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Synopsis

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

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Abstract

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

Methods: The Anti-VEGF In Diabetes project sought to investigate the clinical and cost-effectiveness of using anti-vascular endothelial growth factor to prevent retinopathy progression when compared to panretinal photocoagulation or no treatment. A systematic review with network meta-analysis of randomised controlled trials of anti-vascular endothelial growth factor (alone or in combination with panretinal photocoagulation) to treat retinopathy was conducted. The database searches were updated in May 2023. Individual participant data from larger trials were sought. A systematic review of non-randomised studies was performed.

Existing cost-effectiveness analyses were reviewed, and a new economic model was developed, informed by the individual participant data meta-analysis. The model also estimated the value of undertaking further research to resolve decision uncertainty.

Results: The review found that anti-vascular endothelial growth factors produced a slight, and not clinically meaningful, benefit over panretinal photocoagulation in best corrected visual acuity, after 1 year of follow-up in people with proliferative retinopathy (mean difference of 4.5 ETDRS letters; 95% credible interval −0.7 to 8.2). There was no evidence of a difference in effectiveness among the different anti-vascular endothelial growth factors. The benefit of anti-vascular endothelial growth factor appears to decline over time. Anti-vascular endothelial growth factor therapy may be more effective in people with poorer initial visual acuity. Anti-vascular endothelial growth factor had no impact on vision in people with non-proliferative retinopathy. Anti-vascular endothelial growth factor reduces rates of macular oedema and vitreous haemorrhage and may slow down the progression of retinopathy.

Anti-vascular endothelial growth factors were predicted to be more costly but similarly effective to panretinal photocoagulation, with a net health benefit of −0.214 quality-adjusted life-years at a £20,000 willingness-to-pay threshold. Only under very select conditions might anti-vascular endothelial growth factors have the potential for cost-effectiveness to treat proliferative retinopathy. There is potentially significant value in reducing uncertainty through further primary research.

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Conclusions: Anti-vascular endothelial growth factor has no clinically meaningful benefit over panretinal photocoagulation for preserving visual acuity, but it may delay or prevent progression to macular oedema and vitreous haemorrhage. The long-term effectiveness and safety of anti-vascular endothelial growth factor treatment are unclear, particularly as additional panretinal photocoagulation and anti-vascular endothelial growth factor treatment will be required over time.
Anti-vascular endothelial growth factors are therefore unlikely to be a cost-effective treatment for early proliferative retinopathy compared to panretinal photocoagulation. They are generally associated with higher costs and similar health outcomes across various scenarios. The long-term cost-effectiveness of anti-vascular endothelial growth factor is uncertain due to the lack of long-term clinical evidence.
Future work: Further, robust studies with more than 2 years follow-up are required to evaluate the long-term efficacy and safety of anti-vascular endothelial growth factor use, and the effect of additional anti-vascular endothelial growth factor and panretinal photocoagulation therapy over time. Clinical trials or observational studies focusing on the use of anti-vascular endothelial growth factor in people with poorer vision at time of treatment may also be useful.
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Introduction

Background

Diabetes is a major public health concern that affects about 5 million people in the UK. Diabetic retinopathy is an eye condition that affects blood vessels in the retina and can cause vision loss and blindness in people who have diabetes. It impairs the sight of more than 1700 people in the UK each year.[1] There are several stages of diabetic retinopathy, with proliferative retinopathy being the most severe form. It is associated with a high risk of retinal detachment and vitreous haemorrhage, which may result in severe vision loss.[2,3] In the UK, the cost of treating diabetic retinopathy was estimated to be £57M in 2010–1.[4]

In the UK, proliferative diabetic retinopathy (PDR) is usually treated with laser therapy, specifically panretinal photocoagulation (PRP), where a laser is applied to the retina to stop further proliferation of new (abnormal) blood vessels. PRP is delivered in two or three treatment sessions requiring specialist staff and equipment to administer.[5,6] It is effective and long-lasting[7] but can have adverse effects such as macular oedema and peripheral visual field loss.[6]

Anti-vascular endothelial growth factor (anti-VEGF) drugs are used to treat various eye conditions. Ranibizumab and aflibercept are approved for the treatment of diabetic macular oedema (DMO) in England and Wales[8,9] and have been the main treatment for neovascular ('wet') age-related macular degeneration for several years. Anti-VEGF treatments are injected into the eye, typically once per month. 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 down the progression of retinopathy and prevent oedema.[10] However, these drugs are expensive and there are concerns about their long-term effectiveness.[11,12] Few patients with PDR are at immediate risk of sight loss, and those who do develop macular oedema would be treated with anti-VEGFs as per current guidance. It is therefore unclear whether anti-VEGF treatment could represent a cost-effective option for treating early PDR.

International Council of Ophthalmology guidelines on diabetic eye care[13] support laser photocoagulation and 'appropriate use of anti-VEGF drugs' for the management of diabetic retinopathy. National Institute for Health and Care Excellence (NICE) guidance on the treatment of diabetic retinopathy in England and Wales is in development but may only recommend anti-VEGF if retinopathy continues to progress after PRP treatment, or if cataract or vitreous haemorrhages precludes the delivery of laser.[14]

The Anti-VEGF In Diabetes project

The Anti-VEGF In Diabetes (AVID) project was established to investigate the potential clinical value and cost-effectiveness of using anti-VEGF to manage diabetic retinopathy in people without DMO. It was a collaborative project between experts in health research and health economics based at York University, and clinical experts and patient representatives from around the UK. The project was commissioned and funded by the National Institute for Health and Care Research (NIHR) as project number NIHR132948.

