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Anti-vascular endothelial growth factor for proliferative diabetic retinopathy (Review)

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[Intervention Review]

Anti-vascular endothelial growth factor for proliferative diabetic retinopathy

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ABSTRACT

Background

Proliferative diabetic retinopathy (PDR) is an advanced complication of diabetic retinopathy that can cause blindness. It consists of the presence of new vessels in the retina and vitreous haemorrhage. Although panretinal photocoagulation (PRP) is the treatment of choice for PDR, it has secondary effects that can affect vision. Anti-vascular endothelial growth factor (anti-VEGF), which produces an inhibition of vascular proliferation, could improve the vision of people with PDR.

Objectives

To assess the effectiveness and safety of anti-VEGFs for PDR and summarise any relevant economic evaluations of their use.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register; 2022, Issue 6); Ovid MEDLINE; Ovid Embase; the ISRCTN registry; ClinicalTrials.gov, and the WHO ICTRP. We did not use any date or language restrictions. We last searched the electronic databases on 1 June 2022.

Selection criteria

We included randomised controlled trials (RCTs) comparing anti-VEGFs to another active treatment, sham treatment, or no treatment for people with PDR. We also included studies that assessed the combination of anti-VEGFs with other treatments. We excluded studies that used anti-VEGFs in people undergoing vitrectomy.

Data collection and analysis

Two review authors independently selected studies for inclusion, extracted data, and assessed the risk of bias (RoB) for all included trials. We calculated the risk ratio (RR) or the mean difference (MD), and 95% confidence intervals (CI). We used GRADE to assess the certainty of evidence.

Main results

We included 15 new studies in this update, bringing the total to 23 RCTs with 1755 participants (2334 eyes). Forty-five per cent of participants were women and 55% were men, with a mean age of 56 years (range 48 to 77 years). The mean glycosylated haemoglobin (Hb1Ac) was 8.45% for the PRP group and 8.25% for people receiving anti-VEGFs alone or in combination. Twelve studies included people with PDR, and participants in 11 studies had high-risk PDR (HRPDR).

Twelve studies were of bevacizumab, seven of ranibizumab, one of conbercept, two of pegaptanib, and one of aflibercept. The mean number of participants per RCT was 76 (ranging from 15 to 305). Most studies had an unclear or high RoB, mainly in the blinding of interventions and outcome assessors. A few studies had selective reporting and attrition bias.

No study reported loss or gain of 3 or more lines of visual acuity (VA) at 12 months. Anti-VEGFs ± PRP probably increase VA compared with PRP alone (mean difference (MD) -0.08 logMAR, 95% CI -0.12 to -0.04; I^2 = 28%; 10 RCTS, 1172 eyes; moderate-certainty evidence). Anti-VEGFs ± PRP may increase regression of new vessels (MD -4.14 mm^2, 95% CI -6.84 to -1.43; I^2 = 75%; 4 RCTS, 189 eyes; low-certainty evidence) and probably increase a complete regression of new vessels (RR 1.63, 95% CI 1.19 to 2.24; I^2 = 46%; 5 RCTS, 405 eyes; moderate-certainty evidence). Anti-VEGFs ± PRP probably reduce vitreous haemorrhage (RR 0.72, 95% CI 0.57 to 0.90; I^2 = 0%; 6 RCTS, 1008 eyes; moderate-certainty evidence). Anti-VEGFs ± PRP may reduce the need for vitrectomy compared with eyes that received PRP alone (RR 0.67, 95% CI 0.49 to 0.93; I^2 = 43%; 8 RCTs, 1248 eyes; low-certainty evidence). Anti-VEGFs ± PRP may result in little to no difference in the quality of life compared with PRP alone (MD 0.62, 95% CI -3.99 to 5.23; I^2 = 0%; 2 RCTs, 382 participants; low-certainty evidence). We do not know if anti-VEGFs ± PRP compared with PRP alone had an impact on adverse events (very low-certainty evidence). We did not find differences in visual acuity in subgroup analyses comparing the type of anti-VEGFs, the severity of the disease (PDR versus HRPDR), time to follow-up (< 12 months versus 12 or more months), and treatment with anti-VEGFs + PRP versus anti-VEGFs alone.

The main reasons for downgrading the certainty of evidence included a high RoB, imprecision, and inconsistency of effect estimates.

Authors' conclusions

Anti-VEGFs ± PRP compared with PRP alone probably increase visual acuity, but the degree of improvement is not clinically meaningful. Regarding secondary outcomes, anti-VEGFs ± PRP produce a regression of new vessels, reduce vitreous haemorrhage, and may reduce the need for vitrectomy compared with eyes that received PRP alone. We do not know if anti-VEGFs ± PRP have an impact on the incidence of adverse events and they may have little or no effect on patients' quality of life. Carefully designed and conducted clinical trials are required, assessing the optimal schedule of anti-VEGFs alone compared with PRP, and with a longer follow-up.

PLAIN LANGUAGE SUMMARY

Injections of anti-vascular endothelial growth factor for advanced diabetic retinopathy

Review question

Do injections of anti-vascular endothelial growth factor (anti-VEGF) either with or without laser treatment help people with advanced diabetic retinopathy in terms of vision and progression of the disease? Is this treatment safe?

Key messages

· Anti-VEGFs (combined with or without laser) improve the vision, but the degree of improvement is not clinically meaningful. They also reduce the formation of new vessels, haemorrhages, and the need for removing the vitreous with surgery (vitrectomy).

· The safety of anti-VEGFs (combined with or without laser) remains uncertain because we have very little confidence in the evidence we found.

· More clinical trials of high quality are needed to better establish the appropriate treatment dosage and time of administration of anti-VEGFs.

Background

Proliferative diabetic retinopathy (PDR) is the medical name for advanced damage to the retina. PDR consists of the presence of new vessels in the retina and a vitreous or pre-retinal haemorrhage (leakage of blood in and around the gel that fills the space between the crystalline lens and the retina), and can cause blindness. Panretinal photocoagulation (PRP) using laser is the current treatment. However, it has secondary effects such as loss of vision. Anti-VEGFs stop new vessels from forming. We wanted to find out if anti-VEGFs, either combined with other treatments or alone, were safe and better than a standard alternative to improve PDR.

What did we do?

We searched for randomised controlled trials (RCTs) comparing anti-VEGFs (combined or not with laser) to another active treatment, sham treatment, or no treatment for people with PDR. We also included studies that assessed the combination of anti-VEGFs with other treatments. We excluded studies in people undergoing vitrectomy or treatment to remove some or all of the gel that fills the space between the lens and the retina.

What did we find?

We found 23 studies that took place in North and South America, Europe, the Middle East and Asia. On average, people were studied for eight months, but one study followed participants for two years. In total we included 2334 eyes of 1755 people; 55% were men, and the average age was 56 years. About half of the studies did not declare their funding source and about half of the studies' authors did not report whether or not had any conflicts of interest.

Main results

On average, people treated with anti-VEGF with or without laser probably had better vision than people not treated with anti-VEGF (but the degree of improvement is small and may not be noticeable), and new vessels become smaller. They were also less likely to have bleeding in the eye and may be less likely to need vitrectomy. Only two studies reported on the quality of life, but we have low confidence in the evidence. Side effects were uncommon and there were not enough data to detect a difference in safety between the two groups.

What are the limitations of the evidence?

Some of the studies had flaws in their design/conduct and their results might be biased; in addition, they did not include many people. This leads us to have only little to moderate confidence in the main findings, and very little confidence in the evidence about side effects.

How up-to-date is this evidence?

This review updates our previous review published in 2014. The evidence is up-to-date until June 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Anti-vascular endothelial growth factor (anti-VEGF) with or without pan-retinal photocoagulation (PRP) compared to PRP alone for proliferative diabetic retinopathy

Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) compared to PRP alone for proliferative diabetic retinopathy

Patient or population: people with proliferative diabetic retinopathy
Setting: hospital
Intervention: anti-VEGF with or without PRP
Comparison: PRP alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with PRP alone	Risk with anti-VEGF with or without PRP				
Loss of 3 or more lines of ETDRS visual acuity - not reported	-	-	-	-	-	The included studies did not report this outcome.
LogMAR visual acuity (logMAR scale value of 0 = 6/6 vision, higher score = worse vision) Follow-up: median 12 months (range from 3 to 24 months)	The mean visual acuity ranged from 0.12 to 0.32 logMAR	MD 0.08 logMAR lower (0.12 lower to 0.04 lower)	-	1172 (10 RCTs)	⊕⊕⊕⊝ Moderate[a]	The MD in logMAR corresponds to a mean difference in four letters; 95% CI from 2.5 to 5 letters.
Complete regression of new vessels (dichotomous outcome) Follow-up: median 12 months (range from 12 to 12 months)	Study population		RR 1.63 (1.19 to 2.24)	405 (5 RCTs)	⊕⊕⊕⊝ Moderate[b]	
	377 per 1000	615 per 1000 (449 to 845)				
Regression of new vessels (continuous outcome): mean area of fluorescein leakage (mm^2) fluorescein angiography	The mean area of neovascularisation was 8 mm^2	MD 4.14 mm^2 lower (6.84 lower to 1.43 lower)	-	189 (4 RCTs)	⊕⊕⊝⊝ Low[c]	

Follow-up: median 12 months (range from 12 to 12 months)					
Presence of vitreous haemorrhage[d] Follow-up: median 12 months (range from 7 to 24 months)	Study population		RR 0.72 (0.57 to 0.90)	1008 (6 RCTs)	⊕⊕⊕⊝ Moderate[b]
	264 per 1000	191 per 1000 (115 to 238)			
Need for vitrectomy Follow-up: median 12 months (range from 3 to 24 months)	Study population		RR 0.67 (0.49 to 0.93)	1248 (8 RCTs)	⊕⊕⊝⊝ Low[a,e]
	217 per 1000	145 per 1000 (106 to 201)			
Quality of life (VFQ-25 General health) Follow-up: median 18 months (range from 12 to 24 months)	The mean quality of life (VFQ-25 General health) score was 46.3	MD 0.62 points higher (3.99 lower to 5.23 higher)	-	382 (2 RCTs)	⊕⊕⊝⊝ Low[a,e]
Adverse events Follow-up: median 12 months (range from 12 to 24 months)	Six studies reported adverse events. One study used aflibercept, and five ranibizumab. There were no significant differences in the incidence of angina (1 RCT), cardiovascular events based on APTC[f] (2 RCTs), arterial hypertension (3 RCTs), cataract (1 RCTs), cerebrovascular accident (2 RCTs), cornea-related problems (2 RCTs), endophthalmitis (4 RCT), eye inflammation (1 RCT), macular oedema (2 RCTs), neovascular glaucoma (3 RCTs), ocular discomfort (1 RCT), raised intraocular pressure (4 RCTs), retinal detachment (3 RCTs), retinal tear (1 RCTs), pain (1 RCT), visual disturbances (1 RCT), and vitreoretinal interface abnormalities (1 RCT). There was a reduction in pain scores in the group with anti-VEGFs and PRP (1 RCT).			1070 (6 RCTs)	⊕⊝⊝⊝ Very low[g]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
APTC: Anti-platelet Trialists' Collaboration; anti-VEGF: anti-vascular endothelial growth factor; CI: confidence interval; MD: Mean Difference; RR: risk ratio; VFQ-25: National Eye Institute Vision Functioning Questionnaire 25 (VFQ-25)

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded for risk of bias (-1) (unmasked participants and personnel, attrition bias)
[b]Downgraded for risk of bias (-1) (unmasked participants, personnel and outcome assessor, attrition bias, and selective reporting bias)
[c]Downgraded for risk of bias (-1) (unmasked participants and personnel), and for inconsistency (-1)
[d]Occurrence of new vitreous or pre-retinal haemorrhage from baseline to end of follow-up, or persistence at the end of follow-up if it was at baseline.
[e]Downgraded for imprecision (-1) (wide confidence intervals)
[f]Anti-platelet trialists' Collaboration (APTC) events: death, miocardial infarction and stroke.
[g]Downgraded for risk of bias (-1) (high risk of bias due to unmasked participants, personnel and outcome assessor, and attrition bias), and for imprecision (-2) (the confidence interval included no effect, and the number of events was low).

BACKGROUND

Description of the condition

Introduction and epidemiology

Diabetic retinopathy (DR) is a vascular disorder involving the retina that is characterised by increased vascular permeability, retinal ischaemia and oedema, and the formation of new vessels (Carmeliet 2004). DR produces visual impairment that can progress to blindness. It is a complication of both types of diabetes mellitus (DM), type 1 and type 2. Prevalence of DR is estimated to be 22.27% globally within the diabetic population, while the prevalence of vision-threatening DR (which includes both proliferative DR and diabetic macular oedema) is estimated at 6.17%. The prevalence varies considerably between regions (Teo 2021). DR may develop before a diagnosis of diabetes is made, such that one in five people with type 2 DM has retinopathy at the time of diagnosis. More than 60% of people with type 2 DM and almost all people with type 1 DM develop DR during the first 20 years of the disease (ADA 2006).

According to the Global Burden of Disease Study, diabetic retinopathy is the fifth main cause of blindness and also of moderate and severe vision impairment in adults aged 50 years and older. The relative percentage contribution of DR to the age-standardised prevalence of blindness in adults aged 50 years and older is estimated to be 2.5% (95% CI 1.7 to 6.7) globally (Steinmetz 2020).

A person with diabetes has a three-fold increased risk of blindness compared with the general population (Hayward 2002). In one study conducted by Moss and colleagues, the incidence of blindness 10 years after the onset of DM was 1.8% in people with type 1 DM, 4.0% in people with insulin-treated type 2 DM, and 4.8% in people with non-insulin-treated type 2 DM (Moss 1994). In the same study, the incidence of visual impairment at 10 years was 9.4% in people with type 1 DM, 37.2% in people with insulin-treated type 2 DM, and 23.9% in people with non-insulin-treated type 2 DM. In the USA, in 2002, 17% of blindness was attributed to DR (Resnikoff 2004).

The principal risk factors for developing DR are the duration of DM and the severity of hyperglycaemia (Davis 1998; Klein 1988; UKPDSG 1998a; Van Leiden 2003). Other risk factors are age (in type 1 DM) (Klein 1984), hypertension (Klein 1989; Klein 2002a; UKPDSG 1998b), nephropathy (Mathiesen 1995), hypercholesterolaemia (Chew 1996; Klein 2002b; Van Leiden 2002), abdominal obesity and high body mass index (Van Leiden 2003), anaemia (Davis 1998), pregnancy (Klein 1990), age at onset (Kullberg 2002), smoking and ethnicity (Moss 1996).

In addition to the visual impact of DR on the individual, there are significant impacts on the health care system associated with DR. For example the cost of illness associated with DR in the UK was estimated to be GBP 39 in 2035 to 2036 (Hex 2012). Therefore, the most effective treatment is also important from the perspective of the health care system.

Presentation and diagnosis

People with DR can range from completely asymptomatic to presenting a sudden or progressive loss of visual acuity (acuteness or clearness of vision) of varying severity. The retinal damage progresses sequentially from a mild non-proliferative stage to a severe proliferative stage. Signs of non-proliferative diabetic retinopathy (NPDR) include the presence of microaneurysms, intraretinal haemorrhages, hard exudates (lipid deposits), vascular changes (such as beading and looping or segmentation of the veins), soft exudates or cotton wool spots (which result from the closure of small retinal arterioles), intraretinal microvascular abnormalities and retinal oedema.

There are two important DR clinical classification systems: the Early Treatment Diabetic Retinopathy Study (ETDRS) research group classification (ETDRSRG 1991a; ETDRSRG 1991b; Table 1), and the International Clinical Diabetic Retinopathy Disease Severity (ICRDS) scale (Wilkinson 2003; Table 2).

Approximately 50% of people with very severe NPDR progress to proliferative diabetic retinopathy (PDR) within one year (ETDRSRG 1991c). PDR is characterised by new vessels, which start in the retina but can grow and affect the vitreous. These new vessels are prone to bleeding, which results in vitreous haemorrhage and fibrosis, and may lead to vitreous or retinal detachments (Table 1; Table 2).

Description of the intervention

The treatment strategies for DR include:

1. laser photocoagulation (DRSRG 1978; DRSRG 1981a; DRSRG 1981b; ETDRSRG 1985);
2. vitrectomy (DRVSRG 1985); and
3. pharmacotherapy to prevent both retinal new vessels and blood flow abnormalities affecting metabolic pathways. Generally, the drug is administered by intravitreal injection.

There are several lines of treatment including vascular endothelial growth factor (VEGF) inhibitors (anti-VEGFs), which cause regression of new vessels, macular oedema, or both. Anti-VEGFs include pegaptanib sodium (Adamis 2006; Cunningham 2005), and antibodies such as bevacizumab (Arevalo 2007; Avery 2006a; Avery 2006b; Chen 2006; Haritoglou 2006; Mason 2006; Scott 2007; Spaide 2006), ranibizumab (Chun 2006), brolucizumab *(*Brown 2021; Dugel 2017*)* and faricimab (Sahni 2019; Wykoff 2022); and recombinant fusion proteins such as aflibercept (Korobelnik 2014; Wykoff 2017), and conbercept (Li 2014; Li 2018; Xu 2017), which cause regression of neovascularization, macular oedema, or both.

Other drugs have a non-selective anti-VEGF effect, such as corticosteroids (Boyer 2014; Campochiaro 2011; Jaffe 2006; Martidis 2002; Nauck 1997; Pearson 2011), cyclo-oxygenase inhibitors (Sennlaub 2003), and angiotensin-converting enzyme (ACE) inhibitors (Gilbert 2000). These are not the object of this review.

How the intervention might work

VEGFs are present in the retinal pigment epithelium, pericytes, and endothelial cells of the retina. VEGFs are released physiologically when ischaemia occurs, and they stimulate the formation of new blood vessels. Hyperglycaemia induces chronic retinal hypoxia and leads to the over-expression of VEGFs that stimulate the formation of neovascularisation (Bussolati 2001), and cause vascular disease in the retina.

Selective anti-VEGF drugs inhibit only specific VEGF isoforms: pegaptanib (a modified oligonucleotide) inhibits only the VEGF

165 isoform. Bevacizumab and ranibizumab (a murine humanised monoclonal antibody fragment) inhibit all isoforms of VEGF-A. Aflibercept and conbercept are recombinant fusion proteins that inhibit VEGF-A VEGF-B and placental growth factor (PGF). Faricimab is a humanised bispecific immunoglobulin antibody that inhibits both VEGF-A and angiopoietin-2.

Many studies have shown that local intravitreal administration of these drugs may be useful in macular oedema and neovascularisation, although anti-VEGFs can produce local adverse effects (in 1.27% of cases) such as endophthalmitis (severe inflammation of the intraocular cavities, usually caused by infection) (Shima 2008), and systemic adverse effects (in 1.5% of cases) such as acute elevation of systemic blood pressure or cerebrovascular accident (CVA) (Wu 2008).

In addition to the considerations around the safety and efficacy of the drugs, there are significant resource implications to consider (Sasongko 2020). For example, Hutton 2019 estimated the five-year costs of management with ranibizumab to be 32,300 US dollars (USD) over a period of five years (USD 2018). As such, understanding the costs and benefits associated with each approach is important for healthcare decision-makers.

Why it is important to do this review

Despite the standard of care given for the prevention and treatment of DR, it remains an important cause of vision loss. Due to this, new lines of treatment are being developed, such as selective anti-VEGF drugs. Anti-VEGFs have been extensively studied in neovascular age-related macular degeneration (Solomon 2019), and diabetic macular oedema (Virgili 2018), where they have shown efficacy. We performed a previous review assessing the efficacy and safety of anti-VEGFs for PDR complications. The results, based on 18 RCTs and 1005 participants, showed very low or low-certainty evidence for the efficacy and safety of anti-VEGF agents when used to treat PDR over and above current standard treatments (Martinez-Zapata 2014). However, new RCTs have been published, and it is important to update the review to include the new evidence.

OBJECTIVES

To assess the effectiveness and safety of anti-VEGFs for PDR and summarise any relevant economic evaluations of their use.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs without any date or language restrictions.

Types of participants

We included trials in adults (aged 18 years and over) with proliferative DR (PDR) defined as the presence of neovascularisation, vitreous haemorrhage, and vitreous or retinal detachments secondary to diabetes.

We excluded studies where diabetic macular oedema (DMO) was the principal inclusion criterion because this has been assessed in the Cochrane Review by Virgili 2018. We also excluded studies that assessed people who underwent vitrectomy because of the overlap with the Cochrane Review by Smith 2015.

Types of interventions

We included studies in which selective anti-VEGFs were compared with another active treatment, sham treatment, or no treatment. We also included studies that assessed the combination of anti-VEGFs with other treatments, for example, photocoagulation or other non-surgical treatments.

Types of outcome measures

Primary outcomes

The primary outcome was best-corrected visual acuity at the end of the study follow-up.

We used three measures:

- loss of 3 or more lines of vision on the ETDRS visual acuity charts;
- gain of 3 or more lines of vision on the ETDRS visual acuity charts.

This 3-line change is equivalent to a doubling of the visual angle. For studies that did not use the ETDRS chart, we used the measure of visual acuity reported that corresponded most closely to a doubling of the visual angle.

We also considered mean visual acuity:

- corrected visual acuity measured on a continuous scale (logarithm of the minimum angle of resolution (logMAR) visual acuity or ETDRS letters).

Secondary outcomes

- Regression of new vessels as defined with fundus fluorescein angiography (absence of leakage) or clinical examination (fibrotic new vessels and absence of haemorrhage from new vessels) or any validated DR staging systems, such as ETDRS or ICRDS scales). We measured regression sustained at least three months after the last injection. We assessed complete regression (dichotomous outcome) and regression (continuous outcome) of new vessels.
- Presence of microaneurysms.
- Presence of vitreous haemorrhage: occurrence of new vitreous from baseline to end of follow-up or persistence (if it was presented at baseline) at the end of follow-up.
- Need for laser photocoagulation.
- Need for vitrectomy.
- DMO, measured as a dichotomous variable or as a continuous variable (macular thickness).
- Quality of life measured on any validated scale.
- Any ocular or systemic adverse outcomes.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases. There were no restrictions to language or year of publication. The date of the search was 1 June 2022.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 6) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (Appendix 1).
- MEDLINE Ovid (1946 to 1 June 2022) (Appendix 2).

- MEDLINE Ovid (1946 to 1 June 2022) – economic search (Appendix 3).
- Embase Ovid (1980 to 1 June 2022) (Appendix 4).
- Embase Ovid (1980 to 1 June 2022) – economic search (Appendix 5).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch) (Appendix 6).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 7).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 8).

Searching other resources

For this update, we looked for other published systematic reviews in this area as a source of additional RCTs. We reviewed the reference lists of the identified clinical trials. When necessary, we contacted study authors to obtain more information regarding their published trials.

Data collection and analysis

Selection of studies

Two authors (MJM and DP or ISM) independently assessed the eligibility of the studies identified in the search, first by title and abstract screening and in a second stage by full-text review. When there were disagreements, it was resolved by consensus or a third author (MJM) evaluated the study independently and discussed it with the remainder of the team.

We graded the eligible studies as included or excluded. We contacted one study author to clarify secondary publications of the main clinical trial (Ramos Filho 2011).

One review author (AK) screened the economic studies.

We used Covidence systematic review software to screen the studies.

Data extraction and management

For this update, two pairs of authors (MJM and DP, ISM, JAC or JIP) collected data independently on a previously tested standardised form. The collected information recorded the risk of bias, characteristics of participants in the study, characteristics of the intervention and control groups, and outcome characteristics of each group of participants. One review author (MJM) entered the data into Review Manager 5.4 (RevMan 2020). Some included studies were in Chinese, and they needed language support experts (see Acknowledgements section).

When visual acuity was measured using the ETDRS chart but reported in letters rather than logMAR score, we converted to logMAR score using the following formula: (85 - mean letter score) * 0.02 and for the standard deviation (SD) (letter score * 0.02) (Ferris 1982).

Assessment of risk of bias in included studies

For this update, two pairs of authors (MJM and DP, ISM, IS, JAC or JIP) assessed the risk of bias in the included studies (using the Cochrane risk of bias 1 tool; Higgins 2017), specifically examining the randomisation method (sequence generation and allocation concealment); whether the intervention was masked to the participants, investigators and outcome assessors; incomplete outcome data; selective outcome reporting and percentage of losses to follow-up. We also considered whether the number of postrandomisation losses and exclusions had been made explicit. Once this information was gathered, the authors classified each study into one of the three levels of risk of bias: low, unclear, or high risk of bias. We followed the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

Measures of treatment effect

We considered the following effect measures for each study: risk ratios (RR) for dichotomous variables and mean differences (MD) for continuous variables. We calculated 95% confidence intervals (CIs).

Unit of analysis issues

The unit of analysis was the eye; most studies included one eye per person. We excluded from the analysis nine exclusively within-person studies in which the fellow eye was used as a control (Ahmad 2012; Ali 2018; Ernst 2012; He 2020; Mirshahi 2008; Preti 2013; Preti 2017; Roohipoor 2016; Shahraki 2022). However, we included studies with a low percentage of participants with the fellow eye used as a control and considered as a parallel design trial (DRCR.net 2015; Ergur 2009; Meng 2016; Rebecca 2021; Sameen 2017).

When studies had more than two treatment arms, the main comparison was anti-VEGF plus PRP versus PRP. For a subgroup analysis based on the combination or not of anti-VEGF with PRP, we extracted the data of the arm of anti-VEGF alone and compared it with PRP.

Dealing with missing data

We contacted the study authors to obtain further information. Our main analysis was an 'available-case analysis', analysing data as provided in the individual studies.

Assessment of heterogeneity

We examined the characteristics of each study to detect clinical heterogeneity. We conducted an analysis to detect the presence of heterogeneity. We regarded an I^2 statistic between 50% and 75% as substantial heterogeneity and an I^2 statistic between 75% and 100% as considerable statistical heterogeneity, and we examined sources of heterogeneity. When heterogeneity was more than 75%, we did not pool the studies.

Assessment of reporting biases

In accordance with Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2022), we did not assess whether the review was subject to publication bias by using a funnel plot for visual acuity (main outcome) because the number of clinical trials identified for inclusion in the meta-analyses was fewer than 10.

Data synthesis

We determined the pooled effect estimate for each outcome through a meta-analysis of the individual study effect measures using a random-effects model because we pooled different anti-VEGFs, treatment dosages, times of administration of anti-VEGFs, and periods of follow-up (DerSimonian 1986).

We performed statistical analysis using Review Manager 5.4.1 (RevMan 2020).

Subgroup analysis and investigation of heterogeneity

We compared the effect of treatment according to the type of anti-VEGF agent, that is, aflibercept, bevacizumab, conbercept, pegaptanib, and ranibizumab.

For this update, we compared the results of studies that included people with PDR versus people with high-risk PDR (HRPDR), and 12 months or more of follow-up versus less than 12 months, for the main outcome. In addition, we compared the effect of treatment according to the comparison of anti-VEGF plus PRP or anti-VEGF alone versus PRP alone.

Sensitivity analysis

We compared random-effects models and fixed-effect models for main outcomes that had three or more trials.

We compared the results of high risk of bias trials (i.e. high risk of bias in one or more domains) and low risk trials (i.e. not high risk in any domain) for main outcomes that had more than two trials contributing to the analysis and at least one trial in each high risk/low risk group.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table, including an assessment of the overall certainty of the evidence using the GRADE scheme (GRADEpro GDT). We used the principles of the GRADE system to assess the certainty of the body of evidence associated with the main outcomes listed below.

The GRADE approach appraises the certainty of the body of evidence according to the extent to which one can be confident that an estimate of the effect on the outcome being assessed is correct. The certainty of evidence is graded as high, moderate, low, and very low confidence. Evaluation of the certainty of the body of evidence considers the within-study risk of bias, indirectness of the evidence, inconsistency (heterogeneity in the data), imprecision (precision of effect estimates), and publication bias (Schünemann 2022). For this update, two review authors (MJM and GV) independently assessed the certainty of the body of evidence for the following outcomes, and discordances were resolved by consensus.

1. Visual acuity
2. Complete regression of new vessels (dichotomous)
3. Regression of new vessels (continuous outcomes)
4. Presence of vitreous haemorrhage
5. Need for vitrectomy
6. Quality of life
7. Adverse events

Brief economic commentary

For this update, following the search outlined in search methods for the identification of studies, we developed a brief economic commentary to summarise the availability and principal findings of the full economic evaluations assessing anti-VEGF treatments for the management of PDR (Aluko 2021). This brief economic commentary encompassed full economic evaluations (i.e. cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) conducted as part of a single empirical study, such as an RCT, a model based on a single such study, or a model based on several such studies.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The updated electronic searches yielded 1768 references (Figure 1). After removing duplicate records, we screened 866 records and obtained the full-text reports of 93 new potentially relevant publications. We included 24 reports of 15 new studies in this update of the review and added 69 reports of 45 studies as excluded studies. There are currently three clinical trials that will be assessed for potential inclusion in the review when data become available. The search of economic studies found 267 reports; 261 were not relevant, and we included the remaining six records (five studies).

