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 risk, vitreous haemorrhage, macular oedema and other harms. Laser 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 of anti-VEGF therapy for the treatment of diabetic retinopathy when compared to laser photocoagulation.

Methods

A systematic review and network meta-analysis of all published randomised controlled trials comparing anti-VEGF 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 15 trials were included: 54 of aflibercept, 5 of bevacizumab and 6 of ranibizumab. Two trials were of patients with non-proliferative retinopathy (NPDR); all others were in PDR. Overall anti-VEGF was better than PRP at preventing vison loss at up to two years follow-up (BCVA mean difference in logMAR -0.064, 95% CI -0.122 to -0.015). There was no clear evidence of any difference between the anti-VEGFs, but potential for bias and differences in trial 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 evidence that the effectiveness of anti-VEGF varied over time, but one trial found no benefit of anti-VEGF over laser therapy after 5 years.

Conclusions

Anti-VEGF injection appears to be superior to using laser photocoagulation, but the benefit in preservation of eyesight appears to be modest. Long-duration observational studies are needed to examine how anti-VEGF may be beneficial in the long term.

Background

Diabetes is a major cause of poor health, impairing the sight of more than 1,700 people in the UK each year [1]. Diabetic retinopathy is a "chronic progressive, potentially sight-threatening disease of the retinal microvasculature" [2, 3] and is a major form of sight loss. Prevalence of type 1 diabetes is around 48%, and 28% in type 2 diabetes. [3] Older people, men, South Asian groups, and more deprived populations are at higher risk. [4] Diabetic retinopathy staging allows for stratification for risk of future visual loss, with the most severe form, proliferative diabetic retinopathy (PDR), placing the patients at a very high risk of vitreous haemorrhage bleeding, retinal detachment, neovascular glaucoma and vision loss. [5, 6]

Laser photocoagulation is the primary treatment for proliferative diabetic retinopathy (PDR). Laser is applied to the retina either to prevent proliferation of new blood vessels or encourage fibrosis in those with established new vessels Panretinal photocoagulation (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. 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 the laser burn is accidently placed in the macula or if there is a laser creep into the macula. [8]

Anti-vascular endothelial growth factor (anti-VEGF) drugs are used to treat various eye conditions. NICE has approved ranibizumab and aflibercept for the treatment of diabetic macular oedema (DME). [9, 10] Anti-VEGF treatments are injected into the eye, under local anaesthetic, at regular intervals. They have rare but potentially serious adverse effects including: ocular hypertension, retinal detachment, endophthalmitis and other intraocular inflammation, and cataracts. [11] There are also concerns that effects may not be long-lasting, and patients may have worse outcomes than those who had laser photocoagulation if patients are not carefully followed up. [12 13]

There is no current NICE guidance for the use of anti-VEGF drugs in diabetic retinopathy in people without macular oedema, including for proliferative retinopathy. 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.

There is a growing body of evidence in favour of the various anti-VEGF drugs, so a thorough systematic assessment of the relevant evidence, and network meta-analysis (NMA) is needed to assess the value and rank of all relevant anti-VEGF interventions. This paper presents a review and network meta-analysis of all published randomised controlled trials (RCTs) of the three main anti-VEGFs used to treat diabetic retinopathy: aflibercept, bevacizumab and ranibizumab. The project is funded by the National Institute for Health Research (Project number NIHR132948). The project is ongoing, and the complete project will also include analysis of individual participant data, a wider assessment of anti-VEGF studies, including non-randomised studies, and an economic analysis. The review is registered on PROSPERO [CRD42021272642] and the full protocol is available online from the NIHR [hiips://fundingawards.nihr.ac.uk/award/NIHR132948].

Methods

The review was conducted following CRD's guidance on undertaking systematic reviews [15] and reported according to the principles of the overarching PRISMA statement. [16]

Inclusion criteria

The wider review in the project 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 compared to laser photocoagulation therapy, sham injection or another type of anti-VEGF.

In this paper we consider the most relevant RCTs from the wider review. Specifically, these are RCTs of aflibercept, bevacizumab or ranibizumab for the treatment of diabetic retinopathy. Only trials published in English in full publications (not conference abstracts) are considered here.

A full list of outcomes of interest are reported in the review protocol. This paper focuses on best corrected visual acuity (BCVA) measured on ETDRS or logMAR scales. Other outcomes were not widely reported in publications; we examine here data on key outcomes such as incidence of DME, vitreous haemorrhage and adverse events.