The key aims of the project were to systematically review the existing clinical evidence on the use of anti-VEGF to treat diabetic retinopathy, and to perform a new economic

analysis to assess its cost-effectiveness. The overall aim was to provide evidence to resolve uncertainties around how anti-VEGF should be used, and to inform guidance for UK medical practice.

The AVID protocol is available from the NIHR website (https://fundingawards.nihr.ac.uk/award/NIHR132948), and the project was registered on the PROSPERO database (reference: CRD42021272642).

Objectives

The AVID protocol identified seven key objectives for this project, which were:

1. To identify and critique all randomised controlled trials (RCTs) of anti-VEGF drugs and laser photocoagulation for diabetic retinopathy.
2. To obtain original individual participant data (IPD) for large trials comparing anti-VEGF drugs to photocoagulation.
3. To perform network meta-analyses (NMAs) to compare and rank all treatments, incorporating the IPD collected.
4. Where RCT evidence was limited, to identify high-quality observational evidence, focusing on long-term and safety outcomes, relevant to a UK context, to inform the economic analysis.
5. To identify and critique all UK-relevant cost-effectiveness models for anti-VEGF and laser photocoagulation therapies.
6. To develop a de novo economic model, informed by the review of existing economic evaluations, which will incorporate the NMA results.
7. In collaboration with patients and clinicians, to examine the evidence collected, consider its suitability for the UK health service, or identify priority areas where additional evidence is required.

Publications and outputs

To meet the specified objectives, four papers have been published, along with this synopsis and two supplementary documents. See *Box 1* for details of these papers.

Objectives 1–3 are covered by two systematic reviews and NMAs of RCTs, including analysis of IPD (Papers 1 and 2 in *Box 1*). Some additional trials not included in the meta-analyses are reviewed in a short supplementary paper (Paper 5). We identified very little observational evidence of anti-VEGF therapy, so Objective 4 is covered in a short paper supplied as supplementary material to this synopsis (Paper 6). Objective 5 was covered by a systematic review of the existing economic literature (Paper 3). Objective 6 was addressed with a new economic model for anti-VEGF (Paper 4). Objective 7 is chiefly covered in this synopsis.

BOX 1 Key outputs of the AVID project

Key papers

1. **A systematic review of published RCTs**[15]

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

(published in *Health Technology Assessment*).

2. **A systematic review and IPD NMA of RCTs**[16]

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

(published in *Health Technology Assessment*).

3. **A systematic review of existing economic analyses**[17]

A systematic review of the cost-effectiveness of anti-VEGF *drugs for the treatment of diabetic retinopathy*

(published in *Health Technology Assessment*).

4. **The development of a new cost-effectiveness model**[18]

Anti-VEGF drugs for the treatment of proliferative diabetic retinopathy: a cost-effectiveness analysis

(published in *Value in Health*[18]).

Additional material (see *Report Supplementary Material 1*)

5. A narrative review of RCTs not included in the meta-analyses.
6. A systematic review and narrative synthesis of non-randomised studies.

Methods

Systematic reviews

Three systematic reviews were conducted as part of the AVID project:

1. A review of all RCTs where anti-VEGF was used to treat diabetic retinopathy.
2. A review of all non-randomised studies where anti-VEGF was used to treat diabetic retinopathy.
3. A review of all cost-effectiveness analyses and economic models of anti-VEGF as a treatment for diabetic retinopathy.

The reviews focused on the three most commonly used anti-VEGF drugs: aflibercept, bevacizumab and ranibizumab. These could be used on their own or in combination

with PRP. Trials of non-proliferative and proliferative retinopathy were included, but trials exclusively of DMO or vitreous haemorrhage were excluded. The primary outcome for all reviews was best corrected visual acuity (BCVA), but incidences of DMO, vitreous haemorrhage and adverse events were also included. A full list of inclusion criteria and outcomes is given in the AVID protocol.

All reviews were conducted following Centre for Reviews and Dissemination guidance on undertaking systematic reviews[19] and reported according to the principles of the overarching Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20]

For each review, an information specialist designed and ran appropriate searches in relevant databases. Search strategies are reported in the appendices to each review paper. Two researchers 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. Data extraction forms were developed and piloted for each review. Data were extracted from included publications by one reviewer and checked by the second one. Risk of bias was assessed only for RCTs included in meta-analyses, owing to limited reporting and evidence for other studies. This was assessed by one reviewer and checked by the second one using the RoB 2 tool.[21] Full review processes are described in Papers 1, 2, 3 and 6.

Individual participant data

The project advisory group, along with the research team, considered which trials to request data from. IPD were then requested from larger, high-quality trials; specifically, trials of aflibercept or ranibizumab with at least 80 randomised participants. Data were sought from six trials: three trials were able to supply IPD for analysis (CLARITY,[22] PROTOCOL S[23] and PROTEUS[24]); one trial declined to provide IPD (PANORAMA[10]); two trials could not provide data as analyses were ongoing (PRIDE,[25] PROTOCOL W[26]).

Meta-analysis

For synthesis, all included studies were separated into those considering PDR and those of non-proliferative diabetic retinopathy (NPDR), as these two types of retinopathy were judged to be too different to be considered together.

Among PDR studies, meta-analyses were only feasible for the RCTs of anti-VEGF therapy, as results in non-randomised studies were too inconsistently reported. NMAs were performed to allow comparison of the different types of anti-VEGF. However, these were only feasible for the outcome of BCVA, using Bayesian methods.[27] As most trials had a duration of 1 year or less, NMAs were performed using the longest follow-up time in each trial of up to 1 year. 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.