Figure 1. Study flow diagram

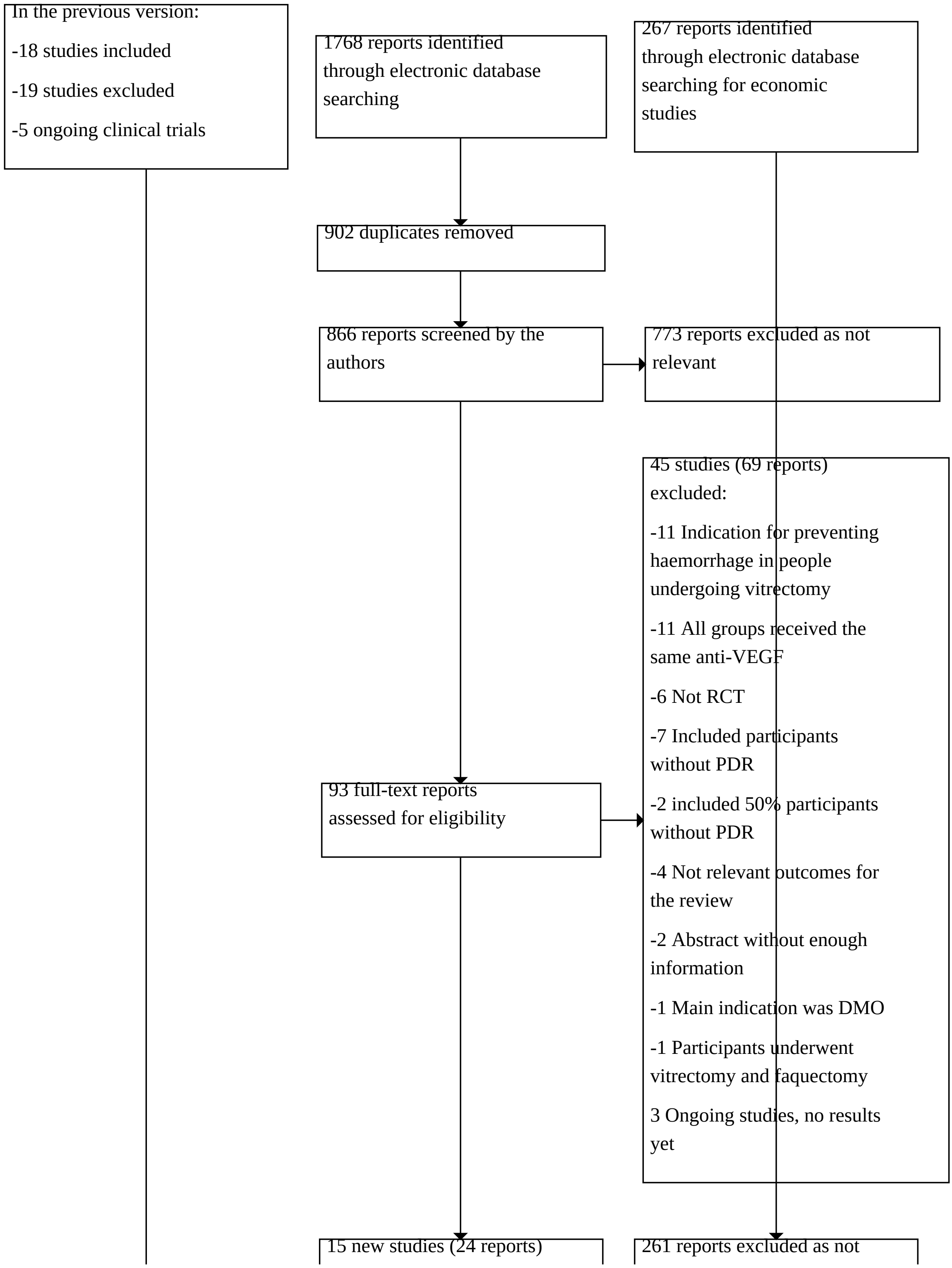
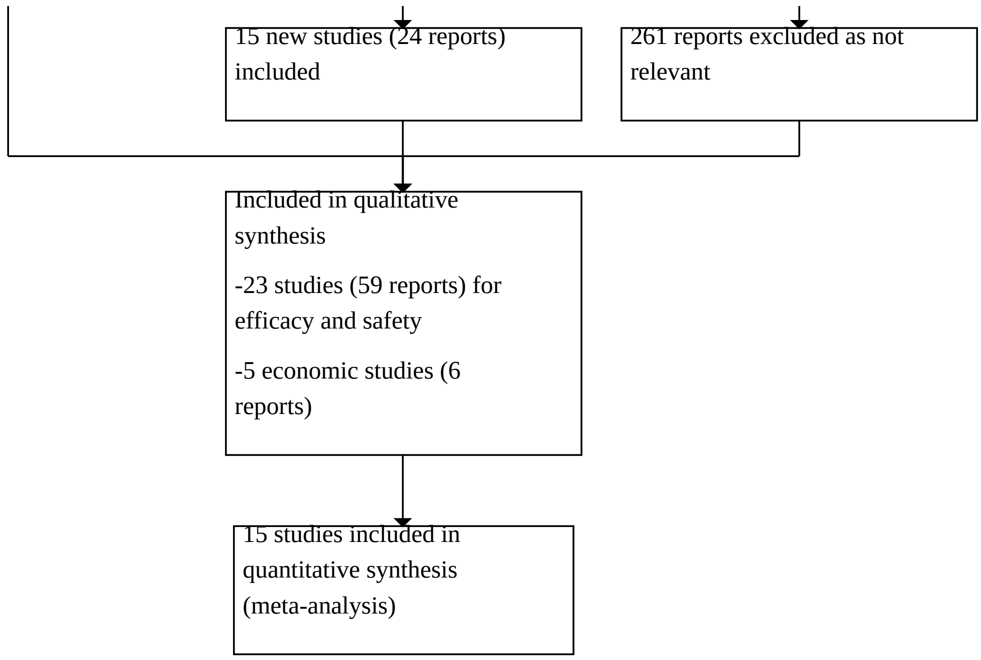


Figure 1. (Continued)



For efficacy and safety, we included 15 new studies for this review, which now includes 23 studies: as the inclusion criteria in this review have changed, only eight of 18 studies that were included in the first version have been added (DRCR.net 2013; Ergur 2009; González 2009; Mirshahi 2008; Preti 2013; Ramos Filho 2011 and two ongoing studies -NCT01941329 and EUCTR2013-003272-12-GB- that have since been published, Figueira 2018 and Sivaprasad 2017); and 15 new studies (Ahmad 2012; Ali 2018; Chelala 2018; DRCR.net 2015; Figueira 2016; Gonzalez 2014; He 2020; Lang 2019; Marashi 2017; Meng 2016; Preti 2017; Rebecca 2021; Roohipoor 2016; Sameen 2017; Shahraki 2022).

For this update, we excluded 79 studies: 34 studies in the first version and 45 new studies in this update. Reasons for excluding studies are in the table Characteristics of excluded studies.

We included five economic studies in the brief economic commentary in this update, described in six reports (Hutton 2017; Hutton 2019; Lin 2016; Lin 2018; Sivaprasad 2018; Yannuzzi 2018), and identified three new ongoing studies (ChiCTR-INR-17013555; NCT02911311; NCT04278417).

We contacted the authors to obtain additional information for two studies (Chen 2019; Ramos Filho 2011). One author responded to our questions (Ramos Filho 2011).

Included studies

Overall, we included data on 1755 participants (2334 eyes) from 23 RCTs in the review. Forty-five per cent of participants were women and 55% were men, with a mean age of 56 years (range 48 to 77 years). The mean of glycosylated haemoglobin (Hb1Ac) was 8.45% for the PRP groups and 8.25% for anti-VEGF groups, alone or in combination (see Table 3). Twelve studies included people with PDR (Ahmad 2012; Ali 2018; Chelala 2018; DRCR.net 2013; DRCR.net 2015; Ergur 2009; Lang 2019; Marashi 2017; Roohipoor 2016; Sameen 2017; Shahraki 2022; Sivaprasad 2017), and 11 studies included people with HRPDR (Figueira 2016; Figueira 2018; González 2009; Gonzalez 2014; He 2020; Meng 2016; Mirshahi 2008; Preti 2013; Preti 2017; Ramos Filho 2011; Rebecca 2021).

The mean number of participants per RCT was 76 (ranging from 15 to 305). Two studies took place in China (He 2020; Lang 2019); four in Pakistan (Ahmad 2012; Ali 2018; Rebecca 2021; Sameen 2017); four in the USA (DRCR.net 2013; DRCR.net 2015; González 2009; Gonzalez 2014); three in Brazil (Preti 2013; Preti 2017; Ramos Filho 2011); three in Iran (Mirshahi 2008; Roohipoor 2016; Shahraki 2022); two in Portugal (Figueira 2016; Figueira 2018), and one each in Germany (Lang 2019), Lebanon (Chelala 2018), Syria (Marashi 2017), Turkey (Ergur 2009), and the UK (Sivaprasad 2017). Seven studies were partially or completely industry-funded (DRCR.net 2013; DRCR.net 2015; Figueira 2016; González 2009; Gonzalez 2014; Lang 2019; Sivaprasad 2017), five studies were only funded by independent institutions (Figueira 2018; He 2020; Preti 2013; Ramos Filho 2011; Sameen 2017), and 11 studies did not declare the funding source (Ahmad 2012; Ali 2018; Chelala 2018; Ergur 2009; Marashi 2017; Meng 2016; Mirshahi 2008; Preti 2017; Rebecca 2021; Roohipoor 2016; Shahraki 2022). Ten studies did not declare their authors' conflicts of interest, eight declared they have received financial fees from industry, and five reported none.

All studies evaluated anti-VEGFs in people with PDR or HRPDR who needed PRP. In 18 of these studies, anti-VEGFs were combined with PRP and compared with PRP alone (Ahmad 2012; Ali 2018; Chelala 2018; DRCR.net 2013; DRCR.net 2015; Ergur 2009; He 2020; Figueira 2016; Figueira 2018; Lang 2019; Mirshahi 2008; Preti 2013; Preti 2017; Ramos Filho 2011; Rebecca 2021; Roohipoor 2016; Sameen 2017; Shahraki 2022). Some of these studies had more than two arms and also compared anti-VEGFs alone with PRP (DRCR.net

2015; Figueira 2016; Lang 2019; Shahraki 2022). Two studies only compared anti-VEGFs alone with PRP (González 2009; Sivaprasad 2017). Marashi 2017 and Meng 2016 used PRP in the anti-VEGF groups only when DR progression was produced. In the Meng 2016 study, 70% of participants in the anti-VEGF group also received PRP; and in the Marashi 2017 study, this information was unclear.

Twelve of these studies used bevacizumab (Ahmad 2012; Ali 2018; Ergur 2009; Marashi 2017; Meng 2016; Mirshahi 2008; Preti 2013; Preti 2017; Rebecca 2021; Roohipoor 2016; Sameen 2017; Shahraki 2022); seven studies used ranibizumab (Chelala 2018; DRCR.net 2013; DRCR.net 2015; Figueira 2016; Figueira 2018; Lang 2019; Ramos Filho 2011), two studies used pegaptanib (González 2009; Gonzalez 2014), one study used aflibercept (Sivaprasad 2017), and one used conbercept (He 2020).

The primary outcome was visual acuity in seven trials (Ali 2018, DRCR.net 2015; Ergur 2009; Marashi 2017; Sameen 2017; Shahraki 2022; Sivaprasad 2017), regression of PDR in nine studies (Ahmad 2012; Figueira 2016; Figueira 2018; González 2009; Gonzalez 2014; He 2020; Lang 2019; Mirshahi 2008; Rebecca 2021), macular thickness in two trials (Preti 2017; Roohipoor 2016), rate of vitrectomy in two trials (Chelala 2018; DRCR.net 2013), clearing of vitreous haemorrhage in one trial (Meng 2016), active neovascularisation in one trial (Ramos Filho 2011), and changes in contrast sensitivity in one trial (Preti 2013).

The mean follow-up of participants was eight months (range one month (Preti 2017) to 24 months (DRCR.net 2015). Thirteen studies had a follow-up of less than 12 months (Ahmad 2012; Ali 2018; Chelala 2018; Ergur 2009; González 2009; He 2020; Meng 2016; Mirshahi 2008; Preti 2013; Preti 2017; Rebecca 2021; Roohipoor 2016; Sameen 2017). Ten studies had 12 or more months of follow-up (DRCR.net 2013; DRCR.net 2015; Figueira 2016; Figueira 2018; Gonzalez 2014; Lang 2019; Marashi 2017; Ramos Filho 2011; Shahraki 2022; Sivaprasad 2017).

The mean total number of anti-VEGF injections in the anti-VEGF group was 3.5 (SD 2.5), specifically 2.1 (SD1.5) for studies with less than 12 months of follow-up, and 5.2 (SD 2.7) for studies with 12 or more months of follow-up.

The mean total number of PRP sessions in the PRP group was 2.7 (SD 1.2); 2.5 (SD 1.3) for studies with less than 12 months of follow-up, and 2.9 (SD 1.1) for studies with 12 or more months of follow-up.

When anti-VEGFs were combined with PRP, the mean total number of PRP sessions was 2.2 (SD 1.3); 2.1 (SD 1.2) for studies with less than 12 months of follow-up, and 2.2 (SD 1.4) for studies with 12 or more months of follow-up.

Additionally, (Table 4) shows the number of injections in the anti-VEGF arm and PRP sessions in the two groups. The anti-VEGF group received a median of two injections (ranging from 1 to 10 injections). In five studies with a follow-up shorter than 12 months, the anti-VEGF arm received a median of one injection, with two in five studies, and three to six injections in three studies. In 10 studies with 12 or more months of follow-up, the median number of injections was five (range 2 to 10 injections). DRCR.net 2015 reached 24 months of follow-up and delivered a median of 10 injections in the PRP arm. The PRP group received a median of three sessions (range: one to five sessions), as did the anti-VEGF group (range one to four sessions). There were no PRP sessions in the anti-VEGF group in two studies (Chelala 2018; González 2009). DRCR.net 2015 and Shahraki 2022 were the only studies allowing for rescue injections in the PRP group if diabetic macular edema (DME) was detected.

Six trials specified the sample size calculation (DRCR.net 2013; DRCR.net 2015; Figueira 2016; Sameen 2017; Shahraki 2022; Sivaprasad 2017).

Excluded studies

We excluded 79 clinical trials. The Characteristics of excluded studies table shows the reasons for exclusion. Briefly, participants in 22 studies underwent vitrectomy (Ahmadieh 2009; Ahn 2011; Albuquerque 2014; Antoszyk 2022; Arevalo 2019; Castillo 2017; Comyn 2014; Di Lauro 2010; El-Batarny 2008; Farahvash 2011; Li 2022; Manabe 2015; Modarres 2009; NCT02857491; Rizzo 2008; Sohn 2012; Su 2016; Sun 2015; Wang 2014; Yang 2016; Yu 2015; Zaman 2013); 19 studies were non-randomised clinical trials (Arimura 2009; Dong 2016; Fulda 2010; Genovesi-Ebert 2007; Gonzalez 2021; Hattori 2010; Hershberger 2018; Huang 2009; Jiang 2009; Jorge 2006; Lee 2014; López-López 2012; Ma 2016; Minnella 2008; Shin 2009; Stergiou 2007; Yeh 2009; Parikakis 2018; Zhang 2019), five trials were in people with macular oedema (Gonzalez 2006; Ip 2012; Michaelides 2010; NCT02207712; Zhou 2010), 11 RCTs included the same anti-VEGF in all groups (Barroso 2020; Chatziralli 2020; Hach 2019; Maguire 2020; Messias 2019; NCT02630277; NCT02976012; NCT03904056; NCT04708145; Toscano 2021; Wykoff 2019); one study had methodological issues (Scott 2008), nine trials were in non-PDR (Cheema 2009; Chen 2019; Dufour 2017; Ferraz 2015; Lanzagorta-Aresti 2009; Maturi 2021; NCT03452657; NCT04782128; Song 2020), four studies included no relevant outcomes (Bressler 2018; Bu 2018; Li 2015; Yu 2021), four trials also included people without PDR (Bi 2020; Cho 2010: Ernst 2012; Wang 2019), two were only reported as an abstract without enough information (Oh 2014; Zhou 2017), in one study participants received vitrectomy and faquectomy (Hu 2017), and one trial was partially randomised (Tonello 2008).

Risk of bias in included studies

Figure 2 and Figure 3 show the risk of bias in included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

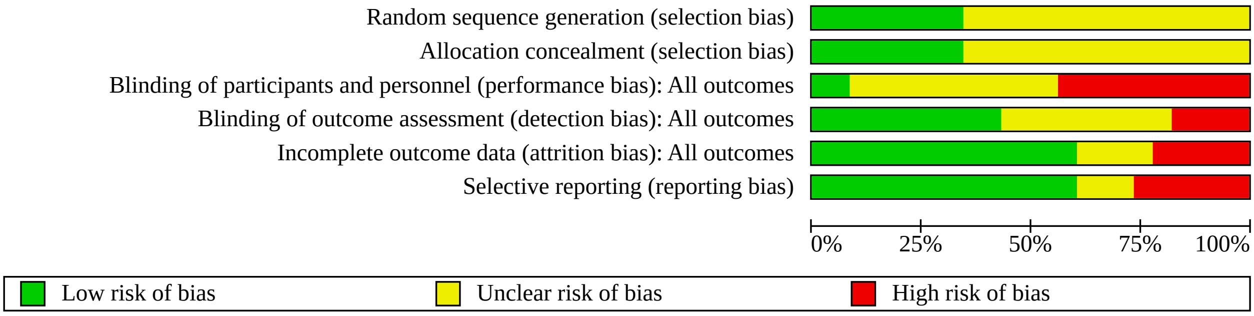


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

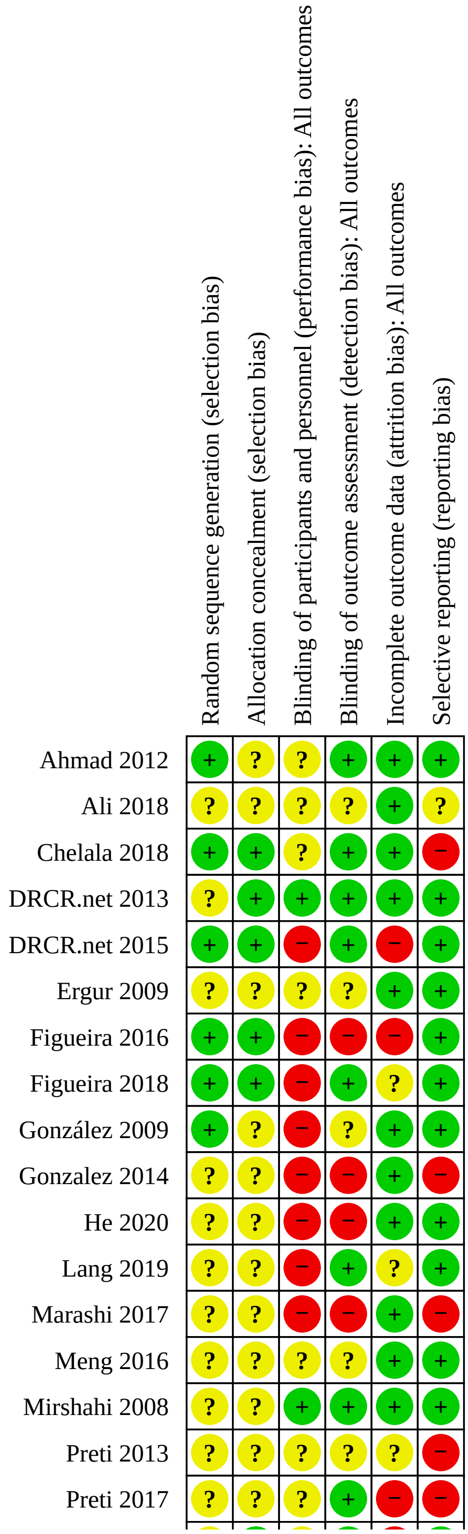
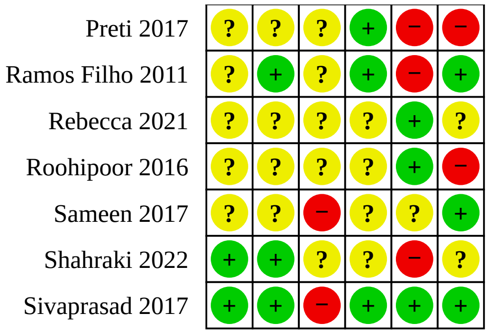


Figure 3. (Continued)



Allocation

Eight studies reported methods of sequence generation that we considered were low risk of bias with mention of computer-generated random allocation lists (Chelala 2018; DRCR.net 2015; Figueira 2016; Figueira 2018; González 2009; Shahraki 2022; Sivaprasad 2017), and one randomised by simple lottery (Ahmad 2012). The remaining studies did not report how they generated the allocation in enough detail to enable us to judge.

Five studies had a central online randomisation system (DRCR.net 2013; DRCR.net 2015; Figueira 2016; Shahraki 2022, Sivaprasad 2017), and one study used sealed opaque envelopes (Ramos Filho 2011). The remainder of the studies did not report allocation.

Blinding

Two studies masked participants, personnel, and outcome assessors, one study by means of a sham injection (Mirshahi 2008), and in another study, both interventions were delivered by injection and these were identified by number only (DRCR.net 2013). Ten studies were at high risk of bias (Figueira 2016; Figueira 2018; González 2009; Gonzalez 2014; He 2020; Lang 2019; Marashi 2017; Sameen 2017; Sivaprasad 2017) and the others had unclear risk of bias.

A further 10 studies reported masking outcome assessors only (Ahmad 2012; Chelala 2018; DRCR.net 2013; DRCR.net 2015; Figueira 2018; Lang 2019; Mirshahi 2008; Preti 2017; Ramos Filho 2011; Sivaprasad 2017). We judged four studies to be at high risk of bias for masking because they were not masked (open-label) (Figueira 2016; Gonzalez 2014; He 2020; Marashi 2017) and the others at unclear risk of bias.

Incomplete outcome data

Most studies did not appear to have a problem with incomplete outcome data (Ahmad 2012; Ali 2018; Chelala 2018; DRCR.net 2013; Ergur 2009; González 2009; Gonzalez 2014; He 2020; Marashi 2017; Meng 2016; Mirshahi 2008; Rebecca 2021; Roohipoor 2016; Sivaprasad 2017) but, four studies had relatively high losses to follow-up so we judged them to be at high risk of attrition bias (DRCR.net 2015Figueira 2016; Preti 2017; Ramos Filho 2011; Shahraki 2022), and the others studies had not clearly reported the losses.

Selective reporting

For most studies, we considered that selective outcome reporting was not a problem because they reported the main outcomes expected, or mentioned them in the methods section of the paper (Ahmad 2012; DRCR.net 2013; DRCR.net 2015; Ergur 2009; Figueira 2016; Figueira 2018; González 2009; He 2020; Lang 2019; Meng 2016; Mirshahi 2008; Ramos Filho 2011; Sameen 2017; Sivaprasad 2017). We judged six studies to be at high risk of bias for selective reporting because the outcomes were reported incompletely (Chelala 2018; Gonzalez 2014; Marashi 2017; Preti 2017), or differed from those stated on the trials register (Preti 2013; Roohipoor 2016); for the others studies, this information was unclear.

Other potential sources of bias

Not included.

Effects of interventions

See: **Summary of findings 1** Anti-vascular endothelial growth factor (anti-VEGF) with or without pan-retinal photocoagulation (PRP) compared to PRP alone for proliferative diabetic retinopathy

Anti-vascular endothelial growth factor with or without pan-retinal photocoagulation versus pan-retinal photocoagulation alone

Loss of 3 or more lines of ETDRS visual acuity

There were no studies including this outcome.

Gain of 3 or more lines of ETDRS visual acuity

There were no studies including this outcome.

Mean visual acuity

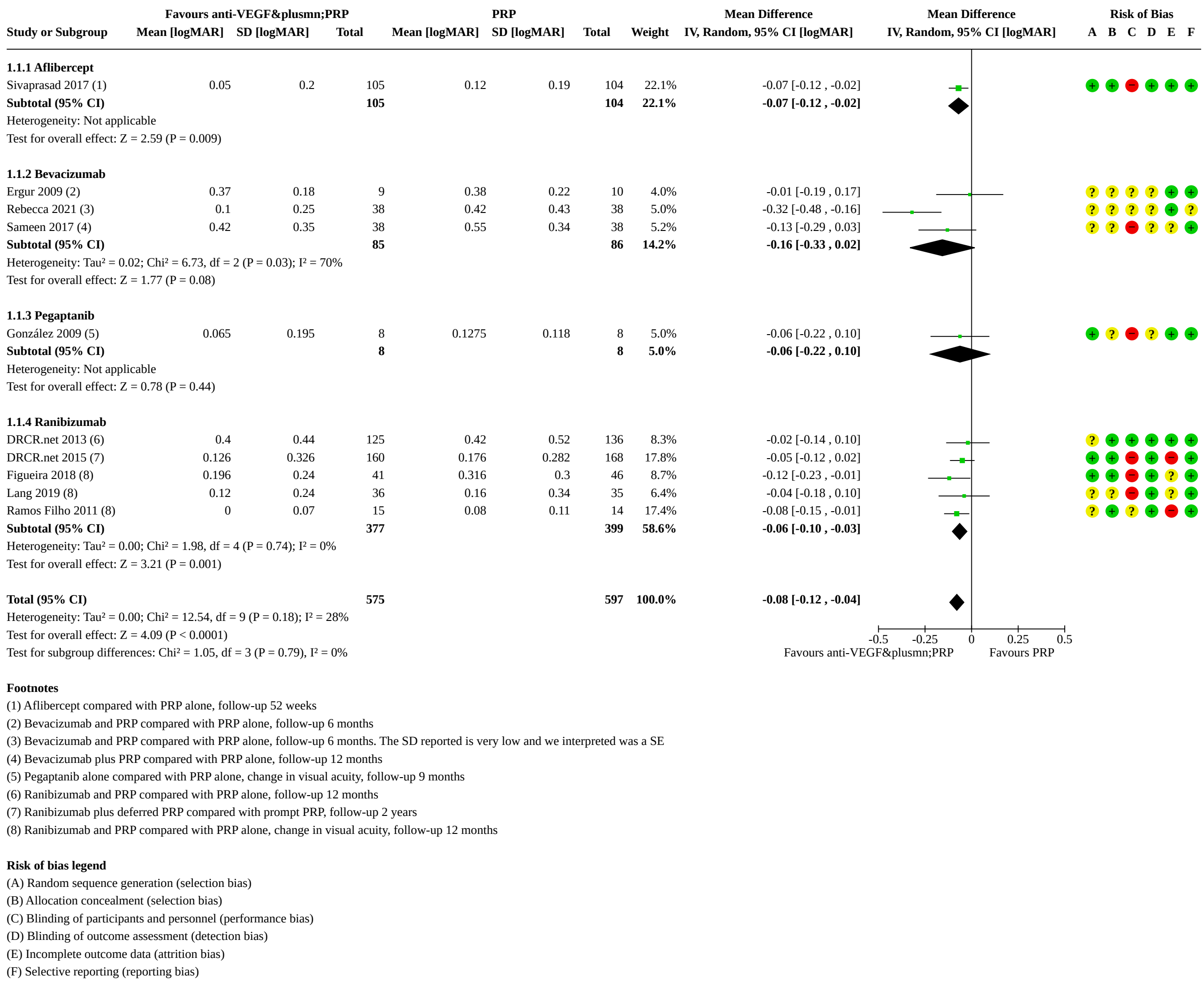
Ten trials contributed to the analyses of mean visual acuity. Two of these reported changes in visual acuity from baseline (González 2009; Ramos Filho 2011), and the remaining eight reported end of follow-up data.

Three of the trials used intravitreal bevacizumab (Ergur 2009; Rebecca 2021; Sameen 2017), one assessed aflibercept (Sivaprasad 2017), one trial used intravitreal pegaptanib (González 2009), and five trials used ranibizumab (DRCR.net 2013; DRCR.net 2015; Figueira 2018; Lang 2019; Ramos Filho 2011).

All studies used an intravitreal injection of anti-VEGF as an adjunct to PRP and compared them with PRP alone, except Sivaprasad 2017 (which used aflibercept), and González 2009 (which used pegaptanib) that compared anti-VEGFs alone with PRP. DRCR.net 2015 compared ranibizumab plus deferred PRP versus prompt PRP, with a follow-up of two years, and only 6% of eyes (12 out 191) received delayed PRP in the anti-VEGF group. Lang 2019 compared ranibizumab alone or in combination with PRP. One trial used an intravitreal injection of bevacizumab injected at the same time or up to three weeks before PRP (Ergur 2009); one study used it one week before or after PRP and at the end of the third session of PRP administered weekly (Rebecca 2021); and another study used it one day after the PRP session and thereafter each month for three months (Sameen 2017). One trial used pegaptanib injected every six weeks for 30 weeks combined with treatment with PRP (González 2009). One trial used three injections of ranibizumab at baseline, fourth and eighth weeks; both groups also received PRP (DRCR.net 2013). One trial only used one injection of ranibizumab after the completion of PRP (Ramos Filho 2011). Two studies assessed the injection of ranibizumab monthly for three months with the standard PRP treatment (Figueira 2018; Lang 2019) or alone (Lang 2019).

Anti-VEGFs (aflibercept, bevacizumab, pegaptanib, or ranibizumab) ± PRP probably increase visual acuity compared with PRP alone (MD -0.08 logMAR, 95% CI -0.12 to -0.04; I^2 = 28%; 10 RCTs, 1172 eyes; moderate-certainty evidence; Analysis 1.1; Figure 4; Summary of findings 1). Overall, there was low heterogeneity (I^2 = 28%) and no evidence for any difference according to the type of anti-VEGF (test for subgroup differences P = 0.79). These results represent an improvement in visual acuity of 4 letters (95% CI from 2 to 6 letters).

Figure 4. Forest plot of comparison: 1 Anti-vascular endothelial growth factor (anti-VEGF) versus photocoagulation, outcome: 1.3 Visual acuity [logMAR]



Sensitivity analysis by random-effects models versus fixed-effect models did not affect the conclusions.

Analysis	The measure of effect in a random-effects model (95% CI)	The measure of effect in a fixed-effect model (95% CI)

Analysis 1.1	MD -0.08 logMAR (-0.12 to -0.04)	MD -0.08 logMAR (-0.10 to -0.05)

We did not carry out sensitivity analysis by a low risk of bias versus a high risk of bias because included trials presented unclear or high risk of bias.

Regression of new vessels (dichotomous outcome)

Five trials reported complete regression of ocular new vessels elsewhere (NVE) of PDR as a dichotomous outcome. One used aflibercept (Sivaprasad 2017), one used bevacizumab (Marashi 2017) and three used ranibizumab (Figueira 2016; Figueira 2018; Lang 2019). Regression of PDR was reported at 12 months in all studies. All studies used fundus fluorescein angiography (FFA) for measuring this outcome except one, Marashi 2017, that used the assessment of fundus photography. Sivaprasad 2017, Figueira 2016, and Figueira 2018 used both methods.

Anti-VEGFs (aflibercept, bevacizumab, or ranibizumab) ± PRP probably increase the chance of a complete regression of new vessels of PDR (RR 1.63, 95% CI 1.19 to 2.24; I^2 = 46%; 5 RCTs, 405 eyes; moderate-certainty evidence; Analysis 1.2; Summary of findings 1). Overall, there was moderate heterogeneity (I^2 = 46%) and no evidence for any difference according to the type of anti-VEGF (test for subgroup differences P = 0.07).

Regression of new vessels (mean area of fluorescein leakage)

Four trials reported regression of diabetic retinopathy as a continuous outcome (Ergur 2009; Figueira 2018; Lang 2019; Ramos Filho 2011). All trials reported this outcome at 12 months, except Ergur 2009 who reported it at six months. Two studies reported differences from baseline in the area (mm^2) of new vessels (Figueira 2018; Ramos Filho 2011). All studies used FFA for measuring this outcome. Ergur 2009 and Figueira 2018 also used fundus photography.

Anti-VEGFs (bevacizumab, or ranibizumab) ± PRP may increase regression of PDR compared with PRP alone (MD -4.14 mm^2, 95% CI -6.84 to -1.43; 4 RCTs, 189 eyes; low-certainty evidence; Analysis 1.3; Summary of findings 1). Overall, there was a high risk of bias, high heterogeneity (I^2 = 75%), and evidence for difference according to the type of anti-VEGF (test for subgroup differences P < 0.001). The bevacizumab group presented more regression of new vessels in comparison with the ranibizumab group, but this result was based on only one study of 19 eyes (Ergur 2009).

Presence of microaneurysms

None of the studies specifically reported the presence of microaneurysms.

Presence of vitreous haemorrhage

Six trials reported the presence of vitreous haemorrhage. One of these trials used intravitreal bevacizumab (Marashi 2017), one trial used intravitreal pegaptanib (González 2009), one used aflibercept (Sivaprasad 2017), and three trials used ranibizumab (DRCR.net 2013; DRCR.net 2015; Lang 2019).

All studies used anti-VEGF as an adjunct to PRP and compared them with PRP alone, except González 2009 and Sivaprasad 2017, who administered anti-VEGFs alone.

The presence of vitreous haemorrhage was assessed at nine months (González 2009), 12 months (DRCR.net 2013; Marashi 2017; Lang 2019; Sivaprasad 2017), and 24 months (DRCR.net 2015).

Anti-VEGFs (aflibercept, bevacizumab, pegaptanib, or ranibizumab) ± PRP probably reduce vitreous haemorrhage compared with PRP alone (RR 0.72, 95% CI 0.57 to 0.90; I^2= 0%; 6 RCTs, 1008 eyes; moderate-certainty evidence; Analysis 1.4; Summary of findings 1). Overall there was no heterogeneity (I^2 = 0%) and no evidence of any difference according to the type of anti-VEGF (test for subgroup differences P = 0.51).

Need for laser photocoagulation

Two studies reported the need for laser photocoagulation in all arms of treatment (DRCR.net 2015; Lang 2019). Anti-VEGFs (ranibizumab) without PRP probably reduce the need for laser photocoagulation (overall pooled RR 0.18, 95% CI 0.11 to 0.28; I^2= 0%; 2 RCTs, 464 eyes; moderate-certainty evidence; Analysis 1.5). We downgraded the certainty of evidence (-1) for the high risk of bias.

Need for vitrectomy

Eight trials reported the need for vitrectomy. One used aflibercept (Sivaprasad 2017), one bevacizumab (Meng 2016), one pegaptanib (González 2009), and five trials used ranibizumab Chelala 2018; DRCR.net 2013; DRCR.net 2015; Figueira 2018; Lang 2019).

