National Institute for Health and Care Excellence

Final

Diabetic retinopathy: management and monitoring

[F] Evidence reviews for vitrectomy

NICE guideline NG242

Evidence reviews underpinning recommendations 1.5.7 to 1.5.9 and 1.6.14

August 2024

Final

These evidence reviews were developed by NICE

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Contents

1 Effectiveness of vitrectomy

1.1 Review question

What is the effectiveness of vitrectomy surgery alone, or in combination with other treatments for treating proliferative diabetic retinopathy and macular oedema?

1.1.1 Introduction

Vitrectomy is a surgical procedure that is sometimes used as a treatment for complications associated with proliferative diabetic retinopathy or diabetic macular oedema. The aim of this evidence review was to determine the effectiveness of vitrectomy compared with other treatments for diabetic retinopathy or diabetic macular oedema to make recommendations on when vitrectomy should be used. The review also covered vitrectomy in combination with other treatments such as anti-VEGF agents and intravitreal steroids.

This evidence review informed recommendations in the NICE guideline on the management and treatment of diabetic retinopathy, which is a new NICE guideline in this area.

1.1.2 Summary of the protocol

Table 1: Vitrectomy for treatment of diabetic retinopathy

Population	People with proliferative diabetic retinopathy. People with diabetic macular oedema
Interventions	• Vitrectomy (surgery) alone or in combination with other treatments listed below

Comparator	• No treatment
	• Standard care, for example:
	  ○ Anti-VEGF agents
	  ○ Laser photocoagulation
	  ○ Intravitreal steroids
	• Combinations of these treatments
	• Vitrectomy alone (when compared with vitrectomy in combination with another treatment)

Outcomes	• Best corrected visual acuity,
	  ○ Best correct visual acuity will be presented per eye when this data is available in the study.
	  ○ Per patient data will only be extracted when this data is not presented in a study.
	• Progression of proliferative diabetic retinopathy or diabetic macular oedema
	• Peripheral vision (assessed using visual field measurement)
	• Quality of life (measured using a validated tool - the overall score as well as mental health domain scores will be reported separately)
	• Retinal detachment
	• Adverse events (Raised intraocular pressure, Cataract, Intraocular infection, Intraocular Inflammation)
	• Acceptability. Qualitative or quantitative data on acceptability collected alongside included randomised controlled trials will be included
	
	Outcomes will be reported at the latest time point reported by the study.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies.

A total of 1846 records were identified in the search and 4 were identified from other sources. After removing duplicate references, 1214 records were screened at title and abstract stage. Following title and abstract screening, 82 studies were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A) and 1 systematic review and 17 RCTs were included. The re-run search identified an additional 90 records, but none met the inclusion criteria for the review. The protocol stated that any qualitative studies that were published alongside the included RCTs would be included in the review. However, no qualitative studies that met this criteria were identified.

As part of the search, one systematic review was identified (Smith & Steel, 2015) which included comparisons between anti-VEGFs with vitrectomy and vitrectomy alone. This Cochrane review was assessed as high quality and directly applicable to the review. The Cochrane review did not extract the outcomes that were in the protocol for this review and so it was used as a source of studies, but the relevant primary studies were assessed by the NICE team to determine if any additional data could be extracted. No relevant data was found in these primary studies, and so no data was available for comparisons between anti-VEGFs with vitrectomy and vitrectomy alone.

Evidence was found for the following population groups and comparisons:

People who have proliferative diabetic retinopathy

- PPV vs Panretinal photocoagulation (1 parallel-group RCT)
- PPV + Anti-VEGF vs Anti-VEGF (1 parallel-group RCT)
- PPV + Intravitreal corticosteroid vs PPV (4 parallel-group RCT)
- PPV + Panretinal photocoagulation vs Anti-VEGF (1 parallel-group RCT)
- PPV + Panretinal photocoagulation vs Panretinal photocoagulation (1 parallel-group RCT)

People who have diabetic macular oedema

- Pars Plana Vitrectomy (PPV) vs No treatment (1 parallel group RCT, 1 within-person RCT)
- PPV vs Intravitreal corticosteroid (1 within-person RCT)
- PPV vs Macular grid photocoagulation (3 parallel-group RCTs, 1 within-person RCT)
- PPV + Anti-VEGF + Intravitreal corticosteroid vs Anti-VEGF + Intravitreal corticosteroid + Macular grid photocoagulation (1 parallel-group RCT)

People who have proliferative diabetic retinopathy with diabetic macular oedema

- PPV + Intravitreal corticosteroid vs PPV (1 parallel-group RCT)

1.1.4.2 Excluded studies

Overall, 63 Studies were excluded following examination of the full text articles. See Appendix J for the list of excluded studies with reasons for their exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Table of included studies

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Altun 2021 Turkey	Parallel-group RCT 6-mo FU	**Inclusion criteria** • Eyes with proliferative diabetic retinopathy (PDR) and vitreomacular traction syndrome **Key exclusion criteria** • Cases with intense vitreous haemorrhage, macular ischemia, retinal detachment • Previous macular laser treatment • Non-tractional diabetic macular oedema • Type I diabetes mellitus	**PPV-ilm + ICS (N = 26)** Intravitreal dexamethasone (IVD) injection 3 days before 23-gauge PPV with internal limiting membrane removal and pan-retinal photocoagulation (PRP)	**PPV (N = 26)** PPV with pan-retinal photocoagulation	• BCVA • Progression of PDR or DME
Antosyk 2020 USA	Parallel-group RCT 2-year FU	**Inclusion criteria** Only one eye from each participant was enrolled. Participants included if they had: • Diagnosis of Type 1 or Type 2 diabetes Eyes included if they had: • Vitreous haemorrhage (VH) from proliferative diabetic retinopathy causing vision impairment (BCVA≤78 [Snellen equivalent 20/32 or worse] with at least light perception) that investigator deemed intervention indicated **Key exclusion criteria**	**PPV + PRP (N=105)** PPV with 23-gauge (or smaller) instrument and intraoperative PRP	**Anti-VEGF (N=100)** Intravitreal aflibercept 2mg injection at baseline and weeks 4, 8 and 12	• BCVA • Progression of PDR or DME • Retinal detachment • Adverse Events

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• PRP or intravitreal anti-VEGF ≤2-mo before onset of VH • Centre-involved diabetic macular oedema • Retinal detachment from fibrosis or scar tissue pulling on retina (i.e., traction) that were involving or threatening macula			
Avitabile 2011 Italy	Parallel-group RCT 1-year FU	**Inclusion criteria** • Eyes with advanced PDR (active neovascular and fibrovascular proliferation on or within 1 disc diameter of optic disc and/or new vessels elsewhere and presence of fibrovascular proliferation with or without tractional retinal detachment not involving macula) **Key exclusion criteria** • Eyes in which PRP performed ≤past 3-month.	**PPV-ilm + PRP (N = 90)** Twenty-gauge PPV with ILM. Focal or grid laser treatment during FU if persistent clinically significant DME detected during FU	**PRP (N = 90)** 532 nm Nd:YAG laser PRP in line with ETDRS guidelines with focal or macular grid laser treatment if clinically significant macular oedema detected at baseline or if persistent during FU. Repeat PRP permitted	• BCVA • Improvement in visual acuity • Retinal detachment • Adverse Events
Blankenship 1991 USA	Parallel-group RCT 6-mo FU	**Inclusion criteria** • Loss of vision due to dense, non-clearing VH • Retinal detachment secondary to diabetic retinopathy complications. **Key exclusion criteria** • Not reported	**PPV + ICS (N = 27)** Three-port PPV with intravitreal dexamethasone 0.8 mg at end of surgery	**PPV (N = 30)** PPV same as intervention group	• Retinal detachment • Adverse Events

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Doi 2012 Japan	Within-person RCT 1-year FU	**Inclusion criteria** • Bilateral diffuse diabetic macular oedema (CMT; 300μm <) determined by OCT • No history of retinal diseases except diabetic retinopathy • BCVA logMAR 0.2-1.0 • ≥20 years-old **Key exclusion criteria** • Signs of vitreo-macular traction on biomicroscopy or OCT • apparent posterior vitreous detachment • Active PDR • History of photocoagulation within 3-mo	**PPV (N = 20)** Twenty-gauge 3-port PPV with endophotocoagulation	**ICS (N = 20)** Single intravitreal triamcinolone acetonide 4 mg injection	• BCVA • Adverse Events
Faghihi 2008 Iran	Parallel-group RCT 6-mo FU	**Inclusion criteria** • Eyes with diabetic non-clearing VH that had indication for pars plana vitrectomy (PPV) **Key exclusion criteria** • patients with previous ocular surgery (except cataract surgery), intravitreal silicone oil or SF6 gas injection, • tractional retinal detachment (detected by B-scan)	**PPV + ICS (N = 38)** Standard three port PPV with PRP and 4 mg intravitreal triamcinolone acetonide at end of surgery	**PPV (N = 34)** PPV same as intervention group	• BCVA • Adverse Events