Review methods

An experienced information specialist (HF) designed search strategies for MEDLINE, EMBASE and CENTRAL which were searched up to July 2022. 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 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. Risk of bias in all included trials was assessed using the RoB 2 tool. [17]

Statistical analysis

Effect estimates were pooled across studies using standard DerSimonian-Laird random effect meta-analysis, separately for each anti-VEGF and according to duration of follow-up. Heterogeneity was be assessed in terms of I^2 [18] and by inspecting the between-study heterogeneity standard deviation (τ) relative to the treatment effect size.

Network meta-analyses were performed using standard Bayesian methods of network meta-analysis using the R package multinma. [12, 19] 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, and on the ranking of the different treatments. [19] 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). [20]

Threshold analysis

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. [21]

Results

General results

Key findings for BCVA, DME, vitrectomy, vitreous haemorrhage and adverse events are presented in this paper. A full presentation of all analyses performed is provided in the two supplementary appendices; one for BCVA data, and one for all other outcomes and adverse events.

Figure 1 shows the PRISMA flow chart for the original searches in this review. Update searches found 850 records, of which 2 publications were eligible for the full project, with 1 new RCT included in this assessment. Overall, 15 RCTs were included in this analysis. The searches also identified 18 other RCTs, which were reported only as conference abstracts, not in English, were published before 2010 (and judged to be out-of-date), or used other types of anti-VEGF not in widespread use. Those trials were therefore judged to ineligible for inclusion in this meta-analysis.

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 four trials of aflibercept (one of which did not have a control arm). Some trials used anti-VEGF as the intervention, but others used anti-VEGF combined with PRP. Nearly all trials were of patients with proliferative retinopathy. Two trials of aflibercept recruited patients with non-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 consistent outcome reported in all trials.