This outcome was assessed at three months (Meng 2016), four months (Chelala 2018), seven months (González 2009), 12 months (DRCR.net 2013; Sivaprasad 2017; Figueira 2018; Lang 2019), and 24 months (DRCR.net 2015).

Anti-VEGFs (aflibercept, bevacizumab, or ranibizumab) ± PRP may reduce the need for vitrectomy compared with PRP alone (RR 0.67, 95% CI 0.49 to 0.93; I^2= 43%; 8 RCTs, 1248 eyes; low-certainty evidence; Analysis 1.6; Summary of findings 1). The heterogeneity (I^2) was moderate (43%) and there was no evidence of any difference according to the type of anti-VEGF (test for subgroup differences P = 0.45).

Diabetic macular oedema measured by macular thickness

Four trials reported DMO as a continuous outcome, measuring the macular thickness in µm. One used bevacizumab (Rebecca 2021), one pegaptanib (González 2009), and two trials used ranibizumab (Lang 2019; Ramos Filho 2011). All studies combined anti-VEGFs with PRP, except González 2009 which used pegaptanib alone and compared it with PRP.

This outcome was assessed at six months (Rebecca 2021), nine months (González 2009), and 12 months (Lang 2019; Ramos Filho 2011). Lang 2019 and Ramos Filho 2011 reported changes in macular thickness with regard to baseline values. Anti-VEGFs (bevacizumab, pegaptanib, ranibizumab) ± PRP may reduce slightly

DMO compared with PRP alone (MD -45.95 µm, 95% CI -80.02 to -11.88; I^2= 52%; 4 RCTs, 175 eyes; low-certainty evidence; Analysis 1.7). The heterogeneity (I^2) was moderate (52%) and there was no subgroup difference according to the type of anti-VEGF (test for subgroup differences P = 0.05).

Quality of life

Two studies reported quality of life using the National Institute Visual Function Questionnaire (NEI VFQ-25) (DRCR.net 2015; Sivaprasad 2017). The NEI VFQ-25 contains 25 questions within 11 vision subscales and one general health subscale. Scoring ranges from 0 (worst) to 100 (best vision-related function). Vision subscales include general, peripheral, and colour vision, difficulty with near- and distance-vision activities, driving, vision-specific dependency, social functioning, mental health, role difficulties, and ocular pain. We do not know if anti-VEGFs (aflibercept, ranibizumab) ± PRP had an impact on quality of life compared with only PRP (MD 0.62, 95% CI -3.99 to 5.23; I^2= 0%; 2 RCTs, 382 participants; very low-certainty evidence; Analysis 1.8; Summary of findings 1).

Adverse events

Six studies reported adverse events, in a total of 981 participants (1070 eyes). One study used aflibercept (Sivaprasad 2017), and five used ranibizumab (DRCR.net 2013; DRCR.net 2015; Figueira 2016; Lang 2019; Ramos Filho 2011). See Analysis 1.9; Summary of findings 1.

Angina

One study with 23 participants reported angina (Figueira 2016). We do not know whether anti-VEGF with or without PRP compared with only PRP had an impact on angina because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 95% 3.82 CI 0.17 to 84.90; 23 participants; Analysis 1.9; Summary of findings 1).

Any Anti-Platelet Trialists' Collaboration (APTC) event

Two trials reported APTC events (DRCR.net 2015; Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on APTC events because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 1.64, 95% CI 0.78 to 3.43; I^2 = 0; 448 participants; Analysis 1.9; Summary of findings 1).

Arterial hypertension

Three trials reported arterial hypertension (DRCR.net 2013; DRCR.net 2015; Figueira 2018). We do not know if anti-VEGF ± PRP compared with PRP had an effect on arterial hypertension compared because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 0.43, 95% CI 0.16 to 1.22; I^2 = 10%; 742 participants; Analysis 1.9; Summary of findings 1).

Progression of cataract

One trial reported cataracts (Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on the progression of cataracts because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 0.33, 95% CI 0.01 to 8.10; 232 eyes; Analysis 1.9; Summary of findings 1).

Cerebrovascular accident

Two trials reported cerebrovascular accidents (CVA) (DRCR.net 2013; Sivaprasad 2017). We do not know if anti-VEGFs ± PRP compared with PRP had an effect on CVA because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 4.92, 95% CI 0.56 to 42.99; I^2 = 0%; 493 participants; Analysis 1.9; Summary of findings 1).

Cornea-related problems

Two trials reported cornea-related problems (Lang 2019; Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on developing cornea-related problems because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 2.34, 95% CI 0.20 to 27.20; I^2 = 64%; 303 eyes; Analysis 1.9; Summary of findings 1).

Endophthalmitis

Four trials reported endophthalmitis (DRCR.net 2013; DRCR.net 2015; Figueira 2018; Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on developing endophthalmitis-related problems because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 1.07, 95% CI 0.11 to 10.27; I^2 = 0%; 887 eyes; Analysis 1.9; Summary of findings 1).

Eye inflammation

One study with 232 participants reported ocular inflammation (Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on ocular inflammation because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 3.00, 95% CI 0.83 to 10.80; Analysis 1.9; Summary of findings 1).

Macular oedema

Two trials reported cornea macular oedema (Lang 2019; Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on developing macular oedema because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 0.49, 95% CI 0.19 to 1.26; I^2 = 0%; 303 eyes; Analysis 1.9; Summary of findings 1).

Neovascular glaucoma

Three trials reported neovascular glaucoma (DRCR.net 2013; DRCR.net 2015; Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on developing neovascular glaucoma because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 0.61, 95% CI 0.18 to 2.09; I^2 = 0%; 887 eyes; Analysis 1.9; Summary of findings 1).

Ocular discomfort

One study with 232 participants reported ocular discomfort (Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on the risk of ocular discomfort because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 1.50, 95% CI 0.43 to 5.18; Analysis 1.9; Summary of findings 1).

Raised intraocular pressure

Four trials reported an increase in intraocular pressure (IOP) (DRCR.net 2013; DRCR.net 2015; Lang 2019; Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on developing raised intraocular pressure, because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 0.88, 95% CI 0.51 to 1.53; 858 eyes; I^2 = 25%; Analysis 1.9; Summary of findings 1).

Retinal detachment

Three trials reported retinal detachment (DRCR.net 2013; DRCR.net 2015; Sivaprasad 2017). We do not know if anti-VEGF with or without PRP compared with PRP had an effect on retinal detachment, because the certainty of evidence was very low and the CIs were wide and compatible with no effect (the certainty of evidence was very low; RR 0.78, 95% CI 0.49 to 1.24; I^2 = 0%; 3 RCTs, 887 eyes; Analysis 1.9; Summary of findings 1).

Retinal tear

One trial reported a retinal tear (Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on a retinal tear because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 3.00, 95% CI 0.12 to 72.89; 232 eyes; Analysis 1.9; Summary of findings 1).

Pain

One trial reported pain, which was measured on a 100-mm visual analogue scale (Ramos Filho 2011). People receiving ranibizumab intravitreal injection and PRP reported a mean pain score of 4.7 (SD 8.4), which was much lower than people receiving PRP who reported a mean pain score of 60.8 (SD 29.2). This gave an MD of -56.1 (95% CI -71.9 to -40.3; 31 participants) in favour of ranibizumab intravitreal injection. However, we do not know if anti-VEGF ± PRP compared with PRP had an effect on pain because the certainty of evidence was very low due to the high risk of bias and the low number of participants.

Visual disturbances

One study with 232 participants reported visual disturbances (Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on visual disturbances because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 95% 0.91 CI 0.40 to 2.06; Analysis 1.9; Summary of findings 1).

Vitreoretinal interface abnormalities

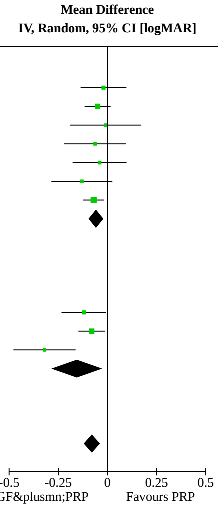
One study with 232 participants reported vitreoretinal interface abnormalities (Sivaprasad 2017). We do not know if anti-VEGF ± PRP compared with PRP had an effect on vitreoretinal interface abnormalities because the certainty of evidence was very low and the CIs were wide and compatible with no effect (RR 2.00, 95% CI 0.18 to 21.75; Analysis 1.9; Summary of findings 1).

Subgroup analysis: comparison by the severity of the disease, PDR versus HRPDR

Stratifying the analysis by the severity of the disease (PDR versus HRPDR), seven RCTs assessed people with PDR (DRCR.net 2013; DRCR.net 2015; Ergur 2009; González 2009; Lang 2019; Sameen 2017; Sivaprasad 2017) and three RCTs people with HRPDR (Figueira 2018; Ramos Filho 2011; Rebecca 2021); 980 eyes were included in the PDR group and 192 eyes in the HRPDR group. The results were similar to the main analysis. There were no differences between subgroups analysed in visual acuity (P = 0.13; Analysis 2.1; Figure 5).

Figure 5. Forest plot of comparison: 4 Stratification by severity of the disease: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, outcome: 4.1 Visual acuity [logMAR]

Study or Subgroup	Favours anti-VEGF±PRP Mean [logMAR]	SD [logMAR]	Total	PRP Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]	A	B	C	D	E	F
2.1.1 PDR														
DRCR.net 2013 (1)	0.4	0.44	125	0.42	0.52	136	8.3%	-0.02 [-0.14 , 0.10]	?	+	+	+	+	+
DRCR.net 2015 (2)	0.126	0.326	160	0.176	0.282	168	17.8%	-0.05 [-0.12 , 0.02]	+	+	−	+	−	+
Ergur 2009 (3)	0.37	0.18	9	0.38	0.22	10	4.0%	-0.01 [-0.19 , 0.17]	?	?	?	?	+	+
González 2009 (4)	0.065	0.195	8	0.1275	0.118	8	5.0%	-0.06 [-0.22 , 0.10]	+	?	−	?	+	+
Lang 2019 (5)	0.12	0.24	36	0.16	0.34	35	6.4%	-0.04 [-0.18 , 0.10]	?	?	−	+	?	+
Sameen 2017 (6)	0.42	0.35	38	0.55	0.34	38	5.2%	-0.13 [-0.29 , 0.03]	?	?	−	?	?	+
Sivaprasad 2017 (7)	0.05	0.2	105	0.12	0.19	104	22.1%	-0.07 [-0.12 , -0.02]	+	+	−	+	+	+
Subtotal (95% CI)			**481**			**499**	**68.9%**	**-0.06 [-0.09 , -0.02]**						
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 6 (P = 0.93); I² = 0%														
Test for overall effect: Z = 3.29 (P = 0.0010)														
2.1.2 HRPDR														
Figueira 2018 (5)	0.196	0.24	41	0.316	0.3	46	8.7%	-0.12 [-0.23 , -0.01]	+	+	−	+	?	+
Ramos Filho 2011 (5)	0	0.07	15	0.08	0.11	14	17.4%	-0.08 [-0.15 , -0.01]	?	+	?	+	−	+
Rebecca 2021 (8)	0.1	0.25	38	0.42	0.43	38	5.0%	-0.32 [-0.48 , -0.16]	?	?	?	?	+	?
Subtotal (95% CI)			**94**			**98**	**31.1%**	**-0.16 [-0.28 , -0.03]**						
Heterogeneity: Tau² = 0.01; Chi² = 7.48, df = 2 (P = 0.02); I² = 73%														
Test for overall effect: Z = 2.50 (P = 0.01)														
Total (95% CI)			**575**			**597**	**100.0%**	**-0.08 [-0.12 , -0.04]**						
Heterogeneity: Tau² = 0.00; Chi² = 12.54, df = 9 (P = 0.18); I² = 28%														
Test for overall effect: Z = 4.09 (P < 0.0001)														
Test for subgroup differences: Chi² = 2.27, df = 1 (P = 0.13), I² = 55.9%														



Footnotes

(1) Ranibizumab and PRP compared with PRP alone, follow-up 12 months
(2) Ranibizumab plus deferred PRP compared with prompt PRP, follow-up 2 years
(3) Bevacizumab and PRP compared with PRP alone, follow-up 6 months
(4) Pegaptanib alone compared with PRP alone, change in visual acuity, follow-up 9 months
(5) Ranibizumab and PRP compared with PRP alone, change in visual acuity, follow-up 12 months
(6) Bevacizumab plus PRP compared with PRP alone, follow-up 12 months
(7) Aflibercept compared with PRP alone, follow-up 52 weeks
(8) Bevacizumab and PRP compared with PRP alone, follow-up 6 months. The SD reported is very low and we interpreted was a SE

Risk of bias legend

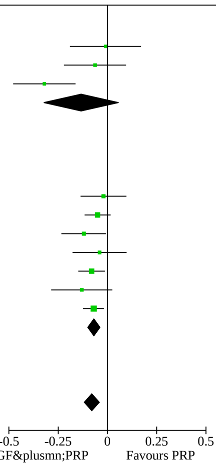
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Subgroup analysis: comparison by the time of follow-up, < 12 months versus 12 months or more

Stratifying the analysis by time of follow-up (< 12 months versus ≥ 12 months), three RCTs presented a follow-up of < 12 months (Ergur 2009; González 2009; Rebecca 2021), and seven RCTs presented a follow-up of 12 or more months (DRCR.net 2013; DRCR.net 2015; Figueira 2018; Lang 2019; Ramos Filho 2011; Sameen 2017; Sivaprasad 2017). The median time of follow-up was four months (from three to seven months) and 12 months (from 12 to 24 months), respectively; 111 eyes were included in the group with < 12 months of follow-up, and 1061 eyes in the group with 12 months or more. The results were similar to the main analysis. There were no differences between subgroups analysed in visual acuity (P = 0.51; Analysis 3.1; Figure 6).

Figure 6. Forest plot of comparison: 2 Analysis stratified by time of follow-up: <12 months vs 12 months or more, outcome: 2.1 Visual acuity [logMAR]

Study or Subgroup	Favours anti-VEGF±PRP Mean [logMAR]	SD [logMAR]	Total	PRP Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]	A	B	C	D	E	F
3.1.1 Less than 12 months of treatment														
Ergur 2009 (1)	0.37	0.18	9	0.38	0.22	10	4.0%	-0.01 [-0.19 , 0.17]	?	?	?	?	+	+
González 2009 (2)	0.065	0.195	8	0.1275	0.118	8	5.0%	-0.06 [-0.22 , 0.10]	+	?	−	?	+	+
Rebecca 2021 (3)	0.1	0.25	38	0.42	0.43	38	5.0%	-0.32 [-0.48 , -0.16]	?	?	?	?	+	?
Subtotal (95% CI)			**55**			**56**	**14.1%**	**-0.13 [-0.32 , 0.06]**						
Heterogeneity: Tau² = 0.02; Chi² = 7.90, df = 2 (P = 0.02); I² = 75%														
Test for overall effect: Z = 1.38 (P = 0.17)														
3.1.2 12 months or more of treatment														
DRCR.net 2013 (4)	0.4	0.44	125	0.42	0.52	136	8.3%	-0.02 [-0.14 , 0.10]	?	+	+	+	+	+
DRCR.net 2015 (5)	0.126	0.326	160	0.176	0.282	168	17.8%	-0.05 [-0.12 , 0.02]	+	+	−	+	−	+
Figueira 2018 (6)	0.196	0.24	41	0.316	0.3	46	8.7%	-0.12 [-0.23 , -0.01]	+	+	−	+	?	+
Lang 2019 (6)	0.12	0.24	36	0.16	0.34	35	6.4%	-0.04 [-0.18 , 0.10]	?	?	−	+	?	+
Ramos Filho 2011 (6)	0	0.07	15	0.08	0.11	14	17.4%	-0.08 [-0.15 , -0.01]	?	+	?	+	−	+
Sameen 2017 (7)	0.42	0.35	38	0.55	0.34	38	5.2%	-0.13 [-0.29 , 0.03]	?	?	−	?	?	+
Sivaprasad 2017 (8)	0.05	0.2	105	0.12	0.19	104	22.1%	-0.07 [-0.12 , -0.02]	+	+	−	+	+	+
Subtotal (95% CI)			**520**			**541**	**85.9%**	**-0.07 [-0.10 , -0.04]**						
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 6 (P = 0.85); I² = 0%														
Test for overall effect: Z = 4.37 (P < 0.0001)														
Total (95% CI)			**575**			**597**	**100.0%**	**-0.08 [-0.12 , -0.04]**						
Heterogeneity: Tau² = 0.00; Chi² = 12.54, df = 9 (P = 0.18); I² = 28%														
Test for overall effect: Z = 4.09 (P < 0.0001)														
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%														



Footnotes

(1) Bevacizumab and PRP compared with PRP alone, follow-up 6 months
(2) Pegaptanib alone compared with PRP alone, change in visual acuity, follow-up 9 months
(3) Bevacizumab and PRP compared with PRP alone, follow-up 6 months. The SD reported is very low and we interpreted was a SE
(4) Ranibizumab and PRP compared with PRP alone, follow-up 12 months
(5) Ranibizumab plus deferred PRP compared with prompt PRP, follow-up 2 years
(6) Ranibizumab and PRP compared with PRP alone, change in visual acuity, follow-up 12 months
(7) Bevacizumab plus PRP compared with PRP alone, follow-up 12 months
(8) Aflibercept compared with PRP alone, follow-up 52 weeks

Risk of bias legend

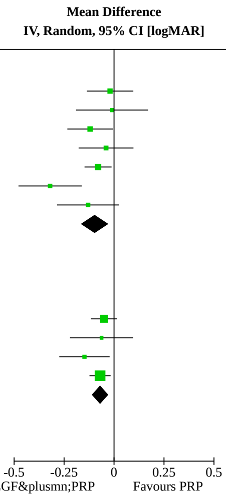
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Subgroup analysis: comparison of anti-VEGF plus PRP or anti-VEGF alone versus PRP alone

Stratifying the analysis by anti-VEGF combined with PRP or not and compared with anti-VEGF alone, seven RCTs (DRCR.net 2013; Ergur 2009; Figueira 2018; Lang 2019; Ramos Filho 2011; Rebecca 2021; Sameen 2017) assessed anti-VEGF combined with PRP, and four RCTs (DRCR.net 2015; González 2009; Lang 2019; Sivaprasad 2017) administered anti-VEGF alone; 619 eyes were included in the group anti-VEGF plus PRP and 623 eyes in the group with anti-VEGF alone. The results were similar to the main analysis and there were no differences between the subgroups analysed in the outcomes of visual acuity (P = 0.48; Analysis 4.1, Figure 7).

Figure 7. Forest plot of comparison: 4 Analysis stratified by anti-vascular endothelial growth factor (anti-VEGF) plus PRP versus anti-VEGF alone, both compared with PRP, outcome: 4.1 Visual acuity [logMAR]

	Anti-VEGF			PRP				Mean Difference	Risk of Bias					
Study or Subgroup	Mean [logMAR]	SD [logMAR]	Total	Mean [logMAR]	SD [logMAR]	Total	Weight	IV, Random, 95% CI [logMAR]	A	B	C	D	E	F
4.1.1 Anti-VEGF plus PRP														
DRCR.net 2013 (1)	0.4	0.44	125	0.42	0.52	136	15.7%	-0.02 [-0.14 , 0.10]	?	+	+	+	+	+
Ergur 2009 (2)	0.37	0.18	9	0.38	0.22	10	9.2%	-0.01 [-0.19 , 0.17]	?	?	?	?	+	+
Figueira 2018 (3)	0.196	0.24	41	0.316	0.3	46	16.1%	-0.12 [-0.23 , -0.01]	+	+	−	+	?	+
Lang 2019 (3)	0.12	0.24	36	0.16	0.34	35	13.1%	-0.04 [-0.18 , 0.10]	?	?	−	+	?	+
Ramos Filho 2011 (3)	0	0.07	15	0.08	0.11	14	23.7%	-0.08 [-0.15 , -0.01]	?	+	?	+	−	+
Rebecca 2021 (4)	0.1	0.25	38	0.42	0.43	38	11.0%	-0.32 [-0.48 , -0.16]	?	?	?	?	+	?
Sameen 2017 (5)	0.42	0.35	38	0.55	0.34	38	11.3%	-0.13 [-0.29 , 0.03]	?	?	−	?	?	+
Subtotal (95% CI)			**302**			**317**	**100.0%**	**-0.10 [-0.16 , -0.03]**						
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.38$, df = 6 (P = 0.08); $I^2 = 47\%$														
Test for overall effect: Z = 2.95 (P = 0.003)														
4.1.2 Anti-VEGF alone														
DRCR.net 2015 (6)	0.126	0.326	160	0.176	0.282	168	33.2%	-0.05 [-0.12 , 0.02]	+	+	−	+	−	+
González 2009 (7)	0.065	0.195	8	0.1275	0.118	8	5.8%	-0.06 [-0.22 , 0.10]	+	?	−	?	+	+
Lang 2019	0.012	0.17	35	0.16	0.34	35	9.1%	-0.15 [-0.27 , -0.02]	?	?	−	+	?	+
Sivaprasad 2017 (8)	0.05	0.2	105	0.12	0.19	104	51.9%	-0.07 [-0.12 , -0.02]	+	+	−	+	+	+
Subtotal (95% CI)			**308**			**315**	**100.0%**	**-0.07 [-0.11 , -0.03]**						
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.83$, df = 3 (P = 0.61); $I^2 = 0\%$														
Test for overall effect: Z = 3.61 (P = 0.0003)														
Test for subgroup differences: $Chi^2 = 0.51$, df = 1 (P = 0.48), $I^2 = 0\%$														



Footnotes

(1) Ranibizumab and PRP compared with PRP alone, follow-up 12 months
(2) Bevacizumab and PRP compared with PRP alone, follow-up 6 months
(3) Ranibizumab and PRP compared with PRP alone, change in visual acuity, follow-up 12 months
(4) Bevacizumab and PRP compared with PRP alone, follow-up 6 months. The SD reported is very low and we interpreted was a SE
(5) Bevacizumab plus PRP compared with PRP alone, follow-up 12 months
(6) Ranibizumab plus deferred PRP compared with prompt PRP, follow-up 2 years. Only 6% of eyes (12 out 191) received delayed PRP in the anti-VEGF group .
(7) Pegaptanib alone compared with PRP alone, change in visual acuity, follow-up 9 months
(8) Aflibercept compared with PRP alone, follow-up 52 weeks

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Brief economic commentary

The reporting of the five included studies was limited. Based on the authors' reports only, there is conflicting evidence about the cost-effectiveness analysis of anti-VEGF treatment for the management of PDR. The two analyses alongside clinical trials both found anti-VEGF treatments to be more costly, but they differed as to whether concurrent DMO is required to offset this cost, with Hutton 2017 and Hutton 2019 concluding it is. Sivaprasad 2018 did not conclude that people with DMO were likely to be more cost-effective to treat, but is also uncertain whether the quality of life outcomes matched up with the clinical results. With respect to the modelling studies, Lin 2016, Lin 2018, and Yannuzzi 2018 all concluded that PRP and PPV are more likely to be cost-effective compared with ranibizumab. However, the three modelling studies utilised methods not consistent with recommended practices for economic modelling (Caro 2012).

DISCUSSION

Summary of main results

The aim of this review was to evaluate the effectiveness and safety of anti-VEGFs in PDR. This update included 23 RCTs with 1755 participants (2334 eyes) who needed laser or surgical treatment for PDR or the complications of PDR. A similar number of PRP sessions was delivered in the anti-VEGF and PRP groups, except in three studies in which no laser was delivered in the anti-VEGF group, whereas only two studies allowed the use of anti-VEGF injections to treat DME in the PRP group (DRCR.net 2015; Shahraki 2022).

People receiving anti-VEGF in association with laser treatment for PDR had better visual acuity at 12 months of follow-up (mean difference of four letters, 95% CI from 2 to 6 letters). They were more likely to have regression of new vessels (23% reduction; 95% CI from 11 to 35%), less likely to experience vitreous haemorrhage (7% reduction; 95% CI from 2 to 12%) and less likely to need vitrectomy (reduction of 6%; 95% CI from 1 to 11%). There was no evidence of any increased risk of adverse events with anti-VEGF.

In addition, we found three ongoing trials; all except one trial will follow participants up for 12 months.

The reporting of the five economic studies included was limited. There is conflicting evidence about the cost-effectiveness of anti-VEGF treatment for the management of PDR.

Overall completeness and applicability of evidence

Participants included in the review presented PDR or HRPDR that needed PRP (23 RCTs). The mean follow-up was eight months.

No studies assessed our primary outcome (gain or loss of 3 or more lines of ETDRS) in PDR. However, there was a sufficient number of studies that calculated visual acuity in logMAR (10 RCTs and 1172 eyes), reported complete regression of ocular new vessels (5 RCTs and 405 eyes) or regression of ocular new vessels as a continuous outcome (4 RCTs and 189 eyes), presented data about vitreous haemorrhage (6 RCTs and 1008 eyes), and macular oedema measuring the macula thickness (4 RCTs and 175 eyes). Only two studies reported quality of life, and their results were uncertain, with very low certainty of evidence. Furthermore, the monitoring of participants was less than one year in most studies. There was no evidence of any increased risk of adverse events with anti-VEGF.

The number of RCTs was variable between anti-VEGFs: bevacizumab (12 RCTs) was the most evaluated, followed by ranibizumab (seven RCTs), pegaptanib (two RCTs), aflibercept (one RCT), and conbercept (one RCT). Although the level of assessment of these drugs was not the same, in the overall analysis there were no significant differences between subgroups for the outcomes visual acuity and vitreous haemorrhage.

In this update, according to the original protocol, we included all studies for the meta-analysis independently of their follow-up, to be more inclusive in the assessment of new anti-VEGFs. We did not observe any relevant difference in visual acuity, stratifying studies with < 12 months (seven RCTs) versus ≥ 12 months (five RCTs) of follow-up. There were secondary publications of the DRCR.net 2015 trial with results at a five-year follow-up, but we did not include them in the meta-analysis because treatments were crossed between groups and there was contamination bias: 14% of eyes received PRP in the ranibizumab group and 58% eyes received at least one injection of ranibizumab for DME in the PRP group during the five years.

We found a mean difference of 0.08 logMAR improvement in the visual acuity that corresponds to four letters (95% CI from 2.5 letters to 5 letters). This result is not clinically relevant because patients only appreciate a change higher than 0.2 log MAR (10 letters or 2 lines) in visual acuity (Rosser 2003). In the subgroup analysis that compared anti-VEGF plus PRP or alone, we did not find evidence of a difference between subgroups in visual acuity. These results reinforce the main analysis comparing Anti-VEGF ± PRP versus PRP alone. We also found no difference in the subgroup analysis that compared visual acuity in studies of people with PDR versus studies of people with HRPDR.

We found three ongoing RCTs that, in the future, may resolve doubts about the efficacy and safety of these drugs for PDR (Characteristics of ongoing studies).

Although we included 23 RCTs, only 13 (56.5%) reported data that were meta-analysed. We excluded 10 studies from the meta-analysis because they had within-person randomisation (9 RCTs) or reported insufficient data to include in the meta-analysis (Gonzalez 2014). From the studies included in the analysis, four studies had attrition bias. One clinical trial did not reach the calculated sample size (Figueira 2016), and three had important losses. DRCR.net 2015 and Ramos Filho 2011 had losses of follow-up (from 16% to 27.5%) that were balanced between groups. However, the PRP group in the Figueira 2018 study lost more participants than the anti-VEGF plus PRP group (40.1% versus 29.3%).

Brief economic commentary

For the brief economic commentary, we summarised the results of identified studies based on what the study authors reported. These studies have not been critically appraised, and the studies may have used methods that are not consistent with accepted practice. For this reason, and because the studies were conducted at different times and in different places, we have not attempted to draw any firm or general conclusions regarding the relative costs or efficiency of anti-VEGF strategies for managing PDR.

We identified five studies (Hutton 2017; Lin 2016; Lin 2018; Sivaprasad 2018; Yannuzzi 2018), one of which was described in two publications (Hutton 2017; Hutton 2019). All the studies compared laser photocoagulation to anti-VEGF injection treatment. Two studies evaluated the effects of ranibizumab (Hutton 2017; Lin 2016), whereas Sivaprasad 2018 and Yannuzzi 2018 evaluated the effects of aflibercept compared to photocoagulation. One study compared pars plana vitrectomy as a treatment strategy in addition to PRP and ranibizumab (Lin 2018). Two studies were economic evaluations carried out alongside clinical trials (Hutton 2017; Sivaprasad 2018). Two studies utilised economic decision models (Lin 2016; Yannuzzi 2018). Hutton 2019 carried out a within-trial analysis of the five-year outcomes from the trial and also simulated the results to a 10-year time horizon. Four studies were carried out in the USA (Hutton 2017; Lin 2016; Lin 2018; Yannuzzi 2018), and one was carried out in the UK (Sivaprasad 2018). The costs used in the commentary were converted to USD 2021 using the Campbell and Cochrane Economics Methods Group (CCEMG) cost converter. A detailed summary of each economic evaluation is reported in Additional Table 5.

Quality of the evidence

The overall certainty of evidence ranged from very low to moderate in this review (Summary of findings 1). We downgraded the certainty of the evidence because 16 of 23 RCTs had a high risk of bias. The high risk of bias was due to not masking the interventions (DRCR.net 2015; Figueira 2016; Figueira 2018; González 2009; Gonzalez 2014; He 2020; Lang 2019; Marashi 2017; Sameen 2017; Sivaprasad 2017), attrition bias (DRCR.net 2015; Figueira 2016; Preti 2017; Ramos Filho 2011; Shahraki 2022), and selective reporting (Chelala 2018; Gonzalez 2014; Marashi 2017; Preti 2013; Preti 2017; Roohipoor 2016). Furthermore, only five trials specified the calculation of the sample size (DRCR.net 2013; DRCR.net 2015; Figueira 2016; Sameen 2017; Sivaprasad 2017).

For some outcomes, the results of the individual studies were heterogeneous and, although we provided a pooled estimate, we downgraded it for inconsistency. Furthermore, only five studies were funded by independent institutions and the authors declared no conflict of interest. Seven studies were partially or completely industry-funded and in eight studies authors declared they have been receiving financial fees from the industry. Eleven studies did not declare the funding source and 10 studies did not declare the authors' conflicts of interest. Therefore, there is an important lack of transparency in these investigations.

Potential biases in the review process

This review has methodological strengths, as it has been successful in obtaining information from trial investigators. Although not all have responded, most investigators have done so. We have also made an exhaustive search of clinical trials (including those in progress), and have assessed the risk of bias and extracted data in a duplicate way. We found no evidence of publication bias.

However, this review is limited by the quality of RCTs, which included a low number of participants per RCT and presented an unclear or high risk of bias. Furthermore, eight studies were not included in the efficacy analysis because the fellow eye was used as a control group (Ahmad 2012; Ali 2018; He 2020; Mirshahi 2008; Preti 2013; Preti 2017; Roohipoor 2016; Shahraki 2022). However, we have included studies with a low percentage of participants with the fellow eye used as a control (DRCR.net 2015; Ergur 2009; Meng 2016; Rebecca 2021; Sameen 2017).

We made some modifications to the protocol (Differences between protocol and review) but did not consider that these changes will have introduced bias.

Agreements and disagreements with other studies or reviews

We have identified four non-Cochrane systematic reviews recently published that assessed anti-VEGF therapy for diabetic retinopathy (Gao 2020; Ngo Ntjam 2021; Yates 2021; Zhang 2022).

Yates 2021 assessed anti-VEGF monotherapy versus panretinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR). In our review, when studies had more than two arms, we prioritised the arm of the combination of the anti-VEGF with PRP over the anti-VEGF alone. For this reason, we only included data from three of 28 RCTs where anti-VEGFs were evaluated alone. Yates 2021 included only five RCTs that were also included in our review. The conclusions were very similar to ours: the anti-VEGF intervention arm had a mean difference of -0.08 logMAR gained when compared with PRP at 12 months. The difference in rates of vitrectomy and vitreous haemorrhage also favoured anti-VEGF alone over PRP.