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Freyler 1980 USA	Parallel-group RCT 1-year FU	**Inclusion criteria** • insulin dependent juvenile type of diabetes • between 12-26 years • asymmetrical proliferative diabetic retinopathy in both eyes (stage 3 according to classification of Zweng) • extensive glial and fibrous strands **Key exclusion criteria** Not reported	**PPV + PRP (N = 12)** PRP with xenon-arc and argon laser and PPV using O'Malley Vitritome	**PRP (N = 12)** PRP same as intervention group	• Improvement in visual acuity • Retinal detachment
Jorge 2021 Brazil	Parallel-group RCT 24-week FU	**Inclusion criteria** • Patient≥18 years-old • Vitreous haemorrhage duration>3-mo • Visual acuity worse than 20/40 in study eye **Key exclusion criteria** • Intraocular surgery ≤past 3-mo • Previous PPV • Associated traction retinal detachment	**PPV + Anti-VEGF (N=35)** Single intravitreal bevacizumab injection 1.5 mg 7 days before 23-gauge PPV and endolaser pan photocoagulation	**Anti-VEGF (N=38)** Total of 3 intravitreal bevacizumab 1.5 mg injections at 8-week intervals	• BCVA • Retinal detachment • Adverse Events
Kumar 2007 India	Parallel-group RCT 6-mo FU	**Inclusion criteria** Patients with • Diffuse macular oedema • Best corrected visual acuity ≤6/60 • HbA1c ≤7.5 mg/dl **Key exclusion criteria** • Underwent cataract surgery ≤past 12-month	**PPV-ilm (N = 12)** Three-port PPV with ILM removal	**Modified MGP (N = 12)** Modified grid laser photocoagulation with frequency-doubled argon green 532 nm laser	• BCVA • Improvement in visual acuity • Retinal detachment

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Previously treated with PRP ≤past 12-mo and grid laser ≤past 6-mo • Evidence of vitreomacular traction			
Limon 2022 Turkey	RCT 6-mo FU	**Inclusion criteria** • Type 2 diabetes mellitus • >49 years-old • Treatment-naive macula-off tractional retinal detachment (Grade-C) secondary to PDR with coexisting grade 3 and 4 cataracts **Key exclusion criteria** • Other causes of TRD except PDR • Previous treatment with macular laser or PRP, ICS, and intravitreal anti-VEGFs • Patients with retina or iris neovascularization at baseline	**PPV + ICS (N = 22)** Intravitreal bevacizumab 4 days before PPV. Combined phacoemulsification and PPV followed by simultaneous silicone tamponade and intravitreal dexamethasone and 360° PRP	**PPV (N = 21)** Same as intervention group without intravitreal dexamethasone injection	• BCVA • Retinal detachment • Adverse Events
Patel 2006 UK	Parallel-group RCT 1-year FU	**Inclusion criteria** • Persistent clinically significant macular oedema involving foveal centre for <2 years. • Previous treatment with macular laser • ETDRS vision score of 65–35 (equivalent Snellen visual acuity 6/15 to 6/60). **Key exclusion criteria**	**PPV (N = 10)** Standard three-port PPV	**MGP (N = 10)** Standard ETDRS argon macular photocoagulation	• Improvement in visual acuity • Adverse Events

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Posterior vitreous detachment diagnosed by the presence of a Weiss ring, • Macular traction as evidenced by retinal striae involving the foveal centre or the taut vitreous face syndrome, • Macular ischaemia as defined by an enlarged foveolar avascular zone			
Saeed 2013 Egypt	Parallel-group RCT 1-year FU	**Inclusion criteria** • Biomicroscopically, angiographically, and tomographically confirmed intractable diffuse diabetic macular oedema • Macular oedema not responsive to or recurred after IVTA and/or macular focal laser photocoagulation • Central foveal thickness >300 µm **Key exclusion criteria** • Presence of vitreomacular traction • Active neovascularization of PDR • Diabetic macular oedema for ≤ past 3-mo •	**PPV-hy + Anti-VEGF + ICS (N = 15)** PPV with posterior hyaloid removal and intravitreal triamcinolone acetonide 0.1 mL (40 mg/mL) and intravitreal bevacizumab 1.25 mg injections	**Anti-VEGF + ICS + MGP (N = 15)** Same intravitreal injection combination as intervention group with MGP 2 weeks after	• BCVA • Improvement in visual acuity • Retinal detachment • Adverse Events
Stolba 2005 Not reported[1]	Parallel-group RCT	**Inclusion criteria**	**PPV-ilm (N = 25)** Standard three-port vitrectomy with removal of the	**No treatment (N = 31)** No treatment but received same postop topical	• Improvement in visual acuity • Adverse Events

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
	6-mo FU	• History of diffuse diabetic macular oedema for minimum of 6 and maximum of 18-mo • Grid laser photocoagulation performed ≥4-mo earlier • Documented attached posterior hyaloid either with B-scan ultrasound examination or presence of a preretinal membrane shown with OCT • No or only mild cataract **Key exclusion criteria** • >3 laser treatments in macula or other pre-treatments before enrolment • Ischemic maculopathy • Proliferative changes with indication for PRP, optic atrophy or advanced glaucoma	posterior hyaloid and internal limiting membrane. Postop topical antibiotic and anti-inflammatory therapy	antibiotic and anti-inflammatory therapy as intervention group	
Takamura 2018 Japan	Parallel-group RCT	**Inclusion criteria** • Patients with type 2 diabetes who required vitrectomy for VH **Key exclusion criteria** • History of injection of anti-VEGF drugs and steroids and retinal photocoagulation ≤3-mo before surgery • Retinal detachment	**PPV + ICS (N = 42)** Standard four-port PPV including posterior hyaloid removal using 25-gauge instrument with 532 nm PRP during, and intravitreal triamcinolone acetonide 0.1mL (4mg) at end of, surgery	**PPV (N = 42)** PPV and PRP same as intervention group	• BCVA • Retinal detachment • Adverse Events
Thomas 2005 UK	Parallel-group RCT 1-year FU	**Inclusion criteria** • Confirmed diagnosis of diabetes mellitus	**PPV-ilm (N = 19)** Standard three-port PPV with internal limiting membrane removal.	**MGP (N = 21)** Further argon laser MGP to areas of	• BCVA

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Clinical and angiographic evidence of diffuse or diffuse and focal macular oedema in an eye which had already received ≥1 argon laser treatment at least previous 3-mo • Visual acuity of 0.30 logMAR (Snellen equivalent 6/12 or 20/40) or worse **Key exclusion criteria** • Ischaemic maculopathy • Active proliferative diabetic retinopathy • Vitreous haemorrhage • Biomicroscopic evidence of macular traction		angiographically-confirmed leakage	
Yanyali 2005 Turkey	Within-person RCT 6-mo FU	**Inclusion criteria** • Diagnosis of bilateral diabetic macular oedema (defined as retinal thickening of ≥2 disk areas involving foveal avascular zone with or without cystoid changes attributable to diffuse leakage from dilated retinal capillaries, retinal pigment epithelium, and ischemic retina • Diastolic blood pressure<100 mm Hg • Glycosylated haemoglobin ≤10 mg/dl **Key exclusion criteria**	**PPV-ilm (N = 12)** Standard three-port PPV with internal limiting membrane peeling. Subconjunctival gentamicin injection at end of surgery.	**Modified GLP (N = 12)** Modified Grid Argon (green 514 nm) Laser Photocoagulation	• BCVA • Improvement in visual acuity • Adverse Events

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Previous macular laser photocoagulation or PRP ≤past 12-moCataract surgery ≤past12-mo • Traction retinal detachment or evidence of vitreomacular traction. • Active neovascularization • Media opacity such as cataract or vitreous haemorrhage			
Yanyali 2006 Turkey	Within-person RCT 1-year FU	**Inclusion criteria** • Diagnosis of bilateral diabetic macular oedema • Prior grid laser photocoagulation treatment • Persistent diabetic macular oedema bilaterally 6-mo post-GLP treatment **Key exclusion criteria** • Only treated with focal laser photocoagulation • Panretinal photocoagulation or cataract surgery ≤past 12-mo • Traction retinal detachment, active neovascularization or evidence of vitreomacular traction. • Media opacity such as cataract or vitreous haemorrhage	**PPV-ilm (N = 10)** Standard three-port PPV with injections of 2mg dexamethasone and 4mg gentamicin at end of surgery	**No treatment (N = 10)** No treatment was given to this group	• BCVA • Improvement in visual acuity • Adverse Events

Notes: 1Study likely conducted in Germany. Abbreviations: Anti-VEGF, Anti-vascular endothelial growth factor therapy; BCVA, Best corrected visual acuity; DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; FU, follow up; HbA1c, Haemoglobin A1c test; ICS, Intravitreal corticosteroid; ilm, inner limiting membrane removal; IVTA, Intravitreal triamcinolone acetonide; MGP, Macular grid photocoagulation; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PPV, Pars plana vitrectomy; PRP, Panretinal photocoagulation; TRD, tractional retinal detachment; VH, vitreous haemorrhage; YAG, yttrium aluminum garnet

1.1.6 Summary of the effectiveness evidence

Pars plana vitrectomy vs No treatment (People with diabetic macular oedema)

Table 3: Pars plana vitrectomy vs No treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity (MD less than 0 favours PPV) *(measured using Snellen logMAR at 12-mo FU)*					
1 (Yanyali 2006)	Within-person RCT	20	Mean Difference; -0.05 [-0.49, 0.39]	High	Could not differentiate
Improvement in visual acuity (RR greater than 1 favours PPV) *(Defined as 'stable' or 'improved')*					
2(Yanyali 2006) (Stolba 2005)	Parallel-group RCT, Within-person RCT	76	Risk Ratio: 1.43 [1.09, 1.88]	Moderate	Favours PPV
Improvement in visual acuity – Subgroup: Stable or improved >=2 line					
1 (Yanyali 2006)	Parallel-group RCT	20	Risk Ratio 1.40 [0.92, 2.14]	High	Could not differentiate
Improvement in visual acuity – Subgroup: Stable or improved >2 lines					
1 (Yanyali 2006)	Parallel-group RCT	58	Risk Ratio 1.45 [1.02, 2.04]	High	Favours PPV
Adverse events during follow up (RR less than 1 favours PPV)					
2 (Yanyali 2006) (Stolba 2005	Parallel-group RCT, Within-person RCT	76	Risk Ratio 3.00 [0.14, 65.90]	High	Could not differentiate

.