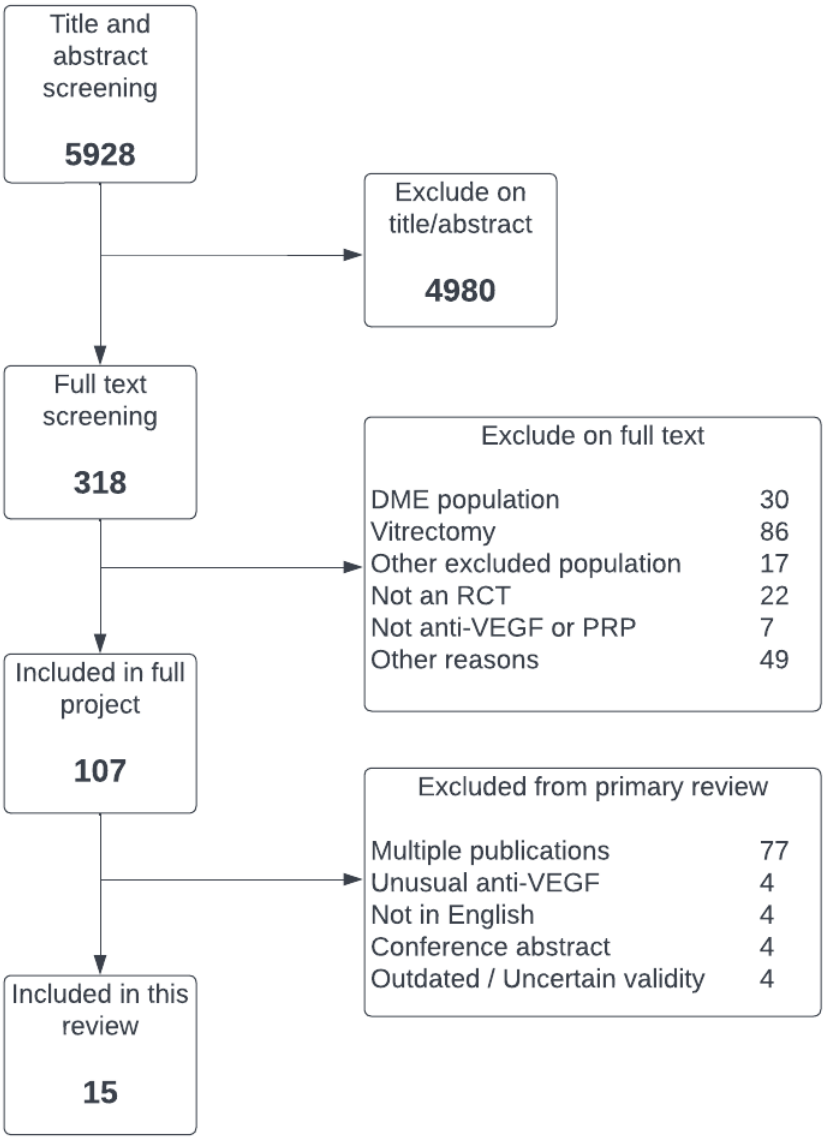

Figure 1 PRISMA flow diagram

Table 1 Summary of the included RCTs

Trial	Year	Anti-VEGF	Comparator	Location	Sample size	Follow-up	Population	Main outcome(s)
CLARITY[22]	2017	Aflibercept	PRP	UK	232 persons	1 year	PDR	BCVA, DR severity, subsequent treatment, complications
DRCRN Protocol W[23]	2021	Aflibercept	Sham injection	USA/Canada	328 persons	2 years	Severe NPDR (some DME)	Time to PDR or DME
PANORAMA [24]	2018	Aflibercept (every 16 weeks vs. 8 weeks)	Sham injection	International	402 persons	1 & 2 years	NPDR	DR severity, subsequent treatment, complications
RECOVERY[25]	2019	Aflibercept (monthly)	Aflibercept (quarterly)	USA	40 eyes	1 year	PDR	BCVA, DR severity, functional impact
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
Roohipour[30]	2016	Bevacizumab (+PRP)	PRP	Iran	64 eyes	10 months	PDR	BCVA
DRCRN Protocol S[31, 32]	2018	Ranibizumab	PRP	USA	305 persons	2 & 5 years	PDR	DR severity, functional impact on vision, subsequent treatment, complications
Ferraz[33]	2015	Ranibizumab (+PRP)	PRP	Brazil	60 eyes	6 months	PDR	BCVA
PRIDE[34]	2019	Ranibizumab (+PRP)	PRP	Germany	106 persons	1 year	PDR	BCVA, DR severity, subsequent treatment
PROTEUS[35]	2018	Ranibizumab (+PRP)	PRP	Europe	87 persons	1 year	PDR	BCVA, subsequent treatment, complications
Sao Paulo B[36]	2011	Ranibizumab (+PRP)	PRP	Brazil	40 persons	1 year	PDR	BCVA, pain
Sao Paulo A[37]	2018	Ranibizumab (+PRP, ETRDS)	Ranibizumab (+PRP, PASCAL)	Brazil	40 eyes	1 year	PDR	BCVA

Risk of bias

The results for the bias assessment of BCVA are shown in Table 2. In general, the larger trials were well reported, with low risk of bias. Smaller trials, particularly bevacizumab trials, were less well reported and consequently had unclear or high risk of bias in many categories. The main risk of bias concern was in how BCVA and other outcomes were assessed; it was generally not possible to blind patients or outcome assessors to the treatment used, and most trials did not state whether the clinicians performing sight tests were blinded to the treatment received.

Table 2 Cochrane Risk of bias assessment of the included RCTS

Impact on vision (BCVA)

Figure 2 summarises in a forest plot all the data on BCVA for anti-VEGF compared to PRP reported across all trials. Results are shown on the logMAR scale; where trials reported ETDRS these results were converted to their logMAR equivalents.

This plot shows several key issues with the available trial data. First, that some trials compare anti-VEGF to PRP directly, while others combine anti-VEGF with PRP. Second, that the time at which BCVA is measured varies enormously across trials, from one month to 5 years. Given these issues, the trials are not combined in a meta-analysis here. However, we note that despite the differences in intervention and timing, there is comparatively little heterogeneity across studies within each drug class.