Gao 2020 assessed the efficacy and safety of intravitreal anti-VEGF therapy with or without the combination of PRP against PRP monotherapy for proliferative diabetic retinopathy. They included 15 RCTs. Results showed superior visual acuity outcomes and fewer PDR-related complications, in line with our review. However, our results are more consistent because they included a lower number of clinical trials (15) than ours. We agree in 13 included clinical trials, except for one RCT, where we differed in our evaluation of the risk of bias. Gao 2020 considered there to be a low risk of bias in the masking of participants and investigators, whereas our evaluation did not. Zhang 2022 assessed the efficacy and safety of PRP combined with intravitreal anti-VEGFs against PRP monotherapy for diabetic retinopathy. They included only 11 clinical trials and their conclusions were similar to our review. We agreed on the inclusion of six studies, but we differed in our evaluation of the risk of bias in the same way as we have described for Gao 2020.

A recent systematic review by Ngo Ntjam 2021 included 74 RCTs and assessed systemic adverse events of anti-VEGFs in people with age-related macular degeneration, diabetic retinopathy (diabetic macular oedema, or proliferative diabetic retinopathy), retinal vein occlusion, and myopic choroidal neovascularisation. Ngo Ntjam 2021 showed that anti-VEGFs were not associated with increased arterial or venous thromboembolic events. This conclusion agrees with our review but we did not find any evidence of the association of anti-VEGFs with adverse events. However, Ngo Ntjam 2021 found non-ocular haemorrhagic events in people with age-related macular degeneration and a small increase in total mortality in people with diabetic retinopathy.

AUTHORS' CONCLUSIONS

Implications for practice

There was very low to moderate-certainty evidence from randomised controlled trials for the efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) drugs when used to treat proliferative diabetic retinopathy (PDR) or high-risk PDR (HRPDR) over and above current standard treatments. The results suggest that anti-VEGFs can improve visual acuity; however, it is not a clinically important improvement. Additionally, anti-VEGFs reduce the formation of new vessels and the risk of intraocular bleeding, and may slightly reduce diabetic macular oedema (DMO) and the need for vitrectomy compared with panretinal photocoagulation (PRP) alone in people with PDR.

Implications for research

There is a clear need for further adequate clinical trials to assess the efficacy of anti-VEGFs for PDR over a longer follow-up period. It is important to study the effect and the optimal posology of anti-VEGFs alone in the long term (more than 12 to 24 months) without PRP as a co-intervention, and to compare it with PRP alone. This proposal is based on the results of our subgroup analysis and the fact that the effect of anti-VEGF is time-limited and requires more than one dose.

If the unit of randomisation is the eye, appropriate modifications of the sample size and statistical analysis are required, i.e. taking into account within-person correlation. The calculations of sample size should be based on relevant clinical differences. The concealment of interventions (e.g. blinding the outcome assessor) and a long-term follow-up (at least 12 months) are necessary to improve the quality of clinical trials. Longer follow-up studies would also be useful to better estimate cost-effectiveness for different types of patients. Future clinical trials should report data about quality of life or patient-reported outcomes.

We identified three ongoing trials registered in trial registries: one of conbercept, one of brolucizumab, and one of bevacizumab. All except one study will assess participants for 12 months.

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Previous version

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmad 2012

Study characteristics

Ahmad 2012 *(Continued)*

Methods	Study design: prospective, parallel, single-blind, within-person randomised study to compare the effect of panretinal photocoagulation (PRP) plus intravitreal injection of bevacizumab in one eye versus PRP alone in the contralateral eye Unit of randomisation: eye Unit of analyses: eye Follow-up: 1 and 3 months after procedure
Participants	Country: Pakistan Setting: Department of Vitreoretinal Surgery, Khyber Institute of Ophthalmic Medical Sciences, Hayatabad Medical Complex, Peshawar Number of participants: 54 Exclusions post-randomisation: none Losses to follow-up: none Age (mean (SD)): experimental group 51.0 ± 6.0 and control group 50.8 ± 6.8 Gender: 33 men and 21 women Inclusion criteria: age ≥ 18 year, first-time PDR with almost same changes in both eyes with no prior retinal laser besides macular laser treatment Exclusion criteria: history of prior PRP or vitrectomy
Interventions	Treatment: PRP in two sessions performed at day 1 and day 15 in both eyes plus bevacizumab 1.25 mg (0.05 ml) 3 hours after PRP Control: PRP alone in two sessions performed at day 1 and day 15 as in both eyes Duration: 2 doses in two weeks Co-intervention: the eyes with clinically significant macular oedema (12 participants in control group and 13 participants in experimental group) received macular laser treatment as per ETDRS protocol before or at the time of initiating PRP
Outcomes	Primary: changes in neo vessels on the disc (NVD; measured in percentage of disc surface diameter) and neo vessels elsewhere (NVE; measured as referred to disc surface diameter) Secondary: best-corrected visual acuity (BCVA; measured with Snellen's chart converted to log MAR) at 1 month and 3 months after the procedure
Notes	Funding: not reported Trial registration: not reported Date conducted: October 2010 to August 2011 Conflict of interest: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Both eyes of each patient were randomly selected by simple lottery method”

Ahmad 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: it is unclear how blinding of the participants and personnel was achieved. No sham procedure was applied to control eyes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The physician did not know which eye has been injected."
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses.
Selective reporting (reporting bias)	Low risk	There was not a previously published protocol, but the outcomes referred to in methods have been specified in results.

Ali 2018

Study characteristics	
Methods	Study design: within-person randomised controlled trial Unit of randomisation: eye Unit of analyses: 60 eyes of 30 participants Follow-up: 6 months
Participants	Country: Pakistan Setting: Department of Ophthalmology, Benazir Bhutto Hospital, Rawalpindi, Pakistan Number of participants: 30 participants Exclusions post-randomisation: not reported Losses to follow-up: not reported Age (mean +/- SD): 52.3 +/- 6.8 years Gender: 11 (36.6%) men; 19 (63.3%) women Inclusion criteria: people with bilateral proliferative diabetic retinopathy with new vessels (NVD or NVE) associated with or without clinically significant macular oedema (CSME), presenting BCVA ≥ 6/60 or ≤ 6/12. The mean duration of diabetes was 10 ± 4.9 years. Age between 40 and 65 years. Exclusion criteria: people with non-proliferative diabetic retinopathy (NPDR) and advanced diabetic eye disease (tractional retinal detachment), an increase in retinal thickness and new vessels found in other ocular disorders such as age-related macular degeneration, central serous chorio-retinopathy (CSCR) and retinal vein occlusion, patients diagnosed with significant cataract and glaucoma.
Interventions	Treatment

Ali 2018 *(Continued)*

	Group A: intravitreal bevacizumab injection (1.25 mg/0.05 ml) 2 weeks before PRP session. Laser parameters: spot 200 to 500 micrometers, energy 300 to 500 W, exposition 50 to 100 msec, 1500 to 2000 burns. The eye undergoing treatment with injection was prepared by applying 5% povidone iodine. Retinal artery perfusion was checked after the injection, and participants were commenced on topical antibiotics for 7 days. Control Group B: PRP. 1 session of PRP. Laser parameters: spot 200 to 500 micrometers, energy 300 to 500 W, exposition 50 to 100 msec. 1500 to 2000 burns. After treatment at day 30, the clinical status of the two eyes in terms of retinal vessels (NVD/NVE) status was compared and evaluated by using BCVA, slit lamp biomicroscopy and fundus photography. Duration: 1 month Co-interventions: no
Outcomes	Primary: mean change in BCVA, NVD, and NVE. Time of assessment: results provided before PRP and on day 30.
Notes	Funding: not reported Trial registration: not reported Date conducted: December 2014 to July 2015 Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: random sequence not described
Allocation concealment (selection bias)	Unclear risk	Comment: allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: blinding not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the publication reports data of all participants. The authors did not refer to losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	Comment: data reported from all the primary and secondary outcomes. No data reported about other common factors in PDR that may affect visual acuity (i.e. vitreous haemorrhage incidence)

Chelala 2018

Study characteristics	
Methods	Study design: randomised clinical trial of intravitreal ranibizumab injections for the treatment of vitreous haemorrhage (VH) related to proliferative diabetic retinopathy. Unit of randomisation: participant Unit of analyses: eye Follow-up: 16 weeks
Participants	Country: Lebanon Setting: Department of Ophthalmology, the Eye and Ear University Hospital, Naccash, Lebanon. Number of participants: 133 (133 eyes): 71 (intervention group) and 62 (control group) Exclusions post-randomisation: 0 Losses to follow-up: 0 Age (mean (SD)): 67.9 (10.2) in ranibizumab group, 69.4 (8.5) in control group. Gender: 71 men and 32 women Inclusion criteria: people with diabetic proliferative retinopathy with VH of more than 2 weeks' duration. Exclusion criteria: people with rubeosis iridis, established neovascular glaucoma, tractional retinal detachment, or extensive fibrovascular tractional membranes; people with VH in whom it was unclear whether diabetic retinopathy was the cause; with a history of thromboembolic events (cerebrovascular accident or myocardial infarction); uncontrolled hypertension (systolic blood pressure 180 mmHg or diastolic blood pressure 110 mmHg); current use of anticoagulative medications or known coagulation abnormalities; with known allergies to the drugs used in the study or with evidence of external ocular infection (significant blepharitis, conjunctivitis, and chalazion)
Interventions	Treatment: intravitreal ranibizumab 0.5 mg at baseline, repeated at 4-week intervals when VH clearing was incomplete (for a maximum of four injections). Control group: observation alone. Co-intervention: in both groups, retinal photocoagulation was performed by independent ophthalmologists unaware of this study, whenever adequate fundus visualisation could be obtained. During this study we considered a PRP to be “complete,” if we had approximately 500 mm burns, 1 to 2 burns apart, on each of the retina 4 quadrants, starting at approximately 1 disk diameter from the macular vessel arcade and extending to the equator. Duration: 16 weeks
Outcomes	Primary: rate of vitrectomy and rate of recurrence of the VH (defined as a participant who had an improvement in his visual acuity (VA) on a follow-up visit because of a VH clearing and on the next follow-up a deterioration in VA was noted and was attributed to a worsening VH) at 16 weeks, and final VA at 2, 4, 6, 8,10, 12, 14 and 16 weeks (using Snellen charts). Secondary: visual acuity improvement, PRP completion rate (approximately 500 mm burns, 1 to 2 burns apart, on each of the retina 4 quadrants, starting at approximately one disk diameter from the macular vessel arcade and extending to the equator) and complications at 16 weeks.
Notes	Funding: not reported Trial registration: not reported

Chelala 2018 *(Continued)*

	Date conducted: June 2006 to June 2010 Conflict of interest: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: automated online randomisation generator
Allocation concealment (selection bias)	Low risk	Comment: automated online randomisation generator
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Study participants and all study personnel were masked to treatment group assignment throughout the study" Comment: due to the nature of the treatment (intravitreal injection vs observation), blinding is not possible; however, that is unlikely to affect the estimated effect related to remission or recurrence of VH.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an independent ophthalmologist was assigned to grade the VH according to the grading system discussed earlier" "retinal photocoagulation was performed by independent ophthalmologists unaware of this study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no patients were lost to follow-up.".
Selective reporting (reporting bias)	High risk	Comment: no trial registration was reported and not all the outcomes were described in detail in the methods section. The severity of VH was dichotomised to show statistical significance.

DRCR.net 2013

Study characteristics

Methods	Study design: phase 3, double-blind, randomised, multicentre clinical trial of intravitreal ranibizumab for VH from PDR Unit of randomisation: eye (1 eye per participant) Unit of analyses: eye Follow-up: at 4, 8, 12,16 weeks and 12 months
Participants	Country: USA Setting: community-based and academic-based ophthalmology practices specialising in retinal diseases (61 centres) Number of participants: 261 (261 eyes) Exclusions post-randomisation: 10 (3 in ranibizumab group and 7 in the control group) Losses to follow-up: 4 (2 in each group) at 16 weeks and 42 at 12 months;5 death during 12 months of follow-up. Age (mean (SD)): 58 (12) years

DRCR.net 2013 *(Continued)*

	Gender: 52% women. By group, 65 (52%) and 70 (51%) women in the ranibizumab and control groups, respectively. Inclusion criteria: ≥ 18 years of age with type 1 or type 2 diabetes. Eyes with VH associated to PDR, causing vision impairment and precluding completion of PRP Exclusion criteria: eyes requiring immediate vitrectomy for reasons such as rhegmatogenous or traction retinal detachment; a vision of no light perception, neovascular glaucoma, active iris new vessels judged or angle new vessels; history of intravitreal anti-VEGF treatment for VH
Interventions	Treatment: intravitreal ranibizumab 0.5 mg at baseline and 4 and 8 weeks Control: intravitreal saline at baseline and 4 and 8 weeks Both groups received PRP as soon as possible after the first injection Duration: 3 doses
Outcomes	Primary: cumulative probability of vitrectomy performed within 16 weeks Secondary: cumulative probability of vitrectomy performed within 12 months, the proportion of eyes with "complete" PRP by 16 weeks in the absence of vitrectomy; improvement in visual acuity from baseline ; extent of VH measured by optical coherence tomography signal strength; systemic and ocular adverse events
Notes	Funding: co-operative agreements EY14231 and EY18817 from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services (USA). Genentech provided the ranibizumab for the study and provided funds to DRCR.net Trial registration: NCT00996437 Date conducted: June 2010 to March 2012 Conflict of interest: Genentech provided the ranibizumab for the study and provided funds to DRCR.net to defray the study's clinical site costs. DRCR.net had complete control over the design of the protocol, conduct, and reporting of the research and retained ownership of the data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: it was not specified how the random sequence was generated. Only specified that a permuted block design stratified by site was used.
Allocation concealment (selection bias)	Low risk	Quote: "randomly assigned on the DRCR.net website" Comment: the randomisation was centralised and the investigators were blinded to the random sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "eyes received an injection of saline or 0.5-mg ranibizumab at randomization, 4 weeks, and 8 weeks using a masked vial provided by the Coordinating Center that was identified by number only"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "eyes received an injection of saline or 0.5-mg ranibizumab at randomization, 4 weeks, and 8 weeks using a masked vial provided by the Coordinating Center that was identified by number only"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the analyses were by intention to treat, and there were 4 losses to follow-up (2 in each group). Overall, 82% of the participants completed a 52-week visit, 2% died, and 16% were lost to follow-up.

DRCR.net 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	All registered outcomes (clinicaltrials.gov/ct2/show/NCT00996437) are reported.

DRCR.net 2015

Study characteristics	
Methods	Study design: phase III, prospective, multicentre randomised clinical trial Unit of randomisation: eye Unit of analyses: eye Follow-up: 2 years (follow-up planned through 5 years)
Participants	Country: USA Setting: 55 United States sites; Jaeb Center for Health Research; National Eye Institute (NEI); Genentech, Inc. Number of participants: 305 participants (394 eyes randomised) but 89 participants with 2 eyes randomised. Exclusions post-randomisation: a per-protocol analysis was conducted excluding eyes not completing the 2-year visit, eyes without PDR on baseline fundus photographs, and eyes receiving alternate PDR treatment. Losses to follow-up: anti-VEGF + Deferred PRP: 31 eyes did not complete 2-year visit; prompt PRP: 35 eyes did not complete 2-year visit Age (mean (SD)): median (interquartile range): 51 (44 to 59) Gender, n (%): 134 (44%) women; 171 (56%) men Inclusion criteria: study participants were at least 18 years old and had type1 or type 2 diabetes, at least 1 eye with PDR, no previous PRP, and a best corrected visual acuity letter score of 24 or higher (approximate Snellen equivalent, 20/320 or better). Eyes with or without DME were eligible. Exclusion criteria: significant renal disease; individuals in poor glucemics control; known allergy to any component of the study drug; blood pressure > 180/110; myocardial infarction or other acute cardiac event requiring hospitalisation; systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomisation; women of child-bearing potential.
Interventions	Treatment: anti-VEGF(0.5 mg Ranibizumab) + deferred PRP Control: prompt PRP Duration: the primary outcome follow-up visit was at 2 years, with follow-up planned through 5 years.
Outcomes	Primary: mean change in visual acuity from baseline to 2 years Secondary outcomes 1. Comparing other visual function outcomes (including Humphrey visual field testing and study participant self-reports of visual function) in eyes receiving anti-VEGF with deferred PRP with those in eyes receiving prompt PRP. 2. Determining percent of eyes not requiring PRP when anti-VEGF is given in the absence of prompt PRP. 3. Comparing safety outcomes between treatment groups. 4. Comparing associated treatment and follow-up exam costs between treatment groups.

DRCR.net 2015 *(Continued)*

Notes	Funding: this study was supported through a co-operative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, US Department of Health and Human Services (grants EY14231, EY23207, and EY18817). Genentech provided ranibizumab for the study and funds to the DRCR.net to defray the study's clinical site costs. Trial registration: NCT01489189 Date conducted: Patients enrolled between February and December 2012 Conflict of interest: all authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gross reports grants and personal fees from Jaeb Center for Health Research, drug samples for office use from Genentech, and grants from Regeneron. Mr Glassman reports grants to his institution from Genentech/Roche and Regeneron. Dr Aiello reports personal fees for consultancy from Thrombogenics, Kalvista, Sanovas, Eisai, Merck, and Lilly. Dr Antoszyk reports honoraria/consulting fees from Alimera Sciences, Novartis, and Iconic Therapeutics and vice chairmanship for Jaeb Center for Health Research. Dr Berger reports research support from Genentech. Dr Bressler reports grants from Northwestern University and grants to his institution from Bayer, Lumenis, the National Institutes of Health, and Novartis. Dr Browning reports grants from Novartis, Regeneron, Genentech, Aerpio, Alcon, and Allergan, personal fees for consultancy from Alimera, book royalties from Springer, and stock in Zeiss. Dr Marcus reports clinical research grants and/or personal fees for consultancy from Genentech, Roche, Regeneron,Thrombogenics, Alimera, Acucela, Lpath, Alcon,Allergan, GlaxoSmithKline, Pfizer, Ophthotech,and Allegro. Ms Melia reports data and safety monitoring board membership for Alimera. Dr Sun reports grants from Genentech, non-financial support from Optovue and Boston Micromachines, research support from Kalvista, and personal fees from Novartis, Regeneron, Eisai, Kowa, Allergan, Bayer, and Abbott.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomization was based on a permuted block design” “Participants with one study eye were randomly assigned using the DRCR.net web site with equal probability”
Allocation concealment (selection bias)	Low risk	Quote: “Participants with one study eye were randomly assigned using the DRCR.net web site with equal probability”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “Study participants, investigators,and study coordinators were not masked because of the nature of the treatments”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Reading center graders and the medical monitor who reviewed all adverse events were masked to treatment assignments. Visual acuity and ocular coherence tomography technicians were masked to treatment group assignments at annual visits”.

DRCR.net 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were 31/191 (16%) losses in the anti-VEGF group and 35/203 (17%) in the PRP group.
Selective reporting (reporting bias)	Low risk	Comment: the results of the outcomes were described in the methods section and in the published protocol.

Ergur 2009

Study characteristics

Methods	Study design: prospective, randomised clinical trial of intravitreal bevacizumab for PDR Unit of randomisation: participant Unit of analyses: eye Follow-up: 1 day, 1 week, 1 and 6 months
Participants	Country: Turkey Setting: M.D., Ministry of Health Atatürk Research and Training Hospital 2st Eye Clinic Ankara, Turkey Number of participants: 16 (19 eyes) Exclusions post-randomisation: 0 Losses to follow-up: 0 Age (mean (SD)): 71.4 (4.6) years in bevacizumab plus PRP group, 68.3 (3.4) years in PRP group Gender: 9 men and 7 women Inclusion criteria: people with PDR Exclusion criteria: people with history of cataract surgery or thromboembolic ictus
Interventions	Treatment: intravitreal bevacizumab 1.25 mg/0.05 mL, 20 days before PRP, 3 sessions Control: PRP/week/3 weeks, 3 sessions
Outcomes	Primary: BCVA, intraocular pressure, biomicroscopic examination, fundus examination, colour fundus photography, fluorescein leakage areas
Notes	Funding: not reported Trial registration: not reported Date conducted: not reported Conflict of interest: none reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not described

Ergur 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were 0 losses
Selective reporting (reporting bias)	Low risk	Comment: the results of the variables were described in the methods section

Figueira 2016

Study characteristics	
Methods	Study design: exploratory open-label phase II randomised controlled parallel trial with 3 treatment arms: (PRP, IVR, PRP+IVR). Comparisons: PRP versus IVR alone and PRP versus PRP + IVR combined treatment. Unit of randomisation: 35 participants (32 used) Unit of analyses: eye Follow-up: 12 months (monthly)
Participants	Country: Portugal Setting: 4 centres Number of participants: 35 subjects Exclusions post-randomisation: 3 subjects Losses to follow-up: 0 losses Age (mean (SD)): 54 (PRP); 61 (IVR); 57(PRP+IVR) Gender: % women: 23% (PRP); 40% (IVR); 17% (PRP+IVR) Inclusion criteria: Type 2 diabetic patients with high-risk PDR, aged 18 years or older, with BCVA at screening > 20/320 (25 letters in the ETDRS chart) in the study eye. Exclusion criteria: (1) treatment with PRP or macular photocoagulation, YAG laser, cryoablation or laser retinopexy within the 6 months prior to inclusion; (2) treatment with any investigational agents for diabetic retinopathy, anti-VEGF agents or corticosteroids in the 90 days prior to inclusion; (3) presence of fibrovascular proliferation with associated retinal traction; (4) presence of atrophy, scarring, fibrosis or hard exudates involving the centre of the macula; (5) history of previous vitrectomy; (6) HbA1c equal or superior to 11% or systemic uncontrolled diabetes; (7) underlying significant systemic diseases (such as severe cardiac disease and significantly impaired renal function, among others), and (8) significant media opacities, which might interfere with visual acuity, assessment of toxicity or fundus photography.

Figueira 2016 *(Continued)*

Interventions	Treatments 1. Intravitreal ranibizumab 0.5 mg alone (rescue treatment with PRP was performed after 3 months of follow-up (6 months after the initial injection) if considered necessary) 2. PRP + intravitreal ranibizumab 0.5 mg Control: PRP Duration: 0, 1 and 2 months (participants could receive additional intravitreal ranibizumab 0.5 mg with a minimum interval of 4 weeks)
Outcomes	Primary: regression of neovascularisation Secondary outcomes: BCVA evaluated using ETDRS charts at a 4 m distance; area of NVD, NVE, the total area of NV and central macular thickness (CMT), number of treatments needed, additional focal or grid laser for Diabetic Macular Edema, adverse events, need for vitrectomy
Notes	Funding: this study was financially supported by Novartis Trial registration: NCT01280929 Date conducted: from November 2010 to November 2012 Conflict of interest: José Cunha-Vaz is a consultant for Alimera Sciences, Allergan, Bayer, Fovea Pharmaceuticals, GeneSignal, Novartis, OM Pharma, Pfizer, Roche and Zeiss. João Figueira is a consultant for Allergan, Bayer, Novartis, Alcon and Kemin Pharma. Paulo Caldeira Rosa is a consultant for Bayer and Novartis. José Henriques is consultant for Alimera Sciences, Bayer, Novartis and Pfizer. Rufino Silva is member of the Advisory Board of Allergan, Alimera, Novartis, Bayer, Alcon and Thea. Inês Laíns, Pedro Melo and Sandrina Gonçalves Nunes have no other conflict of interest to declare. Sample size was calculated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomization was performed by an automated system at a 1: 1:1 ratio to 1 of 3 treatment arms".
Allocation concealment (selection bias)	Low risk	Quote: “Randomization was performed by an automated system at a 1: 1:1 ratio to 1 of 3 treatment arms".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “This randomised, open label, phase II, controlled trial”. Comment: “open trial” means that both the researchers and participants know which treatment is being administered.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: “This randomised, open label, phase II, controlled trial”. Comment: “open trial” means that both the researchers and participants know which treatment is being administered.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 3 participants were excluded from 35 subjects. But the sample size calculated was 54 participants including a 10% of loss. For this reason the study was underpowered.
Selective reporting (reporting bias)	Low risk	Comment: the outcomes finally reported were previously described in the methods section and in the protocol.

Figueira 2018

Study characteristics	
Methods	Study design: randomised, multicenter, open-label, phase II-III trial Unit of randomisation: participant Unit of analyses: one eye per participant Follow-up: 12 months
Participants	Country: Portugal, UK, France, Italy Setting: Departments of Ophtalmology of several European hospitals and European Opthalmology Research Institutes. Number of participants: 87 Exclusions post-randomisation: 2 in the intervention group (1 health problems + 1 event prespecified as meriting exclusion), 8 in the control group (1 dropout + 7 events that qualified for exclusion (vitreous haemorrhage, diabetic macular oedema, subretinal haemorrhage) Losses to follow-up: 1 in the control group (according to the flow-chart, although in the main text authors talk about 10 losses to follow-up) Age (mean (SD)): experimental group was 59 years (13) and the control group was 52 years (12). Gender: intervention group 13 females (31.7%) and control group 19 (41.3%) Inclusion criteria: ≥ 18 years of age, type 1 or 2 diabetes mellitus; BCVA >24 ETDRS letters score (approximate Snellen equivalent 20/320) and HRPDR. Exclusion criteria: people with systolic blood pressure > 170 mmHg or diastolic blood pressure > 100 mmHg, haemoglobin A1C level > 11%, or recent signs of uncontrolled diabetes; any intraocular surgery within 6 months before trial enrolment, other cause of retinal new vessels, atrophy /scarring /fibrosis/hard exudates involving the centre of the macula; DME with central involvement, previous vitrectomy; intraocular pressure > 21 mmHg, and previous anti-VEGF therapy within the last 3 months.
Interventions	Treatment: study participants received, between month 0 and month 2 (loading phase), 3 IVR injections in month 0, month 1, and month 2 combined with the standard PRP treatment, that is, with 1, 2, or 3 laser sessions (according to investigators decision) applied 1 or 2 weeks after each ITV injection to obtain a complete PRP treatment Control: the control participants received between month 0 and month 2 the standard PRP treatment, with 1 mandatory laser session in month 0 and more laser sessions as needed until month 2 to complete the PRP treatment. Duration: up to 3 months Co-intervention: intervention group: from months 3 to 11 option to an additional RBZ ITV injection + PRP session control group: from months 3 to 11 optional additional PRP sessions
Outcomes	Primary: regression of neovascularisation total (NVT) at 12 months Secondary: BCVA change at month 12 from baseline, time to complete NV regression, recurrence of NV (NVT increase after a period of improvement), recidivism of NV (NVT reappearance after NVT complete regression), change in macular retinal thickness at month 12, need for treatment for DME, need for vitrectomy due to the occurrence of vitreous haemorrhage, tractional retinal detachment or other complications of DR, and other adverse events (AEs) related to the treatments.
Notes	Funding: European Clinical Vision Research Network. Association for Innovation and Biomedical Research on Light and Image (Coimbra, Portugal)

Figueira 2018 *(Continued)*

	Trial registration: NCT01941329 Date conducted: April 2014 to May 2016 (recruitment) Conflict of interest: important financial ties between several researchers and pharma companies. Several participating researchers belong to the boards and/or consultants of pharma companies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization list was generated by the sponsor on Stata 12.1 (ralloc package, version 1.4) and implemented through the electronic data capture platform with the following assumptions: ratio 1:1, 47 blocks, block size 2, total number of allocations 94."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization list was generated by the sponsor on Stata 12.1 (ralloc package, version 1.4) and implemented through the electronic data capture platform with the following assumptions: ratio 1:1, 47 blocks, block size 2, total number of allocations 94."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study is open label, cointerventions were different for the two groups."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "images were assessed by masked graders for the presence or absence of the defined lesions and identification of NVD or NVE areas (main outcome)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 30% of participants were lost for per protocol analysis. The PRP group lost more participants than the anti-VEGF plus PRP group (40.1% versus 29.3%). However, authors stated that they used last-observation-carried-forward approach considering 85 from 87 randomised participants.
Selective reporting (reporting bias)	Low risk	Comment: they provide information for all outcomes described in the methods section.

González 2009

Study characteristics

Methods	Study design: randomised, parallel, open-label direct comparison of pegaptanib alone with PRP alone in people with PDR Unit of randomisation: eyes (Quote: "for subjects in whom both eyes were eligible, one eye was selected randomly as the study eye. Fellow eyes of these subjects were treated according to standard clinical guidelines established") Unit of analyses: eye Follow-up: 30 weeks
Participants	Country: USA Setting: Valley Retina Institute Number of participants: 20 (20 eyes)

González 2009 *(Continued)*

	Exclusions post-randomisation: 1 Losses to follow-up: 3 Age (mean): 56.2 years in intravitreal pegaptanib group, 59 years in the PRP group Gender: 13 men and 7 women Inclusion criteria: active PDR, in 1 or both eyes, with at least 1 of the following high-risk characteristics as defined by the Diabetic Retinopathy Study: 1. new vessels within 1 disc diameter of the optic nerve head that was larger than one-third of the disc area; 2. VH or pre-retinal haemorrhage associated with either less extensive new vessels at the optic disc, or with new vessels elsewhere half the disc area or larger; or both 1. and 2. Exclusion criteria: haemorrhage or media opacity obscuring visualisation of the macula and optic nerve; epiretinal membranes involving the macula; proliferative diabetic membranes along the major retinal arcades sufficiently extensive to cause either significant vitreomacular traction or significant impairment in BCVA; any TRD; severe ischaemia involving the foveal avascular zone; neovascular glaucoma; study eye treated with intravitreal steroid injections within 6 months prior to baseline or PRP treatment within 90 days of baseline (or both)
Interventions	Treatment: intravitreal pegaptanib 0.3 mg every 6 weeks for 30 weeks Control: PRP laser every 6 weeks for 30 weeks
Outcomes	Primary: regression of PDR from baseline to week 36, defined as regression of new vessels of the optic disc, new vessels elsewhere, or both Secondary: BCVA assessed by ETDRS letter score, as well as changes in optical coherence tomography assessments of central macular thickness and macular volume
Notes	Funding: grant from Pfizer, New York and (OSI) Eyetech, New York Trial registration: not reported Date conducted: not reported Conflict of interest: first author was a paid consultant and speaker for (OSI) Eyetech Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "eligible eyes were randomly assigned (1:1) to either pegaptanib alone or PRP alone based on a sequence generated by the random number function in Microsoft Excel (Microsoft Corporation, Seattle, Washington)"
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "prospective, randomised, controlled, open-label, exploratory study" Comment: the participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "prospective, randomised, controlled, open-label, exploratory study" Comment: the outcome assessor was not blinded.
Incomplete outcome data (attrition bias)	Low risk	There were 4 losses (2 in each group)

González 2009 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Comment: the results of the outcomes were described in the methods section.