Table 4: **Pars plana vitrectomy (PPV) vs Intravitreal corticosteroid (ICS) (population with diabetic macular oedema)**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity (SMD less than 0 favours PPV) (Intravitreal triamcinolone acetonide) measured using Snellen logMAR					
1 (Doi 2012)	Within-person RCT	40	Std. Mean Difference -0.56 [-1.51, 0.38]	High	Could not differentiate
Adverse Events – Raised intraocular pressure (Intravitreal triamcinolone acetonide)					
1 (Doi 2012)	Within-person RCT	40	Risk Ratio 0.50 [0.05, 5.08]	High	Could not differentiate
Adverse Events – Cataract (Intravitreal triamcinolone acetonide)					
1 (Doi 2012)	Within-person RCT	40	Not estimable[1]	High	Could not differentiate
Adverse Events – Intraocular infection (Intravitreal triamcinolone acetonide)					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 (Doi 2012)	Within-person RCT	40	Not estimable[1]	High	Could not differentiate
Adverse Events – Intraocular inflammation (Intravitreal triamcinolone acetonide)					
1 (Doi 2012)	Within-person RCT	40	Not estimable[1]	High	Could not differentiate

1 not estimable due to no events

Pars plana vitrectomy vs Macular grid photocoagulation (People with diabetic macular oedema)

Table 5 Pars plana vitrectomy vs Macular grid photocoagulation for MGP treatment-naïve patients

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity measured using Snellen logMAR					
2Yanyali 2005 (Kumar 2007)	Parallel-group RCT, Within-person RCT	48	Mean Difference: --0.03 [-0.11, 0.06]	High	Could not differentiate
Improvement in visual acuity – treatment naïve (RR greater than 1 favours PPV)					
2 (Yanyali 2005) (Kumar 2007)	Parallel-group RCT, Within-person RCT	48	Risk Ratio: 1.00 [0.90, 1.11]	High	Could not differentiate
Retinal detachment treatment naïve (RR greater than 1 favours PPV)					
1 (Kumar 2007)	Parallel-group RCT	24	Risk Ratio: 3.00 [0.13, 67.06]	High	Could not differentiate
Adverse Events – Raised intraocular pressure treatment naïve (RR greater than 1 favours PPV					
1 (Yanyali 2005)	Within-person RCT	24	Risk Ratio: 5.00 [0.27, 94.34]	High	Could not differentiate
Adverse Events – Cataract treatment naïve (RR greater than 1 favours PPV)					
1 (Yanyali 2005)	Within-person RCT	24	Risk Ratio 2.00 [0.45, 8.94]	High	Could not differentiate

Table 6: Pars plana vitrectomy vs Macular grid photocoagulation for patients who have received recent laser treatment.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity – recent laser treatment (MD less than 0 favours PPV)					
1 (Thomas 2005)	Parallel-group RCT	33	Mean Difference: 0.15 [-0.08, 0.38]	High	Could not differentiate
Improvement in visual acuity – recent laser treatment (RR greater than 1 favours PPV)					
1 (Patel 2006)	Parallel-group RCT	20	Risk Ratio: 0.83 [0.37, 1.85]	High	Could not differentiate
Retinal detachment – recent laser treatment (RR less than 1 favours PPV)					
1 (Patel 2006)	Parallel-group RCT	20	Not estimable	High	Could not differentiate
Adverse Events – Raised intraocular pressure – recent laser treatment (RR less than 1 favours PPV)					
1 (Patel 2006)	Parallel-group RCT	20	Not estimable	High	Could not differentiate
Adverse Events – Cataract surgery– recent laser treatment (RR less than 1 favours PPV)					
1 (Patel 2006)	Parallel-group RCT	20	Not estimable	High	Could not differentiate

Pars plana vitrectomy (PPV) vs Pan-retinal photocoagulation (PRP) for people with advanced proliferative diabetic retinopathy

Table 7: Pars plana vitrectomy (PPV) vs Pan-retinal photocoagulation (PRP)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity (MD less than 0 favours PPV)					
1 (Avitabile 2012)	Parallel-group RCT	180	Mean Difference 0.08 [-0.08, 0.24]	High	Could not differentiate
Improvement in visual acuity (RR greater than 1 favours PPV)					
1 (Avitabile 2012)	Parallel-group RCT	180	Risk Ratio: 0.70 [0.57, 0.86]	High	Favours PRP
Adverse Events – Raised intraocular pressure					
1 (Avitabile 2012)	Parallel-group RCT	180	Risk Ratio: 17.00 [1.00, 290.19]	High	Favours PRP
Adverse Events – Cataract					
1 (Avitabile 2012)	Parallel-group RCT	180	Risk Ratio: 6.20 [2.53, 15.22]	High	Favours PRP
Adverse Events – Intraocular infection					
1 (Avitabile 2012)	Parallel-group RCT	180	Not estimable	High	Could not differentiate

Pars plana vitrectomy and Anti-VEGF vs Anti-VEGF

Table 8: Pars plana vitrectomy and Anti-VEGF vs Anti-VEGF for people with proliferative diabetic retinopathy

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity measured using Snellen logMAR					
1 (Jorge 2021)	Parallel-group RCT	70	Mean Difference: -0.11 [-1.04, 0.83]	Low	Could not differentiate
Retinal detachment					
1 (Jorge 2021)	Parallel-group RCT	70	Risk ratio: 0.36 [0.02, 8.58]	Low	Could not differentiate
Adverse Events – Raised intraocular pressure					
1 (Jorge 2021)	Parallel-group RCT	70	Risk Ratio: 2.17 [0.21, 22.91]	Low	Could not differentiate
Adverse Events – Cataract					
1 (Jorge 2021)	Parallel-group RCT	70	Not estimable[1]	Low	Could not differentiate
Adverse Events – Intraocular infection					
1 (Jorge 2021)	Parallel-group RCT	70	Not estimable[1]	Low	Could not differentiate
Adverse Events – Intraocular inflammation					
1 (Jorge 2021)	Parallel-group RCT	70	Not estimable[1]	Low	Could not differentiate

1 Effect size not estimable due to no events

Pars plana vitrectomy (PPV) and Intravitreal corticosteroid (ICS) vs Pars plana vitrectomy (PPV) for people with diabetic macular oedema