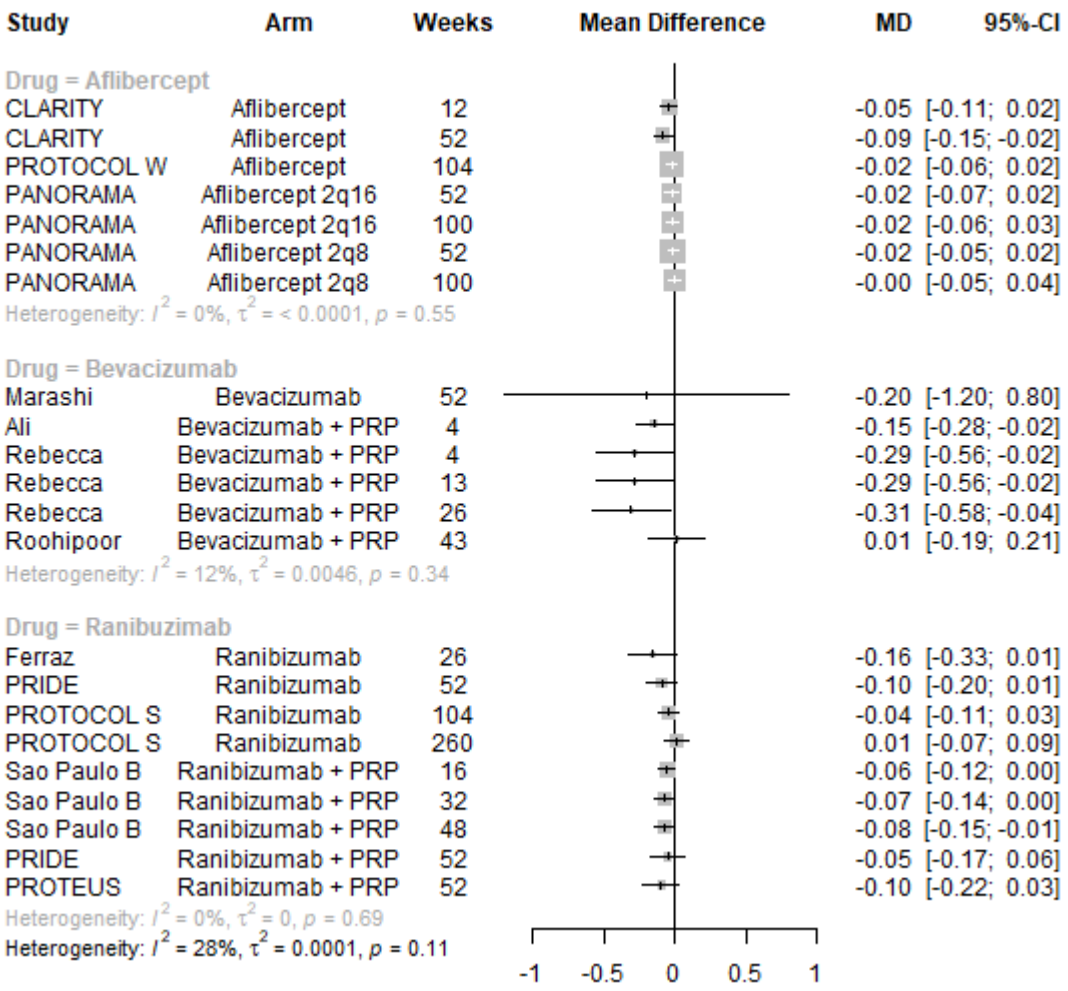

Figure 2 All BCVA data (logMAR scale) from all trials of anti-VEGF

Network meta-analyses of BCVA in proliferative retinopathy

Given the variations in timing at which BCVA results were reported, for the primary network meta-analyses the data were divided into two groups:

1. Up to and including 1 year of follow-up,

2. 1 to 2 years' follow up.

Note that trials reporting at exactly 1 year (52 weeks) were included in both analyses. Given the difference between proliferative and non-proliferative disease, and because the two trials of non-

proliferative disease compared anti-VEGF to sham injection, they were not included in the main network analysis. The network diagrams for both analyses are shown in Figure 3.