For all other outcomes in RCTs of PDR, there were insufficient data to perform a full NMA. Hence, all other meta-analyses assumed that all types of anti-VEGF had the same effectiveness. For outcomes where NMA was not used, summary data (such as number of events or mean outcome and its standard deviation in each trial arm) were used to perform standard random-effects meta-analysis. These meta-analyses evaluated the effectiveness of using anti-VEGF in general, compared to PRP.

Only two trials in NPDR were identified, both comparing aflibercept to sham injection, so these were pooled using standard random-effects meta-analysis.

To investigate the impact of patient characteristics on the effectiveness of anti-VEGFs, analyses of the three trials that provided IPD were performed. Mixed-effect linear and logistic regression was used to investigate the interactions between anti-VEGF use and key participant characteristics, including age, sex, BCVA at the time of randomisation and presence of DMO or vitreous haemorrhage.

All statistical analyses were conducted in R version 4.3 (The R Foundation for Statistical Computing, Vienna, Austria). The R code for all analyses is available via GitHub (https://github.com/marksimmondsyork/avid).

Narrative synthesis

For the reviews of non-randomised studies, meta-analyses were not feasible. There were also a number of RCTs that could not be included in the main meta-analyses. There were various reasons for this, including: absence of a PRP arm, older trials where the laser therapy might be outdated, or publication not in English or only as a conference abstract. A narrative synthesis approach was used for both these reviews (see *Report Supplementary Material 1*). Studies were grouped according to duration, size and anti-VEGF used, and results tabulated and summarised.

A narrative approach was also adopted in the cost-effectiveness review (Paper 3), in which a descriptive summary of each identified study was generated and key features of each analysis were tabulated. Studies were grouped by population (NPDR and PDR) to aid interpretation.

Economic modelling

A de novo model was constructed to assess whether anti-VEGF drugs represent a cost-effective option for the treatment of PDR compared to PRP within the UK NHS context (Paper 4). The model was developed in collaboration with UK clinical and patient experts and captured the impact of treatment on BCVA across both eyes. The model was coded in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) using Visual Basic for Applications. The base-case analysis used a 50-year time horizon (i.e. lifetime), with costs and benefits discounted at 3.5% per annum. The analysis adopted a UK NHS and Personal Social Services perspective. A severity-based quality-adjusted life-year (QALY) weight multiplier would not be applicable in this indication under current NICE methods.

The model adopted a discrete-event simulation approach, enabling the representation of an individual's healthcare journey by simulating various health events, encounters with the healthcare system, and other processes over their lifetime. To capture these events, a system of 'flags' was employed, attaching markers denoting ongoing clinical and treatment history to a patient. Flags included the treatment they were receiving, the presence of DMO, previous vitreous haemorrhage and severe visual impairment/blindness. These flags were used to capture the effect of ongoing monitoring and treatment costs, as well as the probability and timing of subsequent events, for example DMO and death.

The primary source of clinical inputs used in the model was the AVID IPD meta-analysis which informed baseline demographic parameters (including the joint sampling of visual acuity in the best-seeing and worst-seeing eye), patterns of BCVA progression, and the timing of ocular events including DMO, vitreous haemorrhage and other treatment-related adverse events. The primary effect of the treatment was change in visual acuity over time. This was modelled through a linear mixed-effects regression model of BCVA based on the AVID IPD data set at 12 months, and then upon PROTOCOL S alone as the only data source reporting data between 12 and 60 months. Treatment effects on BCVA were propagated through the model via a published regression analysis in DMO patients, which defined current EuroQol-5 Dimensions as a function of visual acuity in both eyes (among other factors). The AVID IPD data set was also used to inform treatment administration frequency. Other parameter inputs including resource utilisation and unit costs were informed by appropriate published data sources.

Results of the model were presented in terms of cost per QALY using incremental cost-effectiveness ratios and net health benefit (NHB) assuming a willingness-to-pay (WTP) threshold of £20,000. The economic analysis also included a value of information on which the expected value of perfect information (EVPI) was estimated.

Results

Systematic review and meta-analysis of randomised controlled trials

Overall, 14 RCTs were included in the meta-analyses, with around 1800 participants.[10,22–26,28–35] Paper 1 includes a PRISMA flow diagram for the review process.[15] 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), which 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. They are discussed in supplementary Paper 5 (see *Report Supplementary Material 1*).

The 14 included 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, all of which used PRP as the control intervention. Two trials recruited patients with NPDR; both of which evaluated aflibercept compared to sham injection.[10,26] All but two trials had a follow-up period of 1 year or less.

Risk of bias

A full risk of bias assessment was performed for the 14 trials included in the meta-analyses. Four trials were classed at low risk of bias, three moderate and seven at high risk of bias. Risk of bias concerns were largely due to the lack of masking of participants and limited reporting in most trials. Larger trials of ranibizumab and aflibercept tended to be better reported and judged to be at low risk of bias. Other concerns included limited description of randomisation and allocation concealment processes, and missing patients and outcome data. The full bias assessment is presented in Paper 1.[15]

Proliferative diabetic retinopathy

In the 12 trials of PDR, NMA at up to 1 year of follow-up found that anti-VEGFs were better in maintaining vision than PRP, when measured as BCVA. Improvements in BCVA

when compared to PRP ranged from 1.7 ETDRS letters [95% credible interval (CrI) −2.6 to 6.7] for aflibercept to 6.9 ETDRS letters (95% CrI 1.5 to 12.2) for bevacizumab in combination with PRP. However, for aflibercept, no difference between aflibercept and PRP was within the CrI. Results were broadly similar across anti-VEGF agents, with no conclusive evidence that any particular anti-VEGF was superior to any other. Similarly, there was no evidence that combining anti-VEGF with PRP was superior to using anti-VEGF alone.