Table 9: Pars plana vitrectomy (PPV) and Intravitreal corticosteroid (ICS) vs Pars plana vitrectomy (PPV)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity by subgroups of indication for vitrectomy: vitreomacular traction syndrome, indication tractional retinal detachment and by vitreous haemorrhage (MD less than 0 favours PPV + ICS)					
3	Parallel-group RCT	248	Mean difference: -0.13 [-0.25, -0.01]	High	Favours PPV + ICS
Best corrected visual acuity –subgroup: Intravitreal dexamethasone, indication vitreomacular traction syndrome					
1 (Altun 2021)	Parallel-group RCT	52	Mean difference: -0.09 [-0.14, -0.04]	High	Favours PPV + ICS
Best corrected visual acuity –subgroup intravitreal dexamethasone, indication tractional retinal detachment					
1 (Limon 2022)	Parallel-group RCT	43	Mean difference: -0.31 [-0.55, -0.07]	High	Favours PPV + ICS
Best corrected visual acuity –subgroup intravitreal triamcinolone acetonide, indication vitreous haemorrhage					
2 (Faghihi 2008) (Takamura 2018)	Parallel-group RCT	153	Mean difference- 0.10 [-0.39, 0.19]	Low	Could not differentiate
Progression of PDR or Diabetic macular oedema (Intravitreal dexamethasone) indication vitreomacular traction syndrome					
1 (Altun 2021)	Parallel-group RCT	63	Risk Ratio: 0.52 [0.10, 2.62]	High	Could not differentiate
Retinal detachment: overall indication tractional retinal detachment & vitreous haemorrhage					
3(Blankenship 1991) (Limon 2022) (Takamura 2018)	Parallel-group RCT	190	Risk Ratio:0.20 [0.04, 1.08]	High	Could not differentiate
Retinal detachment: Intravitreal dexamethasone subgroup indication tractional retinal detachment & vitreous haemorrhage					
2(Blankenship 1991) (Limon 2022)	Parallel-group RCT	106	Risk Ratio: 0.20 [0.04, 1.08]	Moderate	Could not differentiate
Retinal detachment: Intravitreal triamcinolone acetonide subgroup indication vitreous haemorrhage					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 (Takamura 2018)	Parallel-group RCT	84	Not estimable	High	Could not differentiate
Adverse Events – Raised intraocular pressure (Intravitreal dexamethasone) indication tractional retinal detachment and vitreous haemorrhage					
2 Blankenship 1991) (Limon 2022)	Parallel-group RCT	106	Risk Ratio 0.98 [0.24, 3.99]	High	Could not differentiate
Adverse Events – Cataract (Intravitreal dexamethasone) indication tractional retinal detachment and vitreous haemorrhage					
2 Blankenship 1991) (Limon 2022)	Parallel-group RCT	106	Risk Ratio 0.16 [0.02, 1.21]	High	Could not differentiate
Adverse Events – Intraocular inflammation: overall indication tractional retinal detachment, vitreous haemorrhage and vitreomacular traction syndrome					
4 (Altun 2021) Blankenship 1991) (Limon 2022) (Takamura 2018)	Parallel-group RCT	248	Risk Ratio: 0.46 [0.10, 2.18]	Moderate	Could not differentiate
Adverse Events – Intraocular inflammation: Intravitreal dexamethasone subgroup indication tractional retinal detachment and vitreous haemorrhage					
2 Blankenship 1991) (Limon 2022)	Parallel-group RCT	106	Risk Ratio: 0.40 [0.04, 4.47]	Low	Could not differentiate
Adverse Events – Intraocular inflammation: Intravitreal triamcinolone acetonide subgroup indication tractional retinal detachment and vitreous haemorrhage					
2 Blankenship 1991) (Limon 2022)	Parallel-group RCT	156	Risk Ratio: 0.30 [0.01, 7.11]	High	Could not differentiate

Pars plana vitrectomy (PPV) and Pan-retinal photocoagulation (PRP) vs Anti-VEGF for people with proliferative diabetic retinopathy with vitreomacular traction syndrome

Table 10: Pars plana vitrectomy (PPV) and Pan-retinal photocoagulation (PRP) vs Anti-VEGF

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	177	Mean difference: 2.20 [-2.30, 6.70]	High	Could not differentiate
Progression of PDR or DMO (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	205	Risk ratio: 1.08 [0.57, 2.04]	High	Could not differentiate
Retinal detachment (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	205	Risk Ratio :0.62 [0.34, 1.12]	High	Could not differentiate
Retinal detachment – Tractional (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	205	Risk Ratio 0.61 [0.33, 1.12]	High	Could not differentiate
Retinal detachment – Rhegmatogenous (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	205	Risk Ratio 1.19 [0.33, 4.31]	High	Could not differentiate
Adverse Events – Raised intraocular pressure (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	205	Risk Ratio 1.04 [0.63, 1.70]	High	Could not differentiate
Adverse Events – Cataract (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	156	Risk Ratio 0.90 [0.64, 1.26]	High	Could not differentiate
Adverse Events – Intraocular infection (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	205	Risk Ratio 1.90 [0.18, 20.68]	High	Could not differentiate

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse Events – Intraocular inflammation (Intravitreal aflibercept)					
1 (Antosyk 2020)	Parallel-group RCT	205	Risk Ratio 0.63 [0.18, 2.18]	High	Could not differentiate

Pars plana vitrectomy (PPV) and Pan-retinal photocoagulation (PRP) vs Pan-retinal photocoagulation for people with asymmetrical proliferative diabetic retinopathy

Table 11: Pars plana vitrectomy (PPV) and Pan-retinal photocoagulation (PRP) vs Pan-retinal photocoagulation

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Improvement in visual acuity					
1 (Freyler 1980)	Parallel-group RCT	56	Risk ratio 1.88 [0.95, 3.70]	Low	Could not differentiate
Retinal detachment					
1 (Freyler 1980)	Parallel-group RCT	56	Risk ratio: 0.27 [0.09, 0.87]	Low	Favours PPV + PRP

Pars plana vitrectomy (PPV) and Anti-VEGF and Intravitreal corticosteroid (ICS) vs Anti-VEGF and Intravitreal corticosteroid and Macular grid photocoagulation (MGP) for people with intractable diffuse diabetic macular oedema

Table 12: Pars plana vitrectomy (PPV) and Anti-VEGF and Intravitreal corticosteroid (ICS) vs Anti-VEGF and Intravitreal corticosteroid and Macular grid photocoagulation (MGP)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity (Intravitreal triamcinolone acetonide and intravitreal bevacizumab)					
1 (Saeed 2013)	Parallel-group RCT	30	Mean Difference: 0.03 [-0.02, 0.08]	High	Could not differentiate
Improvement in visual acuity (Intravitreal triamcinolone acetonide and intravitreal bevacizumab)					
1 (Saeed 2013)	Parallel-group RCT	30	Risk Ratio: 1.00 [0.88, 1.13]	High	Could not differentiate
Retinal detachment (Intravitreal triamcinolone acetonide and intravitreal bevacizumab)					
1 (Saeed 2013)	Parallel-group RCT	30	Risk Ratio Not estimable	High	Could not differentiate
Adverse Events – Raised intraocular pressure (Intravitreal triamcinolone acetonide and intravitreal bevacizumab)					
1 (Saeed 2013)	Parallel-group RCT	30	Risk Ratio: 2.00 [0.61, 6.55]	High	Could not differentiate
Adverse Events – Cataract (Intravitreal triamcinolone acetonide and intravitreal bevacizumab)					
1 (Saeed 2013)	Parallel-group RCT	30	Risk Ratio: Not estimable	High	Could not differentiate
Adverse Events – Intraocular infection (Intravitreal triamcinolone acetonide and intravitreal bevacizumab)					
1 (Saeed 2013)	Parallel-group RCT	30	Risk Ratio: Not estimable	High	Could not differentiate

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 672 studies. Based on title and abstract screening, 667 of the studies could confidently be excluded for this review question and a further 4 studies excluded following the full-text review (see Appendix G for study selection). Thus, only one study was included in the review (see Appendix G).

1.1.7.2 Excluded studies

Four studies were excluded at full text review (see Appendix J).

1.1.8 Summary of included economic evidence

Table 13: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
Lin et al. (2018) Cost Evaluation of Early Vitrectomy versus Panretinal Photocoagulation and Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy	Partially applicable – US study with a partly applicable perspective to costs, different discount rate and unclear source of utility values	Potentially serious limitations – unclear modelling methods and sensitivity analysis, unclear how the efficacy of PPV was determined, appropriate incremental analysis was not conducted	The total and incremental QALYs are not clearly presented	Total lifetime cost* PRP: $42,182 IVR: $244,192 PPV: $42,369	Not reported	ICER not reported. Absolute cost per QALY: PRP: $61,695 IVR: $338,348 PPV: $63,942	Sensitivity analyses were conducted around the number and frequency of ranibizumab. No other sensitivity analyses were reported.

PRP, panretinal photocoagulation; IVR, intravitreal ranibizumab; PPV, pars plana vitrectomy.,
**These results are from the scenario of the 0.3mg dose of ranibizumab. Scenarios were also run using a 0.5mg dose, and with an assumption that 20/50 BCVA would be maintained. These other scenarios were not considered to be as relevant (dose) or clinically plausible.*

1.1.9 Economic model

No economic modelling was done for this review question.

1.1.10 Unit costs

Table 14: Unit costs of vitrectomies

Resource	Unit costs	Source
Urgent vitrectomy	£2,558.26	National schedule of NHS costs, weighted average of non-elective long and short stay procedures, major vitreous retinal procedures, 19 years and over, with CC score 0-2+ (BZ84A, BZ84B)
Elective vitrectomy	£671.32	National schedule of NHS costs, weighted average of day case procedures, major vitreous retinal procedures, 19 years and over, with CC score 0-2+ (BZ84A, BZ84B)

1.1.11 Evidence statements

Economic evidence statement

- One published cost-utility analysis was identified comparing early vitrectomy with intravitreal ranibizumab and with panretinal photocoagulation in people with proliferative diabetic retinopathy without diabetic macular oedema. This study found that over a lifetime horizon, early vitrectomy and panretinal photocoagulation were more likely to be considered cost-effective than intravitreal ranibizumab. However, this study had some serious limitations with how the analysis was conducted and reported, and did not present an appropriate incremental analysis. Additionally this analysis was conducted in a US healthcare setting which is funded differently to the NHS, so results may not be generalisable to the UK population.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee agreed that best-corrected visual acuity and improvement in visual acuity were important outcomes because visual acuity has a direct impact on a person's quality of life and ability to function. Progression of proliferative diabetic retinopathy or macular oedema, retinal detachment and adverse events were also considered important. The committee wanted to consider evidence on outcomes of peripheral vision and quality of life, however no evidence was available for this.

The committee wanted to consider qualitative evidence on the acceptability of vitrectomy and adjuvant treatments to a vitrectomy surgery such as anti-VEGF and steroid injections because they are known to cause patients anxiety. However, no studies were identified that reported on these outcomes.