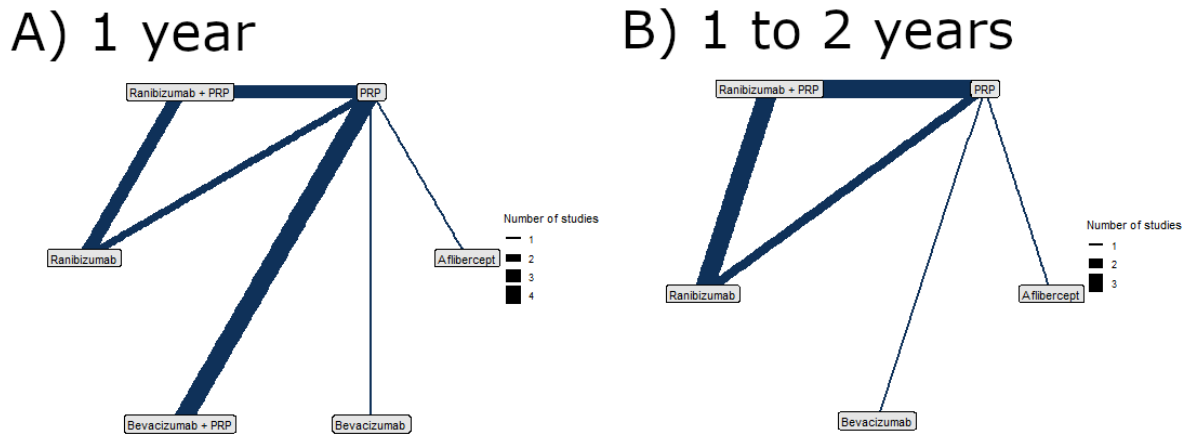

Figure 3 Network diagrams at A) Up to 1 year and B) 1 to 2 years

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. For the primary comparisons with PRP all anti-VEGF agents favour anti-VEGF over PRP and reduce logMAR scores (improved BCVA). However, the effects are not statistically significant for aflibercept at either one or two years, or for ranibizumab at 2 years. Results are broadly similar across ant-VEGF agents and at both 1 year and 2 years. Results for bevacizumab (without PRP) are inconclusive because of the very limited data on this treatment group. For full results see Section 3 of the supplementary appendix.

Given the similarity in magnitude of effect for the various anti-VEGF agents it is not surprising that the indirect comparisons between agents show no conclusive evidence of difference between any of the agents, suggesting that all three anti-VEGFs have similar efficacy. There appears to be no difference between using ranibizumab alone vs ranibizumab combined with PRP, particularly at 2 years.

Treatment rankings are shown in the supplementary appendix for BCVA (Figures 14 and 17). 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.