A NMA was fitted to allow the effectiveness of anti-VEGFs to vary with follow-up time in each trial and with BCVA at randomisation. This 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 in 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).

Individual participant data were available for three trials: PROTOCOL S (ranibizumab vs. PRP, 305 patients), CLARITY (aflibercept vs. PRP, 202 patients) and PROTEUS (ranibizumab + PRP vs. PRP, 87 patients). These 3 trials included 54% of the patients with PDR across the 12 trials. Analyses of this IPD were conducted to investigate the impact of protocol-specified patient characteristics on the effectiveness of anti-VEGF at preserving BCVA (see Paper 2[16]). These analyses found that the following patient characteristics modified the effect of anti-VEGF: sex, where men benefit more than women (by 3.5 ETRDS letters); vision at randomisation, where people with poorer vision before treatment have greater benefits from anti-VEGF (by 0.14 ETDRS letters per letter poorer at baseline); vitreous haemorrhage at baseline, where people with haemorrhage benefit more from anti-VEGF (by 6.4 ETDRS letters); glycated haemoglobin (HbA1c), where people with higher HbA1c benefit more from anti-VEGF (by 0.1 ETDRS letters per unit HbA1c). There was no clear evidence that presence of DMO at the time of treatment altered the effectiveness of anti-VEGF.

Analysis of the IPD also found that vision on PRP improves with increasing follow-up duration (by 0.64 ETDRS letters per year), whereas vision with anti-VEGF declines by comparison (by 1.86 ETDRS letters per year). This would suggest that any benefit in vision with anti-VEGF over PRP may be lost within 3 years.

Anti-VEGF reduced the incidence of DMO after 1 year by about half when compared to using PRP [relative risk (RR) 0.48, 95% confidence interval (CI) 0.28 to 0.83, four trials]. Using anti-VEGF also reduced the incidence of vitreous haemorrhage by around 28%, but this was not conclusive (RR 0.72, 95% CI 0.47 to 1.10, six trials). 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 (RR 0.63, 95% CI 0.16 to 2.42, four trials).

Adverse events were not widely reported, with little consistency across trials as to which adverse events were reported. Meta-analyses were performed for adverse event types reported in two or more trials. 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, and because of inconsistent reporting across trials.

In the three IPD trials, most patients received additional treatment after their initial therapy. In CLARITY and PROTEUS, most patients received at least one further round of the treatment to which they were randomised within 1 year of follow-up. 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 the 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.

Non-proliferative diabetic retinopathy

Only two trials, with a total of 630 participants, examined anti-VEGF in people with NPDR; both compared aflibercept to sham injection. Meta-analysis of their BCVA results found only a very small benefit of aflibercept over sham injection (mean difference 0.93 ETDRS, 95% CI 0.13 to 1.73). 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 (RR 0.283, 95% CI 0.18 to 0.44). Both trials found some evidence that aflibercept may slow down the progression of retinopathy.

Review of non-randomised studies

The review identified 27 relevant non-randomised studies where anti-VEGF was used to treat diabetic retinopathy. Of these, 19 had both fewer than 100 patients and a follow-up of 1 year or less. Given their small size and short duration, these studies were judged as being unlikely to meaningfully add to the RCT evidence and were not

examined further. This left eight studies for full review. A summary of the included studies is given in supplementary Paper 6 (see *Report Supplementary Material 1*).

Five of the eight included studies had a follow-up period of 2 years or more; only one of which included over 100 patients. Two studies had a follow-up of < 2 years, and one was a cross-sectional study without follow-up. The diverse nature of the eight studies made it difficult to synthesise findings across the studies.

The studies generally found benefits of using anti-VEGF to treat diabetic retinopathy, with some noting comparability with RCTs such as PROTOCOL S. Most notably, two of the studies[36,37] found that an initial benefit of anti-VEGF in the first year of use was followed by a decline in benefit in the second year. This may have been due to discontinuation of anti-VEGF use. This supports the finding of declining benefit of anti-VEGF over time found in the PROTOCOL S trial.[23] Two studies presented limited data on quality-of-life outcomes. While treatment did improve quality of life, there was no evidence that anti-VEGF offered any benefit over PRP.

Systematic review of cost-effectiveness studies

The cost-effectiveness analysis review identified seven studies, five in PDR and two in NDPR. The five studies in a PDR population all evaluated one or more anti-VEGF compared with PRP. In the two studies within a NPDR population, one evaluated the use of aflibercept compared with best supportive care, while the second evaluated treatment with PRP at the onset of NPDR versus treatment with PRP at the onset of PDR. For full results, see Paper 3.[17]

All five PDR studies suggested that anti-VEGF treatments offer additional benefits in terms of preserved visual acuity but also incur substantial additional costs relative to PRP. Authors generally expressed scepticism about the value of anti-VEGF treatments, as they believed that the limited benefits of these treatments did not justify the, often substantial, additional costs. This was particularly evident in subgroups of patients without DMO at baseline, where the benefits of anti-VEGF treatment were smaller.

