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

|  |  |
| --- | --- |
| Authors | Robert Hodgson1, Matthew Walton1, Helen Fulbright1, Laura Bojke2, Ruth Walker1, Alexis Llewellyn1, Sofia Dias1, Lesley A Stewart1, David Steel3, John G Lawrenson4, Tunde Peto5, Mark Simmonds1 |
| Affiliations: | 1 Centre for Reviews and Dissemination, University of York, United Kingdom; 2 Centre for Health Economics, University of York, United Kingdom; 3 International Centre for Life, Newcastle University, United Kingdom; 4 Department of Optometry and Visual Sciences City, University of London, United Kingdom; 5 Centre for Public Health, Queen’s University Belfast, United Kingdom |

Corresponding Author: Robert Hodgson [rob.hodgson@york.ac.uk](mailto:rob.hodgson@york.ac.uk); tel: 01904 321069

**Word count: TBD**

**Declarations**

**Funding**

This paper presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. This paper is based on work completed as part of the NIHR commissioned HTA: Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy: a systematic review and economic analysis, project number 132948.

**Conflicts of interest/Competing interests**

All authors declare no conflict of interest.

**Availability of data and material**

All data used in this analysis are provided in the main body of text and the supplementary material.

**Contributors and guarantor of information**

RH and MW were involved in all aspects of the systematic review process including study selection, data extraction, validity assessment, synthesis of the included studies and drafting the protocol and manuscript. MS was the principal investigator who led the application for funding and took overall managerial responsibility for the project. All authors discussed the direction of the research and commented on the early drafts and the final version of the manuscript.

# Abstract

**Background**

Non-proliferative and proliferative diabetic retinopathy (DR) are common complications of diabetes and a major cause of sight loss. Anti-vascular endothelial growth factor (anti-VEGF) drugs represent a treatment option for people with DR and are routinely used to treat various other eye conditions. Anti-VEGF drugs are, however, expensive relative to current care options and it is unclear whether this additional cost would be justified in DR, where immediate risks of sight loss are low compared to those for patients with more aggressive ophthalmological conditions.

**Objective**

To systematically review the existing evidence supporting the cost-effectiveness of alternative treatments for DR considering a UK decision-making perspective.

**Methods**

A systematic review of all comparative cost-effectiveness studies was conducted evaluating any treatment for DR. Included studies were synthesised narratively and evaluated with reference to UK decision-making. Studies were grouped by population, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

**Results**

The review identified five studies in the PDR population, all of which examined the cost-effectiveness of anti-VEGF treatments compared to pan-retinal photocoagulation (PRP). Results of these studies suggest that anti-VEGF treatments offer some additional benefits in terms of preserved visual acuity, but also incur substantial additional costs relative to PRP. Most authors expressed reservations about the additional costs outweighing the limited benefits, especially in certain patient subgroups without pre-existing oedema. The majority of the identified evidence considered a US perspective, it is unclear how these results would translate to a UK setting.

Two studies were identified in the NDPR population. There was limited evidence to support the early use of anti-VEGF treatment. One UK study, however, suggested that early treatment of NPDR with PRP is cost-effective compared to delayed PRP.

**Conclusions**

Overall, there is a dearth of cost-effectiveness evidence considering the UK context. The identified studies raised doubts about the cost-effectiveness of anti-VEGF treatments for PDR. No conclusions can be made regarding the cost-effectiveness of anti-VEGF for NPDR. Future research should focus on developing rigorous model-based cost-effectiveness analyses integrating all available evidence.

# Plain English Summary

Anti-vascular endothelial growth factor (VEGF) medications have been proposed as a treatment for diabetic retinopathy (DR) a common complication of diabetes. Currently in the UK use of anti-VEGF medications are not used to treat DR, instead, pan-retinal photocoagulation (PRP), commonly known as laser therapy is used as standard care. While evidence suggests that anti-VEGFs are an effective treatment for the management of DR, it is unclear if they would represent good value for money.

This study looks to review the existing evidence on the cost-effectiveness (value for money) of treatments for DR. This has been done by systematically searching for relevant studies and collating the findings. The results of our review consider two types of DR: non-proliferative and proliferative.

In patients with proliferative DR, we found five studies that compared anti-VEGFs with laser treatment. These studies suggest that anti-VEGF medications may help preserve vision but are also more costly than laser therapy. The study authors didn’t think that anti-VEGFs were worth the additional cost. A limitation of the majority of the studies identified in the review is that they were conducted in the United States; it is difficult to extrapolate evidence on value for money from one country to another.

In patients with non-proliferative DR, we identified two studies. One study compared anti-VEGFs with laser but didn’t report their findings in a way that could be interpreted. The other, a UK-based study, suggested that early use of laser therapy may help preserve vision and save money. This second study, however, did not look at the possibility of using anti-VEGFs.