1.1.12.2 The quality of the evidence

17 RCTs were included in the review, and the evidence for the outcomes ranged from high to low quality, with most of the evidence being high quality. The studies were separated by population, so results for people with proliferative diabetic retinopathy and those with diabetic macula oedema were analysed separately.

People with proliferative diabetic retinopathy

For people with proliferative retinopathy, the quality of the evidence for most comparisons was high. However, the committee noted that some of the evidence included a range of populations

who would usually fall under different pathways. For example, when comparing vitrectomy with pan-retinal photocoagulation, the evidence included people with advanced proliferative diabetic retinopathy. However, the study reported that 50% of people also had retinal detachment at baseline. This made it difficult for the committee to draw conclusions about each individual indication for a vitrectomy.

In the comparison of vitrectomy with intravitreal corticosteroids to vitrectomy only, most participants had vitreous haemorrhage or vitreomacular traction syndrome. However, there was a small number of people in each study and the evidence was heterogeneous, and so decision-making was difficult. The committee agreed that the evidence should therefore be considered for each population separately rather than as a whole.

The committee also highlighted that the short follow up periods made it difficult to assess the true effects of interventions. While 12 months follow-up can show side effects or post-operative adverse events, the benefits of treatment are likely to be clearer with longer follow-up periods.

For the comparison of vitrectomy against pan-retinal photocoagulation, 66% of the participants were phakic. The inclusion of people with their natural lens would influence differences in visual acuity because a cataract is a recognised complication of vitrectomy in this subgroup of people. This could account for the reversible reduction in vision seen in the short follow up period after treatment.

The comparison between vitrectomy with anti-VEGFs and anti-VEGFs alone, was comprised of 1 study with a small number of participants. The outcomes reported in this comparison were downgraded for high risk of bias. The committee's ability to make recommendations based on this evidence was therefore limited.

The evidence for comparisons of vitrectomy with intravitreal corticosteroid to pars plana vitrectomy included people with varying indications for vitrectomy surgery. One study showed a benefit of vitrectomy with intravitreal corticosteroids, but this was downgraded for risk of bias due to unclear method of randomisation, lack of blinding and selective reporting.

Single studies made up the evidence base for vitrectomy with panretinal photocoagulation compared to anti-VEGFs and for vitrectomy with panretinal photocoagulation compared to panretinal photocoagulation alone. Both studies had small sample sizes, and for the comparison with panretinal photocoagulation alone, the committee were concerned that the comparator did not reflect current practice.

People with diabetic macula oedema

For the effectiveness of vitrectomy for people with diabetic macula oedema, 8 RCTs were identified. The evidence for the outcomes ranged from high to moderate quality.

While most of the evidence was directly applicable to the review, the committee were concerned about the study design that compared vitrectomy to no treatment. The people randomised to the comparator arm were not treated with steroids, anti-VEGFs or any of the 1st - 3rd line therapies currently available in practice. Therefore, they decided that this evidence has limited applicability to current practice, as this group of people would not be left without treatment.

Imprecision and clinical importance of effects

The committee noted that while there were a large number of trials overall, there were many comparisons and participants had a range of different indications for vitrectomy. This meant that not all of the evidence could be pooled, and most of the analysis was either based on a small number of studies, or single studies. This meant that the much of the evidence had a high degree of imprecision and the wide confidence intervals often crossed the line of no effect. This made it difficult for the committee to draw strong conclusions on which to base recommendations.

The committee also noted that some studies reported no adverse events, such as raised intraocular pressure. This did not match the committee's experience, particularly for the use of intravitreal steroids. The zero events also meant that confidence intervals could not be calculated, meaning that the imprecision of these results could not be determined, and it was not possible to base decisions on these results.

1.1.12.3 Benefits and harms

People with proliferative diabetic retinopathy

The committee agreed that the evidence for this review failed to show a clear benefit of vitrectomy for people with proliferative diabetic retinopathy. The committee attributed this to the limitations in the evidence base, rather than a lack of effect, as they were confident that, based on their clinical knowledge and experience, vitrectomy does have benefits for certain groups.

The committee agreed that people who have proliferative diabetic retinopathy with macular-involving or macular-threatening retinal detachment should be offered vitrectomy. While there was no evidence for this group, the committee highlighted that if this group of people go untreated, they are at high risk of sight-threatening progression. They therefore used their clinical experience to recommend that vitrectomy should be offered to these people. They were also aware that when retinal detachment is non-macular involving or threatening, there can still be benefits from early vitrectomy. They therefore recommended that where there is progression of proliferative diabetic retinopathy due to unresponsiveness to panretinal photocoagulation treatment, a vitrectomy should be considered.

For people with non-proliferative and proliferative retinopathy with no secondary complication there is no evidence of benefit to early vitrectomy. For people that fall under this criterion, the first line of treatment of panretinal photocoagulation is effective and appropriate. The committee therefore made no recommendations for this group based on this review, because this was covered in the review on treatment strategies for proliferative diabetic retinopathy (see evidence review E).

People with diabetic macular oedema

The committee agreed that there was no evidence to support the use of vitrectomy to treat diabetic macular oedema. However, they were aware that vitrectomy can have benefits for a subgroup of people who have diabetic macular oedema with evidence of vitreoretinal traction or epiretinal membrane (see evidence review B).Based on their clinical knowledge and experience, the committee recommended that vitrectomy should be considered for these people. This should be done early enough after a person's condition shows no response to anti-VEGF treatment so that the eye does not incur any permanent damage. The committee were aware that there is no evidence for this group of people and discussed whether a research recommendation should be made so that stronger recommendations could be made about this in future. However, they were aware that the small number of people that make up this group means it has been hard to meet recruitment targets for previous trials.

There was some evidence of a benefit of vitrectomy combined with intravitreal steroids over vitrectomy alone in terms of visual acuity for people with tractional retinal detachment or vitreomacular tractional syndrome. The committee considered whether it was possible to make a recommendation to use intravitreal steroids with vitrectomy based on this evidence. However, they were concerned that the study on tractional retinal detachment included additional treatment with silicone oil which does not reflect standard practice. They also questioned why the study failed to report rates of raised intraocular pressure, which is a common adverse event associated with the use of intravitreal corticosteroids. (see evidence review G). They therefore decided that the evidence was not sufficient to recommend the use of vitrectomy in combination with intravitreal steroids.

1.1.12.4 Cost effectiveness and resource use

The committee considered one economic analysis addressing the cost-effectiveness of vitrectomy for proliferative diabetic retinopathy when making their recommendations, and they noted the costs may not be representative of those in current UK clinical practice because of the US setting and that the study had applicability issues and some serious limitations. Despite these issues the committee felt that the study supported their clinical experience that early vitrectomy can be effective, and that there is some economic value in considering early vitrectomy, however the overall evidence was insufficient to make recommendations on vitrectomy in the full population of people with diabetic retinopathy. Given the limited economic evidence, vitrectomy was only recommended for a subpopulation of people with non-clearing vitreous haemorrhage or macular- involving or threatening retinal detachment, as the committee agreed treatment of these conditions was likely to offset future costs around sight-threatening progression of their retinopathy. To minimise the potential resource implications of a wider recommendation, only a consider recommendation was made for those with non-macular-involving or non-macular-threatening retinal detachment because of a lack of evidence that vitrectomy in this group would offset the need for future treatment or prevent progression. The committee agreed that these recommendations would be unlikely to have a resource impact as they are broadly aligned with current clinical practice, and offering vitrectomy in the specific population discussed is anticipated to prevent future costs which would offset the upfront costs of the vitrectomy.

No economic evidence was identified addressing the cost-effectiveness of vitrectomy for people with diabetic macular oedema. Due to a lack of both clinical and economic evidence the recommendations firstly highlight this lack of evidence and recommend that vitrectomy is only to be considered for a specific subgroup of people with DMO. Given the population indicated in this recommendation is likely to be small, and vitrectomy is recommended before permanent damage occurs (and therefore likely to prevent or delay future treatment costs and costs associated with low vision) the committee did not anticipate a substantial resource impact.

1.1.12.5 Other factors the committee took into account

While the evidence from this review did not show a clear benefit of vitrectomy for people with diabetic retinopathy, the committee were aware of the DRVS (1990) study in the review on effectiveness of different thresholds or criteria for starting treatment (see evidence review B) that showed there is benefit to an early vitrectomy for people with severe vitreous haemorrhage secondary to proliferative diabetic retinopathy. The DRVS study did not meet the inclusion criteria for this review, as it compared timing of vitrectomy rather than different treatment options, but moderate quality evidence showed that early vitrectomy resulted in better visual acuity and fewer retinal detachments at 2 years than deferred vitrectomy. The committee also highlighted that, in their experience, vitrectomy is important as it can be used for clearance of a vitreous haemorrhage. Vitreous haemorrhage can otherwise obscure the view of the retina, meaning that other complications, such as the development of retinal tears and retinal detachment cannot be identified. Therefore, they used a combination of this evidence and their clinical experience to make a recommendation in favour of vitrectomy for people who have non-clearing vitreous haemorrhage. Given that this recommendation was based on evidence from one study which was at moderate risk of bias, it was recommended that vitrectomy is considered, rather than offered, for this group of people. However, based on their clinical experience of the benefits of vitrectomy, the committee thought it was important that this recommendation was included. They recommended that this should happen within 3 months, as their clinical experience reflected that this was the time period within which vitrectomy needs to take place to reduce the risk of associated complications, such as vision loss.