The main exception was an analysis presented by Sivaprasad *et al.*,[38] the only UK study identified in a PDR population. The authors were more positive about the potential value of anti-VEGF drugs in this population, though it is notable that the cost–utility analysis results showed aflibercept to be dominated (more costly and less effective) by PRP. Several studies[39,40] also considered the use of bevacizumab as a low-cost alternative to ranibizumab and aflibercept, which led to substantial cost reductions in incremental costs associated and more favourable cost-effectiveness estimates. The majority of studies identified in a PDR population considered a US perspective, and it is unclear how these results would translate to a UK setting. In patients with NPDR, the one study that compared anti-VEGFs with PRP used a cost–benefit rather cost–utility approach, meaning that the results could not be easily interpreted in the context of this review. The other study suggested that early use of PRP in patients with NPDR may help preserve vision and save money. This second study did not address the use of anti-VEGFs in these patients.

Economic model

A full presentation of the AVID economic model is given in Paper 4.[18]

In the base-case economic analysis, anti-VEGF drugs were found to be more costly but of similar effectiveness to PRP, generating 0.029 fewer QALYs at an additional cost of £3688. Anti-VEGFs generated a NHB of −0.214, assuming a £20,000 threshold. PRP was the more cost-effective treatment option in 99.4% of parameter permutations.

Anti-VEGFs generated similar total QALYs compared to PRP across a range of scenario analyses. Small 1-year BCVA improvements appeared to be short-lived on the basis of data from PROTOCOL S, which over 5 years suggested slow decline in ranibizumab, and stability in PRP. Extrapolating these trends over longer time periods – even just 1 additional year – consistently showed PRP to be increasingly effective versus anti-VEGFs.

Costs in the model were primarily driven by acquisition and administration costs associated with anti-VEGFs. This was true in both arms, as the primary driver of costs in the PRP arm was subsequent treatment of DMO with anti-VEGFs. Any confidential discounts on the acquisition cost of anti-VEGFs available to the NHS therefore also reduce the total costs associated with PRP and are unlikely to impact model results.

Scenario analysis results suggest that only under very select conditions may anti-VEGFs offer significant potential for cost-effective use in early treatment of PDR. Anti-VEGFs had the highest probability of cost-effectiveness (75.57%) when combining scenarios assuming BCVA outcomes at 1 year are maintained indefinitely, anti-VEGFs are administered by a nurse rather than consultant, and a discount of 80% on the acquisition costs of ranibizumab biosimilar (Ximluci) is applied. In this analysis, anti-VEGFs

generated a nominally positive NHB of 0.027, owing to lower treatment costs and a small QALY benefit. Despite the use of optimistic assumptions, incremental QALYs generated on anti-VEGFs remained close to zero.

Value of information (VoI) analysis suggested that, at a £20,000 WTP threshold, the expected value of resolving all decision uncertainty over 10 years is only £143,524 in the base-case analysis. This increased substantially to £93,531,171 under the most optimistic assumptions regarding the long-term effectiveness of anti-VEGFs, but decreased to an EVPI of £0 under more conservative assumptions.

Discussion

A summary of the project findings and main research recommendation is given in *Box 2*.

BOX 2 Key findings of the AVID project, with implications for practice and research recommendations

Key findings

1. Anti-VEGF is better than PRP in maintaining eyesight in people with PDR, but the benefit is small and may not be long-lasting.
2. Anti-VEGF had no meaningful impact on vision in people with NPDR.
3. Aflibercept, ranibizumab and bevacizumab are broadly similar in efficacy.
4. Combining anti-VEGF injection with PRP therapy is no more effective in maintaining eyesight than anti-VEGF alone.
5. Anti-VEGF may prevent, or delay, progression to macular oedema and vitreous haemorrhage.
6. People with poorer vision, or with vitreous haemorrhage, at time of treatment may benefit more from anti-VEGF therapy.
7. Anti-VEGF is very unlikely to represent a cost-effective treatment option for the early treatment of PDR compared with PRP.

Implications for decision-making

1. Anti-VEGF should probably not be used in people with NPDR.
2. PRP should generally be preferred over anti-VEGF in people with newly diagnosed PDR on cost grounds.
3. Anti-VEGF may be useful for people for whom PRP is initially unsuitable, such as people with vitreous haemorrhage or before cataract surgery.

Research recommendations

1. Future RCTs comparing anti-VEGF to PRP in people with PDR should be in targeted populations, particularly:
   - people of South Asian ethnicity
   - people with poorer eyesight at presentation
   - people at high risk of developing DMO.
2. Future trials should include outcomes on how vision impacts quality of life in ways that are meaningful to patients, beyond measuring only BCVA.
3. Long-term follow-up of 5 years or more is needed in both new and existing trials.
4. Trials of anti-VEGF to treat severe NPDR are needed.

Clinical value of anti-vascular endothelial growth factor

The systematic review and NMA of PDR trials found that all anti-VEGF therapies are better in maintaining vision than PRP therapy at up to 1 year of follow-up. However, this benefit appears to be small. On average, across the three types of anti-VEGF, it was around 4.5 ETDRS letters (95% CrI −0.7 to 8.2). This is within the region of variation that might be expected between visual acuity measurements without any intervention.[41] Evidence from the PROTOCOL S trial suggests that even this benefit also may be lost within 5 years.[23]

When considering changes in vision, there was no clear evidence to suggest that the three anti-VEGFs (aflibercept, ranibizumab and bevacizumab) differ in effectiveness, and 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 in improving vision than anti-VEGF alone.

Anti-VEGF injection is therefore only marginally better than PRP in maintaining vision, and the benefit is not clinically meaningful and may disappear entirely within 3–5 years. This suggests that people with PDR are unlikely to notice any meaningful improvement in vision, and hence in quality of life, if treated with anti-VEGF instead of PRP. By contrast, there is good evidence that anti-VEGF may prevent, or delay, progression to macular oedema and vitreous haemorrhage. There is also some, but more limited, evidence that anti-VEGF slows down the progression of diabetic retinopathy generally.