Overall, we found few studies that sought to evaluate the cost-effectiveness of treatments for DR. Further studies are necessary to understand whether anti-VEGF medications are likely to represent value for money in the UK.

# Introduction

Diabetic retinopathy (DR) is a common complication of diabetes, which occurs when high levels of blood sugar damage the blood vessels in the retina which over time, can lead to vision loss, particularly when left untreated. Globally, 22% of people (103 million) living with diabetes have diabetic retinopathy with 6% (29 million) having vision-threatening diabetic retinopathy It represents a leading cause of visual impairment in working-age adults. In the UK the cost of treating sight-threatening DR in 2010/2011 was estimated to be £57 million and is predicted to reach £97 million by 2035/2036.1

Treatment of DR depends on the stage of the disease. In the early non-proliferative stages of DR, treatment aims to control metabolic dysfunction and includes careful monitoring of blood sugar levels, blood pressure, and cholesterol. In the more advanced proliferative form of DR, proliferative diabetic retinopathy (PDR), the current standard of care is laser photocoagulation. Treatment with laser photocoagulation (pan-retinal photocoagulation (PRP)) aims to prevent disease progression and effect regression of existing proliferative disease, to preserve visual function.2

Anti-vascular endothelial growth factor (VEGF) medications have been proposed as an alternative treatment for DR, principally in PDR, and are already used to treat a variety of ophthalmological conditions including diabetic macular oedema (DMO) and neovascular age-related macular degeneration (nAMD), where they have been shown to be cost-effective.3-5 Treatment with anti-VEGF has been shown to be similarly effective to PRP.6 However, using anti-VEGF drugs to treat DR would potentially also significantly increase treatment expenses, and it is unclear whether they would be a cost-effective treatment for DR, where immediate risks of sight loss are low compared to those for patients with DMO and nAMD.

Given uncertainties about the relative clinical benefits of anti-VEGF treatments for DR and the potential for additional costs, the UK National Institute for Health and Care Research (NIHR) funded the Anti-VEGF in Diabetic Retinopathy (AVID) project to evaluate whether anti-VEGF drugs are clinically- and cost-effective for the treatment of DR and its complications, either as a replacement for, or in addition to, laser photocoagulation, within the UK National Health Service (NHS). The project included several components: i) a systematic review and individual participant data (IPD) meta-analysis of existing evidence on the clinical effectiveness of anti-VEGF drugs for the management of DR, ii) a systematic review of existing evidence on the cost-effectiveness of anti-VEGF drugs for the management of DR, and iii) the development of a *de novo* model evaluating the cost-effectiveness of anti-VEGF drugs for the management of DR in a UK setting. This manuscript focuses on the second of these components and aims to systematically review and synthesise cost-effectiveness evidence evaluating treatments for both NPDR and PDR. The review was conducted to provide a summary of the existing cost-effectiveness evidence and to ascertain its suitability to inform decision making in the UK. The findings from the review were also used to help inform the development of a new decision-analytic model conducted in part three of the AVID project.

# Methods

The AVID study followed a protocol registered on PROSPERO (CRD42021272642). Findings are reported in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews Meta-Analysis) statement.7, 8

## **Inclusion criteria**

The review considered a broad range of economic studies including trial-based economic evaluations, modelling studies and analyses of administrative databases. Studies were eligible for inclusion if they:

* Included patients with DR (proliferative and non-proliferative). Studies modelling patients with a principal indication of DMO were excluded, as were patients with vitreous haemorrhage.
* Patients received any treatment including, but not limited to, the following anti-VEGF therapies: aflibercept, bevacizumab, ranibizumab, or their biosimilars. Either alone or in combination with PRP.
* Reported full economic evaluations comparing two or more alternative interventions in terms of both costs and consequences, i.e., cost-minimisation, cost-effectiveness, cost-utility or cost-benefit analyses.

No restriction was placed on outcomes reported. Outcomes of relevant study designs were, however, expected to include one of the following: Functional impact on vision, progression of retinopathy (non-proliferative to proliferative), health-related quality of life (NEI-VFQ-25, EQ-5D, SF-36), quality-adjusted life years (QALYs), costs, resource use, incremental costs and QALYs, or incremental cost-effectiveness ratios (ICERs). Non-comparative costing studies were excluded. There was no restriction by language or date of publication.