Gonzalez 2014

Study characteristics	
Methods	Study design: randomised, open-label, parallel (three arms) clinical trial Unit of randomisation: participant Unit of analyses: eye/participant Follow-up: baseline, week 3, week 6, and every 6 weeks until week 52 (12 months)
Participants	Country: USA Setting: Valley Retina Institute PA, Edinburg, Texas Number of participants: 30 Exclusions post-randomisation: not reported Losses to follow-up: 4 Age (mean (SD)): older than 18 years. No more information specified. Gender: both. No more information specified. Inclusion criteria: people with proliferative diabetic retinopathy with high-risk characteristics. All eyes must meet at least one or both of the following criteria: mild neovascularisation of the disc (NVD) of at least 1/4 to 1/3 disc area as shown in standard photograph 10A of the DRS. Moderate neovascularisation of the retina elsewhere (NVE) of at least 1/2 disc area as shown in standard photograph 7 of the DRS. 2. ETDRS visual acuity score greater than or equal to 24 letters (approximately 20/320) and less than or equal to 85 letters (approximately 20/20) by the ETDRS visual acuity protocol at the screening visit. 3. Eyes with mild pre-retinal haemorrhage (PRH) or mild vitreous haemorrhage (VH) that does not interfere with clear visualisation of the macula and optic disc are eligible for this study. 4. Evaluating physician believes that PRP can be safely withheld for 3 weeks. Exclusion criteria: 1. Presence of moderate or dense PRH or VH that prevents clear visualisation of the macula and/or optic disc. 2. Presence of either: significant epiretinal membranes involving the macula, OR proliferative diabetic membranes along the major retinal arcades that are extensive enough to cause either: significant vitreomacular traction, OR significant impairment in visual acuity. 3. Presence of any tractional retinal detachment. 4. Severe ischaemia involving the foveal avascular zone as determined by fluorescein angiography performed at the initial screening visit. 5. Significant media opacity (due to cornea, anterior chamber, or lens) precluding clear visualisation of the macula or optic disc. 6. Presence of neovascular glaucoma with or without hyphema. 7. Previous treatment with intravitreal steroid injections in the study eye within 6 months of baseline. 8. Previous treatment with peribulbar steroid injections in the study eye within 90 days of baseline 9. Previous PRP laser treatment in the study eye within 90 days of baseline visit.
Interventions	Treatments 1. Three intravitreal pegaptanib (IVP) injections every 6 weeks, then additional injections every 12 weeks. 2. Three IVP every 6 weeks followed by selective laser treatment. Control: Standard PRP

Gonzalez 2014 *(Continued)*

	Duration: 12 months
Outcomes	Primary: regression of high-risk proliferative diabetic retinopathy. Treatment failure was defined as: 1) Development of increased neovascularisation 2) neovascularisation that is not regressed at least 50% compared to the baseline amount within 3 weeks; 3) Development of significant vitreous haemorrhage that is sufficient in quantity to obscure visualisation of the entire macula, optic disc, and the major temporal arcade vessels. Secondary: loss of BCVA measured by comparing the percentages of participants that lost 3 or more lines on ETDRS chart in the study arms. Humphrey Visual Fields, dark adaptation, ETDRS, BCVA, FA, and OCT were performed in all groups at baseline and at variable pre-determined times.
Notes	Funding: Pfizer MPDRS-ED Trial registration: NCT01486771 Date conducted: not reported Conflict of interest: specified (the authors have collaborated with Allergan, Ampio, Genentech, Kalvista, Ophthotec, Pfizer, Regeneron and Valeant).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised into three arms" Comment: not described.
Allocation concealment (selection bias)	Unclear risk	Comment: not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote in the protocol: "open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote in the protocol: "open label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only four participants were lost.
Selective reporting (reporting bias)	High risk	There are not details of regression of PDR.

He 2020

Study characteristics

Methods	Study design: pilot within-person randomised controlled trial Unit of randomisation: eye within participant (each eye randomly allocated to one of the treatment groups) Unit of analyses: eye

He 2020 *(Continued)*

	Follow-up: 6 months
Participants	Country: China Setting: hospital Number of participants: 15 (30 eyes) Exclusions post-randomisation: not reported Losses to follow-up: not reported Age (mean (SD)): 47.7 years (11.6) Gender: 8 female (53.3%) Inclusion criteria: people diagnosed with treatment-naive high-risk PDR in both eyes as confirmed by fluorescein fundus angiography. Exclusion criteria: people with: 1) fibrovascular proliferation with retinal traction; 2) obvious optical media blurring affecting the evaluation of retina condition; 3) other causes of NV such as retinal vein occlusion; 4) atrophy, scarring, fibrosis, and hard exudates involving the central macula; or 5) a history of vitrectomy, optic neuropathy and uncontrolled glaucoma.
Interventions	Treatment: eyes in the combination group received one intravitreal injection of 0.5 mg/0.05 mL conbercept (Chengdu Kanghong Biotech Co., Ltd., Chengdu, Sichuan, China) twice, i.e. one week before PRP and one week after PRP. Control: PRP was performed in three sessions at a one-week interval according to the EDTRS guidelines Duration: 2 weeks for the intervention groups and 3 weeks for the control group. Co-intervention: no reported
Outcomes	No identification of primary and secondary outcomes. Outcomes: NV leakage area, total regression rate of NV, BCVA, central retinal thickness, foveal avascular zone assessed monthly until six months.
Notes	Funding: National Key R&D Program of China under grant number SQ2018YFC200148-03 and the Fundamental Research Funds for the Central Universities under number 3332018033. Dr Yang's research was supported by the National Natural Science Foundation of China (No. 81771493), NIH/NIA grant R01AG036042 and the Illinois Department of Public Health. Trial registration: No reported Date conducted: from October 2017 to October 2018 (recruitment) Conflict of interest: there was no conflict of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: the generation of random sequence was not described.
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment was not described.
Blinding of participants and personnel (performance bias)	High risk	Comment: it seems clear that neither trial personnel nor participants were blinded as to the treatment received.

He 2020 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: it seems clear that neither trial personnel nor participants were blinded as to the treatment received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no losses.
Selective reporting (reporting bias)	Low risk	Comment: authors show results of all outcome variables specified in the methods section.

Lang 2019

Study characteristics	
Methods	Study design: phase 2, multicentre, open-label, reading-centre blinded, randomised, active-controlled clinical trial Unit of randomisation: participant Unit of analyses: participant Follow-up: 12 months
Participants	Country: Germany Setting: hospitals Number of participants: 106; 35 ranibizumab group; 36 combination group; 35 PRP (control) group Exclusions post-randomisation: 2 (participants withdrew) Losses to follow-up: 25; 7 ranibizumab group; 10 PRP group; 8 combination group. Reasons: withdrawn before the first treatment (n = 2); adverse events (n = 12); protocol violation (n = 1); lost to follow-up (n = 6); and death (n= 4). Age (mean (SD)): ranibizumab group: 52.5 (11); combination group: 55.0 (13.4); control group: 53.0 (12.1) Gender: 68.9% male, 31.1% female Inclusion criteria: PDR secondary to type 1 or type 2 diabetes under medical surveillance/with stabilised treatment; age ≥ 18 years; best-corrected visual acuity (BCVA) ≥ 20 ETDRS letters (Snellen equivalent 20/400); HbA1c ≤ 12% Exclusion criteria: clinically significant DME with centre involvement large areas of NV (≥ 2 disc areas) within the macula proliferative vitreoretinopathy (PVR); severe vitreous haemorrhage impairing imaging/treatment; previous treatment with PRP (> 300 laser burns within the previous 6 months); treatment with anti-VEGF within the past 3 months; treatment with corticosteroids within the past 6 months
Interventions	Treatments 1. Ranibizumab monotherapy. Three initial monthly intravitreal injections of ranibizumab 0.5 mg. 2. Ranibizumab + PRP. Three initial monthly intravitreal injections of ranibizumab 0.5 mg and 1200 to 1600 laser spots (500 lm spot size at the retina) were applied in three sessions between baseline and month 3.

Lang 2019 *(Continued)*

	In both intervention groups, further injections were given monthly until stability of morphological parameters was reached, as determined by the Investigator, that is no further improvement of morphology or no worsening of morphology (inactive NVs) was seen over three consecutive months while on ranibizumab treatment as assessed by ophthalmoscopy and, if applicable, FFA. - If worsening or reperfusion of NVs occurred or new NVs were detected by the Investigator, retreatment was initiated with at least two monthly injections. Control group: 1200 to 1600 laser spots (500 lm spot size at the retina) were applied in three sessions between baseline and month 3. If worsening or reperfusion of NVs occurred or new NVs were detected by the Investigator, retreatment was initiated. Duration: 12 months Co-intervention: PRP rescue treatment was allowed in this study and was possible for participants in the ranibizumab monotherapy group beginning at month 2 (after two injections of ranibizumab), and only if a sufficient progression of NV, with associated threat to visual loss, was evident.
Outcomes	Primary: Change in total area of NV [mm^2] (calculated as sum of area of NVE and NVD) on FFA early/mid-phase frames from baseline to month 12 Secondary outcomes: change in BCVA (ETDRS letters); complete regression of leakage from NVs; change in the ETDRS severity scale stage; change in central subfield thickness; treatment frequency over the course of the study; safety. All outcomes measured at 12 months.
Notes	Funding: Novartis Pharma GmbH Germany, Nuremberg Trial registration: NCT01594281 Date conducted: study start date: 11 December 2012; primary completion date: 30 November 2016 Study completion date: 5 December 2017; Conflict of interest: different authors received funding from different companies.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: generation of randomisation sequence not described.
Allocation concealment (selection bias)	Unclear risk	Comment: allocation to interventions not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Colour fundus photography, FFA and SD-OCT images were analysed by certified graders at the Cologne Image Reading Center (CIRCL, Cologne, Germany) using a two-grader system. Discrepancies were solved by open adjudication. Graders were masked to the treatment group."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17% participants were lost. The reasons for each dropout was described.

Lang 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the study reported data for all the outcomes.

Marashi 2017

Study characteristics	
Methods	Study design: randomised, parallel, open-label clinical trial Unit of randomisation: participants Unit of analyses: 30 eyes of 30 participants Follow-up: 12 months
Participants	Country: Syria Setting: Marashi eye clinic, AlBashir Hospital, Yamman Shuman Retina specialist at advanced ocular centre Alkalmat Hospital Number of participants: 30 (15 per group) Exclusions post-randomisation: not reported Losses to follow-up: not reported Age (mean (range)): bevacizumab group 52 (46 to 59) years and control group 53 (48 to 61) years Gender: 7 men and 23 women Inclusion criteria: age >= 18 years, presence of PDR which the investigator intends to manage with PRP alone but for which PRP can be deferred for at least 4 weeks in the setting of intravitreal bevacizumab; best corrected Snellen equivalent 20/320 or higher on the day of randomisation; media clarity, pupillary dilation, and study participant co-operation sufficient to administer PRP and obtain adequate fundus photographs and OCT. Exclusion criteria: chronic renal failure requiring dialysis or kidney transplant; ischaemic systemic events; pregnant or lactating women; tractional retinal detachment involving the macula; macular oedema related to ocular surgery; ocular infection; glaucoma; aphakia; previous treatment with anti-VEGFs or corticosteroids.
Interventions	Treatment: bevacizumab (1.25 mg three injections every 4 weeks and PDR was reassessed at week 18 to 20) with deferred panretinal photocoagulation (PRP) if it was necessary (and it was stopped whenever a stable PDR was achieved for the last 2 injections) Control: prompt PRP Duration: 12 months Co-intervention: both groups could have received intravitreal bevacizumab or focal/grid laser for diabetic macular oedema; 12 participants had DME in the experimental group and 3 in the control group.
Outcomes	Primary: proportion of visual acuity improvement using Snellen chart or equivalent from baseline and 12 months Secondary outcomes: treatment cost at 1 year; per cent of eyes with vitreous haemorrhage at 1 year; the proportion of eyes with complete regression of neovascularisation on fundus photograph at 1 year; the proportion of eyes with progression to central sub-field involved diabetic macular oedema at 1 year; the proportion of eyes need for vitrectomy at 12 months

Marashi 2017 *(Continued)*

Notes	Funding: not reported Trial registration: NCT02705274 Date conducted: between February and April 2016 Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized multicenter and open label double arm interventional study"
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomized multicenter and open label double arm interventional study"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the publication reports data for all participants. The authors did not refer to losses.
Selective reporting (reporting bias)	High risk	Quote: "PDR complications such as vitreous haemorrhage and tractional retinal detachment along with the need of vitrectomy were not included in this study due to the small number of recruitment and short term follow-up" Comment: The cost included in the protocol was not reported. For some continuous data (e.g. visual acuity) there were no standard deviations reported.

Meng 2016

Study characteristics

Methods	Study design: randomised, parallel, controlled study Unit of randomisation: eyes Unit of analyses: eyes Follow-up: 3 months
Participants	Country: China Setting: Department of Ophthalmology, Second Affiliated Hospital of Henan University of Science and Technology Number of participants: intervention: 30 eyes of 28 participants; control: 20 eyes of 18 participants Exclusions post-randomisation: 0

Meng 2016 *(Continued)*

	Losses to follow-up:0 Age (mean (SD)): bevacizumab group: 47.53±3.34; control group:49.17±3.52. Gender: bevacizumab group: 12 males and 16 females. Control group: 8 males and 10 females. Inclusion criteria: people with vitreous haemorrhage and with vision affected or who have significant bloody vitreous opacity, fundus examination can see or vaguely see the retina, or thick vitreous haemorrhage, the fundus is not possible to see. No significant retinal traction and retinal detachment by B-ultrasound. Blood glucose control within 8 mmol/L. Hypertensive participants with blood pressure control under 130/80 mmHg Exclusion criteria: PDR patients with neovascular glaucoma and/or severe cataracts, other causes of vitreous haemorrhage. Someone who had serious systemic disease, was older, or had recent cardiovascular and cerebrovascular accidents. Those that cannot use bevacizumab. Patients with glaucoma or with ocular diseases that may affect vision. Those with abnormal coagulopathy.	
Interventions	Treatment: 1.25 mg intravitreal injection of bevacizumab (one dose) before PRP (if it was DR progression) Control: PRP Duration: (one dose) At 4 weeks after treatment, if the haemorrhage was not absorbed and became even worse, or retinal detachment occurred during the follow-ups, pars plana vitrectomy (PPV) was taken	
Outcomes	Primary: absorption of vitreous haemorrhage (after 4 weeks) Secondary outcomes: vision after surgery (after 3 months); re-bleeding after surgery (after 3 months)	
Notes	Funding: not reported Trial registration: not reported Date conducted: From January 2013 to August 2015 Conflict of interest: not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not reported.
Allocation concealment (selection bias)	Unclear risk	Comment: not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no losses.

Meng 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all outcomes in methods have results.

Mirshahi 2008

Study characteristics	
Methods	Study design: prospective, randomised, double-blind clinical trial of intravitreal bevacizumab in PDR Unit of randomisation: eye Unit of analyses: eye Follow-up: 6 and 16 weeks
Participants	Country: Iran Setting: Eye Research Center, Farabi Eye Hospital, Medical Sciences/University of Tehran Number of participants: 40 (80 eyes) Exclusions post-randomisation: 0 Losses to follow-up: 0 Age (median (range)): 52 (39-68) years Gender: 12 men and 28 women Inclusion criteria: people with high-risk characteristics identified by Diabetic Retinopathy Study criteria: new vessels of the disc ≥ one-quarter to one/third disc area, any amount of disc new vessels with VH or pre-retinal haemorrhage, or new vessels elsewhere ≥ one-half disc area with VH or pre-retinal haemorrhage (with or without macular oedema) Exclusion criteria: people with uncontrolled hypertension, recent (in the past 6 months) myocardial infarction or cerebrovascular accident, uncontrolled glaucoma, a history of any type of retinal photocoagulation, a diagnosis of TRD
Interventions	Treatment: intravitreal injection bevacizumab 1.25 mg/0.05 mL at the first session of laser photocoagulation and 3 sessions of laser photocoagulation (1 week apart) Control: sham injection in the fellow eye at the first session of laser photocoagulation and 3 sessions of laser photocoagulation (1 week apart) Duration: only 1 dose
Outcomes	Primary: regression response was defined angiographically Secondary: recurrence of PDR and complications of treatment
Notes	Funding: not reported Trial registration: not reported Date conducted: December 2005 to September 2006 Conflict of interest: none reported This study was designed using both treatments in the same participant: intravitreal bevacizumab in 1 eye compared with PRP in the contralateral eye

Mirshahi 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "fellow eyes of each case were randomly assigned to receive Avastin [bevacizumab] or sham" Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "fellow eye injection was mimicked with a needleless syringe" Comment: personnel were not blinded, but the participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "this assessment was carried out by two independent masked observers; in case of conflict it was resolved through discussion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 0 losses
Selective reporting (reporting bias)	Low risk	Comment: the results of the variables were described in the methods section

Preti 2013

Study characteristics	
Methods	Study design: within-person randomised, blinded, controlled trial comparing of PRP with intravitreal bevacizumab injections versus PRP alone in high-risk PDR Unit of randomisation: eye, within-person study Unit of analyses: eye but not pair-matched analysis Follow-up: 6 months
Participants	Country: Brazil Setting: Department of Ophthalmology, University of Sap Paulo Medical School Number of participants: 42 (84 eyes) Exclusions post-randomisation: 7 people with VH Losses to follow-up: 0 Age (mean (range)): 56 (43-73) years Gender: 28 men and 14 women Inclusion criteria: aged ≥ 18 years, high-risk PDR with or without diabetic macular oedema; visual acuity ≥ 20/200

Preti 2013 *(Continued)*

	Exclusion criteria: pretreatment for diabetic retinopathy (laser, intraocular medications and surgeries); pre-retinal haemorrhage and VH; presence of changes in the vitreous-retinal interface (epiretinal membrane, macular hole and vitreoretinal traction syndrome); evidence of active external eye infection such as blepharitis; prior thromboembolic events, including myocardial infarction, stroke and deep vein thrombosis; systolic blood pressure > 180 mm Hg and diastolic blood pressure > 110 mm Hg; glycated haemoglobin levels > 15%; chronic renal failure; major surgery within 1 month; previous systemic anti-VEGF
Interventions	Treatment: 2 intravitreal bevacizumab injections 1.25 mg/0.05 mL, 1 dose 1 week before the PRP, and the other dose after the last session of PRP. The PRP was performed weekly over 3 weeks Control: PRP performed weekly over 3 weeks Duration: 4 weeks
Outcomes	Primary: changes in contrast sensitivity measured with Vistech Consultants Incorporation® (VCTS) at 1, 3 and 6 months between the groups with and without diabetic macular oedema Secondary: changes in VCTS within each group with and without diabetic macular oedema; ocular safety (ocular hypertension, lens opacity progression and anterior chamber reaction arterial); systemic safety (thromboembolic events)
Notes	Funding: study was supported by the São Paulo Research Foundation (FAPESP) No 2009/08895-1 Trial registration: NCT01389505 Date conducted: February 2011 to June 2012 Conflict of interest: none reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 post-randomisation losses, not specified by group
Selective reporting (reporting bias)	High risk	Comments: outcome measures on clinical trials.gov were different to those reported in the paper: Primary outcome measures: functional macular evaluation [timeframe: 24 weeks] [designated as safety issue: yes]; during this 24 weeks of follow-up the visual acuity (ETDRS), contrast vision will be measured at baseline, 4, 12 and finally at 24 weeks.

Preti 2013 *(Continued)*

	Secondary outcome measures: structural macular evaluation [timeframe: 24 weeks] [designated as safety issue: yes]; during the 24 weeks of follow-up the following measured will be made: optical coherence tomography

Preti 2017

Study characteristics	
Methods	Study design: blinded within-person randomised clinical trial Unit of randomisation: eye Unit of analyses: 38 eyes of 19 participants Follow-up: 1 month
Participants	Country: Brazil Setting: Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo, Oftalmologia, Sao Paulo/SP, Brazil Number of participants: 19 Exclusions post-randomisation: not reported Losses to follow-up: 4 participants: 2 participants due to unreliable CT measurements + 2 participants due to vitreous haemorrhage Age (mean (range)): 53.4 +/- 9.3 years Gender: 9 males, 10 females Inclusion criteria: best corrected visual acuity (BCVA) > or = 20/200; type 2 DM; similar high risk PDR in both eyes with or without DME Exclusion criteria: pretreatment of diabetic retinopathy (laser photocoagulation or intraocular surgery); vitreous haemorrhage; vitreous-retinal interface alteration (epiretinal membrane, macular hole, or vitreoretinal traction syndrome); active external eye disease; systolic or diastolic blood pressures greater than 180 or 110 mmHg respectively; Haemoglobin A1C levels exceeding 15%; chronic renal failure
Interventions	Treatment: intravitreal bevacizumab (1.25 mg/0.05 mL) on the day of randomisation and at the end of the third PRP episode (interval between the two injections: 3 weeks). PRP once per week for 3 consecutive weeks beginning 1 week after the first IVB (300 to 500 shots per episode, spot size of 250 mm, exposure time between 0.1 and 0.2 msec, intensity 200 to 500 mW) Control: PRP once per week for 3 consecutive weeks beginning on the same day as randomisation (300 to 500 shots per episode, spot size 250 mm, exposure time between 0.1 and 0.2 msec, intensity 200 to 500 mW) Duration: 1 month Co-intervention: When concomitant DME was present, it was treated during the first episode of PRP based on Olk 1986 and the ETDRS guidelines (= macular grid laser)
Outcomes	Primary: comparison between macular CT measurements of the eyes in the experimental and control groups at baseline and at a 1-month follow-up

Preti 2017 *(Continued)*

	Secondaries: Longitudinal comparison of macular CT measurements within each group at baseline and at a 1-month follow-up
Notes	Funding: São Paulo Research Foundation (FAPESP) Trial registration: NCT01389505 Date conducted: not reported Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: randomisation sequence not described
Allocation concealment (selection bias)	Unclear risk	Comment: allocation method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no reference to blinding of personnel or participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An investigator blinded to the study design performed all measurements in one afternoon. On a different occasion, another examiner independently measured the same group of OCTs. To calculate intra- and inter-observer variability, the same two observers repeated their measurements unaware of the previous results"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Three patients were excluded before randomization, 2 because of unreliable CT measurements and one because of vitreous haemorrhage. Nineteen patients (38 eyes) were randomized and treated, but at the one-month follow-up, 4 patients were excluded (2 because of vitreous haemorrhage and 2 because of unreliable CT measurements at follow-up). The fourth excluded patient had one eye (from the control group) excluded due to unreliable CT measurements, whereas the eye subjected to PRP and IVB injections was suitable for study" Comment: follow-up losses 4/19 participants (21%), although losses were proportionate in both groups.
Selective reporting (reporting bias)	High risk	Comment: in the Clinicaltrials.gov registration, the primary outcome is "Functional Macular Evaluation", but only structural data is provided in this article. There is another publication from the author referring the same Clinicaltrials.gov registry, but neither the N nor the time frame match.

Ramos Filho 2011

Study characteristics

Methods	Study design: randomised, clinical trial that assessed efficacy of ranibizumab in people with high-risk PDR Unit of randomisation: participant

Ramos Filho 2011 *(Continued)*

	Unit of analyses: participant/eye Follow-up: 16, 32 and 48 weeks
Participants	Country: Brazil Setting: Department of Ophthalmology, School of Medicine Number of participants: 40 (40 eyes) Exclusions post-randomisation: 1 Losses to follow-up: 10 Age (mean): 50.5 years in ranibizumab plus PRP group, 63.3 years in PRP alone group Gender: 18 men and 11 women Inclusion criteria: people with high-risk PDR, which was defined according to the guidelines set forth by the ETDRS: 1. presence of new vessels at the disc > ETDRS standard photograph 10A, 2. presence of new vessels at the disc associated with VH or pre-retinal haemorrhage or 3. new vessels elsewhere with more than one-half disk area associated with VH or pre-retinal haemorrhage Exclusion criteria: 1. history of prior laser treatment or vitrectomy in the study eye; 2. history of a thromboembolic event, 3. major surgery within the prior 6 months or planned within the next 28 days; 4. uncontrolled hypertension, 5. known coagulation abnormalities or current use of anticoagulative medication other than aspirin or 6. any condition affecting documentation
Interventions	Treatment: intravitreal ranibizumab 0.5 mg, 60 minutes after the completion of PRP Control: PRP Duration: only 1 dose
Outcomes	Primary: total area (mm^2) of fluorescein leakage from active new vessels Secondary: BCVA (logMAR) and the central subfield macular thickness
Notes	Funding: Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP). Grant number: 2009/01036-3 Trial registration: NCT01988246 Trial registration: not reported Date conducted: February 2009 to December 2009 Conflict of interest: none reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The technician was asked to pick up one of two identical opaque envelopes; one contained the designation for PRP, and the other contained the designation for PRP plus treatment" Comment: the method of randomisation was not described. There was an imbalance between groups in the age of the participants (mean (SD): 63.3 (2.5) with intravitreal ranibizumab + PRP vs. 50.5 (3.0) with PRP alone; P = 0.0036)), which suggest doubts about if they were correctly randomised.

Ramos Filho 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "the technician was asked to pick up one of two identical opaque envelopes; one contained the designation for PRP, and the other contained the designation for PRP plus treatment"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: blinding of participants and personnel were not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a single masked certified examiner performed Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) measurements prior to any other study procedure. A single retinal specialist performed the ophthalmic evaluations (JARF) and the stereoscopic fundus photography (FPPA). Study data were analysed and interpreted by AM, RAC, IUS, JASR, RJ"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "twenty-nine of 40 patients initially included in this trial completed the 48-week follow-up evaluation" Comment: there were 11 losses (27.5%; 25% in ant-VEGF group and 30% in PRP group).
Selective reporting (reporting bias)	Low risk	Comment: the results of the variables were described in the methods section.

Rebecca 2021

Study characteristics	
Methods	Study design: randomised controlled trial Unit of randomisation: eye Unit of analyses: 76 eyes of 52 participants Follow-up: 6 months
Participants	Country: Pakistan Setting: Department of Ophthalmology, Isra University Hospital, Hyderabad, Pakistan Number of participants: 52 participants (38 eyes per group) Exclusions post-randomisation: not reported Losses to follow-up: not reported Age (mean (SD)): experimental group: 51.1 (5.9) years; control group: 50.7 (6.9) years Gender: experimental group: 58.25% men, 41.75% women; control group: 62.96% men, 37.04% women Inclusion criteria: people with Type-1 and Type-2 diabetes mellitus with high risk PDR. Age between 18 years to 65 years of age. No previous treatment for diabetic retinopathy. Exclusion criteria: history of intravitreal bevacizumab (IVB) or steroids, retinal laser therapy, vitrectomy. Any media opacity like cataract that prevents the visualization of fundus.
Interventions	Treatment: intravitreal bevacizumab injection (1.25 mg/0.05 ml) 1 week before first PRP session and a second injection at the end of the third PRP session.

Rebecca 2021 *(Continued)*

	PRP starting 1 week after intravitreal injection: 3 sessions of PRP with 1 week interval. 2 additional sessions at 1 month and 2 months if needed. Laser parameters: spot 200 micrometers, energy 400 to 500 mW, exposition 20 msec. 2000 to 3000 burns. Control: 3 sessions of PRP with 1 week interval. 2 additional sessions at 1 month and 2 months if needed. Laser parameters: spot 200 micrometers, energy 400 to 500 mW, exposition 20 msec. 2000 to 3000 burns Duration: 1 month (if additional laser, duration 3 months) Co-intervention: post-injection topical antibiotics four times a day given for three days.
Outcomes	Primary: 1. timing of regression of neovessels (complete, partial neovascular regression); 2. BCVA before and after treatment Time of assessment: results provided at baseline, 4 weeks, 3 months, and 6 months. Primary endpoint not reported. Secondary outcomes: central macular thickness before and after treatment. Time of assessment: results provided at baseline, 4 weeks, 3 months, and 6 months. Primary endpoint not reported.
Notes	Funding: not reported Trial registration: not reported Date conducted: June 2018 to December 2018 Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: random sequence not described
Allocation concealment (selection bias)	Unclear risk	Comment: allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: blinding not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the publication reports data for all participants. The authors did not refer to losses.
Selective reporting (reporting bias)	Unclear risk	Comment: data reported from all the primary and secondary outcomes. No data reported about other common factors in PDR that may affect visual acuity (i.e. vitreous haemorrhage incidence).

Roohipoor 2016

Study characteristics	
Methods	Study design: within-person randomised clinical trial to compare choroidal thickness (CT) and retinal thickness (RT) between eyes with proliferative diabetic retinopathy treated with panretinal photocoagulation (PRP) or PRP with intravitreal bevacizumab (PRP + VB) Unit of randomisation: eye Unit of analyses: eye Follow-up: 10 months
Participants	Country: Iran Setting: Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Science Number of participants: 33 (66 eyes) Exclusions post-randomisation: none Losses to follow-up: none Age (mean (SD)): 54 (7) Gender: 6 (18%) males, 27 (82%) females Inclusion criteria: treatment-naive eyes in people with Type 1 or 2 diabetes mellitus with PDR Exclusion criteria: any previous retinal treatment, significant media opacities that precluded fundus examination or imaging, other retinal pathology, optic nerve pathology (including ocular hypertension and glaucoma), diffuse macular oedema or focal fovea involving macular oedema that would require IVB, uncontrolled systemic hypertension, and/or refractive error more than ± 3 diopters
Interventions	Treatment: PRP (3 sessions separated by 1-week interval) + bevacizumab 1.25 mg (0.05 mL) after the first session of PRP Control: PRP alone (3 sessions separated by 1-week interval) Duration: 1 month, but at months 3 and 6 if active new vessels were detected, participants could receive additional fill-in PRP. Additionally, if clinically significant macular oedema was present, participants could be retreated with laser/macular photocoagulation in the PRP group and additional IVB in PRP + IVB group.
Outcomes	Primary: choroidal thickness, macular thickness Secondary: BCVA
Notes	Funding: not reported Trial registration: clinical registration number: IRCT2014030116782N1 Date conducted: October 2013 to March 2014 Conflict of interest: declared (none)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "One eye was randomly assigned to PRP only... and the other eye was assigned to PRP + IVB injection..."

Roohipoor 2016 *(Continued)*

		Comment: no detail regarding random sequence generation is given.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although the registration details indicate that the study was single-blinded, this is not reflected in the article.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were accounted for.
Selective reporting (reporting bias)	High risk	One of the preregistered primary outcomes (peripapillary nerve fibre layer thickness) was not reported.

Sameen 2017

Study characteristics	
Methods	Study design: randomised clinical trial Unit of randomisation: eyes Unit of analyses:eyes (76 eyes and 50 participants) Follow-up: 3 months
Participants	Country: Pakistan Setting: Armed Forces Institute of Ophthalmology, Rawalpindi. Number of participants: 50 participants (76 eyes) having proliferative diabetic retinopathy (PDR) and diabetic macular oedema (DME) Exclusions post-randomisation: not described Losses to follow-up: not described Age (mean (SD)): 57.47 (6.08) in PRP; 55.69 (6.58) in PRP + IVB Gender: Females 24% (PRP); 36% (PRP + IVB) Inclusion criteria: people having PDR with DME and no history of previous treatment. Exclusion criteria: people with poor diabetic control (HbA1C > 7.0%), hypertension (> 140/90), significant lenticular changes, traction, advanced diabetic retinopathy, cystoid macular oedema (CMO) and subretinal serous elevation were also excluded from the study.
Interventions	Treatment: PRP + intravitreal bevacizumab 2.5 mg/0.1ml (IVB) Control: PRP alone Duration: IVB injection one day after PRP session and repeated monthly for 3 months.

Sameen 2017 *(Continued)*

Outcomes	Primary: BCVA and Optical coherence tomography (OCT)
Notes	Funding: none. Trial registration: not described Date conducted: from January 2016 to August 2016 Conflict of interest: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “All sessions of laser and IVB injections were performed by the second author.”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: not described
Selective reporting (reporting bias)	Low risk	Comment: the results of the outcomes were described in the methods section.

Shahraki 2022

Study characteristics

Methods	Study design: randomised, triple-masked (participant, care provider, investigator) trial. "In bilateral cases, each eye was randomly allocated individually; however, both eyes were not allocated to the same arm". Comment: most participants received different treatments for each eye. Therefore, we considered the design as a within-person randomised clinical trial. Unit of randomisation: eye Unit of analyses: eye Follow-up: 12 months
Participants	Country: Iran Setting: Ophthalmic Research Center, Research Institute for Ophthalmology and Vision Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Number of participants: 105 participants (only reported in the published protocol) / 207 eyes (1 or 2 eyes per participant)

Shahraki 2022 *(Continued)*

Exclusions post-randomisation (eyes): PRP group: 7; IVB group: 17; modified combination group: 9

Losses to follow-up (eyes): PRP group: 9; IVB group: 5; modified combination group: 7

Age (mean (range)

Total: 53 ± 7.78 years

PRP group: 53.52 ± 7.25 years

IVB group: 51.96 ± 9.90 years

Modified combination group: 54.70 ± 5.82 years

Gender: males

Total: 51.6%

PRP group: 47%

IVB group: 55.7%

Modified combination group: 52%

Inclusion criteria:

- Age ≥ 18 years.
- Type 1 or type 2 diabetes.
- Presence of PDR.
- Best corrected E-ETDRS visual acuity letter score ≥ 24 (20/320 or better)
- Media clarity, pupillary dilation, and individual cooperation sufficient to administer PRP and obtain wide-field FAG and optical coherence tomography (OCT).

