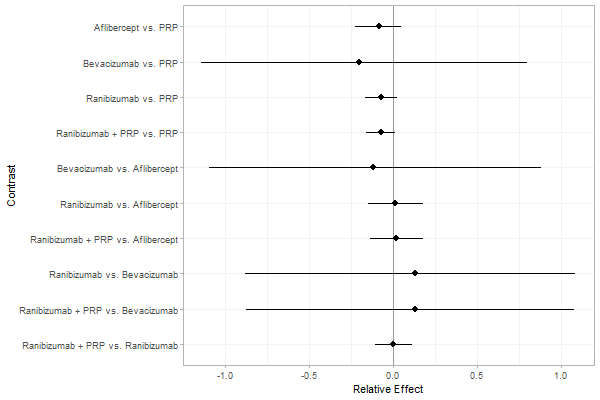


Figure 5 Comparison of interventions from NMA of BCVA from 1 to 2 years

## 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 2.4).

Overall, results were very similar to the NMAs at up to 1 year and 1 to 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 at baseline across all trials (logMAR 0.3). The pattern of effect sizes is very similar to that seen in Figures 4 and 5, but credible intervals 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



Figure 6 NMA of logMAR with adjustment for follow-up time and BCVA at baseline

## Further network meta-analyses

To further compare the anti-VEGFs to each other, simplified network meta-analyses 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 2.5. 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 (MD -0.089, 95% CrI -0.180 to -0.019); as did anti-VEGF combined with PRP compared to PRP alone (MD -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 (MD -0.003, 95% CI -0.166 to 0.163).

### Threshold analysis

Threshold analyses of the network meta-analyses of BCVA are reported in Appendix 2.6. 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 the supplementary material, for all outcomes reported in more than one trial. The limited data meant than network meta-analyses 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 two 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 neovascularization of the disc (NVD) and neovascularization elsewhere (NVE) are shown in Appendix 3.1. These suggest that of neovascularisation was reduced when using anti-VEGF. The results of meta-analyses for other non-vison outcomes are shown in Figure 7. For full results by trial see Section 1 of the supplementary appendix. 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.



Figure 7 Meta-analysis of non-vision outcomes

### 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 two 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 rate of ocular pain, but it was unclear whether this was procedure-related or post-intervention pain.



Figure 8 Meta-analyses of adverse event outcomes

## Non-proliferative retinopathy

Two trials compared aflibercept to sham injection in patients with non-proliferative retinopathy with a follow-up of two 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 (logMAR) -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 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).

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 network meta-analysis 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 logMAR (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.38 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 two years after initialising therapy. However, the one trial with a longer follow-up (Protocol S) found no benefit of ranibizumab over PRP after five 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 is not possible to make 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, network meta-analyses 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.

# Conclusion

Anti-VEGF injection is only marginally better than PRP at maintaining vision and the benefit is unlikely to be 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. Some concern over bias in the trials remains.

The benefits of anti-VEGFs appear consistent to at least two 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 one 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.

# References

1. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the uk: A cohort study in the clinical practice research datalink 2004-2014. *BMJ Open* 2017;**7**:e014444.

2. Ghanchi F, Diabetic Retinopathy Guidelines Working G. The royal college of ophthalmologists' clinical guidelines for diabetic retinopathy: A summary. *Eye Vis (Lond)* 2013;**27**:285-7.

3. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BEK. The wisconsin epidemiologic study of diabetic retinopathy: Xxii the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology* 2008;**115**:1859-68.

4. Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, et al. Global causes of blindness and distance vision impairment 1990-2020: A systematic review and meta-analysis. *Lancet Glob Health* 2017;**5**:e1221-e34.

5. The Diabetic Retinopathy Study Research Group. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the diabetic retinopathy study. The diabetic retinopathy study research group. *Arch Ophthalmol* 1979;**97**:654-5.

6. Parikh R, Shah RJ, VanHouten JP, Cherney EF. Ocular findings at initial pan retinal photocoagulation for proliferative diabetic retinopathy predict the need for future pars plana vitrectomy. *Retina* 2014;**34**:1997-2002.

7. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. *Ophthalmology* 1991;**98**:823-33.

8. Royle P, Mistry H, Auguste P, Shyangdan D, Freeman K, Lois N, et al. Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: Systematic review and economic evaluation. *Health Technol Assess (Winchester)* 2015;**19**:v-247.

9. National Institute for Health and Care Excellence. *Aflibercept for treating diabetic macular oedema*. NICE; 2015. Available from: <https://www.nice.org.uk/guidance/ta346/resources/aflibercept-for-treating-diabetic-macular-oedema-pdf-82602611201221> [accessed 05/07/2023)

10. National Institute for Health and Care Excellence. *Ranibizumab for treating diabetic macular oedema*. NICE; 2013. Available from: <https://www.nice.org.uk/guidance/ta274/resources/ranibizumab-for-treating-diabetic-macular-oedema-pdf-82600612458181> [accessed 05/07/2023)

11. Wubben TJ, Johnson MW, Anti VTISG. Anti-vascular endothelial growth factor therapy for diabetic retinopathy: Consequences of inadvertent treatment interruptions. *Am J Ophthalmol* 2019;**204**:13-8.