## **Study Identification and Selection Process**

Bibliographic searches were carried out to identify studies reporting on the cost-effectiveness of treatments for DR. An Information Specialist (HF) designed a preliminary search strategy in Ovid MEDLINE in consultation with the research team. The final MEDLINE strategy was then adapted for use in all resources searched. The initial searches were performed on 8th November 2021 and were updated on 28th April 2023. The following databases were searched: Ovid MEDLINE(R) ALL, Embase (Ovid), Econlit (Ovid), Cochrane Database of Systematic Reviews (Wiley), Science Citation Index Expanded (Web of Science), Social Sciences Citation Index (Web of Science), International HTA database, NHS EED (CRD), and HTA (CRD). Search results were imported into EndNote 20 (Clarivate Analytics, US) and deduplicated. All search strategies are presented in full in Appendix 1.

The protocol for the selection of relevant studies defined two selection stages: i) assessment and screening for possible inclusion of titles and abstracts identified by the search strategy, and ii) acquisition and screening for inclusion of the full texts of potentially relevant studies. Two researchers (RH and MW) independently screened the titles and abstracts of all reports identified by the bibliographic searches. Full texts of potentially relevant studies and screened in duplicate against the eligibility criteria. Discrepancies were resolved by discussion.

## **Data Extraction and Quality Assessment Strategy**

Details of eligible studies including setting, population, technologies assessed, study type and where applicable modelling approach were extracted and entered into a data extraction template developed in Microsoft ExcelTM. Data were extracted by one reviewer (RH) and then subsequently checked by a second reviewer (MW). Discrepancies between reviewers were resolved through discussion. Quality assessment of the included studies was also conducted using the CHEERs checklist developed by Drummond *et al*.9 In line with the data extraction process, this was completed by one review and checked by a second.

## **Data analysis**

No formal synthesis of identified studies was attempted. Instead, studies were synthesised narratively. A descriptive summary of each identified study was generated, while key features were tabulated. Studies were grouped by population (NPDR and PDR).

# Results

The systematic searches yielded a total of 8357 articles ([Fig 1](about:blank#pntd-0010822-g001)). After the removal of 2274 duplicates, the remaining 6083 titles and abstracts, were screened against the inclusion criteria. A total of 33 studies were considered potentially relevant and were taken forward for full-text examination. Overall, we identified seven studies that reported on economic evaluations for treatments for DR (Table 1). Only two of the identified studies considered a UK setting,10, 11 with all remaining studies considering a US setting. There were five studies that evaluated treatments for PDR,11-15 all of which evaluated one or more anti-VEGF compared with PRP. The study by Lin (2018)15 and colleagues also additionally considered pars plana vitrectomy (PPV) as a comparator. The two remaining studies evaluated whether early treatment of patients with non-proliferative diabetic retinopathy (NPDR) was cost-effective. The first, Patel (2022),16 considered the use of aflibercept compared with best supportive care. The second, Royle (2015),10 evaluated treatment with PRP at the onset of NPDR versus treatment with PRP at the onset of PDR.

Results of the quality assessment identified several limitations in the included studies, see Appendix 2 for details.

Two studies by Hutton et al. were largely methodologically sound, with key concerns relating to the perspective of the analysis (which was not stated) and the justification of discount rates which appear not have been applied. Related studies reported in Lin et al. (2016) and Lin et al. (2018) which both presented modelled based analysis were poorly reported. This meant that it was not possible to fully establish the model structure and assumptions made in the model. There were substantive issues with how cost-effectiveness was assessed which do not conform with standard practice of estimating incremental cost-effectiveness ratios. No methodological concerns were identified regards Sivaprasad et al (2018).

The key limitations of Patel et al (2022) related to the perspective and discount rate applied which were not stated. The studied use of a cost-consequence approach, the motivation for which was explained in the manuscript but not fully justified. And it was not clear how the outcomes selected were informative decision makers. Limitations with the Royale study centred on key assumptions made regarding the durability of the treatment effect, these were however, largely consequence of underlying limitations with the available data rather than the analysis conducted.

Figure 1: PRISMA Flow diagram showing study selection

Records Identified

(n=8357)

Records screened

(n=6082)

Full-texts articles assessed for eligibility (n=33)

Studies included in qualitative synthesis (n= 7 studies)

Duplicates removed

(n=2275)

Records excluded

(n=6050)

Full-text articles excluded based on:

* Study design (n=16)
* Population (n=9)
* Abstract only (n=1)