1.1.13 Recommendations supported by this evidence review.

This evidence review supports recommendations 1.5.7 to 1.5.9 and 1.6.15

1.1.14 References – included studies

1.1.14.1 Effectiveness

Altun, Ahmet, Kanar, Hatice Selen, Aki, Suat Fazil et al. (2021) Effectiveness and Safety of Coadministration of Intravitreal Dexamethasone Implant and Silicone Oil Endotamponade for Proliferative Diabetic Retinopathy with Tractional Diabetic Macular Edema. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 37(2): 131-137

Antoszyk, Andrew N, Glassman, Adam R, Beaulieu, Wesley T et al. (2020) Effect of Intravitreous Aflibercept vs Vitrectomy With Panretinal Photocoagulation on Visual Acuity in Patients With Vitreous Hemorrhage From Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA 324(23): 2383-2395

Avitabile, Teresio, Bonfiglio, Vincenza, Castiglione, Francesco et al. (2011) Severe proliferative diabetic retinopathy treated with vitrectomy or panretinal photocoagulation: a monocenter randomized controlled clinical trial. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie 46(4): 345-51

Blankenship, G W (1991) Evaluation of a single intravitreal injection of dexamethasone phosphate in vitrectomy surgery for diabetic retinopathy complications. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 229(1): 62-5

Doi, Norihito, Sakamoto, Taiji, Sonoda, Yasushi et al. (2012) Comparative study of vitrectomy versus intravitreous triamcinolone for diabetic macular edema on randomized paired-eyes. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 250(1): 71-8

Faghihi, H., Taheri, A., Farahvash, M.S. et al. (2008) Intravitreal triamcinolone acetonide injection at the end of vitrectomy for diabetic vitreous hemorrhage a randomized, clinical trial. Retina 28(9): 1241-1246

Freyler, H., Klemen, U., Prskavec, F. et al. (1980) Treatment of advanced proliferative diabetic retinopathy: photocoagulation or vitrectomy?. Metabolic Ophthalmology 4(3): 129-132

Jorge, D.M., Tavares Neto, J.E.S., Poli-Neto, O.B. et al. (2021) Intravitreal bevacizumab (IVB) versus IVB in combination with pars plana vitrectomy for vitreous hemorrhage secondary to proliferative diabetic retinopathy: a randomized clinical trial. International Journal of Retina and Vitreous 7(1): 35

Kumar, Atul, Sinha, Subijay, Azad, Rajvardhan et al. (2007) Comparative evaluation of vitrectomy and dye-enhanced ILM peel with grid laser in diffuse diabetic macular edema. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 245(3): 360-8

Limon, Utku and Sezgin Akcay, Betul Ilkay (2022) Efficacy of Intravitreal Dexamethasone After Combined Phacoemulsification and Pars Plana Vitrectomy for Diabetic Tractional Retinal Detachments. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 38(2): 176-182

Patel, J I, Hykin, P G, Schadt, M et al. (2006) Diabetic macular oedema: pilot randomised trial of pars plana vitrectomy vs macular argon photocoagulation. Eye (London, England) 20(8): 873-81

Saeed, A.M. (2013) Combined vitrectomy and intravitreal injection versus combined laser and injection for treatment of intractable diffuse diabetic macular edema. Clinical Ophthalmology 7: 283-297

Smith JM, Steel DHW. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD008214. DOI: 10.1002/14651858.CD008214.pub3.

Stolba, Ulrike, Binder, Susanne, Gruber, Diego et al. (2005) Vitrectomy for persistent diffuse diabetic macular edema. American journal of ophthalmology 140(2): 295-301

Takamura, Yoshihiro, Shimura, Masahiko, Katome, Takashi et al. (2018) Effect of intravitreal triamcinolone acetonide injection at the end of vitrectomy for vitreous haemorrhage related to proliferative diabetic retinopathy. The British journal of ophthalmology 102(10): 1351-1357

Thomas, D, Bunce, C, Moorman, C et al. (2005) A randomised controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema. The British journal of ophthalmology 89(1): 81-6

Yanyali, A, Horozoglu, F, Celik, E et al. (2006) Pars plana vitrectomy and removal of the internal limiting membrane in diabetic macular edema unresponsive to grid laser photocoagulation. European journal of ophthalmology 16(4): 573-81

Yanyali, Ates, Nohutcu, Ahmet F, Horozoglu, Fatih et al. (2005) Modified grid laser photocoagulation versus pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema. American journal of ophthalmology 139(5): 795-801

1.1.14.2 Economic

Lin, James, Chang, Jonathan S, Yannuzzi, Nicolas A et al. (2018) Cost Evaluation of Early Vitrectomy versus Panretinal Photocoagulation and Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy. Ophthalmology 125(9): 1393-1400

Appendices

Appendix A – Review protocols

Review protocol for effectiveness of vitrectomy surgery alone, or in combination with other treatments for treating proliferative diabetic retinopathy and macular oedema?

ID	Field	Content
0.	PROSPERO registration number	CRD42022354251
1.	Review title	What is the effectiveness of vitrectomy surgery alone, or in combination with other treatments for treating proliferative diabetic retinopathy and macular oedema?
2.	Review question	Q6: What is the effectiveness of vitrectomy surgery alone, or in combination with other treatments for treating proliferative diabetic retinopathy and macular oedema
3.	Objective	The aim is to inform recommendations for the effect of vitrectomy surgery alone, or in combination with other treatments such as anti-VEGF or Laser photocoagulation in people diagnosed with proliferative diabetic retinopathy and/or macular oedema
4.	Searches	The following databases will be searched for the clinical review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • HTA (legacy records) • INAHTA • MEDLINE

ID	Field	Content
		• Medline in Process • Medline EPub Ahead of Print For the economics review the following databases will be searched on population only: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Studies reported in English • Study design RCT will be applied. The Cochrane RCT classifier will be used. • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit will be set unless specified by the protocol • Cost Utility (specific) and Cohort Studies for the economic search Other searches: • None identified The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for all databases will be published in the final review.

ID	Field	Content
5.	Condition or domain being studied	Diabetic retinopathy
6.	Population	Inclusion: People with proliferative diabetic retinopathy. People with diabetic macular oedema.
7.	Intervention	Vitrectomy (surgery) alone or in combination with other treatments listed in section 8.
8.	Comparators	• No treatment • Standard care: for example, Anti-VEGF agents, Laser photocoagulation, Intravitreal steroids or combinations of these treatments) • Vitrectomy alone (when compared with vitrectomy in combination with another treatment)
9.	Types of study to be included	Randomised controlled trials Qualitative studies running alongside included randomised trials (sibling studies) reporting qualitative data on acceptability will also be included.
10.	Other exclusion criteria	Trials that were not reported in English

ID	Field	Content
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom.

12.	Primary outcomes (critical outcomes)	• Best corrected visual acuity,
		  ○ Best correct visual acuity will be presented per eye when this data is available in the study.
		  ○ Per patient data will only be extracted when this data is not presented in a study.

13.	Secondary outcomes (important outcomes)	• Progression of proliferative diabetic retinopathy or diabetic macular oedema • Peripheral vision, assessed using visual field measurement • Quality of life, measured using a validated tool (the overall score as well as mental health domain scores will be reported separately) • Retinal detachment • Adverse events (raised intraocular pressure, Cataract, Intraocular infection, Intraocular Inflammation) • Acceptability qualitative or quantitative data on acceptability collected alongside included randomised controlled trials will be included. Outcomes will be reported at the latest time point reported by the study. Reporting at earlier timepoints will be considered to facilitate meta-analysis or where dropout means that earlier timepoints are associated with substantially more precision.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include: study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.

ID	Field	Content
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. Risk of bias in RCTs will be assessed using the Cochrane risk of bias version 2 tool.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I2≥50%, when random effects models will be used instead. A modified version of GRADE will be used to assess the quality of the outcomes. Imprecision will not be assessed in the GRADE profile but will be summarised narratively in the committee discussion section of the evidence review. Outcomes using evidence from RCTs and comparative observational studies assessed with ROBINS-I will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered. Qualitative evidence about the acceptability of interventions will be combined using a thematic synthesis. Themes will be generated using emergent coding, but are expected to include the following: • Factors that increase acceptability of interventions • Factors that reduce acceptability of interventions By examining the findings of each included study, descriptive themes will be independently identified and coded in NVivo v.11. The qualitative synthesis will interrogate these 'descriptive themes' to develop 'analytical themes', using the theoretical

ID	Field	Content
		framework derived from overarching qualitative review questions. Themes will also be organised at the level of recipients of care and providers of care. CERQual will be used to assess the confidence we have in the summary findings of each of the identified themes.
17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women • Proliferative diabetic retinopathy, Diabetic Macular Oedema • Presence of vitreous haemorrhage, presence of retinal detachment If data is available a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Socioeconomic status • Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80) • Severity of vitreous haemorrhage
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative

ID	Field	Content		
		☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	April 2022		
22.	Anticipated completion date	April 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches		
		Piloting of the study selection process		

ID	Field	Content		
		Formal screening of search results against eligibility criteria		
		Data extraction		
		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	**5a. Named contact** NICE Guideline Development Team **5b Named contact e-mail** Diabeticretinopathy@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team		
25.	Review team members	From the Guideline development team: • Kathryn Hopkins • Ahmed Yosef • Linyun Fou • Syed MohiuddinHannah Lomax		

ID	Field	Content
		• Kirsty Hounsell • Jenny Craven • Jenny Kendrick
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline development team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10160
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

ID	Field	Content
		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic retinopathy, diabetic macular oedema, vitrectomy
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Search design and peer review

NICE information specialists conducted the literature searches for the evidence review. The searches were run in July 2022. Update searches were run in Feb 2023.This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review Management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, conference abstract or conference paper or "conference review" were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ, 309(6964), 1286.