Exclusion criteria:

- Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant
- A condition that, in the opinion of the investigator, would preclude participation (e.g. unstable medical status including blood pressure, cardiovascular disease, and glycaemic control).
- Blood pressure > 180 (systolic)/110 (diastolic).
- Myocardial infarction, other acute cardiac event requiring hospitalisation, stroke, transient ischaemic attack, or treatment for acute congestive heart failure within 4 months prior to randomisation.
- Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomisation.
- Women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 3 years.
- History of prior PRP, defined as ≥ 100 burns outside of the posterior pole.
- Traction retinal detachment involving the macula.
- Neovascularisation of the angle.
- Macular oedema due to a cause other than diabetic macular oedema that, in the opinion of the investigator, might alter visual acuity during the course of the study (e.g. retinal vein or artery occlusion, uveitis or another ocular inflammatory disease, neovascular glaucoma, etc.).
- Substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more.
- History of intravitreal anti-VEGF treatment at any time in the past 2 months
- Use of corticosteroid treatment (intravitreal or peribulbar) at any time in the past 4 months.
- Major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months following randomisation.
- Capsulotomy performed within 2 months prior to randomisation.
- Aphakia.
- Uncontrolled glaucoma (in the investigator's judgment).

Shahraki 2022 *(Continued)*

	• Exam evidence of severe external ocular infection, including conjunctivitis, chalazion, or substantial blepharitis
Interventions	**Modified combination group** 2 intravitreal injections of 0.125 mg of bevacizumab (IVB) injections and modified laser (1 session of retinal laser delivered only to the retina anterior to the equator either by conventional or pattern modes during the first 4 months. In the cases with worsening neovascularisation or new vitreous haemorrhage at either the fourth or eighth months, four monthly IVB injections were administered. If neovascularisation persisted (not worsened) at these visits, two monthly or bimonthly IVB injections were performed. In the cases with improved neovascularisation, no further intervention was considered. One session of rescue laser was also performed if worsening of neovascularisation was still noted in the eighth month. **PRP group** 2 or 3 PRP sessions during 3 months either through conventional or pattern modes. At the fourth and eighth months, if the eyes demonstrated worsened neovascularisation (at iris, retina, or optic disk) or developed new vitreous haemorrhage, two rescue IVB injections were planned, either monthly or bimonthly. If neovascularisation persisted (not worsened), one rescue IVB was performed. For the eyes with improved neovascularisation at the fourth and eighth months, no further intervention was considered. **IVB group** 4 intravitreal injections of 0.125 mg of IVB through 4 months. At a 4-month visit if the iris, retinal, or optic disk neovascularisation worsened or if new vitreous haemorrhage occurred, 4 monthly IVB were added. The eyes with persistent neovascularisation in the fourth month received two additional monthly or bimonthly IVB injections. In the eyes with the improved neovascularisation, no additional injection was performed. The same strategy was applied in eighth month; however, if neovascularisation worsened at that time, rescue laser was applied in addition to four monthly IVB injections. All included eyes with visual acuity (VA) ≤ 20/32 and centre-involving DME (defined as central macular thickness ≥ 300 mm based on Heidelberg Spectralis optical coherence tomography) received IVB injection(s). Duration: 4 months
Outcomes	Primary: BCVA (logMAR) at month 12 Secondary outcomes • Change in the number and area of neovessels at month 12 • Changes in MD of visual field at month 12 • Complications (retinal detachment needing vitrectomy, neovascular glaucoma, iris neovascularisation, new vitreous haemorrhage) • Number of visits during 1 year • Number of intravitreal injections needed for treating DME during 1 year
Notes	Funding: not reported Trial registration: NCT04800679 Date conducted: From February 2017 to February 2021 Conflict of interest: not reported

Shahraki 2022 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a randomized parallel assignment with triple-blind protocol (participant, care provider, and investigator) was used. An allocation sequence produced by computer was prepared (A.R.) to be used for enrollment of the eyes."
Allocation concealment (selection bias)	Low risk	Quote: "a randomized parallel assignment with triple-blind protocol (participant, care provider, and investigator) was used. An allocation sequence produced by computer was prepared (A.R.) to be used for enrollment of the eyes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "a randomized parallel assignment with triple-blind protocol (participant, care provider, and investigator) was used. An allocation sequence produced by computer was prepared (A.R.) to be used for enrollment of the eyes." Comment: placebo was not used. In addition, it is difficult to conceal the administration of the treatments assessed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a randomized parallel assignment with triple-blind protocol (participant, care provider, and investigator) was used. An allocation sequence produced by computer was prepared (A.R.) to be used for enrollment of the eyes." Comment: placebo was not used. It is difficult to conceal the administration of the treatments. The masking of investigators/assessors was not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 207 eyes were randomized. After deletion of the missing data, 153 eyes were included in the final analysis" Comment: high percentage (26%) of losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Comment: the number of participants is not reported.

Sivaprasad 2017

Study characteristics	
Methods	Study design: multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial to assess efficacy and safety of intravitreal aflibercept in the management of PDR Unit of randomisation: participant Unit of analyses: participant Follow-up: 52 weeks
Participants	Country: UK Setting: 22 UK National Health Service hospitals Number of participants: 232 Exclusions post-randomisation: none Losses to follow-up: none Age (mean (SD)): 50.8 (13.2) and 51.5 (14.6) in the anti-VEGF and PRP groups

Sivaprasad 2017 *(Continued)*

	Gender: 72 (62%) and 83 (72%) men in the anti-VEGF and PRP groups Inclusion criteria: type 1 or 2 diabetes, aged 18 years or older, with clinical evidence of previously untreated PDR or persistent retinal neovascularisation after initial PRP requiring additional PRP (i.e., previously treated). BCVA or 54 or more (ETDRS) letters, equivalent to 6/24 Snellen BCVA with sufficient media clarity and pupillary dilatation for adequate fundus photographs. The fellow eye Snellen BCVA of 2/60 or higher. Women used effective contraception or were post-menopausal for 12 months or more before trial entry, or were surgically sterile. Exclusion criteria: Coexistent ocular disease that affected or might affect visual acuity or prevent treatment delivery. Diabetic MA and spectral domain optical coherence tomography showing a central subfield thickness of 300 µm or more due to macular oedema were excluded. Other ocular exclusions were moderate or dense vitreous haemorrhage preventing clear visualisation of the macula or optic disc or preventing laser treatment, fibrovascular proliferation, or tractional retinal detachment in the posterior pole, previous history of vitrectomy, other causes of retinal neovascularisation, and anticipated need for cataract extraction or vitrectomy within 12 months. Patients treated with intravitreal anti-VEGF or steroid for diabetic macular oedema within 4 months or PRP within 8 weeks before screening were excluded. Systemic exclusion criteria included glycated haemoglobin (HbA1c) of 12% or higher, blood pressure of 170/110 mm Hg or higher, and any medical condition that, in the opinion of the investigator, precluded participation in the study
Interventions	Treatment: aflibercept intravitreal injection 2 mg/0·05 mL at baseline, 4 weeks, and 8 weeks. From week 12, participants were reviewed every 4 weeks and aflibercept injections were given as needed Control: PRP alone single spot or multispot laser at baseline, fractionated fortnightly thereafter, and from week 12 participants were assessed every 8 weeks and treated with PRP as needed.
Outcomes	Primary: BCVA letter change from baseline to 52 weeks
Notes	Funding: funded by MRC and managed by NIHR on behalf of the MRC-NIHR partnership (EME 12/66/15) and Bayer Plc Trial registration: ISRCTN registry, number 32207582. EUDRA CT number 2013-003272-12 Date conducted: August 2014 to November 2015 Conflict of interest: declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated (1:1) to either <the study drug> or PRP... with the method of minimisation, concealed before allocation, stratified by site, baseline PDR status (previously untreated vs previously treated), best corrected visual acuity, HbA1c, diastolic blood pressure by collaborating site investigators via the King's Clinical Trials Unit web-based randomisation service."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated (1:1) to either <the study drug> or PRP... with the method of minimisation, concealed before allocation, stratified by site, baseline PDR status (previously untreated vs previously treated), best corrected visual acuity, HbA1c, diastolic blood pressure by collaborating site investigators via the King's Clinical Trials Unit web-based randomisation service."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and clinical investigators were unmasked due to the anatomical changes induced by the comparator"

Sivaprasad 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcome assessors including optometrists, visual field technicians, imaging technicians, and the staff at the independent reading centre... were masked to treatment allocation. The primary outcome assessors completed a treatment guess form to establish masking success"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all the randomised participants were accounted for.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were prespecified and previously published (Sivaprasad 2015)

DME: diabetes macular oedema; BCVA: best-corrected visual acuity; CMT: central macular thickness; CT: computerised tomography; CSME: clinically significant macular oedema; DR: diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study; FA: fluorescein angiography; IVR: Intravitreal ranibizumab; HRPDR: high-risk proliferative diabetic retinopathy; NV: neovascularisation; NVD: neo vessels on the disc; NVE: neo vessels elsewhere; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PRP: panretinal photocoagulation; SD: standard deviation; TRD: tractional retinal detachment; VA: visual acuity; VEGF: vascular endothelial growth factor; VH: vitreous haemorrhage.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmadieh 2009	Participants received vitrectomy
Ahn 2011	Participants received vitrectomy
Albuquerque 2014	Participants underwent vitrectomy
Antoszyk 2022	Participants underwent vitrectomy
Arevalo 2019	Participants underwent vitrectomy
Arimura 2009	Retrospective, comparative study
Barroso 2020	All groups received ranibizumab
Bi 2020	50% of included participants had NPDR
Bressler 2018	This clinical trial assessed baseline factors associated with vision and edema outcomes
Bu 2018	This trial explored the effects of conbercept combined with laser on inflammatory factors, oxidative stress levels and retinal haemodynamics in diabetic retinopathy.
Castillo 2017	Participants underwent vitrectomy
Chatziralli 2020	The two groups in the comparison received the same anti-VEGF (ranibizumab)
Cheema 2009	Only 3 included participants had PDR
Chen 2019	Not clear participants had PDR
Cho 2010	Included both participants with NPDR with severe risk of PDR and participants with PDR
Comyn 2014	Participants received vitrectomy

Study	Reason for exclusion
Di Lauro 2010	Participants underwent eye surgery
Dong 2016	Not a randomised and retrospective controlled study. Participants underwent ocular surgery
Dufour 2017	This is an abstract with limited information. The study includes participants without PDR. The main outcome was time to recurrence of retinal neovascularization after anti-VEGF injection
El-Batarny 2008	Participants received vitrectomy
Ernst 2012	50% of included participants had NPDR
Farahvash 2011	Participants received vitrectomy
Ferraz 2015	Non–high-risk PDR in both eyes
Fulda 2010	Not a randomised clinical trial. Each participant received the 2 evaluated interventions. The right eye received intravitreal bevacizumab and 1 session of 800 scattered laser spots. The left eye underwent a full 1600 laser panretinal photocoagulation
Genovesi-Ebert 2007	Not a randomised clinical trial
Gonzalez 2006	RCT assessed the efficacy and safety of pegaptanib in treating diabetic macular oedema and diabetic retinopathy. The publication was an abstract and there was insufficient information to include the study. The principal focus is of participants with macular oedema
Gonzalez 2021	Post hoc analysis of two RCTs (RICE and Rise) in DME.
Hach 2019	Both groups received anti-VEGF
Hattori 2010	Not a randomised clinical trial
Hershberger 2018	Results of 3 RCTs in DME (RICE; RIDE and protocol S)
Hu 2017	Participants underwent vitrectomy and faquectomy
Huang 2009	Compared with historical controls. Not randomised
Ip 2012	2 years of follow-up to evaluate effects of intravitreal ranibizumab on diabetic retinopathy severity over time in 2 phase 3 clinical trials (RIDE, NCT00473382; RISE, NCT00473330) for diabetic macular oedema
Jiang 2009	Retrospective study
Jorge 2006	Non-randomised study
Lanzagorta-Aresti 2009	The included participants did not have proliferative diabetic retinopathy. The outcomes measured were central macular thickness and visual acuity in participants with a moderate retinopathy not proliferative that needed a cataract surgery
Lee 2014	Retrospective study
Li 2015	Subrogate outcomes (levels of bFGF and VEGF in vitreous samples)
Li 2022	Participants underwent vitrectomy

Study	Reason for exclusion
López-López 2012	Anti-VEGF group was not randomised
Ma 2016	No randomised. Participants were divided into observation group and control group, according to the condition of the disease and the participants will.
Maguire 2020	Participants with DME and anti-VEGF was administered in both groups in the comparison.
Manabe 2015	Participants underwent eye surgery
Maturi 2021	Eyes with moderate to severe non-proliferative diabetic retinopathy
Messias 2019	All 3-compared groups received anti-VEGF
Michaelides 2010	Focus of the clinical trial was diabetic macular oedema
Minnella 2008	Non-controlled clinical trial
Modarres 2009	Participants underwent vitrectomy
NCT02207712	The study assess light masks (Noctura 400) added to anti-VEGF in DMO
NCT02630277	This is a phase II clinical trial that compares two groups of participants with PDR treated with intravitreal aflibercept Injection at different posologies
NCT02857491	Participants underwent vitrectomy
NCT02976012	RCT that compares two posologies of Intravitreal Aflibercept in participants undergoing vitrectomy.
NCT03452657	The aim is to prevent high-risk DR
NCT03904056	Both comparison groups received anti-VEGF
NCT04708145	All participants receive anti-VEGF
NCT04782128	Phase II study to evaluate RC28-E injection in people with NPDR
Oh 2014	This is an abstract (ARVOS 2014), that does not present results.
Parikakis 2018	This is not a primary study.
Rizzo 2008	Participants underwent vitrectomy
Scott 2008	Study evaluated agreement in diabetic retinopathy severity classification by retina specialists performing ophthalmoscopy vs reading centre grading of 7-field stereoscopic fundus photographs in a phase 2 clinical trial of intravitreal bevacizumab for centre-involved diabetic macular oedema.
Shin 2009	Data were collected retrospectively.
Sohn 2012	Participants underwent vitrectomy
Song 2020	Participants with non-proliferative diabetic retinopathy
Stergiou 2007	Retrospective case series

Study	Reason for exclusion
Su 2016	Participants underwent vitrectomy
Sun 2015	Participants underwent vitrectomy
Tonello 2008	Quote: "for patients (n= 8) presenting with high-risk PDR [proliferative diabetic retinopathy] in both eyes, the eye with worse BCVA [best-corrected visual acuity] was selected to receive PRP [panretinal photocoagulation] plus intravitreal bevacizumab (eight eyes) and the fellow eye was treated with PRP alone (eight eyes)" Comment: clinical trial partially randomised
Toscano 2021	All comparison groups received anti-VEGF.
Wang 2014	Participants underwent vitrectomy
Wang 2019	50% of included participants had NPDR
Wykoff 2019	The RECOVERY study (NCT02863354) evaluated the effect of intravitreal aflibercept on diabetic retinopathy severity. Subjects were randomized into monthly and quarterly 2 mg aflibercept injection. There is not a group of participants without anti-VEGF.
Yang 2016	Participants underwent vitrectomy
Yeh 2009	Not a randomised study. The treatment assignment was alternative.
Yu 2015	Participants underwent vitrectomy
Yu 2021	Phase II RCT analysed 2 imaging-based biomarkers to guide management of treatment with anti-VEGF
Zaman 2013	Participants underwent vitrectomy
Zhang 2019	This is not a randomized study
Zhou 2010	Focus of the clinical trial is diabetic macular oedema
Zhou 2017	It is an abstract without enough information.

BCVA: best-corrected visual acuity; bFGF: basic fibroblast growth factor; DME: diabetic macular oedema; DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; PRP: panretinal photocoagulation; RCTs: randomized clinical trials; VEGF: vascular endothelial growth factor

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-INR-17013555

Study name	Study on the treatment mode of stage IV diabetic retinopathy
Methods	Parallel unicentric clinical trial
Participants	60 participants (20 participants per group) **Inclusion criteria** 1. Signed the informed consent form and can be followed up according to the test plan.

ChiCTR-INR-17013555 *(Continued)*

	2. Target eye with stage IV diabetic retinopathy: retinal new vascularisation (NVE) or optic disc new vascularisation (NVD), when NVD > 1/4-1/3DA or NVE is greater than 1/2DA, or with anterior retinal haemorrhage or vitreous haemorrhage, is called high-risk proliferative phase 3. Aged over 18 years, male and female 4. Patient confirmed with diabetes whose blood sugar has been controlled and stable. 5. Glycosylated haemoglobin (HbAlc) less than 8.0%. **Exclusion criteria** 1. Patients who have been treated with laser therapy. 2. Patients with severe cataracts, glaucoma, or ocular active inflammation. 3. The target eye has traction retinal detachment, with or without vitreous haemorrhage; the target eye has been accepted within 3 months before the screening, or needs intraocular surgery during the study period. 4. The affected eye is the only functional eye. 5. The target eye is associated with other retinal diseases, including central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), ocular Ischaemic syndrome, hypertensive retinopathy, etc. 6. Target eye, nontarget eye, or whole-body system were treated with anti-vascular endothelial growth factor (VEGF) and other drugs within 3 months before screening. 7. Preoperative routine examination results are abnormal, and not suitable for eye surgery. 8. The researchers found that they were not suitable for inclusion.
Interventions	1. Intravitreal injection of Lucentis combined with PRP 20 laser treatment 2. Intravitreal injection of Lucentis 3. PRP 20 laser treatment
Outcomes	Primary outcomes Ultra wide angle fundus photography and shadow Color Optical Coherence Tomography Optometry
Starting date	26 November 2017
Contact information	Dr Fy Min e-mail: min_fu1212@163.com Zhongshan Ophthalmic Center, Sun Yat-sen University. 54 Xianlie Road South, Guangzhou, Guangdong, China.
Notes	Self-financed

NCT02911311

Study name	Conbercept vs Panretinal Photocoagulation for the Management of Proliferative Diabetic Retinopathy
Methods	Randomised, parallel, single-blind (assessor) clinical trial
Participants	226 participants, of either sex, aged 18 years or over, diagnosis of diabetes mellitus (type 1 or 2). BCVA in the study eye better than or equal to 30 ETDRS letters. PDR with no evidence of previous PRP. Media clarity, pupillary dilation and participant co-operation sufficient for adequate fundus photographs.

NCT02911311 *(Continued)*

Interventions	Experimental: intravitreal injection of conbercept 2 mg/ 0.05 mL at baseline and at 1 and 2 months. Further treatment since month 3 is determined by the degree of regression of new vascularisation (NV) of disc and elsewhere on clinical examination Control: PRP in 1 to 2 two-weekly sessions as per routine clinical practice with emphasis on targeting retinal non-perfusion areas
Outcomes	Primary Mean visual acuity change (BCVA) at 12 months measured in the ETDRS letter score at 4 m Secondary 1. Visual acuity outcomes in terms of visual gain or loss at 6 months and 12 months (visual gain refers to the proportion of visual improvement ≥ 15 letters at 6-month follow-up, visual loss refers to the proportion of visual reduction ≤ 15 letters at 6-month and 12-month follow-up) 2. Complete regression of new vessels at: 6 months and 12 months (evaluated by the fundus photography and fundus fluorescein angiography) 3. Proportion of participants developing macular oedema, vitreous haemorrhage and vitrectomy [at 12 months 4. Change of visual field at 12 months
Starting date	October 2017
Contact information	Chenjin Jin, Dr. (PI); Zhongshan Ophthalmic Center, Sun Yet-sen University
Notes	Sponsor: Sun Yat-sen University

NCT04278417

Study name	A 96-week, two-arm, randomized, single-masked, multi-center,phase III study assessing the efficacy and safety of brolucizumab 6 mg compared to panretinal photocoagulation laser in patients with proliferative diabetic retinopathy
Methods	Randomised, parallel, single-masking (assessor) trial
Participants	706 participants. 18 years or older, either sex. Diagnosis of type 1 or 2 diabetes mellitus (DM) and HbA1c less than or equal to 12% at screening, with DM treatment stable for at least 3 months and with PDR diagnosis with no previous PRP treatment in the study eye
Interventions	Experimental: brolucizumab intra-vitreal injection, 6 mg every 6 weeks per 3 times loading injections, followed by every 12 weeks maintenance through week 90 Other name: RTH258 Active comparator: panretinal photocoagulation laser initial treatment in 1 to 4 sessions up to week 12, followed with additional PRP treatment as needed Other name: PRP.
Outcomes	Primary outcome 1. Change from baseline in BCVA at week 54 Secondary outcomes 1. Proportion of participants with no PDR at week 54 2. Proportion of participants with center-involved DME up to weeks 54 and 96 3. Prevention of DME up to week 54

NCT04278417 *(Continued)*

	4. Area under the curve in change from baseline in BCVA up to week 54 and Week 96 5. Visual acuity change from baseline in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at week 54 and week 96 6. Diabetic retinopathy status 7. Proportion of participants with no PDR at week 96 8. Diabetic retinopathy status 9. Proportion of study eyes developing vision-threatening complications associated with diabetic retinopathy up to week 54 and week 96 10. Ocular complications
Starting date	19 November 2020
Contact information	Contact: Novartis Pharmaceuticals 1-888-669-6682 novartis.email@novartis.com Contact: Novartis Pharmaceuticals +41613241111
Notes	Sponsor: Novartis Pharmaceuticals Other study ID numbers: CRTH258D2301 Estimated primary completion date: 29 November 2024

BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; PDR: proliferative diabetic retinopathy; PRP: panretinal photocoagulation; VEGF: vascular endothelial growth factor.

DATA AND ANALYSES

Comparison 1. Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP

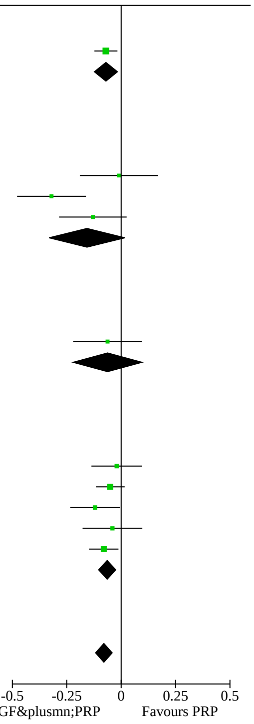
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Visual acuity stratified by anti-VEGF	10	1172	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.12, -0.04]
1.1.1 Aflibercept	1	209	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.12, -0.02]
1.1.2 Bevacizumab	3	171	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.33, 0.02]
1.1.3 Pegaptanib	1	16	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.22, 0.10]
1.1.4 Ranibizumab	5	776	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.10, -0.03]
1.2 Complete regression of new vessels (dichotomous outcome)	5	405	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.19, 2.24]
1.2.1 Aflibercept	1	211	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.39, 2.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Bevacizumab	1	30	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.13, 6.72]
1.2.3 Ranibizumab	3	164	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.09, 1.64]
1.3 Regression of new vessels (continuous outcome): mean area of fluorescein leakage	4	189	Mean Difference (IV, Random, 95% CI)	-4.14 [-6.84, -1.43]
1.3.1 Bevacizumab	1	19	Mean Difference (IV, Random, 95% CI)	-8.13 [-10.94, -5.32]
1.3.2 Ranibizumab	3	170	Mean Difference (IV, Random, 95% CI)	-2.75 [-4.00, -1.49]
1.4 Presence of vitreous haemorrhage	6	1008	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.57, 0.90]
1.4.1 Aflibercept	1	232	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.23, 0.97]
1.4.2 Bevacizumab	1	30	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.26]
1.4.3 Pegaptanib	1	20	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.17, 5.77]
1.4.4 Ranibizumab	3	726	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.58, 0.95]
1.5 Need for laser photocoagulation	2	464	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.11, 0.28]
1.5.1 Ranibizumab	2	464	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.11, 0.28]
1.6 Need for vitrectomy	8	1248	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.49, 0.93]
1.6.1 Aflibercept	1	232	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.14]
1.6.2 Bevacizumab	1	50	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.95]
1.6.3 Pegaptanib	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.6.4 Ranibizumab	5	946	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.41, 1.13]
1.7 Oedema as measured by macular thickness (µm) (participant)	4	175	Mean Difference (IV, Random, 95% CI)	-45.95 [-80.02, -11.88]
1.7.1 Bevacizumab	1	76	Mean Difference (IV, Random, 95% CI)	-58.70 [-92.24, -25.16]
1.7.2 Pegaptanip	1	16	Mean Difference (IV, Random, 95% CI)	-112.00 [-197.38, -26.62]
1.7.3 Ranibizumab	2	83	Mean Difference (IV, Random, 95% CI)	-20.15 [-46.19, 5.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Quality of Life (VFQ-25 General health)	2	382	Mean Difference (IV, Random, 95% CI)	0.62 [-3.99, 5.23]
1.8.1 Aflibercept	1	207	Mean Difference (IV, Random, 95% CI)	0.30 [-5.96, 6.56]
1.8.2 Ranibizumab	1	175	Mean Difference (IV, Random, 95% CI)	1.00 [-5.82, 7.82]
1.9 Adverse events	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 Angina	1	23	Risk Ratio (M-H, Random, 95% CI)	3.82 [0.17, 84.90]
1.9.2 Any APTC event	2	448	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.78, 3.43]
1.9.3 Arterial hypertension	3	742	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.16, 1.22]
1.9.4 Progression of cataract	1	232	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.10]
1.9.5 Cerebrovascular accident	2	493	Risk Ratio (M-H, Random, 95% CI)	4.92 [0.56, 42.99]
1.9.6 Cornea-related problems	2	303	Risk Ratio (M-H, Random, 95% CI)	2.34 [0.20, 27.20]
1.9.7 Endophalmitis	4	974	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.11, 10.27]
1.9.8 Inflammation	1	232	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.83, 10.80]
1.9.9 Macular oedema	2	303	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.19, 1.26]
1.9.10 Neovascular glaucoma	3	887	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.18, 2.09]
1.9.11 Ocular discomfort	1	232	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.43, 5.18]
1.9.12 Raised intraocular pressure	4	958	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.51, 1.53]
1.9.13 Retinal detachment	3	887	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.49, 1.24]
1.9.14 Retinal tear	2	319	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.89]
1.9.15 Visual disturbances	1	232	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.40, 2.06]
1.9.16 Vitreoretinal interface abnormalities	1	232	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.18, 21.75]

Analysis 1.1. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 1: Visual acuity stratified by anti-VEGF

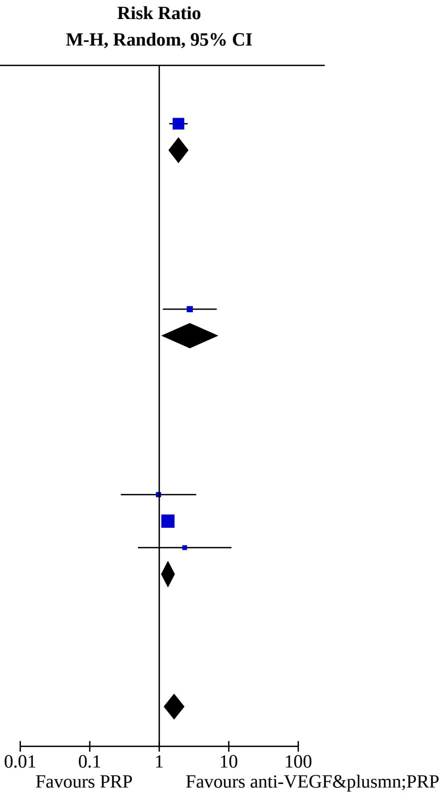
Study or Subgroup	Favours anti-VEGF±PRP Mean [logMAR]	SD [logMAR]	Total	PRP Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]
1.1.1 Aflibercept								
Sivaprasad 2017 (1)	0.05	0.2	105	0.12	0.19	104	22.1%	-0.07 [-0.12 , -0.02]
Subtotal (95% CI)			**105**			**104**	**22.1%**	**-0.07 [-0.12 , -0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.59 (P = 0.009)								
1.1.2 Bevacizumab								
Ergur 2009 (2)	0.37	0.18	9	0.38	0.22	10	4.0%	-0.01 [-0.19 , 0.17]
Rebecca 2021 (3)	0.1	0.25	38	0.42	0.43	38	5.0%	-0.32 [-0.48 , -0.16]
Sameen 2017 (4)	0.42	0.35	38	0.55	0.34	38	5.2%	-0.13 [-0.29 , 0.03]
Subtotal (95% CI)			**85**			**86**	**14.2%**	**-0.16 [-0.33 , 0.02]**
Heterogeneity: Tau² = 0.02; Chi² = 6.73, df = 2 (P = 0.03); I² = 70%								
Test for overall effect: Z = 1.77 (P = 0.08)								
1.1.3 Pegaptanib								
González 2009 (5)	0.065	0.195	8	0.1275	0.118	8	5.0%	-0.06 [-0.22 , 0.10]
Subtotal (95% CI)			**8**			**8**	**5.0%**	**-0.06 [-0.22 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.44)								
1.1.4 Ranibizumab								
DRCR.net 2013 (6)	0.4	0.44	125	0.42	0.52	136	8.3%	-0.02 [-0.14 , 0.10]
DRCR.net 2015 (7)	0.126	0.326	160	0.176	0.282	168	17.8%	-0.05 [-0.12 , 0.02]
Figueira 2018 (8)	0.196	0.24	41	0.316	0.3	46	8.7%	-0.12 [-0.23 , -0.01]
Lang 2019 (8)	0.12	0.24	36	0.16	0.34	35	6.4%	-0.04 [-0.18 , 0.10]
Ramos Filho 2011 (8)	0	0.07	15	0.08	0.11	14	17.4%	-0.08 [-0.15 , -0.01]
Subtotal (95% CI)			**377**			**399**	**58.6%**	**-0.06 [-0.10 , -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 4 (P = 0.74); I² = 0%								
Test for overall effect: Z = 3.21 (P = 0.001)								
Total (95% CI)			**575**			**597**	**100.0%**	**-0.08 [-0.12 , -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 12.54, df = 9 (P = 0.18); I² = 28%								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.05, df = 3 (P = 0.79), I² = 0%								



Footnotes
(1) Aflibercept compared with PRP alone, follow-up 52 weeks
(2) Bevacizumab and PRP compared with PRP alone, follow-up 6 months
(3) Bevacizumab and PRP compared with PRP alone, follow-up 6 months. The SD reported is very low and we interpreted was a SE
(4) Bevacizumab plus PRP compared with PRP alone, follow-up 12 months
(5) Pegaptanib alone compared with PRP alone, change in visual acuity, follow-up 9 months
(6) Ranibizumab and PRP compared with PRP alone, follow-up 12 months
(7) Ranibizumab plus deferred PRP compared with prompt PRP, follow-up 2 years
(8) Ranibizumab and PRP compared with PRP alone, change in visual acuity, follow-up 12 months

Analysis 1.2. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 2: Complete regression of new vessels (dichotomous outcome)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Aflibercept						
Sivaprasad 2017 (1)	68	107	35	104	36.1%	1.89 [1.39 , 2.56]
Subtotal (95% CI)		**107**		**104**	**36.1%**	**1.89 [1.39 , 2.56]**
Total events:	68		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.08 (P < 0.0001)						
1.2.2 Bevacizumab						
Marashi 2017 (2)	11	15	4	15	10.3%	2.75 [1.13 , 6.72]
Subtotal (95% CI)		**15**		**15**	**10.3%**	**2.75 [1.13 , 6.72]**
Total events:	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
1.2.3 Ranibizumab						
Figueira 2016 (2)	3	10	4	13	5.8%	0.97 [0.28 , 3.40]
Figueira 2018 (2)	38	41	32	46	43.9%	1.33 [1.08 , 1.64]
Lang 2019 (3)	5	28	2	26	3.9%	2.32 [0.49 , 10.94]
Subtotal (95% CI)		**79**		**85**	**53.6%**	**1.33 [1.09 , 1.64]**
Total events:	46		38			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.76 (P = 0.006)						
Total (95% CI)		**201**		**204**	**100.0%**	**1.63 [1.19 , 2.24]**
Total events:	125		77			
Heterogeneity: Tau² = 0.05; Chi² = 7.34, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Test for subgroup differences: Chi² = 5.19, df = 2 (P = 0.07), I² = 61.4%						



Footnotes

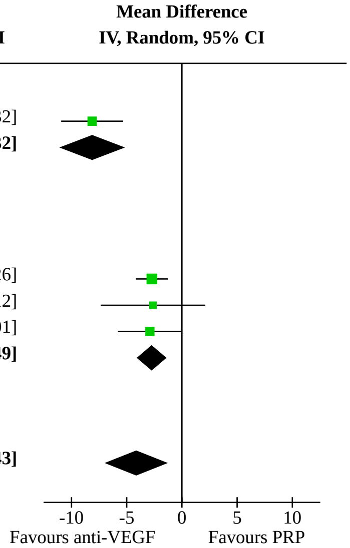
(1) AntiVEGF vs PRP.12-month follow-up

(2) Combination of antiVEGF plus PRP vs PRP. 12-month follow-up

(3) Combination of antiVEGF plus PRP vs PRP. Follow-uo 12 months.