Identification

Screening

Eligibility

Included

Table Summary of study characteristics.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study (country)** | **Interventions under consideration** | **Population (base-case where clearly stated)** | **Type of economic evaluation** | **Perspective, discounting and time horizon** | **Results** |
| Hutton, 201712 (US) | 1. Intravitreal ranibizumab (0.5 mg)  2. PRP | PDR | Trial-based, cost-utility analysis | Perspective: Not stated  Discounting benefits: 0%  Discounting costs: 0%  Time horizon: 2 years | Patients with baseline DMO: $55,568/QALY. Patients without baseline DMO $662,978/quality-adjusted life-year. |
| Hutton, 201913 (US) | 1. Intravitreal ranibizumab (0.5 mg)  2. PRP | PDR | Trial-based, cost-utility analysis | Perspective: Not stated  Discounting benefits:3%  Discounting costs: 3%  Time horizon: 5 years | Base case (5-year) results: Patients with baseline DMO: $65,576/QALY. Patients without baseline DMO $582,268/quality-adjusted life-year. Scenario analysis (10-year) results: Patients with baseline DME: $63,3906/QALY. Patients without baseline DMO $742,202/quality-adjusted life-year. |
| Lin, 2016,14  (US) | 1. Intravitreal ranibizumab (0.5 mg)  2. PRP | PDR | Model-based, cost-utility analysis using Markov modelling approach. | Perspective: Not stated  Discounting benefits: Not state  Discounting costs: Not stated  Time horizon: 2 years (Lifetime explored in scenario analysis) | Results were presented as cost per QALY for each intervention, no incremental results were presented. Cost per QALY for PRP in the facility setting was $7,988, in the non-facility setting cost per QALY was $6,297. Cost per QALY for ranibizumab in the facility setting was $19,150, in the non-facility setting the cost per QALY was $16,238. |
| Lin, 2018,15  (US) | 1. Intravitreal ranibizumab (0.3 mg)  2. PRP  3. PPV | PDR | Model-based, cost-utility analysis using a Markov modelling approach. | Perspective: Not stated  Discounting benefits: 0%  Discounting costs: 3%  Time horizon: 2 years (Lifetime explored in scenario analysis) | Results were presented as cost per QALY for each intervention, no incremental results were presented. Cost per QALY for PRP in the facility setting was $163,988, in the non-facility setting cost per QALY was $102,559. Cost per QALY for ranibizumab n the facility setting was $436,992, in the non-facility setting the cost per QALY was $326,424. Cost per QALY for PPV in the facility setting was $181,144, in the non-facility setting cost per QALY was $107,965. |
| Sivaprasad 2018,11  (UK) | 1. Intravitreal Aflibercept  2. PRP | PDR | Trial-based, cost-effectiveness and cost-utility analysis | Perspective: Payer  Discounting benefits: Not applied  Discounting costs: Not applied  Time horizon: 1 year | Cost-effectiveness analysis: Incremental costs per BCVA letter were £1393 for aflibercept as compared with PRP laser treatment. Sensitivity analysis showed that at the threshold of WTP threshold of £1400 per BCVA letter there was a 57% probability of aflibercept being cost-effective. Cost-utility analysis results found aflibercept to be less effective and more costly compared with PRP. Results were presented as a negative ICER: –£252,827 per QALY. |
| Patel, 202216  (US) | 1. Intravitreal aflibercept (0.5 mg)  2. Standard of care | Moderate to severe NPDR | Trial-based, cost- effectiveness analysis | Perspective: Not stated  Discounting benefits: Not state  Discounting costs: Not stated  Time horizon: 2 years | Cost/ per point change in DRSS was $2700 (hospital-based) and $2400 (non-hospital-based). Using Protocol W data, cost per PDR case prevented was $83,700 (hospital-based) and $72400 (non-hospital-based). Using PANORAMA data, cost per PDR case prevented was $89,400 (hospital-based) and $75,000 (non-hospital-based). Using Protocol W data, cost to prevent one case of DMO was $154,000 (hospital-based) and $133,000 (non-hospital-based). Using PANORAMA data, cost to prevent one case of DM was $70,900 (hospital-based) and $59,500 (non-hospital-based). |
| Royle, 201510  (UK) | 1.PRP initiated at the onset of severe NPDR  2. Watchful waiting, PRP initiated at the onset of PDR | NPDR | Model-based, cost-utility analysis | Perspective: Payer  Discounting benefits: 3.5%  Discounting costs: 3.5%  Time horizon: 30 years | Results showed early intervention with PRP was less costly (-£1112) and more effective (01292 QALYs). Results from probabilistic sensitivity analysis suggested there was a 60% probability of cost-effectiveness assuming a £20,000 WTP threshold. |

Abbreviations: Best Corrected Visual Acuity (BCVA), Diabetic macular oedema (DMO), Diabetic Retinopathy Severity Scale (DRSS), Non proliferative diabetic retinopathy (NPDR), Pan retinal Photocoagulation (PRP), Pars plana vitrectomy (PPV), Proliferative diabetic retinopathy (PDR), Quality adjusted life year (QALY), Willingness to pay threshold (WTP).