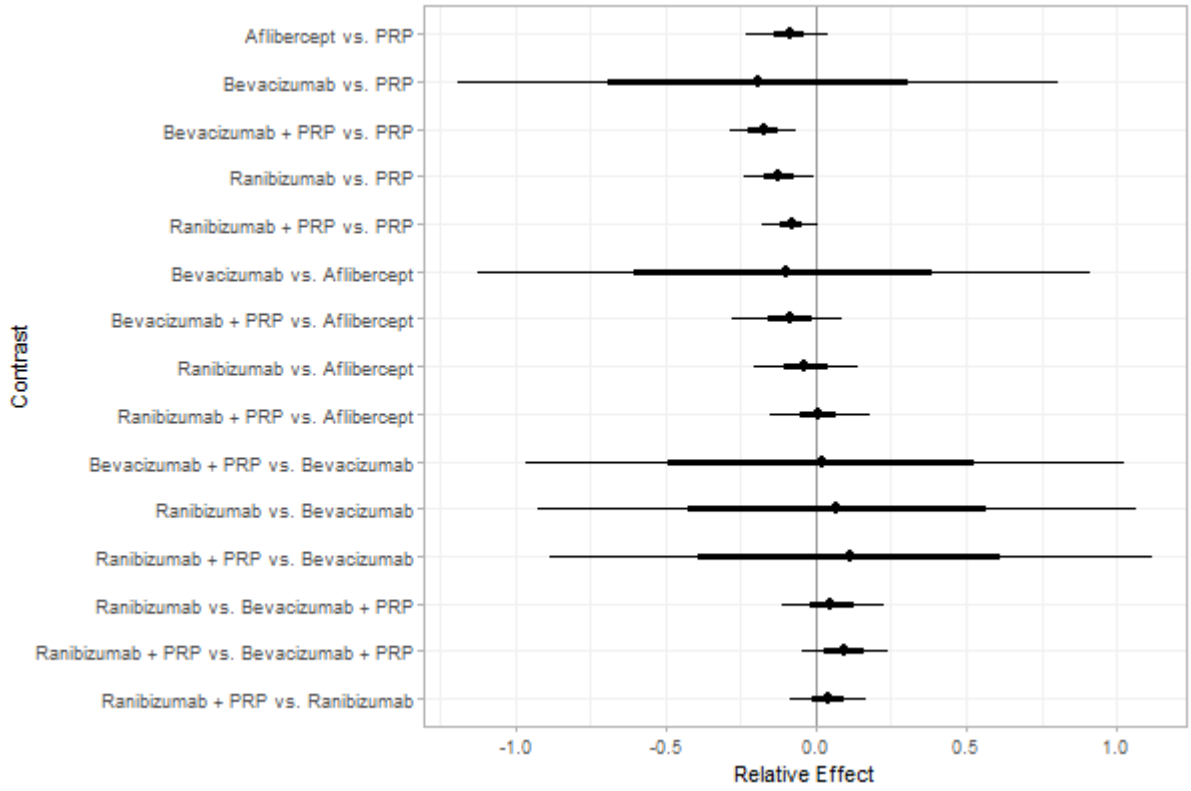

Figure 4 Comparison of interventions from NMA of BCVA up to 1 year

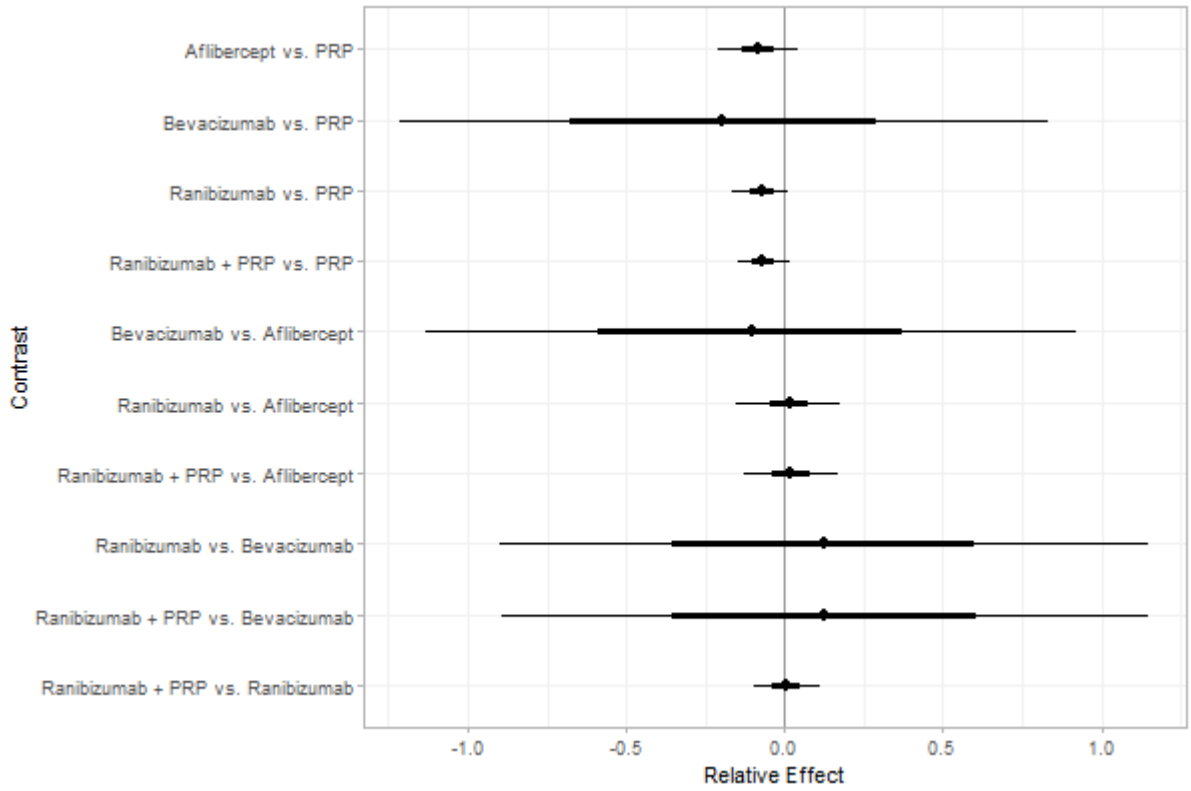

Figure 5 Comparison of interventions from NMA of BCVA from 1 to 2 years

Impact of time and vision at randomisation

To further examine the impact of time on the effectiveness of anti-VEGFs we fitted a range of models including time as a covariate. This meant that all data could be combined in a single NMA, without excluding data, and whether the effectiveness of anti-VEGFs varied with time could be investigated. Several models were fitted, including simple linear changes in effectiveness over time, and more complex models such as exponential time trends. Models were also fitted including BCVA at randomisation, as there was some evidence that this might alter the effectiveness of the anti-VEGFs (see Supplementary appendix Section 4).

Overall, results were very similar to the NMAs at 1 and 2 years. As an example, Figure 6 shows the effect estimates for anti-VEGFs compared to PRP alone from a model with a linear time trend and adjustment for BCVA at randomisation. The pattern of effect sizes is very similar to that seen in Figures 4 and 5.

The various models found no clear evidence that the effectiveness of anti-VEGFs varied with time. However, it should be noted that almost all the data are 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.