Analysis of the IPD found some evidence that the effectiveness of anti-VEGF may vary across patients. People with poorer vision, or with vitreous haemorrhage, at the time of treatment may benefit more from anti-VEGF therapy; however, given the limited IPD collected for this review, this finding remains speculative. There is possibility that men might benefit more than women. People with PDR and concomitant DMO appeared to have the same benefit to vision when treated with anti-VEGF as people without DMO; however, there were few patients with concomitant DMO, so this finding is uncertain.

Evidence on the value of anti-VEGF in treating NPDR was limited to two trials. Those trials found that anti-VEGF had no meaningful impact on vision, when compared to sham treatment, but it might slow down the rate of progression of retinopathy and reduce the incidence of DMO.

Economic impact of anti-vascular endothelial growth factor

Our findings suggest that anti-VEGFs are very unlikely to represent a cost-effective treatment option for the early treatment of PDR compared with PRP. In our base-case analysis, anti-VEGFs were associated with higher costs and similar health outcomes over a lifetime time horizon. Scenario analyses confirm the robustness of the primary model results and indicated that BCVA changes on each treatment are unlikely to be clinically valuable at the magnitude observed in current trial evidence.

Our analysis indicates that structural barriers constrain the potential for anti-VEGFs or new technologies to demonstrate cost-effectiveness in early PDR when PRP is readily available. Firstly, costs in the PRP arm of the model were largely driven by subsequent anti-VEGF use for DMO treatment, making it improbable for drug discounts or off-label use of bevacizumab to significantly enhance the cost-effectiveness of anti-VEGFs as a primary therapy. Secondly, in its early stages, PDR is rarely associated with significant vision loss, which limits the capacity to restore and maintain vision in the short term. Consequently, new technologies are unlikely to yield clinically substantial short-term improvements in BCVA, leading to insufficient QALY gains to justify additional acquisition costs. The potential for cost-effective use of alternatives to PRP instead largely hinges on their ability to prevent complications such as DMO which may cause significant BCVA decline and incur extra costs. Despite demonstrating reduced rates of DMO, anti-VEGFs did not avoid sufficient cases to offset the substantial additional drug acquisition costs.

Despite these structural constraints, the VoI analysis indicates that there may remain some potential economic value from resolving remaining uncertainty around the treatment of early PDR if long-term results from PROTOCOL S are disregarded. This is driven in part by a large incident population, but also uncertainty in several components of the modelled treatment effect, namely medium-term BCVA progression and avoidance of complications. Evidence informing these parameters is more limited than for short-term BCVA outcomes – and is essentially limited to PROTOCOL S. Therefore, despite the existence of a number of high-quality trials of anti-VEGFs in PDR, several key drivers of model outcomes remain subject to uncertainty. The cost-effectiveness results presented here are heavily reliant upon the external validity of the PROTOCOL S study, such that it remains possible that anti-VEGFs are more cost-effective than PRP.

Strengths and limitations

This is the latest, and most comprehensive, systematic review examining the use of anti-VEGF to treat diabetic retinopathy, and the first to include both proliferative and non-proliferative retinopathy. It is also the first review to make full use of NMA to compare different types of anti-VEGF, and to use NMA to investigate variation over time and variation by vision at randomisation.

A key strength of this review was the inclusion of IPD. Although only 3 of the 6 trials for which it was requested could provide IPD, this still represented around 33% of all the relevant RCT data (across all 14 included trials), and 72% of all trial data where aflibercept or ranibizumab was used to treat PDR. The IPD allowed for a deeper analysis of the effectiveness of anti-VEGF, particularly around how patient characteristics alter effectiveness and change in effectiveness over time.

The project team collaborated closely with the NICE guidelines team who were developing guidance on the management of diabetic retinopathy. This ensured that the project findings will be available to stakeholders and inform clinical practice immediately.

It was unfortunate that IPD was available for only three trials, and that IPD could not be obtained for the two NPDR trials. This limited our ability to investigate how the effectiveness of anti-VEGF might vary by patient characteristics. In particular, it was not possible to investigate whether findings were consistent between proliferative and non-proliferative retinopathy. IPD for PROTCOL W will be available in 2024, but whether there will be future access to IPD from PANORAMA is unknown. Ideally, IPD from these two trials should be meta-analysed along similar lines to the IPD analyses performed in this project, and their results compared.

As IPD was only available from three trials, the findings of analyses based on IPD are inconclusive. Although analyses found some evidence that the effectiveness of anti-VEGF may vary with vision at the time of treatment, this would require further research to confirm our findings. Analysis of the IPD also found that patients frequently receive additional treatment with either anti-VEGF or PRP, and the impact this has on relative effectiveness of the treatments is uncertain.

Other limitations were mostly due to the overall quality and extent of the evidence base. Most trials were of short duration, of small size, and at high risk of bias. This meant that there were only six trials judged to be of sufficient

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quality and size to merit requesting their original data. This was particularly an issue for trials of bevacizumab, raising doubts about the validity of comparing bevacizumab to the larger, higher-quality trials of aflibercept and ranibizumab.

All but one trial had a follow-up duration of a year or less. This makes it difficult to assess the long-term implications of using anti-VEGF, particularly as the only studies with longer duration found evidence of a declining benefit of anti-VEGF over time. However, the PROTOCOL S trial had substantial loss to follow-up over the 5 years of follow-up, and included 20% of patients with DMO at baseline.

We identified very few non-randomised studies of anti-VEGF use, with none reporting adverse outcomes and only two with follow-up of over 1 year. This increases uncertainty as to the long-term effects of anti-VEGF use.