## **Studies evaluating treatments for PDR**

Hutton (2017)12 and Hutton (2019)13 were primarily trial-based analyses of PROTOCOL S17, 18, which included a within study prospective cost-effectiveness analysis at 2- and 5-years follow-up. The analysis utilised outcome data on visual acuity, safety and resource use. Visual acuity scores from the best-seeing eye were mapped to health state utilities using the Brown et al.19 algorithm and were used to estimate total QALYs, while resource data from the trial was supplemented by unit cost data from the Medicare fee schedule and used to estimate total costs. Safety data was only used in scenario analysis to estimate costs associated with managing adverse events.

Across both studies, results were stratified based on baseline DMO, which was a key driver of both clinical benefits and cost-effectiveness. Results for both subgroups showed that while ranibizumab was associated with improved visual acuity outcomes at 2 and 5 years, incremental QALY benefits were small. Further, ranibizumab was associated with substantial incremental costs compared to PRP primarily as a consequence of the high drug acquisition costs. Estimated ICERs were therefore high across all analyses (Table 1). These, however, varied substantively across analyses and were considerably lower in the baseline DMO subgroup. This was primarily driven by larger incremental QALY benefits in the baseline DMO subgroup. Hutton (2019)13 also reported analysis using a 10-year time horizon which extrapolated the 5-year data from PROTOCOL S17, 18 assuming visual acuity is maintained at the level reported at the end of 5 year follow up. Results from this analysis were largely similar to those considering a 5-year time horizon.

Lin (2016) and Lin (2018)15 were both model-based analyses. Both studies used the same underlying model but addressed different populations. The modelled population in Lin (2016) 14 reflected the whole population recruited to PROTOCOL S17, 18,17, 18 which included patients both with and without DMO at baseline, while Lin (2018) addressed a subgroup of patients without DMO at baseline. Reporting on the model structure adopted was limited in both study reports, making it difficult to establish the approach taken. The authors described the model as a Markov-style decision tree, and it appears that health states were defined with respect to the treatment received but few other details were provided. The benefits of treatment were evaluated using the diabetic retinopathy severity scale (DRSS) as a surrogate for severe vision loss, assuming 9 lines would be saved on the EDTRS visual acuity chart. This was then converted to QALYs based on published algorithm20 suggesting a conversion factor of 0.03 QALYs per line of vision saved. In scenarios using a lifetime time horizon, it was assumed that any QALY benefits were retained throughout the time horizon. Costs were modelled using Medicare fee schedule data with resource use data informed by values reported in PROTOCOL S17, 18 and appear to have primarily focused on procedure and drug administration and acquisition costs. Poor reporting hampered a thorough quality assessment, in particular, it was difficult to establish the structural assumptions made in the model and consequently the key mechanisms of benefit.

Results from Lin (2016)14 and Lin (2018)15 were not expressed in comparative terms; instead, costs per QALY were estimated individually for each arm and compared. The lack of incremental analysis prevents meaningful interpretation of the results. The authors noted that PRP is less costly than ranibizumab per QALY gained, but also noted that cost-utility ratios for both comparators fall well below the accepted cost per QALY upper limit of $100,000 per QALY. There was no discussion as to why this threshold was adopted. In Lin (2018), which also evaluated PPV as an alternative, the authors concluded that PPV demonstrates similar cost-utility ratios to PRP and favourable cost-utility ratios compared with ranibizumab (Table 1).

Sivaprasad (2018)11 carried out a cost-effectiveness and cost-utility analysis. Both were trial-based analyses that were conducted alongside the CLARITY21 clinical trial which compared aflibercept (2mg) with PRP in patients with PDR. Analysis of CLARITY21 showed that aflibercept was associated with additional costs but also resulted in improved visual acuity. For the cost-effectiveness analysis, the incremental cost of an additional Best Corrected Visual Acuity (BCVA) letter was £1393. For the cost-utility analysis, QALY benefits were derived directly from EQ-5D-3L data collected in the CLARITY21 trial. This analysis found aflibercept to be less effective and more costly compared with PRP. On the basis of the cost-effectiveness analysis, the authors concluded that aflibercept was more costly and more effective. The authors did not consider the results of the cost-utility analysis robust and noted that the measures of quality of life were not sensitive enough to capture the clinical difference between treatments.