12. Obeid A, Su D, Patel SN, Uhr JH, Borkar D, Gao X, et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti-vascular endothelial growth factor. *Ophthalmology* 2019;**126**:407-13.

13. Royal National Institute of Blind People (RNIB). *Anti-VEGF treatment*. RNIB; n.d. Available from: <https://www.rnib.org.uk/eye-health/eye-conditions/anti-vegf-treatment> [accessed 05/07/2023)

14. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, et al. Guidelines on diabetic eye care: The international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. *Ophthalmology* 2018;**125**:1608-22.

15. NICE;. *Diabetic retinopathy (guidance in development)*. 2023. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ng10256> [accessed 03/10/2023

16. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. CRD; n.d. Available from: <https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf> [accessed 17/09/2020)

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 2009;**151**:264-9, W64.

18. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. Rob 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

20. Phillippo DM, Dias S, Ades AE, Belger M, Brnabic A, Schacht A, et al. Multilevel network meta-regression for population-adjusted treatment comparisons. *J R Stat Soc Ser A Stat Soc* 2020;**183**:1189-210.

21. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: Inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013;**33**:641-56.

22. Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE. Threshold analysis as an alternative to grade for assessing confidence in guideline recommendations based on network meta-analyses. *Ann Intern Med* 2019;**170**:538-46.

23. Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (clarity): A multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet* 2017;**389**:2193-203.

24. Maturi RK, Glassman AR, Josic K, Antoszyk AN, Blodi BA, Jampol LM, et al. Effect of intravitreous anti–vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: The protocol w randomized clinical trial. *JAMA Ophthalmol* 2021;**139**:701-12.

25. Brown DM, Wykoff CC, Boyer D, Heier JS, Clark WL, Emanuelli A, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: Results from the panorama randomized clinical trial. *JAMA Ophthalmol* 2021;**05**:05.

26. Mirshahi A, Roohipoor R, Lashay A, Mohammadi SF, Abdoallahi A, Faghihi H. Bevacizumab-augmented retinal laser photocoagulation in proliferative diabetic retinopathy: A randomized double-masked clinical trial. *Eur J Ophthalmol* 2008;**18**:263-9.

27. Ahmad M, Jan S. Comparison between panretinal photocoagulation and panretinal photocoagulation plus intravitreal bevacizumab in proliferative diabetic retinopathy. *J Ayub Med Coll Abbottabad* 2012;**24**:10-3.

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

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

30. Roohipoor R, Sharifian E, Ghassemi F, Riazi-Esfahani M, Karkhaneh R, Fard MA, et al. Choroidal thickness changes in proliferative diabetic retinopathy treated with panretinal photocoagulation versus panretinal photocoagulation with intravitreal bevacizumab. *Retina* 2016;**36**:1997-2005.

31. Gross JG, Glassman AR, Jampol LM. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: A randomized clinical trial (vol ,314 pg 2137, 2015). *JAMA* 2019;**321**:1008-.

32. Gross JG, Glassman AR, Jampol LM. Writing committee for the diabetic retinopathy clinical research network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: A randomized clinical trial (vol 314, pg 2137, 2015). *JAMA* 2016;**315**:944-.

33. Ferraz DA, Vasquez LM, Preti RC, Motta A, Sophie R, Bittencourt MG, et al. A randomized controlled trial of panretinal photocoagulation with and without intravitreal ranibizumab in treatment-naive eyes with non-high-risk proliferative diabetic retinopathy. *Retina* 2015;**35**:280-7.

34. Lang GE, Stahl A, Voegeler J, Quiering C, Lorenz K, Spital G, et al. Efficacy and safety of ranibizumab with or without panretinal laser photocoagulation versus laser photocoagulation alone in proliferative diabetic retinopathy - the pride study. *Acta Ophthalmol* 2020;**98**:e530-e9.

35. Figueira J, Fletcher E, Massin P, Silva R, Bandello F, Midena E, et al. Ranibizumab plus panretinal photocoagulation versus panretinal photocoagulation alone for high-risk proliferative diabetic retinopathy (proteus study). *Ophthalmology* 2018;**125**:691-700.

36. Filho JA, Messias A, Almeida FP, Ribeiro JA, Costa RA, Scott IU, et al. Panretinal photocoagulation (prp) versus prp plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy. *Acta Ophthalmol* 2011;**89**:e567-72.

37. Messias A, Toscano L, Messias K, Ribeiro JAS, Jorge R. Retinal function in proliferative diabetic retinopathy treated with intravitreal ranibizumab and laser photocoagulation targeted to ischemic retina. *Doc Ophthalmol* 2018;**136 (Supplement 1)**:30.

38. Rosser DA, Cousens SN, Murdoch IE, Fitzke FW, Laidlaw DAH. How Sensitive to Clinical Change are ETDRS logMAR Visual Acuity Measurements? *Investigative Ophthalmology & Visual Science* 2003;**44**:3278-81. Available from: <https://doi.org/10.1167/iovs.02-1100>