The economic model represents the first simulation model built in this indication. The model used IPD to explore the complex time-varying two-eye relationships between the treatment effect and patient characteristics. A key strength of the approach presented here is the capacity to explicitly capture the impact important exacerbations of DR such as DMO and vitreous haemorrhage. An important limitation of the economic analysis is its reliance upon a single trial (PROTOCOL S) to make predictions about long-term visual acuity trends.

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 all aspects of the project and its findings, and writing of all papers arising from the project, including this synopsis. Further patient and stakeholder involvement was engaged through the NICE committee currently developing guidance on diabetic retinopathy management.

Patient involvement directed the project to focus key issues that matter to patients and improve their quality of life, particularly in ensuring that how improvements in vision and other outcomes actually can improve life was investigated, for example, whether patients are more able to continue working, or driving, and ability to care for children, grandchildren or other family members.

Patient and clinician perspectives informed both the structural design and validation of the economic model. This included capturing the most important health and management consequences of adverse events, and the most relevant sources of utility data to model the impact of the condition upon patients' quality of life.

On considering all the evidence found in the AVID project, patient representatives noted several key areas of continued concern. Most critical was that most trials of anti-VEGF used BCVA as their primary outcome, without any consideration of how that impacted the quality of life, ability to work, drive or care for family, as noted above. Data on those patient-focused outcomes were only available, in a limited way, in the trials that supplied IPD. Those data were therefore too limited to properly evaluate the impact anti-VEGF treatment might have on the quality of life. The trial evidence also demonstrated that patients treated with anti-VEGF often require a large number of repeated anti-VEGF eye injections over time. By comparison, treatment with PRP was usually complete in one or two treatment rounds. Hence, anti-VEGF treatment places a heavier burden on patient time, given the larger number of regular clinic visits that are required.

The lack of long-term evidence also raised concerns because there is substantial uncertainty about how PDR will be managed and treated in the long term. For example, it is unclear whether anti-VEGF would be required over many years and exactly what symptoms would be required to trigger further rounds of treatment. There is a risk of non-compliance with extended rounds of therapy, which may mean that progression of retinopathy goes undetected.

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 absent in trial publications and economic evaluations and was only available in limited form in the IPD.

Diabetes is more common in people of South Asian ethnicity or heritage and in more socioeconomically deprived groups. No trial publications reported outcomes specifically by ethnicity or socioeconomic status, and data on ethnicity were only available in one of the IPD trials. Trials of bevacizumab, mostly conducted in Middle Eastern and South Asian countries, had generally greater benefits of anti-VEGF than European or American trials. This might suggest that anti-VEGF is more beneficial in those countries or populations, but this benefit may be confounded with other factors, including short trial duration and higher risk of bias. Therefore, there is no current clear evidence as to whether ethnicity or socioeconomic status alters the relative effectiveness of anti-VEGF versus PRP.

We found that anti-VEGF may be more beneficial in people with poorer eyesight or vitreous haemorrhage at

presentation, which may be more common in people with limited access to health care, such as people not attending for regular eye tests. This may lead to equality issues, because differing disease severity might suggest different types of treatment.

The evidence suggested that men may benefit more from anti-VEGF therapy than women. This may be a consequence of men not being diagnosed until their vision has worsened, but this is uncertain. This suggests that gender equality is an important issue for the management of diabetic retinopathy that requires further consideration and investigation.

The IPD showed that patients receiving anti-VEGF typically receive multiple rounds of treatment, whereas PRP typically only requires one or two rounds. This may lead to problems accessing anti-VEGF therapy, particularly where people need to travel for treatment.

Impact

Throughout the AVID project, the project team have collaborated with NICE in their creation of new guidance on the treatment and management of diabetic retinopathy.[14] This included sharing the results of our systematic review and meta-analyses, as well as advising on economic modelling. This project therefore will have a direct impact on the treatment of diabetic retinopathy in England and Wales. We will continue to work with NICE to disseminative the findings of this project, to support final guidance development, and any future changes to the guidance.

The NICE guidance is expected to recommend that anti-VEGF treatment should not be used as the initial treatment for diabetic retinopathy (PDR or NPDR). PRP should remain the primary treatment for PDR, and anti-VEGF should only generally be used to treat DMO. Anti-VEGF might be used in people where PRP is initially unsuitable, such as people with vitreous haemorrhage or before cataract surgery. These expected recommendations concur with the findings of the AVID project, in that anti-VEGF does little to improve vision when compared to PRP, that the effect may reduce over time, and therefore anti-VEGF is not cost-effective.

Implications for decision-makers

The project found that anti-VEGF does not improve vision in people with NPDR and offers at best a modest improvement in vision when compared to PRP in people with PDR. Anti-VEGF does probably reduce the risk of macular oedema and vitreous haemorrhage and may slow down the progression of retinopathy. However, our analyses found that anti-VEGF is very unlikely to represent a cost-effective treatment option compared to PRP, even if these drugs can be acquired very cheaply.

We therefore conclude that:

- Anti-VEGF should probably not be used in people with NPDR.
- PRP should generally be preferred over anti-VEGF in people with newly diagnosed PDR on cost grounds.
- Anti-VEGF may be useful for people for whom PRP is initially unsuitable, such as people with vitreous haemorrhage or before cataract surgery. Patients could then proceed to PRP, if required, once it becomes feasible.