## **Studies evaluating treatments for NPDR**

Patel (2022) was a trial-based analysis that leveraged data from two randomised trials: PROTOCOL W and PANORAMA.22 Both studies evaluated aflibercept compared with sham injection in patients with moderate to severe NPDR without DMO, though each considered a different aflibercept posology. The outcomes of both studies indicated small benefits in terms of visual acuity. The authors therefore considered that cost-utility analysis would be futile and unhelpful. Instead, the analysis was structured as a cost-effectiveness analysis estimating the cost per case of PDR and DMO avoided. The analysis also considered the costs per case of a change in DRSS scores using data from PROTOCOL W only. Patel (2022)16 was a trial-based analysis that leveraged data from two randomised trials: PROTOCOL W23 and PANORAMA.22 Both studies evaluated aflibercept compared with sham injection in patients with moderate to severe NPDR without DME, though each considered a different aflibercept posology. The outcomes of both studies indicated small benefits in terms of visual acuity. The authors therefore considered that cost-utility analysis would be futile and unhelpful. Instead, the analysis was structured as a cost-effectiveness analysis estimating the cost per case of PDR and DMO avoided. The analysis also considered the costs per case of a change in DRSS scores using data from PROTOCOL W only.23

Outcome data (PDR, DMO and DRSS scores) were estimated using published data from PROTOCOL W and PANORAMA22 using values reported at two years. Resource use considered only injection frequency and was also informed by published trial data from PROTOCOL W and PANORAMA.22 This was combined with unit cost data from the Medicare fee schedule to estimate total costs. In the base-case analysis, only aflibercept was considered as an alternative to usual care, however, scenario analysis also considered the costs of bevacizumab assuming equal efficacy with aflibercept. Outcome data (PDR, DMO and DRSS scores) were estimated using published data from PROTOCOL W23 and PANORAMA22 using values reported at two years. Resource use considered only injection frequency and was also informed by published trial data from PROTOCOL W23 and PANORAMA.22 This was combined with unit cost data from the Medicare fee schedule to estimate total costs. In the base-case analysis, only aflibercept was considered as an alternative to usual care, however, scenario analysis also considered the costs of bevacizumab assuming equal efficacy with aflibercept.

Key results from Patel (2022)16 are summarised in Table 1. The authors concluded that treatment with Anti-VEGF was associated with substantial costs per case of PDR, DMO (avoided) and DRSS improvement.

Royle (2015)10 developed a Markov model to determine whether offering PRP treatment to patients with severe NPDR is cost-effective compared with delaying treatment until the onset of PDR. The model structure was based on 18 health states which were defined with respect to the severity of DR and whether patients had DMO. Each health state in the model was associated with one of four levels of visual acuity defined on the EDTRS visual acuity chart with more severe health states associated with lower visual acuity. The onset of DMO was also associated with an additional utility decrement. Delaying progression of the disease and onset of DMO, therefore, represented the main mechanism via which benefits were generated in the model.

Transition probabilities were estimated using data from a range of published sources. Primary sources included Klein *et al*. (1998), Klein *et al*. (2008), EDTRS report #9 and EDTRS report #12. Where data were unavailable, it was assumed that early PRP resulted in a 20% reduction in the risk of progression to a subsequent health state. Utility values were sourced from three studies: Brown *et al*. (1999), Fong *et al*. (2002) and Smith *et al*. (2008). Resource use information was based on RCOphth guidelines24 and expert clinical opinion. Costs modelled included: PRP procedure costs, clinic visits, vitrectomy surgery and annual blindness costs. Cost information was based on national reference costs and values published in the literature. Transition probabilities were estimated using data from a range of published sources. Primary sources included Klein *et al*. (1998),25 Klein *et al*. (2008),26 EDTRS report #927 and EDTRS report #12.28 Where data were unavailable it was assumed that early PRP resulted in a 20% reduction in the risk of progression to a subsequent health state. Utility values were sourced from three studies: Brown *et al*. (1999),29 Fong *et al*. (2002)30 and Smith *et al*. (2008).31 Resource use information was based on RCOphth guidelines and expert clinical opinion. Costs modelled included: PRP procedure costs, clinic visits, vitrectomy surgery and annual blindness costs. Cost information was based on national reference costs and values published in the literature.

Results from the Royle (2015)10 analysis showed early PRP treatment was more effective and less costly than treatment upon the onset of PDR (Table 1). The benefits of early treatment were driven by slowed disease progression and retention of visual acuity. Slowed disease progression also resulted in cost savings due to more severe health states being associated with increased management and subsequent treatment costs. Uncertainties around the cost-effectiveness of PRP at NPDR or early PDR stage, were explored in a range of scenario analyses and found to be robust with early PRP either dominating delayed PRP or generating low ICERs below accepted WTP norms.

# Discussion

Our systematic review aimed to identify existing studies assessing the cost-effectiveness of treatments for DR focusing on a UK decision making perspective. We identified several relevant analyses considering both proliferative and non-proliferative forms of DR.

## **Proliferative diabetic retinopathy**

The review identified five studies in the PDR population, all of which examined the cost-effectiveness of anti-VEGF treatments compared to PRP. While individual studies used different sources of data and made a variety of different assumptions, several common themes emerged.