Analysis 1.3. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 3: Regression of new vessels (continuous outcome): mean area of fluorescein leakage

	Favours anti-VEGF			PRP				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.3.1 Bevacizumab								
Ergur 2009 (1)	4.15	2.26	9	12.28	3.85	10	25.7%	-8.13 [-10.94 , -5.32]
Subtotal (95% CI)			**9**			**10**	**25.7%**	**-8.13 [-10.94 , -5.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.68 (P < 0.00001)								
1.3.2 Ranibizumab								
Figueira 2018 (2)	-0.52	1.04	41	2.2	4.92	46	32.2%	-2.72 [-4.18 , -1.26]
Lang 2019 (2)	1.96	4.91	28	4.58	11.39	26	17.0%	-2.62 [-7.36 , 2.12]
Ramos Filho 2011 (3)	-5.8	2.7	15	-2.9	4.9	14	25.2%	-2.90 [-5.81 , 0.01]
Subtotal (95% CI)			**84**			**86**	**74.3%**	**-2.75 [-4.00 , -1.49]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%								
Test for overall effect: Z = 4.29 (P < 0.0001)								
Total (95% CI)			**93**			**96**	**100.0%**	**-4.14 [-6.84 , -1.43]**
Heterogeneity: Tau² = 5.36; Chi² = 11.79, df = 3 (P = 0.008); I² = 75%								
Test for overall effect: Z = 3.00 (P = 0.003)								
Test for subgroup differences: Chi² = 11.78, df = 1 (P = 0.0006), I² = 91.5%								



Footnotes

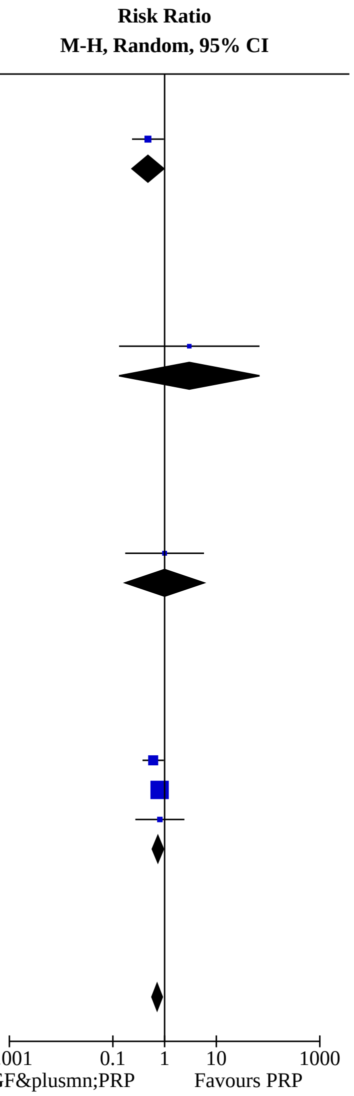
(1) Bevacizumab and PRP compared to PRP alone, Follow-up 6 months

(2) Ranibizumab and PRP compared to PRP alone,12-month follow-up.

(3) Ranibizumab and PRP compared to PRP alone, change in area of fluorescein leakage, follow-up 12 months

Analysis 1.4. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 4: Presence of vitreous haemorrhage

Study or Subgroup	Anti-VEGF Events	Anti-VEGF Total	PRP Events	PRP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Aflibercept						
Sivaprasad 2017 (1)	10	116	21	116	10.6%	0.48 [0.23 , 0.97]
Subtotal (95% CI)		**116**		**116**	**10.6%**	**0.48 [0.23 , 0.97]**
Total events:	10		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.4.2 Bevacizumab						
Marashi 2017 (2)	1	15	0	15	0.5%	3.00 [0.13 , 68.26]
Subtotal (95% CI)		**15**		**15**	**0.5%**	**3.00 [0.13 , 68.26]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.4.3 Pegaptanib						
González 2009 (3)	2	10	2	10	1.7%	1.00 [0.17 , 5.77]
Subtotal (95% CI)		**10**		**10**	**1.7%**	**1.00 [0.17 , 5.77]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.4.4 Ranibizumab						
DRCR.net 2013 (4)	21	125	38	136	23.7%	0.60 [0.37 , 0.97]
DRCR.net 2015 (5)	52	191	69	203	58.9%	0.80 [0.59 , 1.08]
Lang 2019 (6)	5	36	6	35	4.5%	0.81 [0.27 , 2.41]
Subtotal (95% CI)		**352**		**374**	**87.1%**	**0.74 [0.58 , 0.95]**
Total events:	78		113			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.03$, df = 2 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 2.37 (P = 0.02)						
Total (95% CI)		**493**		**515**	**100.0%**	**0.72 [0.57 , 0.90]**
Total events:	91		136			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.34$, df = 5 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 2.83 (P = 0.005)						
Test for subgroup differences: $Chi^2 = 2.30$, df = 3 (P = 0.51), $I^2 = 0\%$						

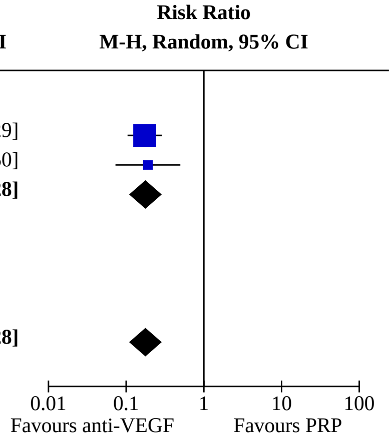


Footnotes

(1) Aflibercept compared with PRP alone, follow-up 52 weeks
(2) Bevacizumab plus deferred PRP versus prompt PRP, follow-up 12 months
(3) Pegaptanib alone compared to PRP alone, follow-up 9 months
(4) Ranibizumab and PRP compared to saline and PRP, follow-up 12 months
(5) Ranibizumab plus deferred PRP versus prompt PRP, follow-up 2 years
(6) combination antiVEGF plus PRP vs PRP; 12 months of follow-up

Analysis 1.5. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 5: Need for laser photocoagulation

Study or Subgroup	Anti-VEGF Events	Anti-VEGF Total	PRP Events	PRP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Ranibizumab						
DRCR.net 2015 (1)	15	191	92	203	78.1%	0.17 [0.10 , 0.29]
Lang 2019 (2)	4	35	21	35	21.9%	0.19 [0.07 , 0.50]
Subtotal (95% CI)		**226**		**238**	**100.0%**	**0.18 [0.11 , 0.28]**
Total events:	19		113			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 7.55 (P < 0.00001)						
Total (95% CI)		**226**		**238**	**100.0%**	**0.18 [0.11 , 0.28]**
Total events:	19		113			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 7.55 (P < 0.00001)						
Test for subgroup differences: Not applicable						



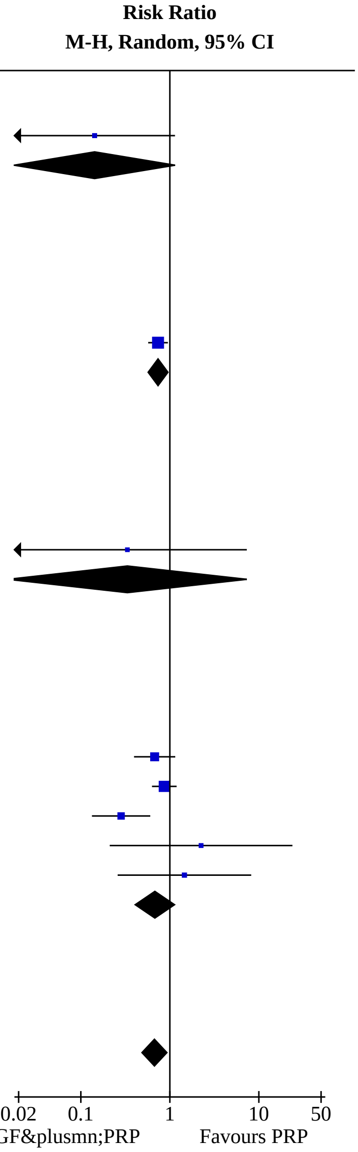
Footnotes

(1) Ranibizumab plus deferred PRP versus prompt PRP, follow-up 2 years

(2) AntiVEGF alone vs PRP. Follow-uo 12 months.

Analysis 1.6. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 6: Need for vitrectomy

Study or Subgroup	Anti-VEGF Events	Anti-VEGF Total	PRP Events	PRP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Aflibercept						
Sivaprasad 2017 (1)	1	116	7	116	2.3%	0.14 [0.02 , 1.14]
Subtotal (95% CI)		**116**		**116**	**2.3%**	**0.14 [0.02 , 1.14]**
Total events:	1		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.6.2 Bevacizumab						
Meng 2016 (2)	21	30	19	20	31.8%	0.74 [0.57 , 0.95]
Subtotal (95% CI)		**30**		**20**	**31.8%**	**0.74 [0.57 , 0.95]**
Total events:	21		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.35 (P = 0.02)						
1.6.3 Pegaptanib						
González 2009 (3)	0	10	1	10	1.1%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**1.1%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.6.4 Ranibizumab						
Chelala 2018 (4)	17	71	22	62	19.0%	0.67 [0.40 , 1.15]
DRCR.net 2013 (5)	43	125	54	136	28.6%	0.87 [0.63 , 1.19]
DRCR.net 2015 (6)	8	191	30	203	12.5%	0.28 [0.13 , 0.60]
Figueira 2018 (7)	2	41	1	46	1.8%	2.24 [0.21 , 23.84]
Lang 2019 (8)	3	36	2	35	3.2%	1.46 [0.26 , 8.21]
Subtotal (95% CI)		**464**		**482**	**64.9%**	**0.68 [0.41 , 1.13]**
Total events:	73		109			
Heterogeneity: Tau² = 0.15; Chi² = 8.99, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 1.50 (P = 0.13)						
Total (95% CI)		**620**		**628**	**100.0%**	**0.67 [0.49 , 0.93]**
Total events:	95		136			
Heterogeneity: Tau² = 0.07; Chi² = 12.26, df = 7 (P = 0.09); I² = 43%						
Test for overall effect: Z = 2.43 (P = 0.02)						
Test for subgroup differences: Chi² = 2.63, df = 3 (P = 0.45), I² = 0%						

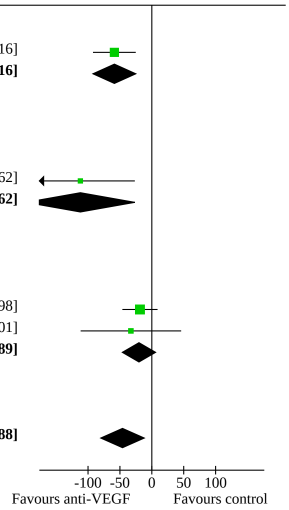


Footnotes

(1) AntiVEGF vs PRP. 12-month follow-up.
(2) Combination of antiVEGF plus PRP vs PRP. 3-month follow-up
(3) Pegaptanib alone compared to PRP alone, follow-up 9 months
(4) AntiVEGF plus PRP. 4-month follow-up
(5) Combination of antiVEGF plus PRP vs PRP.12-month follow-up
(6) Combination of antiVEGF plus PRP vs PRP. 24-month follow-up
(7) Combination of antiVEGF plus PRP vs PRP. 12-month follow-up
(8) Combination antiVEGF plus PRP vs PRP. Follow-up 12 months.

Analysis 1.7. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 7: Oedema as measured by macular thickness (µm) (participant)

Study or Subgroup	AntiVEGF Mean [patient]	AntiVEGF SD [patient]	AntiVEGF Total	PRP Mean [patient]	PRP SD [patient]	PRP Total	Weight	Mean Difference IV, Random, 95% CI [patient]
1.7.1 Bevacizumab								
Rebecca 2021 (1)	240.3	86.91	38	299	59.79	38	34.9%	-58.70 [-92.24 , -25.16]
Subtotal (95% CI)			**38**			**38**	**34.9%**	**-58.70 [-92.24 , -25.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								
1.7.2 Pegaptanip								
González 2009 (2)	191	54	8	303	110.75	8	12.2%	-112.00 [-197.38 , -26.62]
Subtotal (95% CI)			**8**			**8**	**12.2%**	**-112.00 [-197.38 , -26.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.57 (P = 0.01)								
1.7.3 Ranibizumab								
Lang 2019 (3)	17.6	46.7	28	36.2	55.9	26	39.1%	-18.60 [-46.18 , 8.98]
Ramos Filho 2011 (4)	-14.7	151.4	15	18.1	35.2	14	13.8%	-32.80 [-111.61 , 46.01]
Subtotal (95% CI)			**43**			**40**	**52.9%**	**-20.15 [-46.19 , 5.89]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%								
Test for overall effect: Z = 1.52 (P = 0.13)								
Total (95% CI)			**89**			**86**	**100.0%**	**-45.95 [-80.02 , -11.88]**
Heterogeneity: Tau² = 574.20; Chi² = 6.26, df = 3 (P = 0.10); I² = 52%								
Test for overall effect: Z = 2.64 (P = 0.008)								
Test for subgroup differences: Chi² = 6.15, df = 2 (P = 0.05), I² = 67.5%								



Footnotes

(1) Combination of antiVEGF plus PRP vs PRP. 6-month of follow-up

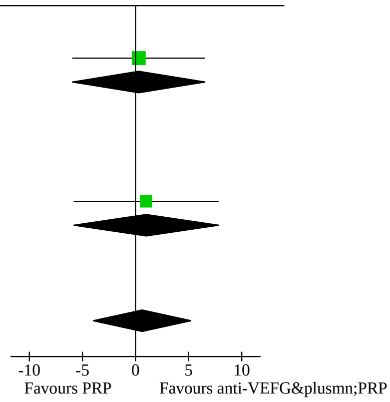
(2) AntiVEGF vs PRP. Assessed at 36 weeks of follow-up

(3) Combination of antiVEGF plus PRP vs PRP. 12-month of follow-up. Mean change from baseline.

(4) Combination of antiVEGF plus PRP vs PRP. 12-month follow-up. Mean change from baseline

Analysis 1.8. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 8: Quality of Life (VFQ-25 General health)

Study or Subgroup	Anti-VEGF±PRP Mean	Anti-VEGF±PRP SD	Anti-VEGF±PRP Total	PRP Mean	PRP SD	PRP Total	Weight	Mean Difference IV, Random, 95% CI
1.8.1 Aflibercept								
Sivaprasad 2017 (1)	46.9	21.9	104	46.6	24	103	54.3%	0.30 [-5.96 , 6.56]
Subtotal (95% CI)			**104**			**103**	**54.3%**	**0.30 [-5.96 , 6.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
1.8.2 Ranibizumab								
DRCR.net 2015 (2)	47	23	83	46	23	92	45.7%	1.00 [-5.82 , 7.82]
Subtotal (95% CI)			**83**			**92**	**45.7%**	**1.00 [-5.82 , 7.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
Total (95% CI)			**187**			**195**	**100.0%**	**0.62 [-3.99 , 5.23]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 0.26 (P = 0.79)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%								



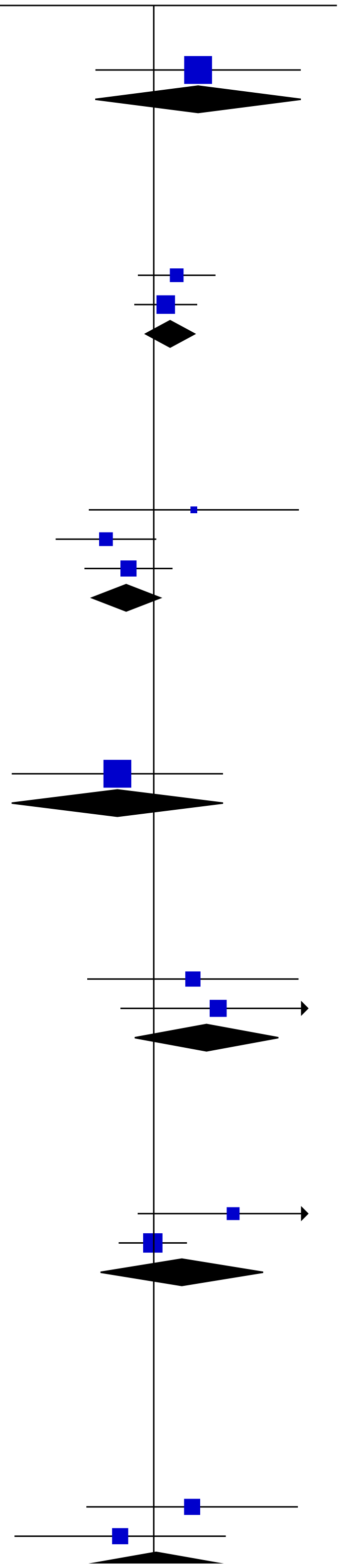
Footnotes

(1) AntiVEGF vs PRP. 12 months of follow-up.

(2) Combination of antiVEGF plus PRP vs PRP. 24 months of follow-up

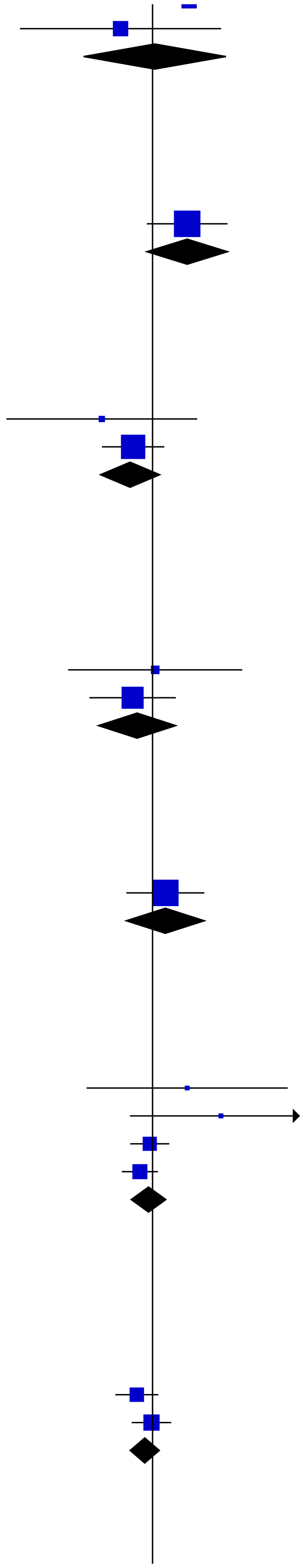
Analysis 1.9. Comparison 1: Anti-vascular endothelial growth factor (anti-VEGF) with or without panretinal photocoagulation (PRP) versus PRP, Outcome 9: Adverse events

Study or Subgroup	Anti-VEGF Events	Anti-VEGF Total	PRP Events	PRP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Angina						
Figueira 2016	1	10	0	13	100.0%	3.82 [0.17 , 84.90]
Subtotal (95% CI)		**10**		**13**	**100.0%**	**3.82 [0.17 , 84.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
1.9.2 Any APTC event						
Sivaprasad 2017	8	116	4	116	39.7%	2.00 [0.62 , 6.46]
DRCR.net 2015	9	102	7	114	60.3%	1.44 [0.56 , 3.72]
Subtotal (95% CI)		**218**		**230**	**100.0%**	**1.64 [0.78 , 3.43]**
Total events:	17		11			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 1.31 (P = 0.19)						
1.9.3 Arterial hypertension						
Figueira 2018	1	41	0	46	10.2%	3.36 [0.14 , 80.20]
DRCR.net 2015	2	191	9	203	39.9%	0.24 [0.05 , 1.08]
DRCR.net 2013	3	125	7	136	50.0%	0.47 [0.12 , 1.76]
Subtotal (95% CI)		**357**		**385**	**100.0%**	**0.43 [0.16 , 1.22]**
Total events:	6		16			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 2.22$, df = 2 (P = 0.33); $I^2 = 10\%$						
Test for overall effect: Z = 1.58 (P = 0.11)						
1.9.4 Progression of cataract						
Sivaprasad 2017	0	116	1	116	100.0%	0.33 [0.01 , 8.10]
Subtotal (95% CI)		**116**		**116**	**100.0%**	**0.33 [0.01 , 8.10]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.9.5 Cerebrovascular accident						
DRCR.net 2013	1	125	0	136	46.1%	3.26 [0.13 , 79.34]
Sivaprasad 2017	3	116	0	116	53.9%	7.00 [0.37 , 134.02]
Subtotal (95% CI)		**241**		**252**	**100.0%**	**4.92 [0.56 , 42.99]**
Total events:	4		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.9.6 Cornea-related problems						
Sivaprasad 2017	5	116	0	116	36.1%	11.00 [0.62 , 196.68]
Lang 2019	6	36	6	35	63.9%	0.97 [0.35 , 2.73]
Subtotal (95% CI)		**152**		**151**	**100.0%**	**2.34 [0.20 , 27.20]**
Total events:	11		6			
Heterogeneity: $Tau^2 = 2.18$; $Chi^2 = 2.78$, df = 1 (P = 0.10); $I^2 = 64\%$						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.9.7 Endophalmitis						
Sivaprasad 2017	0	116	0	116		Not estimable
Figueira 2018	0	41	0	46		Not estimable
DRCR.net 2015	1	191	0	203	50.0%	3.19 [0.13 , 77.77]
DRCR.net 2013	0	125	1	136	50.0%	0.36 [0.01 , 8.82]
Subtotal (95% CI)		**473**		**501**	**100.0%**	**1.07 [0.11 , 10.27]**



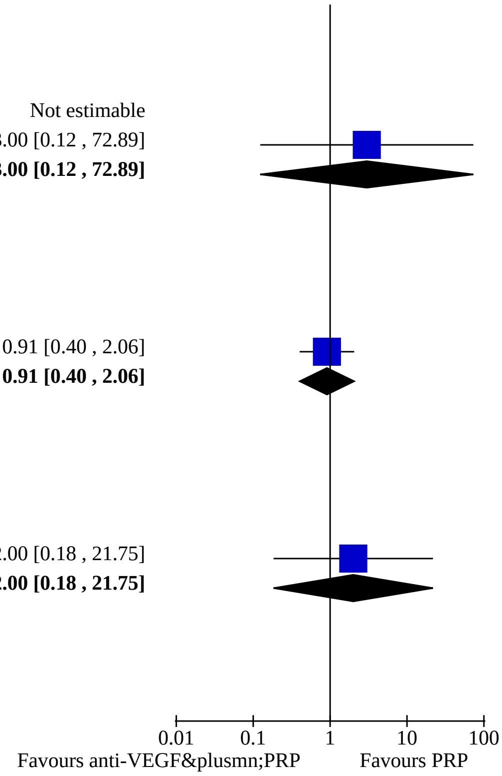
Analysis 1.9. (Continued)

DRCR.net 2013	0	125	1	136	50.0%	0.36 [0.01 , 8.82]
Subtotal (95% CI)		**473**		**501**	**100.0%**	**1.07 [0.11 , 10.27]**
Total events:	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.9.8 Inflammation						
Sivaprasad 2017	9	116	3	116	100.0%	3.00 [0.83 , 10.80]
Subtotal (95% CI)		**116**		**116**	**100.0%**	**3.00 [0.83 , 10.80]**
Total events:	9		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
1.9.9 Macular oedema						
Sivaprasad 2017	0	116	2	116	9.7%	0.20 [0.01 , 4.12]
Lang 2019	5	36	9	35	90.3%	0.54 [0.20 , 1.45]
Subtotal (95% CI)		**152**		**151**	**100.0%**	**0.49 [0.19 , 1.26]**
Total events:	5		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
1.9.10 Neovascular glaucoma						
Sivaprasad 2017	0	116	0	116		Not estimable
DRCR.net 2013	1	125	1	136	19.8%	1.09 [0.07 , 17.21]
DRCR.net 2015	3	191	6	203	80.2%	0.53 [0.13 , 2.09]
Subtotal (95% CI)		**432**		**455**	**100.0%**	**0.61 [0.18 , 2.09]**
Total events:	4		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
1.9.11 Ocular discomfort						
Sivaprasad 2017	6	116	4	116	100.0%	1.50 [0.43 , 5.18]
Subtotal (95% CI)		**116**		**116**	**100.0%**	**1.50 [0.43 , 5.18]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.9.12 Raised intraocular pressure						
Sivaprasad 2017	1	116	0	116	2.9%	3.00 [0.12 , 72.89]
Lang 2019	4	36	0	35	3.5%	8.76 [0.49 , 156.85]
DRCR.net 2013	16	125	19	136	44.8%	0.92 [0.49 , 1.70]
DRCR.net 2015	17	191	27	203	48.8%	0.67 [0.38 , 1.19]
Subtotal (95% CI)		**468**		**490**	**100.0%**	**0.88 [0.51 , 1.53]**
Total events:	38		46			
Heterogeneity: Tau² = 0.08; Chi² = 3.91, df = 3 (P = 0.27); I² = 23%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.9.13 Retinal detachment						
Sivaprasad 2017	0	116	0	116		Not estimable
DRCR.net 2015	12	191	21	203	46.0%	0.61 [0.31 , 1.20]
DRCR.net 2013	16	125	18	136	54.0%	0.97 [0.52 , 1.81]
Subtotal (95% CI)		**432**		**455**	**100.0%**	**0.78 [0.49 , 1.24]**
Total events:	28		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						



Analysis 1.9. (Continued)

Test for overall effect: Z = 1.05 (P = 0.29)						
1.9.14 Retinal tear						
Figueira 2018	0	41	0	46		Not estimable
Sivaprasad 2017	1	116	0	116	100.0%	3.00 [0.12 , 72.89]
Subtotal (95% CI)		**157**		**162**	**100.0%**	**3.00 [0.12 , 72.89]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.9.15 Visual disturbances						
Sivaprasad 2017	10	116	11	116	100.0%	0.91 [0.40 , 2.06]
Subtotal (95% CI)		**116**		**116**	**100.0%**	**0.91 [0.40 , 2.06]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
1.9.16 Vitreoretinal interface abnormalities						
Sivaprasad 2017	2	116	1	116	100.0%	2.00 [0.18 , 21.75]
Subtotal (95% CI)		**116**		**116**	**100.0%**	**2.00 [0.18 , 21.75]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						

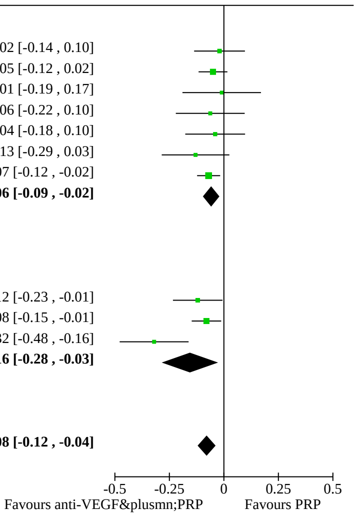


Comparison 2. Analysis stratified by severity of the disease: anti-VEGF with or without PRP versus PRP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Visual acuity stratified by severity of retinopathy	10	1172	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.12, -0.04]
2.1.1 PDR	7	980	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.09, -0.02]
2.1.2 HRPDR	3	192	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.28, -0.03]

Analysis 2.1. Comparison 2: Analysis stratified by severity of the disease: anti-VEGF with or without PRP versus PRP, Outcome 1: Visual acuity stratified by severity of retinopathy

Study or Subgroup	Favours anti-VEGF±PRP Mean [logMAR]	SD [logMAR]	Total	PRP Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]
2.1.1 PDR								
DRCR.net 2013 (1)	0.4	0.44	125	0.42	0.52	136	8.3%	-0.02 [-0.14 , 0.10]
DRCR.net 2015 (2)	0.126	0.326	160	0.176	0.282	168	17.8%	-0.05 [-0.12 , 0.02]
Ergur 2009 (3)	0.37	0.18	9	0.38	0.22	10	4.0%	-0.01 [-0.19 , 0.17]
González 2009 (4)	0.065	0.195	8	0.1275	0.118	8	5.0%	-0.06 [-0.22 , 0.10]
Lang 2019 (5)	0.12	0.24	36	0.16	0.34	35	6.4%	-0.04 [-0.18 , 0.10]
Sameen 2017 (6)	0.42	0.35	38	0.55	0.34	38	5.2%	-0.13 [-0.29 , 0.03]
Sivaprasad 2017 (7)	0.05	0.2	105	0.12	0.19	104	22.1%	-0.07 [-0.12 , -0.02]
Subtotal (95% CI)			**481**			**499**	**68.9%**	**-0.06 [-0.09 , -0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 6 (P = 0.93); I² = 0%								
Test for overall effect: Z = 3.29 (P = 0.0010)								
2.1.2 HRPDR								
Figueira 2018 (5)	0.196	0.24	41	0.316	0.3	46	8.7%	-0.12 [-0.23 , -0.01]
Ramos Filho 2011 (5)	0	0.07	15	0.08	0.11	14	17.4%	-0.08 [-0.15 , -0.01]
Rebecca 2021 (8)	0.1	0.25	38	0.42	0.43	38	5.0%	-0.32 [-0.48 , -0.16]
Subtotal (95% CI)			**94**			**98**	**31.1%**	**-0.16 [-0.28 , -0.03]**
Heterogeneity: Tau² = 0.01; Chi² = 7.48, df = 2 (P = 0.02); I² = 73%								
Test for overall effect: Z = 2.50 (P = 0.01)								
Total (95% CI)			**575**			**597**	**100.0%**	**-0.08 [-0.12 , -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 12.54, df = 9 (P = 0.18); I² = 28%								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Test for subgroup differences: Chi² = 2.27, df = 1 (P = 0.13), I² = 55.9%								



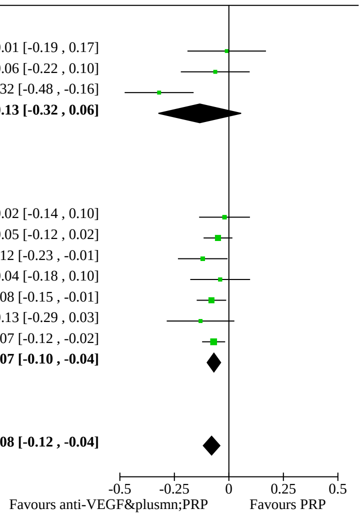
Footnotes
(1) Ranibizumab and PRP compared with PRP alone, follow-up 12 months
(2) Ranibizumab plus deferred PRP compared with prompt PRP, follow-up 2 years
(3) Bevacizumab and PRP compared with PRP alone, follow-up 6 months
(4) Pegaptanib alone compared with PRP alone, change in visual acuity, follow-up 9 months
(5) Ranibizumab and PRP compared with PRP alone, change in visual acuity, follow-up 12 months
(6) Bevacizumab plus PRP compared with PRP alone, follow-up 12 months
(7) Aflibercept compared with PRP alone, follow-up 52 weeks
(8) Bevacizumab and PRP compared with PRP alone, follow-up 6 months. The SD reported is very low and we interpreted was a SE