Search filters

The following search filters were applied to the clinical searches in MEDLINE and Embase to identify:

RCTs

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Qualitative studies

The terms used for qualitative studies are standard NICE practice that have been developed in house. Additional terms were added to end of this filter to find sibling studies.

Clinical search strategies

Database	Date searched	Database Platform	Database segment or version
Cochrane Central Register of Controlled Trials (CENTRAL)	26/07/2022	Wiley	Issue 7 of 12, July 2022
Cochrane Database of Systematic Reviews (CDSR)	26/07/2022	Wiley	Issue 7 of 12, July 2022
Embase	26/07/2022	Ovid	1974 to 2022 July 25
Epistemonikos	26/07/2022	Epistemonikos	Search run on 26 July 2022
HTA	26/07/2022	CRD	Search run on 26 July 2022
INAHTA	26/07/2022	n/a	Search run on 26 July 2022
MEDLINE	26/07/2022	Ovid	1946 to July 25, 2022
MEDLINE-in-Process	26/07/2022	Ovid	1946 to July 25, 2022
MEDLINE ePub Ahead-of-Print	26/07/2022	Ovid	July 25, 2022

Database: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)
#1 MeSH descriptor: [Diabetic Retinopathy] explode all trees 1575 #2 MeSH descriptor: [Macular Edema] explode all trees 1274 #3 (diabet* near/6 (retin* or eye* or macular* or maculopath*)).:ti,ab,kw 1718 #4 {or #1-#3} 4034 #5 MeSH descriptor: [Ophthalmologic Surgical Procedures] explode all trees 6268 #6 ((ophthalm* or ocular* or eye*) near/4 (surg* or operat* or proced* or resect* or re-sect* or remov*)):ti,ab,kw 6332 #7 MeSH descriptor: [Vitrectomy] explode all trees 568 #8 MeSH descriptor: [Vitreoretinal Surgery] explode all trees 36 #9 vitrectom*:ti,ab,kw 1845 #10 (vitreous* near/4 (surg* or operat* or proced* or resect* or re-sect* or remov*)):ti,ab,kw 371

#11 ((vitreoretinal* or vitreo-retinal*) near/4 (surg* or operat* or proced* or resect* or re-sect* or remov*)):ti,ab,kw 342
#12 {or #5-#11} 12011
#13 #4 and #12 744

Database: Embase

1 diabetic retinopathy/ 46711
2 macular edema/ 6170
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 51699
4 or/1-3 70173
5 eye surgery/ 20205
6 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 42666
7 vitrectomy/ or vitreoretinal surgery/ 26064
8 vitrectom*.tw. 21871
9 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 3388
10 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 3193
11 or/5-10 83690
12 4 and 11 6714
13 random:.tw. 1815360
14 placebo:.mp. 499252
15 double-blind:.tw. 232123
16 or/13-15 2084463
17 12 and 16 630
18 Nonhuman/ not Humans/ 5538579
19 17 not 18 597
20 limit 19 to english language 523
21 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5240114
22 20 not 21 437
23 Qualitative Research/ 102554
24 exp Interview/ 335135
25 exp Questionnaire/ 843860
26 exp Observational Method/ 7195
27 Narrative/ 18485
28 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 2349246
29 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 153047
30 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 15242
31 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 2378
32 "critical interpretive synthes*".tw. 166
33 (realist adj (review* or synthes*)).tw. 791
34 (noblit and hare).tw. 100
35 (meta adj (method or triangulation)).tw. 43
36 (CERQUAL or CONQUAL).tw. 336

37 ((thematic or framework) adj synthes*).tw. 1694
38 trial-sibling stud*.tw. 1
39 (sibling adj2 (qualitative* or stud*)).tw. 1002
40 or/23-39 2612185
41 12 and 40 229
42 Nonhuman/ not Humans/ 5538579
43 41 not 42 228
44 limit 43 to english language 206
45 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5240114
46 44 not 45 164
47 22 or 46 570

Database: Epistemonikos

(title:(Diabetic retinopath* OR macular edema OR macular oedema OR diabetic maculopath*) OR abstract:(Diabetic retinopath* OR macular edema OR macular oedema OR diabetic maculopath*))

AND

(title:(Vitrectom* OR vitreous* OR vitreoretinal OR vitreo-retinal*) OR abstract:(Vitrectom* OR vitreous* OR vitreoretinal OR vitreo-retinal*))

Database: Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82
3 ((diabet* near (retin* or eye* or macular* or maculopath*))) 225
4 #1 OR #2 OR #3 254
5 MeSH DESCRIPTOR Ophthalmologic Surgical Procedures EXPLODE ALL TREES 379
6 (((ophthalm* or ocular* or eye*) near (surg* or operat* or proced* or resect* or re-sect* or remov*))) 140
7 MeSH DESCRIPTOR Vitrectomy EXPLODE ALL TREES 30
8 MeSH DESCRIPTOR Vitreoretinal Surgery EXPLODE ALL TREES 3
9 (vitrectom*) 50
10 ((vitreous* near (surg* or operat* or proced* or resect* or re-sect* or remov*))) 2
11 (((vitreoretinal* or vitreo-retinal*) near (surg* or operat* or proced* or resect* or re-sect* or remov*))) 6
12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 464
13 #4 AND #12 42
14 * IN HTA 17351
15 #13 AND #14 4

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

13 #12 AND #4 9
12 #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 145
11 ((vitreoretinal* or vitreo-retinal*) AND (surg* or operat* or proced* or resect* or re-sect* or remov*)) 21
10 (vitreous* AND (surg* or operat* or proced* or resect* or re-sect* or remov*)) 2
9 vitrectom* 6
8 "Vitreoretinal Surgery"[mh] 2
7 "Vitrectomy"[mh] 7
6 ((ophthalm* or ocular* or eye*) AND (surg* or operat* or proced* or resect* or re-sect* or remov*))
5 "Ophthalmologic Surgical Procedures"[mh] 21
4 #3 OR #2 OR #1 95
3 (diabet* AND (retin* or eye* or macular* or maculopath*)) 87
2 "Macular Edema"[mh] 28

Database: Ovid MEDLINE(R)

1 Diabetic Retinopathy/ 28293
2 Macular Edema/ 8490
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 32717
4 or/1-3 42949
5 Ophthalmologic Surgical Procedures/ 13020
6 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 30137
7 Vitrectomy/ or Vitreoretinal Surgery/ 15752
8 vitrectom*.tw. 14981
9 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 2233
10 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 2270
11 or/5-10 57558
12 4 and 11 4197
13 randomized controlled trial.pt. 575177
14 randomi?ed.mp. 928566
15 placebo.mp. 218792
16 or/13-15 984716
17 12 and 16 371
18 Animals/ not Humans/ 5005769
19 17 not 18 371
20 limit 19 to english language 352
21 Qualitative Research/ 76126
22 Nursing Methodology Research/ 16406
23 Interview.pt. 29571
24 exp Interviews as Topic/ 66803
25 Questionnaires/ 542548
26 Narration/ 9739
27 Health Care Surveys/ 33957

28 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 1558785
29 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 105274
30 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 11009
31 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 1810
32 "critical interpretive synthes*".tw. 138
33 (realist adj (review* or synthes*)).tw. 647
34 (noblit and hare).tw. 79
35 (meta adj (method or triangulation)).tw. 33
36 (CERQUAL or CONQUAL).tw. 264
37 ((thematic or framework) adj synthes*).tw. 1252
38 trial-sibling stud*.tw. 1
39 (sibling adj2 (qualitative* or stud*)).tw. 613
40 or/21-39 1777125
41 12 and 40 131
42 Animals/ not Humans/ 5005769
43 41 not 42 130
44 limit 43 to english language 116
45 20 or 44 454

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 7
4 or/1-3 7
5 Ophthalmologic Surgical Procedures/ 0
6 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 10
7 Vitrectomy/ or Vitreoretinal Surgery/ 0
8 vitrectom*.tw. 8
9 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 0
10 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 1
11 or/5-10 17
12 4 and 11 1
13 randomized controlled trial.pt. 0
14 randomi?ed.mp. 272
15 placebo.mp. 66
16 or/13-15 288
17 12 and 16 0
18 Animals/ not Humans/ 0
19 17 not 18 0
20 limit 19 to english language 0
21 Qualitative Research/ 0
22 Nursing Methodology Research/ 0