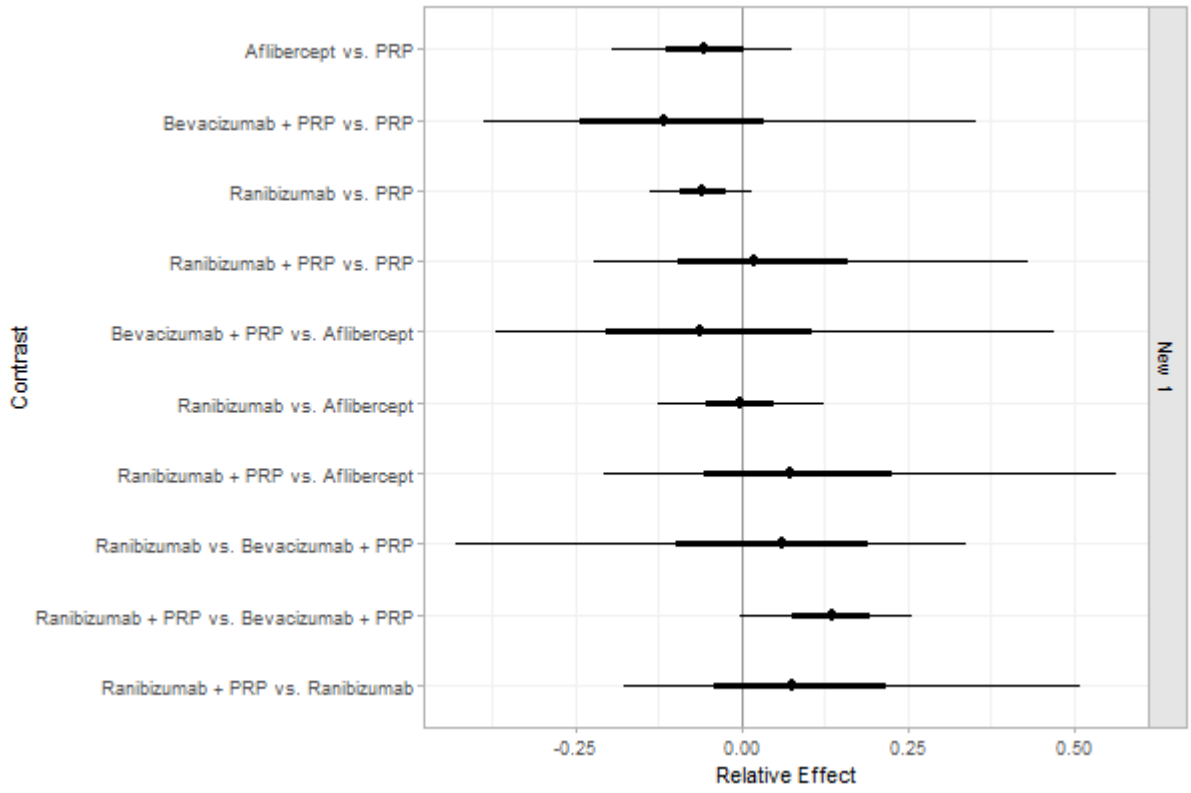

Figure 6 NMA of logMAR with adjustment for follow-up time and BCVA at baseline

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.

Full results for these NMAs are presented in Section 5 of the BCVA supplementary appendix. In summary, there was good evidence that, when all types of anti-VEGF were combined, that anti-VEGF in general improved BCVA when compared to PRP (MD -0.064, 95% CI -0.122 to -0.015). When comparing anti-VEGF combined with PRP to PRP alone the evidence was in the direction of favouring combination therapy, but was not statistically significant (MD -0.044, 95% CI -0.115 to 0.021).

When comparing the three anti-VEGFs (with or without concomitant PRP) bevacizumab was superior to ranibizumab (MD -0.121, 95% CI -0.214 to -0.026) and to aflibercept, although the result was not quite statistically significant (MD -0.122, 95% CI -0.246 to 0.003). There was no difference between aflibercept and ranibizumab (MD -0.002, 95% CI -0.083 to 0.079).

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 the supplementary appendix Figures 1 and 2. These suggest that rates of neovascularisation are substantially lowered 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 are limited, the results suggest that anti-VEGF treatment substantially reduces the rate of macular oedema (DME) and the need for vitrectomy, and reduces the rates of vitreous haemorrhage. No data on progression of diabetic retinopathy (e.g. from non-proliferative to proliferative, or according to severity of disease) were reported.