Comparison 3. Analysis stratified by time of follow-up: < 12 months vs 12 months or more

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Visual acuity stratified by time of follow-up (12-month or more vs <12 month)	10	1172	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.12, -0.04]
3.1.1 Less than 12 months of treatment	3	111	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.32, 0.06]
3.1.2 12 months or more of treatment	7	1061	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.10, -0.04]

Analysis 3.1. Comparison 3: Analysis stratified by time of follow-up: < 12 months vs 12 months or more, Outcome 1: Visual acuity stratified by time of follow-up (12-month or more vs <12 month)

Study or Subgroup	Favours anti-VEGF±PRP Mean [logMAR]	SD [logMAR]	Total	PRP Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]
3.1.1 Less than 12 months of treatment								
Ergur 2009 (1)	0.37	0.18	9	0.38	0.22	10	4.0%	-0.01 [-0.19 , 0.17]
González 2009 (2)	0.065	0.195	8	0.1275	0.118	8	5.0%	-0.06 [-0.22 , 0.10]
Rebecca 2021 (3)	0.1	0.25	38	0.42	0.43	38	5.0%	-0.32 [-0.48 , -0.16]
Subtotal (95% CI)			**55**			**56**	**14.1%**	**-0.13 [-0.32 , 0.06]**
Heterogeneity: Tau² = 0.02; Chi² = 7.90, df = 2 (P = 0.02); I² = 75%								
Test for overall effect: Z = 1.38 (P = 0.17)								
3.1.2 12 months or more of treatment								
DRCR.net 2013 (4)	0.4	0.44	125	0.42	0.52	136	8.3%	-0.02 [-0.14 , 0.10]
DRCR.net 2015 (5)	0.126	0.326	160	0.176	0.282	168	17.8%	-0.05 [-0.12 , 0.02]
Figueira 2018 (6)	0.196	0.24	41	0.316	0.3	46	8.7%	-0.12 [-0.23 , -0.01]
Lang 2019 (6)	0.12	0.24	36	0.16	0.34	35	6.4%	-0.04 [-0.18 , 0.10]
Ramos Filho 2011 (6)	0	0.07	15	0.08	0.11	14	17.4%	-0.08 [-0.15 , -0.01]
Sameen 2017 (7)	0.42	0.35	38	0.55	0.34	38	5.2%	-0.13 [-0.29 , 0.03]
Sivaprasad 2017 (8)	0.05	0.2	105	0.12	0.19	104	22.1%	-0.07 [-0.12 , -0.02]
Subtotal (95% CI)			**520**			**541**	**85.9%**	**-0.07 [-0.10 , -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 6 (P = 0.85); I² = 0%								
Test for overall effect: Z = 4.37 (P < 0.0001)								
Total (95% CI)			**575**			**597**	**100.0%**	**-0.08 [-0.12 , -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 12.54, df = 9 (P = 0.18); I² = 28%								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%								



Footnotes

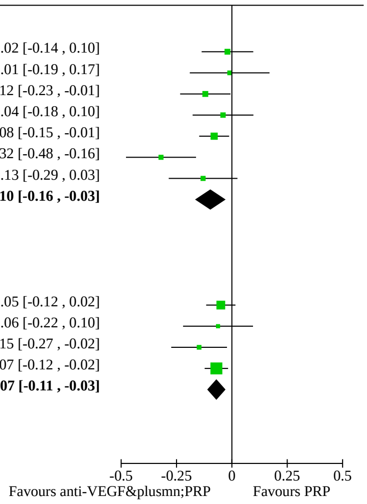
(1) Bevacizumab and PRP compared with PRP alone, follow-up 6 months
(2) Pegaptanib alone compared with PRP alone, change in visual acuity, follow-up 9 months
(3) Bevacizumab and PRP compared with PRP alone, follow-up 6 months. The SD reported is very low and we interpreted was a SE
(4) Ranibizumab and PRP compared with PRP alone, follow-up 12 months
(5) Ranibizumab plus deferred PRP compared with prompt PRP, follow-up 2 years
(6) Ranibizumab and PRP compared with PRP alone, change in visual acuity, follow-up 12 months
(7) Bevacizumab plus PRP compared with PRP alone, follow-up 12 months
(8) Aflibercept compared with PRP alone, follow-up 52 weeks

Comparison 4. Analysis stratified by anti-VEGF plus PRP versus anti-VEGF alone, both compared with PRP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Visual acuity comparing anti-VEGFs plus PRP versus anti-VEGF alone	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1.1 Anti-VEGF plus PRP	7	619	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.16, -0.03]
4.1.2 Anti-VEGF alone	4	623	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.11, -0.03]

Analysis 4.1. Comparison 4: Analysis stratified by anti-VEGF plus PRP versus anti-VEGF alone, both compared with PRP, Outcome 1: Visual acuity comparing anti-VEGFs plus PRP versus anti-VEGF alone

Study or Subgroup	Anti-VEGF Mean [logMAR]	Anti-VEGF SD [logMAR]	Anti-VEGF Total	PRP Mean [logMAR]	PRP SD [logMAR]	PRP Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]
4.1.1 Anti-VEGF plus PRP								
DRCR.net 2013 (1)	0.4	0.44	125	0.42	0.52	136	15.7%	-0.02 [-0.14 , 0.10]
Ergur 2009 (2)	0.37	0.18	9	0.38	0.22	10	9.2%	-0.01 [-0.19 , 0.17]
Figueira 2018 (3)	0.196	0.24	41	0.316	0.3	46	16.1%	-0.12 [-0.23 , -0.01]
Lang 2019 (3)	0.12	0.24	36	0.16	0.34	35	13.1%	-0.04 [-0.18 , 0.10]
Ramos Filho 2011 (3)	0	0.07	15	0.08	0.11	14	23.7%	-0.08 [-0.15 , -0.01]
Rebecca 2021 (4)	0.1	0.25	38	0.42	0.43	38	11.0%	-0.32 [-0.48 , -0.16]
Sameen 2017 (5)	0.42	0.35	38	0.55	0.34	38	11.3%	-0.13 [-0.29 , 0.03]
Subtotal (95% CI)			**302**			**317**	**100.0%**	**-0.10 [-0.16 , -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 11.38, df = 6 (P = 0.08); I² = 47%								
Test for overall effect: Z = 2.95 (P = 0.003)								
4.1.2 Anti-VEGF alone								
DRCR.net 2015 (6)	0.126	0.326	160	0.176	0.282	168	33.2%	-0.05 [-0.12 , 0.02]
González 2009 (7)	0.065	0.195	8	0.1275	0.118	8	5.8%	-0.06 [-0.22 , 0.10]
Lang 2019	0.012	0.17	35	0.16	0.34	35	9.1%	-0.15 [-0.27 , -0.02]
Sivaprasad 2017 (8)	0.05	0.2	105	0.12	0.19	104	51.9%	-0.07 [-0.12 , -0.02]
Subtotal (95% CI)			**308**			**315**	**100.0%**	**-0.07 [-0.11 , -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 3 (P = 0.61); I² = 0%								
Test for overall effect: Z = 3.61 (P = 0.0003)								
Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.48), I² = 0%								



Footnotes

(1) Ranibizumab and PRP compared with PRP alone, follow-up 12 months
(2) Bevacizumab and PRP compared with PRP alone, follow-up 6 months
(3) Ranibizumab and PRP compared with PRP alone, change in visual acuity, follow-up 12 months
(4) Bevacizumab and PRP compared with PRP alone, follow-up 6 months. The SD reported is very low and we interpreted was a SE
(5) Bevacizumab plus PRP compared with PRP alone, follow-up 12 months
(6) Ranibizumab plus deferred PRP compared with prompt PRP, follow-up 2 years. Only 6% of eyes (12 out 191) received delayed PRP in the anti-VEGF group .
(7) Pegaptanib alone compared with PRP alone, change in visual acuity, follow-up 9 months
(8) Aflibercept compared with PRP alone, follow-up 52 weeks

ADDITIONAL TABLES

Table 1. ETDRS classification of diabetic retinopathy

Mild	Presence of at least 1 microaneurysm
Moderate	Haemorrhages or microaneurysms (or both) more than standard photo 2A, presence of soft exudates, venous beading, IRMA definitively present
Severe	Haemorrhages or microaneurysms (or both) more than standard photo 2A in all 4 quadrants, or venous beading in ≥ 2 quadrants, or IRMA more than standard photo 8A in at least 1 quadrant
Very severe	Any ≥ 2 of the changes seen in severe NPDR
Early PDR	Presence of new vessels
High Risk PDR	Any of the following: NVD more than one-third to one-quarter disc diameter, NVD less than one-third to one-quarter disc diameter with vitreous or pre-retinal haemorrhage, new vessels elsewhere with vitreous or pre-retinal haemorrhage

ETDRS: Early Treatment Diabetic Retinopathy Study; IRMA: intraretinal microaneurysm; NPDR: non-proliferative diabetic retinopathy; NVD: new vessels at optic disc; PDR: proliferative diabetic retinopathy.

Table 2. ICDRDS scale

Non-apparent retinopathy	No abnormalities

Table 2. ICDRDS scale *(Continued)*

Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following: > 20 intraretinal haemorrhages in each of 4 quadrants; definite venous beading in 2 quadrants; prominent intraretinal microvascular abnormalities in 1 quadrant and no signs of proliferative retinopathy
Proliferative diabetic retinopathy	≥ 1 of the following: new vessels, vitreous or pre-retinal haemorrhage

ICDRDS: International Clinical Diabetic Retinopathy Disease Severity scale; NPDR: non-proliferative diabetic retinopathy.

Table 3. Glycosylated haemoglobin (HbA1c)

Study	PRP (control group)	Anti-VEGF ± PRP	Comment
Ahmad 2012	7.9	7.3	
Ali 2018	7.6	7.6	
Chelala 2018	8.1	7.9	
DRCR.net 2013	8.3	7.8	
DRCR.net 2015	8.9	8.6	
Ergur 2009	9.12	9.12	
Figueira 2016	8	7.5	
Figueira 2018	8.5	8.1	
González 2009	8.62	7.41	
Gonzalez 2014	-	-	No information
He 2020	7.9	7.9	
Lang 2019	8.1	8.3	
Marashi 2017	-	-	No information
Meng 2016	-	-	No information
Mirshahi 2008	8.4	8.4	
Preti 2013	9.1	9.1	
Preti 2017	8.89	8.89	
Ramos Filho 2011	9.3	9.4	
Rebecca 2021	-	-	No information

Table 3. Glycosylated haemoglobin (HbA1c) *(Continued)*

Roohipoor 2016	8.4	8.4	
Sameen 2017	-	-	No information, but people with poor diabetic control (HbA1C > 7.0%) were excluded.
Shahraki 2022	8.54	8.53	
Sivaprasad 2017	-	-	63% of participants have HbA1c between 8 and 12%, and 47% have HbA1c < 8%.

HbA1c: measured as %; PRP: panretinal photocoagulation

Table 4. Treatment administration per eye

Included studies	Anti-VEGF	Anti-VEGF group		PRP group		
		Anti-VEGF injections	PRP sessions	Rescue anti-VEGF injections	PRP sessions	Follow-up (months)
		Median N	Median N	Median N	Median N	Mean N
Ahmad 2012	Bevacizumab	2	2	NA	2	3
Ali 2018	Bevacizumab	1	1	NA	1	6
Chelala 2018	Ranibizumab	4	NA	NA	NA	4
DRCR.net 2013	Ranibizumab	5	4	NA	3	12
DRCR.net 2015	Ranibizumab	10 (14 if DMO at baseline)	1 (6% eyes repeated dose)	4 (9 if DMO at baseline)	1 (45% eyes repeated dose)	24
Ergur 2009	Bevacizumab	1	3	NA	3	6
Figueira 2016	Ranibizumab	5	4	NA	3	12
Figueira 2018[a]	Ranibizumab	4	3	NA	5	12
González 2009	Pegaptanib	6	NA	NA	2	7
Gonzalez 2014[a]	Pegaptanib	3	1	NA	1	12
He 2020	Conbercept	2	3	NA	3	6
Lang 2019[a]	Ranibizumab	5	3	NA	3	12
Marashi 2017	Bevacizumab	9	Not reported	NA	4	12
Mirshahi 2008	Bevacizumab	1	3	NA	3	4
Meng 2016[b]	Bevacizumab	1	1	NA	1	3

Table 4. Treatment administration per eye *(Continued)*

Preti 2013	Bevacizumab	2	3	NA	3	6
Preti 2017	Bevacizumab	2	3	NA	3	1
Ramos Filho 2011	Ranibizumab	2	2	NA	3	12
Rebecca 2021	Bevacizumab	2	3	NA	5	6
Roohipoor 2016	Bevacizumab	1	3	NA	3	10
Sameen 2017	Bevacizumab	3	3	NA	3	3
Shahraki 2022[a]	Bevacizumab	4	1	2	3	12
Sivaprasad 2017	Aflibercept	4	Only 2% participants needed additional PRP	NA	3	12

[a]Some studies had three or more arms of treatments; one of them was anti-VEGF administered alone.
[b]PRP was administered to 70% of participants in the anti-VEGF group in Meng 2016.
DME: diabetic macular oedema; NA: not applicable because this intervention was not administered.

Table 5. Description of economic included studies

Included study	Description
Hutton 2017	Hutton 2017 carried out a within-trial cost-utility analysis (CUA) with outcomes in quality adjusted life years (QALYs). Costs were initially reported as USD 2016 before conversion. Hutton 2017 found that for participants with PDR and vision-impairing DMO at baseline, the ICER of ranibizumab compared with PRP during a 2-year horizon was USD 61,412/QALY. The study found that participants who had PDR with no DMO had a higher ICER of USD 732,702/QALY. Therefore, ranibizumab was likely to be more cost effective, as such, for participants with no DMO PRP compared with ranibizumab for participants who had PDR with DMO. Sensitivity analysis found that the cost of the anti-VEGF drug was the biggest driver of cost effectiveness. Hutton 2019 used the 5-year trial outcomes to extend the time horizon of the economic evaluation to 5 years and then used these data to extrapolate the results to a longer 10-year horizon. Costs were initially reported as USD 2018 before conversion. The results of analysis with the 5-year time horizon gave an incremental cost per QALY gained of USD 69,552/QALY for ranibizumab compared with PRP for those with PDR and vision-impairing DMO at baseline. The incremental cost per QALY gained was USD 617,573/QALY for those without vision-impairing DMO. When extrapolating the results to a 10-year time horizon, the assumption was made that the last observed visual acuity and utilities remained the same for the remainder of the 10-year time horizon and that any serious systemic events would need care continuing to year 10. The incremental cost per QALY gained for the 10-year time horizon was USD 67,806 for those with PDR and vision-impairing DMO at baseline and USD 787,205 for those without vision-impairing DMO. Sensitivity analysis found that ranibizumab injections had a 37% chance of being cost effective at a threshold of USD 50,000 per QALY, 82% at a threshold of USD 100,000 per QALY, and 93% at a threshold of USD 150,000 per QALY for participants with DMO and PRP. However, there was only a 9% chance that ranibizumab injections might be cost effective at a high threshold of USD 250,000 per QALY for those without CI-DMO and vision loss. The authors concluded that the use of ranibizumab is within an acceptable cost-effectiveness threshold for those with PDR with vision-impairing DMO but not for those without.
Lin 2016	Lin 2016 carried out what was described as a “A Markov-style model of cost-effectiveness and cost utility” which compares ranibizumab and PRP. The exact format of the model used was not described. The results are presented at 2 years and across a patient’s lifetime. The model was based

Table 5. Description of economic included studies *(Continued)*

	on the results of Gross 2015 and expressed as the incremental cost per line of vision saved and "cost per line of vision year". Life expectancy was based on the actuarial tables of the Social Security Administration. For the cost utility analysis, a QALY gain of 0.03 per line-year of vision saved was applied to produce QALYs. The costs were derived from the Centers for Medicare and Medicaid Services (CMS) and costs were reported in USD. Costs were calculated for both a hospital-based facility and a nonfacility in the same geographic area to demonstrate the range of potential reimbursement settings. Professional and facility fees were included in the calculations. Costs were initially reported as USD 2016 before conversion. The results were presented as cost per line of vision saved, cost per line-year saved and the cost per QALY. The results of PRP arm, for the facility billing were: cost per line of vision saved was USD 7252, cost per line-year saved was USD 240 and cost per QALY was USD 7988. In the non-facility setting, the cost per line of vision saved was USD 5717, the cost per line-year saved was USD 189 and the cost per QALY was USD 6297. The results of ranibizumab arm (0.5 mg) for the facility setting were as follows: cost per line saved was USD 16,849, the cost per line-year saved was USD 575, and the cost per QALY was USD 19,150. In the non-facility setting, the cost per line was USD 25,716, the cost per line-year saved was USD 487, and the cost per QALY was USD 16,287. Cost per QALY results were extrapolated beyond 2 years and over the lifetime. In this circumstance the average costs per QALY with PRP treatment of USD 14,219 (non-facility setting) to USD 24,005 (facility setting) and with ranibizumab of USD 138,852 (non-facility setting) to USD 164,360 (facility setting). The authors conclude that PRP compared with ranibizumab as primary treatment for PDR is less expensive over 2 years, but both fall well below the accepted cost per QALY upper limit of USD 100,000 per QALY. There is no discussion as to why this threshold is used. No incremental results were presented and no sensitivity analysis was carried out on these results.
Lin 2018	Lin 2018 conducted a further model based on the study in 2018. The model is described as a "decision analysis model of cost-utility" but no further description of the modelling approach used was given. The model also compared ranibizumab and PRP, but with the additional comparator of Pars Plana Vitrectomy (PPV) with a 2-year time horizon, which was then extrapolated across the patient's lifetime. This model focused on those with PDR without baseline DMO. It should be noted that the cost-utility values for PPV were derived from the author's clinical experience and not from a published source. Other utility values were derived from previous published studies valuing visual impairment. Costs were based on Centers for Medicare and Medicaid Services (CMS) values and again separated into facility and non-facility costs. Costs were initially reported as USD 2017 before conversion. The results for the PRP group were presented as an average cost per QALY utility. In the facility group, this was USD 177,853 and in the non-facility group this was USD 111,230. The costs in the ranibizumab group were: faculty costs of USD 473,939 per QALY and non-faculty cost per QALY of USD 354,023. The PPV group had results of faculty costs per QALY of USD 196,459 and non-faculty cost of USD 117,093. A one-way sensitivity analysis showed that both ranibizumab and PPV groups would have equivalent costs per QALY over the first 2 years if 78% (facility) and 80% (non-facility) of participants in the PPV group required additional treatment with ranibizumab. The costs were then extrapolated across the patients' lifetimes: the faculty cost was calculated as USD 66,911 and the non-faculty costs calculated as USD 23,591 for the PRP group. In the ranibizumab group, faculty costs were USD 366,955 and non-faculty costs were USD 260,011. For PPV the faculty costs were USD 69,348, and non-faculty costs were USD 24,143. The authors concluded that PPV as a strategy for treatment of PDR without DMO demonstrates cost-utility similar to management with PRP and more favourable cost-utility compared with IVR in the short term. This advantage over ranibizumab continued when lifetime costs were factored in. Again, no incremental analysis or probabilistic sensitivity analysis were presented.
Sivaprasad 2018	Sivaprasad 2018 carried out a cost-effectiveness analysis (CEA) using BCVA as the outcome measure, and CUA. Costs were initially reported as GBP 2016 before conversion. Both of these analyses were conducted alongside a clinical trial. For the CEA, the incremental cost of an additional BCVA letter was USD 2207 for aflibercept as compared with PRP laser treatment. Sensitivity analysis showed that at the threshold of GBP 1400 (USD 2218 at USD 2021 values) there was a 57% probability of aflibercept being cost effective at its list price of USD 1292 per 0.1-ml vial, 40 mg/ml. The reasons for the choice of a GBP 1400 (USD 2218 at USD 2021 values) threshold was not described nor justified. For the CUA, the utility values were derived from the trial data using the EQ-5D-3L,

Table 5. Description of economic included studies *(Continued)*

	which was administered at baseline and 52 weeks' follow-up. The results found the aflibercept intervention to be less effective and more costly. The authors reported an ICER of -USD 400,578 for the CUA (it did not explain why this ICER is reported as a negative value) due to a very small difference in the EQ-5D-5L scores between the two groups. The ICE-CAP-A quality of life instrument was also measured at baseline and 52 weeks. For this instrument there was no evidence of a difference between aflibercept compared with PRP. The authors assumed that finding no evidence of a difference was the same as there being evidence of no difference and hence did not calculate an ICER. This study also found that the most important determinant of cost effectiveness is the price of aflibercept. Subgroup analysis was undertaken to assess those with DMO compared with those without. Unlike Hutton 2017, however, this study found no evidence of a difference between those with DMO in at least one eye and those without (USD 2208 per change in BCVA score in the DMO at baseline group compared to USD 2197 per change in BCVA score in the no-DMO at baseline group). The authors concluded that aflibercept was most costly and more effective based on the results of the CEA. The authors considered the evidence to be mixed, and noted that the measures of quality of life were not sensitive enough to measure the clinical difference between treatments.
Yannuzzi 2018	Yannuzzi 2018 carried out a decision analysis model but they provided no further details about the structure of this model. This model used data from the CLARITY trial carried out by Sivaprasad 2018. Medicare fee data for the Miami, Florida area were used to calculate the costs' range from facility to non-facility. Costs were initially reported as USD 2017 before conversion. The utility values were also referenced from the CLARITY trial, though the study did not report which specific values were utilised. The trial reported a faculty cost per QALY over a 1-year time horizon as USD 42,627 for PRP and USD 485,127 for ranibizumab. There were insufficient details to understand how these conclusions were reached.

BCVA: best corrected visual acuity; CEA: cost-effectiveness analysis; ICE-CAP-A: icepop capability measure for adults; CMS: Centers for Medicare and Medicaid Services; CUA: cost-utility analysis; DMO: diabetic macular edema; EQ-5D-3L: Euro Quality of life questionnaire 5 Dimensions 3-level; GBP: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; PDR: proliferative diabetic retinopathy; PPV: pars plana vitrectomy; USD: united stated dollar.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Diabetic Retinopathy] explode all trees
#2 (diabet* or proliferative or non-proliferative) near/4 retinopath*
#3 DR near/3 (eye* or vision or visual* or sight)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees
#6 MeSH descriptor: [Angiogenesis Inducing Agents] this term only
#7 MeSH descriptor: [Endothelial Growth Factors] this term only
#8 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees
#9 macugen or pegaptanib or lucentis or rhufab or ranibizumab or bevacizumab or avastin or aflibercept or conbercept or OPT 302 or Opthea or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol
#10 anti near/2 VEGF*
#11 anti near/1 angiogen*
#12 endothelial near/2 growth near/2 factor*
#13 VEGF TRAP*
#14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 #4 and #14

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.

7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. diabetic retinopathy/
14. ((diabet$ or proliferative or non-proliferative) adj4 retinopath$).tw.
15. diabetic retinopathy.kw.
16. (DR adj3 (eye$ or vision or visual$ or sight$)).tw.
17. or/13-16
18. exp angiogenesis inhibitors/
19. angiogenesis inducing agents/
20. endothelial growth factors/
21. exp vascular endothelial growth factors/
22. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin$ or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol).tw.
23. (anti adj2 VEGF$).tw.
24. (anti adj1 angiogen$).tw.
25. (endothelial adj2 growth adj2 factor$).tw.
26. VEGF TRAP$.tw.
27. or/18-26
28. 12 and 17 and 27

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. MEDLINE Ovid economics search strategy

1. Economics/
2. exp "costs and cost analysis"/
3. Economics, Dental/
4. exp economics, hospital/
5. Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
9. (expenditure$ not energy).ti,ab.
10. value for money.ti,ab.
11. budget$.ti,ab.
12. or/1-11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13-15
17. 12 not 16
18. letter.pt.
19. editorial.pt.
20. historical article.pt.
21. or/18-20
22. 17 not 21
23. exp animals/ not humans/
24. 22 not 23
25. bmj.jn.
26. "cochrane database of systematic reviews".jn.
27. health technology assessment winchester england.jn.
28. or/25-27
29. 24 not 28
30. diabetic retinopathy/
31. ((diabet$ or proliferative or non-proliferative) adj4 retinopath$).tw.
32. diabetic retinopathy.kw.
33. (DR adj3 (eye$ or vision or visual$ or sight$)).tw.
34. or/30-33

35. exp angiogenesis inhibitors/
36. angiogenesis inducing agents/
37. endothelial growth factors/
38. exp vascular endothelial growth factors/
39. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin$ or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol).tw.
40. (anti adj2 VEGF$).tw.
41. (anti adj1 angiogen$).tw.
42. (endothelial adj2 growth adj2 factor$).tw.
43. VEGF TRAP$.tw.
44. or/35-43
45. 34 and 44
46. 29 and 45

Appendix 4. EMBASE Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp diabetic retinopathy/
34. ((diabet$ or proliferative or non-proliferative) adj4 retinopath$).tw.
35. (proliferat$ adj3 retinopath$).tw.
36. (DR adj3 (eye$ or vision or visual$ or sight$)).tw.
37. or/33-36
38. angiogenesis/
39. angiogenesis inhibitors/
40. angiogenesis factor/
41. monoclonal antibody/
42. exp endothelial cell growth factor/
43. vasculotropin/
44. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin$ or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol).tw.
45. (anti adj2 VEGF$).tw.

46. (endothelial adj2 growth adj2 factor$).tw.
47. (anti adj1 angiogen$).tw.
48. VEGF TRAP$.tw.
49. or/38-48
50. 37 and 49
51. 32 and 50

Appendix 5. Embase Ovid economics search strategy

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. pharmacoeconomics/
5. or/1-4
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7. (expenditure$ not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget$.ti,ab.
10. or/6-9
11. 5 or 10
12. letter.pt.
13. editorial.pt.
14. note.pt.
15. or/12-14
16. 11 not 15
17. (metabolic adj cost).ti,ab.
18. ((energy or oxygen) adj cost).ti,ab.
19. ((energy or oxygen) adj expenditure).ti,ab.
20. or/17-19
21. 16 not 20
22. animal/
23. exp animal experiment/
24. nonhuman/
25. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
26. or/22-25
27. exp human/
28. human experiment/
29. or/27-28
30. 26 not (26 and 29)
31. 21 not 30
32. 0959-8146.is.
33. (1469-493X or 1366-5278).is.
34. 1756-1833.en.
35. or/32-34
36. 31 not 35
37. Conference abstract.pt.
38. 36 not 37
39. exp diabetic retinopathy/
40. ((diabet$ or proliferative or non-proliferative) adj4 retinopath$).tw.
41. (proliferat$ adj3 retinopath$).tw.
42. (DR adj3 (eye$ or vision or visual$ or sight$)).tw.
43. or/39-42
44. angiogenesis/
45. angiogenesis inhibitors/
46. angiogenesis factor/
47. monoclonal antibody/
48. exp endothelial cell growth factor/
49. vasculotropin/
50. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin$ or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol).tw.
51. (anti adj2 VEGF$).tw.
52. (endothelial adj2 growth adj2 factor$).tw.

53. (anti adj1 angiogen$).tw.
54. VEGF TRAP$.tw.
55. or/44-54
56. 43 and 55
57. 38 and 56

Appendix 6. ISRCTN registry search strategy

Diabetic retinopathy AND (macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept OR conbercept OR Opthea OR RTH258 OR faricimab OR brolucizumab OR leizumabor)

Appendix 7. ClinicalTrials.gov search strategy

(Diabetic retinopathy) AND (macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept OR conbercept OR Opthea OR RTH258 OR faricimab OR brolucizumab OR leizumabor)

Appendix 8. WHO ICTRP search strategy

Diabetic Retinopathy = Condition AND Macugen OR Pegaptanib OR Lucentis OR Rhufab OR Ranibizumab OR Bevacizumab OR Avastin OR Aflibercept OR Conbercept OR Opthea OR RTH258 OR Faricimab OR Brolucizumab OR Leizumabor = Intervention

WHAT'S NEW

Date	Event	Description
17 March 2023	New citation required and conclusions have changed	Update of a previous version
17 March 2023	New search has been performed	Electronic searches updated and new studies included

HISTORY

Protocol first published: Issue 9, 2010
Review first published: Issue 11, 2014

CONTRIBUTIONS OF AUTHORS

Conceiving the review: MJM.
Designing the review: MJM, AM.
Co-ordinating the review: MJM.
Designing electronic search strategy: Cochrane Eyes and Vision Group editorial base.
Screening search results: MJM, DP, ISM.
Obtaining copies of trials: ISM, MJM, DP.
Appraising quality of papers: MJM, DP, JAC, JIP, ISM, AK, IS.
Abstracting data from papers: MJM, DP, JAC, JIP, ISM, AK.
Data management for the review: MJM.
Entering data into Review Manager 5: MJM
Analysis of data: MJM, ISM, JAC.
Summary of findings: MJM, GV
Interpretation of data: all authors.
Writing the review: MJM, AK, GV
Draft the final review: all authors.
Guarantor for the review: MJM.

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IS: None known
GV: None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following amendments to the protocol (Martinez-Zapata 2010).

1. In the protocol, we had not considered that anti-VEGFs would be used in different patient groups with PDR (i.e. people eligible for laser treatment, people eligible for vitrectomy and people undergoing cataract surgery). In the first version of this review, we felt that clinically it did not make sense to combine these different patient groups and so presented the results separately. In this update, we excluded people who underwent surgery to treat complications of PDR because this overlaps with the Smith 2015 review.
2. In the protocol, the primary outcome was regression of proliferative retinopathy and visual acuity was a secondary outcome. On reflection, we felt this was the wrong emphasis and considered that the effect on visual acuity was more relevant for the person than checking if anti-VEGFs could produce regression of new vessels. We have changed visual acuity to the primary outcome and considered regression of proliferative retinopathy as a secondary outcome.
3. In the protocol a secondary outcome was presence of vitreous or pre-retinal haemorrhage. In this update, this outcome is only presence of vitreous haemorrhage, because vitreous haemorrhage is more relevant.
4. In the protocol, secondary outcomes included regression of neovascularisation (dichotomous and continuous variables). We have changed to regression of new vessels because neovascularisation is used in relation to the retina to refer to neovessels coming from the choroid, in general, as it occurs in age-related macular degeneration. In diabetic retinopathy, the term used is 'new vessels'.
5. In the protocol, we planned to exclude from the analysis studies where the fellow eye was used as a control (i.e. the within-person studies). However, some studies had a parallel-group design but included a low percentage of participants with the fellow eye used as a control. We included these studies in the analysis.
6. We did not calculate the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) due to the low certainty of the evidence.
7. In the protocol, we planned to do a sensitivity analysis by intention-to-treat considering the 'worst-case scenario'. In the event, we did not do this, partly due to the characteristics of the majority of studies and partly because, on reflection, we felt that this analysis was too extreme and unlikely to be informative.
8. We planned to do a sensitivity analysis excluding unpublished studies but did not have any data on unpublished studies to do this.
9. In this update we have added three subgroup analyses considering: i) a comparison between anti-VEGF plus PRP or anti-VEG alone compared with PRP alone; ii) the comparison of PDR versus HRPDR; and iii) by time of follow-up (< 12 months versus 12 months or more).
10. In this review we have included studies that assessed cost and the relation between costs and effectiveness of interventions.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diabetes Mellitus [drug therapy]; *Diabetic Retinopathy [complications] [drug therapy]; Ranibizumab [therapeutic use]; Vascular Endothelial Growth Factor A [antagonists & inhibitors]; Vitreous Hemorrhage [drug therapy] [etiology] [surgery]

MeSH check words

Aged; Female; Humans; Male; Middle Aged