All the studies concluded that anti-VEGF treatments incurred additional costs compared to PRP. These increased costs were primarily driven by drug acquisition costs. Several studies14, 15 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 with anti-VEGF treatment. The studies also found that the differences in visual acuity outcomes between anti-VEGF and PRP groups were small, resulting in modest quality-adjusted life year (QALY) benefits. This is consistent with the results of the systematic review and IPD meta-analysis we have conducted which showed consistent short-term small visual acuity gains in patients receiving anti-VEGFs.

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 to this narrative was Sivaprasad (2018),11 which was the only UK study identified in the PDR population. The authors were more positive about the value of anti-VEGF treatment in this population, though it is notable that the results of their cost-utility analysis showed aflibercept to be dominated (more costly and less effective) by PRP.

Overall, the reviewed studies raised doubts about the cost-effectiveness of anti-VEGF treatments for PDR, with most authors expressing reservations about the additional costs outweighing the limited benefits, especially in certain patient subgroups without pre-existing DMO. It is, however, important to interpret these conclusions with a degree of caution, particularly when considering the UK context. Most studies identified were conducted with a US payer perspective and there are likely to be important differences between settings that may impact estimates of cost-effectiveness. This limits the reliability and relevance of these studies to UK decision-making. This may be addressed by forthcoming NICE Guidelines on DR, which it is understood will include an economic model conducted from an NHS perspective. However, currently no existing cost-effectiveness analyses fully account for the therapeutic value of anti-VEGFs. Most evaluations considered relatively short time horizons based on the maximum follow-up of the trial data used to underpin the analysis. This represents a significant limitation in the context of evaluating cost-effectiveness in PDR. The therapeutic aims of treating DR reflect not only a desire to prevent retinopathy-related vision loss but also to prevent the escalation of disease to DMO as well as the avoidance of complications such as vitreous haemorrhage and tractional retinal detachment. The limited time horizons used in the identified studies mean that these downstream consequences, which may negatively impact visual acuity and management costs, cannot be adequately accounted for and therefore potentially do not fully reflect the costs and benefits of treatment. More sophisticated model-based approaches considering a lifetime time horizon may more fully address these limitations, allowing for better integration of other forms of evidence to inform long-term patient outcomes. Moreover, a model-based analysis may more appropriately integrate a synthesis of all RCT evidence, addressing a weakness of the current literature which is all based on individual RCTs, and therefore does not reflect the totality of the available clinical effectiveness evidence appropriately synthesised.

## **Non-Proliferative diabetic retinopathy**

Just two studies were identified in the NPDR population, each of which considered different interventions and comparators. Results from Patel (2022)16 suggested substantial incremental costs associated with anti-VEGF treatments compared with standard of care, but the nature of their analysis, which is based on a cost-effectiveness analysis, means it is not possible to qualify whether these incremental costs are justified. Patel and colleagues discussed extensively the need for metrics to evaluate value for money in these circumstances. However, at least in the UK, where there is an established value assessment framework, we would disagree with this approach and would suggest instead that future research focus on the development of rigorous cost-effectiveness analyses using model-based approaches that link intermediate outcomes to long-term QALY gains.

Results from Royle (2015)10 are more informative, as they utilised a model-based analysis considering both a lifetime time horizon and a UK payer perspective. Their results strongly support the early use of PRP in NPRP and were robust to a range of alternative scenarios and assumptions. However, there are some limitations with their analysis. First, the analysis is underpinned by non-randomised studies and makes extensive assumptions about the ability of PRP to preserve visual acuity in the NPDR population, which are not borne out by clinical evidence. Second, as acknowledged by the study authors, the deferred PRP arms in the studies may not reflect routine care, where delays in treatment may result in patients having vitreous bleeds or other complications. Finally, an important limitation in the context of the AVID NIHR HTA project, is that the Royle study did not evaluate anti-VEGF treatments for NDPR and therefore offers no insights into the cost-effectiveness of these treatments within the NPDR population.

# Conclusions

We carried out a systematic review of studies evaluating the cost-effectiveness of anti-VEGF or laser photocoagulation therapies for the treatment DR with a specific focus on UK-relevant studies. We identified several studies considering both PDR and NPDR. The majority of the identified evidence was, however, in patients with PDR. Results of these studies suggest that anti-VEGF treatments offer some additional benefits in terms of preserved visual acuity, but also incur substantial additional costs relative to PRP. It is unclear if these additional costs are justified. Study authors generally considered the magnitude of these costs unjustified in patients without DMO at baseline. 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, limiting the relevance of the identified evidence to UK decision-makers. In an NDPR population, there was limited evidence to support the early use of anti-VEGF treatment. One UK study, however, suggested that early treatment of NPDR with PRP is cost-effective compared to delayed PRP. Limitations in the data underpinning this analysis along with questions regarding specific modelling assumptions limit the strength of conclusions that can be drawn. Overall, there is a dearth of cost-effectiveness evidence considering the UK context.