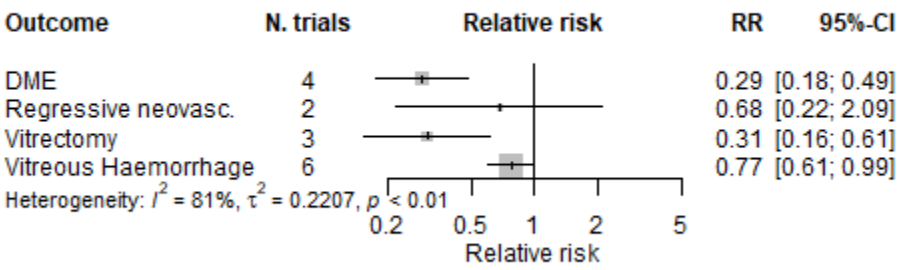

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Figure 7 Meta-analysis of non-vision outcomes

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 appears to reduce the incidence of retinal detachment. It appears to increase the rate of ocular pain, but it was unclear whether this was procedure-related or post-intervention pain.

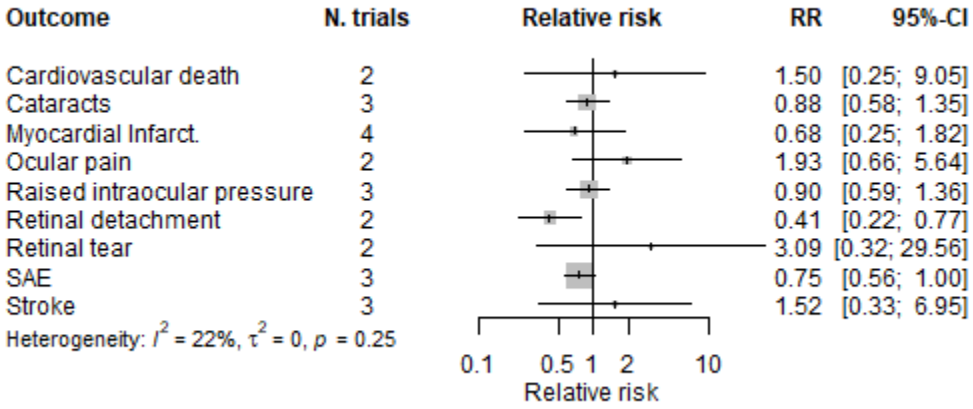

Figure 8 Meta-analyses of adverse event outcomes

Non-proliferative retinopathy

Two trials compared aflibercept to sham injection in patients with non-proliferative retinopathy with a follow-up of two years. Meta-analysis of their BCVA results found no clear evidence of any benefit of anti-VEGF 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).

Discussion

This systematic review included 15 trials of anti-VEGFs used to treat diabetic retinopathy. 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 0.064 points on the logMAR scale (95% CI -0.122 to -0.015). This could be as low as 0.026 for aflibercept and as high as 0.146 for bevacizumab. This is broadly equivalent to a benefit of between 1 and 5 points using ETDRS, which is within the region of variation that might be expected between eye tests without any intervention. There was no compelling evidence to suggest that the three anti-VEGFs (aflibercept, ranibizumab and bevacizumab) differ in effectiveness; it is plausible that any observed differences were due to different trial populations and 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. There was, similarly, some evidence that the benefit of anti-VEGF over PRP is greater in people with poorer eyesight at time of injection. This suggests that the benefits of anti-VEGF may depend on disease severity and eyesight at time of treatment. However, it is not possible to make any firm conclusions on this from data presented in trial publications alone.

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. 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.

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 incidence of macular oedema (RR 0.29, 95% CI 0.21 to 0.41), vitreous haemorrhage (RR 0.78, 95% CI 0.61 to 0.99) and need for vitrectomy (RR 0.31, 95% CI 0.15 to 0.60). This suggests that anti-VEGF may be valuable in preventing progression of diabetic retinopathy, even if its impact on vision itself is more modest.

Evidence on adverse events was limited due to inconsistent reporting, and small numbers of events. There was some evidence that ant-VRGF reduces the risk of retinal detachment (RR 0.45, 95% CI 0.25 to 0.81) but might increase the risk of ocular pain (RR 1.76, 95% CI 0.86 to 3.61). For other types of adverse events anti-VEGF seems to have a similar risk profile as PRP.

Conclusion

Anti-VEGF injection appears to be plausibly superior to using laser photocoagulation in people with proliferative retinopathy, by better preserving eyesight and reducing the risk of progression to macular oedema and vitreous haemorrhage. However, the benefit in preservation of eyesight appears to be modest. Some concern over bias in the trials remains.

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 trial data might aid in resolving this. The benefits of anti-VEGFs appear consistent to at least two years after initiation of

treatment, but longer-term benefits are uncertain. Long-duration observational studies are needed to examine how anti-VEGF may be beneficial in the long term.

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