We note that these recommendations are in line with the draft NICE guidance on treatment of retinopathy.[14]

Research recommendations

The AVID project has found that anti-VEGF therapy has limited benefits and is not cost-effective as a treatment for diabetic retinopathy. We suggest that further randomised trials are unlikely to change the broad conclusions. Future RCTs comparing anti-VEGF to PRP in people with PDR should be in targeted populations, rather than in general populations. In particular, more evidence is needed in people of South Asian ethnicity or heritage, and in more socioeconomically deprived groups. Trials should focus on outcomes beyond measuring only impact on vision using BCVA. This could include more assessment of visual field testing and capillary non-perfusion, which was not widely reported in the existing trials.

The project found some evidence that anti-VEGF may be more effective in people with poorer eyesight or poorer health generally. Therefore, future RCTs should be aimed at comparing anti-VEGF to PRP in such people (e.g. people with initial BCVA below 70 ETDRS letters). Such trials would be useful to confirm the finding from the existing IPD, and to investigate any possible causes of this association, such as presence of, or high risk of, DMO at the time of treatment. Existing trials did not distinguish between different extents and severities of PDR. As our analyses suggest that anti-VEGF may be more beneficial in patients with more extensive PDR, future trials should

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evaluate the effect of anti-VEGF at different levels of PDR severity.

As the project found that anti-VEGF was particularly effective in reducing the 1-year incidence of macular oedema, there may be value in conducting RCTs or observational trials in people at high risk of oedema to test whether anti-VEGF is particularly beneficial to those people. We note that this may require developing a robust means of assessing oedema risk.

Although there was no evidence that anti-VEGF use is beneficial in patients with NPDR, data were limited in this area, and the possible value of anti-VEGF use in severe NPDR should be investigated.

The AVID project found that the key area of uncertainty is in the long-term impact of using anti-VEGF. This is because most trials were of 1-year duration or less, and there is a lack of long-term evidence. While long-term RCTs would be the best option to address this issue, these may be difficult to maintain for long-term follow-up. We suggest that long-term observational studies, of 2-year duration or more, of people who have received anti-VEGF or PRP, are therefore also needed. These studies should test vision repeatedly over time to investigate whether the change in effectiveness over time found by the PROTOCOL S trial is matched in other settings. These studies should also record additional use of anti-VEGF or PRP and the reasons for additional use, such as onset of macular oedema. While these studies could be newly established, continuing follow-up of existing RCTs may be the best way to obtain this data.

Future studies should also assess how treatment and change in vision impact quality of life in ways that are meaningful to patients, such as recording ability to drive, work, read, and care for children and grandchildren.

Conclusions

The AVID project found that anti-VEGF injection is only marginally better than PRP in maintaining vision in people with PDR, and the benefit is not clinically meaningful. In people with non-proliferative retinopathy, anti-VEGF did not improve vision. Aflibercept, ranibizumab and bevacizumab appear to be similar in effectiveness, with no evidence that combining anti-VEGF with PRP improves effectiveness. However, anti-VEGF may prevent, or delay, the progression of retinopathy, and progression to macular oedema or vitreous haemorrhage. Consequently, our economic analysis found that anti-VEGFs are unlikely to be a cost-effective treatment option for treating early PDR in the UK when compared with PRP. Anti-VEGF use appears to have higher costs than PRP but similar health outcomes over a lifetime.

The project findings have been shared with the NICE in the UK in order to support development of new guidance on the management of diabetic retinopathy. The guidance is currently not to recommend anti-VEGF as a treatment for non-proliferative or proliferative retinopathy. It may, however, be used for patients for whom PRP is unsuitable. These recommendations concur with the findings of the AVID project.

One remaining area of uncertainty is around how anti-VEGF effectiveness varies with vision and health at the time of treatment, because this project found some evidence that anti-VEGFs may be more effective in maintaining visual acuity in people with poorer vision or health. Future trials or observational studies that focus on using anti-VEGF in patients with more severe retinopathy or poorer vision would be useful to determine exactly which patients might benefit most from receiving anti-VEGF therapy, and whether there are patients for whom anti-VEGF is a cost-effective option.

The main area of uncertainty is the long-term effectiveness of anti-VEGF, because of the short duration of most trials. Patients will continue to receive PRP and anti-VEGF treatment over time, particularly if they develop macular oedema, and the impact of such continued treatment is unclear. Further trials or observational studies focusing on long-term visual acuity trends on anti-VEGFs and PRP, and rates of vision-threatening complications such as macular oedema are needed. Such studies should examine repeated long-term use of PRP and anti-VEGF, and the adherence to treatments over time. A better understanding of the long-term implications of anti-VEGF use is needed to determine if it can be a useful and cost-effective treatment option for diabetic retinopathy.

Additional information

CRediT contribution statement

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Data-sharing statement

Data and code to reproduce the meta-analyses using published data are available on GitHub (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 and in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for the University of York Data Protection Officer here (www.york.ac.uk/records-management/dp/).

Disclosure of interests

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

Study registration

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About this synopsis

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List of abbreviations

anti-VEGF	anti-vascular endothelial growth factor
AVID	Anti-VEGF In Diabetes
BCVA	best corrected visual acuity
CI	confidence interval
CrI	credible interval
DMO	diabetic macular oedema
ETDRS	Early Treatment Diabetic Retinopathy Study
EVPI	expected value of perfect information
HbA1c	glycated haemoglobin
IPD	individual participant data
NHB	net health benefit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NPDR	non-proliferative diabetic retinopathy
PDR	proliferative diabetic retinopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	panretinal photocoagulation
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
VoI	value of information
WTP	willingness to pay

List of supplementary material

Report Supplementary Material 1
Supplementary material

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/KRWP1264).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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