# References

1. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of type 1 and type 2 diabetes in the uk, including direct health costs and indirect societal and productivity costs. *Diabet Med* 2012;**29**:855-62.

2. The Royal College of Ophthalmologists. *Diabetic retinopathy guidelines*. RCO; 2013. Available from: <https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf> [accessed 04/09/2020)

3. 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)

4. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013*. NICE; 2013. Available from: <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781> [accessed 11/09/2020)

5. 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)

6. Simmonds MC, Llewellyn A, Walker RAE, Fulbright HA, Walton MJ, Hodgson R, et al. Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy : a systematic review and meta -analysis. *NIHR Journals Library* 2023. Available from: <https://eprints.whiterose.ac.uk/201744/>

7. 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.

8. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: The PRISMA-ipd statement. *JAMA* 2015;**313**:1657-65.

9. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press; 2015.

10. 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.

11. Sivaprasad S, Hykin P, Prevost AT, Vasconcelos J, Riddell A, Ramu J, et al. Intravitreal aflibercept compared with panretinal photocoagulation for proliferative diabetic retinopathy: The clarity non-inferiority rct. *Efficacy and Mechanism Evaluation* 2018;**5**.

12. Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR, et al. Cost-effectiveness of intravitreous ranibizumab compared with panretinal photocoagulation for proliferative diabetic retinopathy: Secondary analysis from a diabetic retinopathy clinical research network randomized clinical trial. *JAMA Ophthalmol* 2017;**135**:576-84.

13. Hutton DW, Stein JD, Glassman AR, Bressler NM, Jampol LM, Sun JK, et al. Five-year cost-effectiveness of intravitreous ranibizumab therapy vs panretinal photocoagulation for treating proliferative diabetic retinopathy: A secondary analysis of a randomized clinical trial. *JAMA Ophthalmol* 2019;**137**:1-9.

14. Lin J, Chang JS, Smiddy WE. Cost evaluation of panretinal photocoagulation versus intravitreal ranibizumab for proliferative diabetic retinopathy. *Ophthalmology* 2016;**123**:1912-8.

15. Lin J, Chang JS, Yannuzzi NA, Smiddy WE. Cost evaluation of early vitrectomy versus panretinal photocoagulation and intravitreal ranibizumab for proliferative diabetic retinopathy. *Ophthalmology* 2018;**125**:1393-400.

16. Patel NA, Yannuzzi NA, Lin J, Smiddy WE. A cost-effectiveness analysis of intravitreal aflibercept for the prevention of progressive diabetic retinopathy. *Ophthalmol Retina* 2022;**6**:213-8.

17. Gross JG, Glassman AR, Liu D, Sun JK, Antoszyk AN, Baker CW, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: A randomized clinical trial. *JAMA Ophthalmol* 2018;**136**:1138-48.

18. 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-.

19. Brown MM, Brown GC, Sharma S, Landy J. Health care economic analyses and value-based medicine. *Surv Ophthalmol* 2003;**48**:204-23.

20. Brown MM, Brown GC, Lieske HB, Lieske PA. Preference-based comparative effectiveness and cost–effectiveness: A review and relevance of value-based medicine for vitreoretinal interventions. *Curr Opin Ophthalmol* 2012;**23**:163-74.

21. 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.

22. 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.

23. 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.

24. The Royal College of Ophthalmologists. *Guidelines for diabetic retinopathy*. 2012. Available from: <www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines> [accessed 24 September 2023)

25. Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The wisconsin epidemiologic study of diabetic retinopathy: Xvii. *Ophthalmology* 1998;**105**:1801-15.

26. 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.

27. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: Etdrs report number 9. *Ophthalmology* 1991;**98**:766-85.

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

29. Brown MM, Brown GC, Sharma S, Shah G. Utility values and diabetic retinopathy. *Am J Ophthalmol* 1999;**128**:324-30.

30. Fong DS, Sharza M, Chen W, Paschal JF, Ariyasu RG, Lee PP. Vision loss among diabetics in a group model health maintenance organization (hmo). *Am J Ophthalmol* 2002;**133**:236-41.

31. Smith DH, Johnson ES, Russell A, Hazlehurst B, Muraki C, Nichols GA, et al. Lower visual acuity predicts worse utility values among patients with type 2 diabetes. *Qual Life Res* 2008;**17**:1277-84.