23 Interview.pt. 0
24 exp Interviews as Topic/ 0
25 Questionnaires/ 0
26 Narration/ 0
27 Health Care Surveys/ 0
28 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 628
29 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 57
30 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 0
31 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 2
32 "critical interpretive synthes*".tw. 1
33 (realist adj (review* or synthes*)).tw. 0
34 (noblit and hare).tw. 0
35 (meta adj (method or triangulation)).tw. 0
36 (CERQUAL or CONQUAL).tw. 0
37 ((thematic or framework) adj synthes*).tw. 3
38 trial-sibling stud*.tw. 0
39 (sibling adj2 (qualitative* or stud*)).tw. 0
40 or/21-39 636
41 12 and 40 0
42 Animals/ not Humans/ 0
43 41 not 42 0
44 limit 43 to english language 0
45 20 or 44 0

Database: Ovid MEDLINE(R) Epub Ahead of Print

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 519
4 or/1-3 519
5 Ophthalmologic Surgical Procedures/ 0
6 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 561
7 Vitrectomy/ or Vitreoretinal Surgery/ 0
8 vitrectom*.tw. 331
9 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 18
10 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 43
11 or/5-10 854
12 4 and 11 42
13 randomized controlled trial.pt. 1
14 randomi?ed.mp. 13081
15 placebo.mp. 2635
16 or/13-15 13913
17 12 and 16 6
18 Animals/ not Humans/ 0

19 17 not 18 6
20 limit 19 to english language 6
21 Qualitative Research/ 0
22 Nursing Methodology Research/ 0
23 Interview.pt. 0
24 exp Interviews as Topic/ 0
25 "Questionnaires"/ 0
26 Narration/ 0
27 Health Care Surveys/ 0
28 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 36965
29 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 4183
30 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 251
31 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 108
32 "critical interpretive synthes*".tw. 8
33 (realist adj (review* or synthes*)).tw. 58
34 (noblit and hare).tw. 1
35 (meta adj (method or triangulation)).tw. 0
36 (CERQUAL or CONQUAL).tw. 28
37 ((thematic or framework) adj synthes*).tw. 93
38 trial-sibling stud*.tw. 0
39 (sibling adj2 (qualitative* or stud*)).tw. 17
40 or/21-39 37940
41 12 and 40 2
42 Animals/ not Humans/ 0
43 41 not 42 2
44 limit 43 to english language 2
45 20 or 44 6

Cost effectiveness searches

A broad search covering the diabetic retinopathy population was used to identify studies on cost effectiveness. The searches were run in February 2022.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, comment or letter or editorial or historical articles or conference abstract or conference paper or "conference review" or letter or case report were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ, 309(6964), 1286.

Search filters

Cost utility

The NICE cost utility filter was applied to the search strategies in MEDLINE and Embase to identify cost-utility studies.

Hubbard W, et al. Development of a validated search filer to identify cost utility studies for NICE economic evidence reviews. NICE Information Services.

Cohort studies

For the modelling, cohort/registry terms were used from the NICE observational filter that was developed in-house.

The NICE Organisation for Economic Co-operation and Development (OECD) filter was also applied to search strategies in MEDLINE and Embase.

Ayiku, L., Hudson, T., et al (2021)The NICE OECD countries geographic search filters: Part 2 – Validation of the MEDLINE and Embase (Ovid) filters. Journal of the Medical Library Association)

Cost effectiveness search strategies

Database	Date searched	Database Platform	Database segment or version
EconLit	16/02/2022	OVID	<1886 to February 13, 2022>
Embase (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1974 to 2022 February 16>
HTA	16/02/2022	CRD	16-Feb-2022
INAHTA	16/02/2022	INAHTA	16-Feb-2022
MEDLINE (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1946 to February 16, 2022>
MEDLINE-in-Process (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<1946 to February 16, 2022>
MEDLINE Epub Ahead-of-Print (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<February 16, 2022>
NHS EED	16/02/2022	CRD	N/A

Database: EconLit
1 Diabetic Retinopathy/ 0 2 Macular Edema/ 0 3 (diabet* adj4 (retin* or eye* or macular*)).tw. 14 4 1 or 2 or 3 14

Database: Embase

Cost utility search:

1 diabetic retinopathy/ 45217
2 macular edema/ 5687
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47443
4 1 or 2 or 3 65931
5 cost utility analysis/ 10912
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 26154
7 ((incremental* adj2 cost*) or ICER).tw. 26757
8 (cost adj2 utilit*).tw. 9655
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 2715
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 31906
11 (cost and (effect* or utilit*)).ti. 51363
12 or/5-11 81030
13 4 and 12 417
14 nonhuman/ not human/ 4929899
15 13 not 14 415
16 (conference abstract or conference paper or conference proceeding or "conference review").pt. 5091583
17 15 not 16 302

Cohort studies:

1 diabetic Retinopathy/ 45440
2 macular Edema/ 5828
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47762
4 or/1-3 66388
5 cohort analysis/ 811098
6 Retrospective study/ 1206857
7 Prospective study/ 748103
8 (Cohort adj (study or studies)).tw. 380594
9 (cohort adj (analy* or regist*)).tw. 16437
10 (follow up adj (study or studies)).tw. 68508
11 longitudinal.tw. 384899
12 prospective.tw. 981024
13 retrospective.tw. 1068301
14 or/5-13 3358085
15 4 and 14 13743
16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or

equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1511773
17 exp "organisation for economic co-operation and development"/ 1933
18 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 3545238
19 european union/ 29144
20 developed country/ 34415
21 or/17-20 3576072
22 16 not 21 1373176
23 15 not 22 12938
24 limit 23 to english language 12133
25 nonhuman/ not human/ 4938000
26 24 not 25 12067
27 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 7072757
28 26 not 27 8733
29 limit 28 to dc=20120101-20220228 6467

Database: Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82
3 ((diabet* adj4 (retin* or eye* or macular*))) 216
4 #1 OR #2 OR #3 245
5 * IN HTA FROM 2012 TO 2022 5598
6 #4 AND #5 26

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

6 #5 AND #4 47
5 * FROM 2012 TO 2022 7610
4 #3 OR #2 OR #1 92
3 ((diabet* AND (retin* or eye* or macular*))) 84
2 "Macular Edema"[mh] 27
1 "Diabetic Retinopathy"[mh] 39

Database: Ovid MEDLINE(R)

Cost utility search:

1 Diabetic Retinopathy/ 27250
2 Macular Edema/ 8126
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29608
4 1 or 2 or 3 40314
5 Cost-Benefit Analysis/ 88398
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 13197
7 ((incremental* adj2 cost*) or ICER).tw. 13599
8 (cost adj2 utilit*).tw. 5176
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 1698
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 17986
11 (cost and (effect* or utilit*)).ti. 30223
12 or/5-11 100083
13 4 and 12 287
14 animals/ not humans/ 4924997
15 13 not 14 287

Cohort studies:

1 Diabetic Retinopathy/ 27317
2 Macular Edema/ 8133
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29694
4 or/1-3 40407
5 exp Cohort Studies/ 2302163
6 (cohort adj (study or studies)).tw. 225137

7 (cohort adj (analy* or regist*)).tw. 8773
8 (follow up adj (study or studies)).tw. 48799
9 longitudinal.tw. 243228
10 prospective.tw. 570236
11 retrospective.tw. 546033
12 or/5-11 2652900
13 4 and 12 10289
14 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1201994
15 "organisation for economic co-operation and development"/ 417
16 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3386234
17 european union/ 17116
18 developed countries/ 21089
19 or/15-18 3401513
20 14 not 19 1115138

21 13 not 20 9710
22 limit 21 to english language 8875
23 Animals/ not Humans/ 4930479
24 22 not 23 8825
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 2225022
26 24 not 25 8658
27 limit 26 to ed=20120101-20220228 4813

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations

Cost utility search:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 335
4 1 or 2 or 3 335
5 Cost-Benefit Analysis/ 0
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 196
7 ((incremental* adj2 cost*) or ICER).tw. 177
8 (cost adj2 utilit*).tw. 74
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 29
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 242
11 (cost and (effect* or utilit*)).ti. 286
12 or/5-11 450
13 4 and 12 2
14 animals/ not humans/ 0
15 13 not 14 2

Cohort studies:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 336
4 or/1-3 336
5 exp Cohort Studies/ 0
6 (cohort adj (study or studies)).tw. 4157
7 (cohort adj (analy* or regist*)).tw. 155
8 (follow up adj (study or studies)).tw. 263
9 longitudinal.tw. 3119
10 prospective.tw. 5190
11 retrospective.tw. 6965
12 or/5-11 15689
13 4 and 12 71
14 limit 13 to english language 71
15 limit 14 to dt=20120101-20220228 70

Database: Ovid MEDLINE(R) Epub Ahead of Print

Cost utility search:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 585
4 1 or 2 or 3 585
5 Cost-Benefit Analysis/ 0
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 459
7 ((incremental* adj2 cost*) or ICER).tw. 395
8 (cost adj2 utilit*).tw. 195
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 59
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 625
11 (cost and (effect* or utilit*)).ti. 615
12 or/5-11 1199
13 4 and 12 9
14 animals/ not humans/ 0
15 13 not 14 9

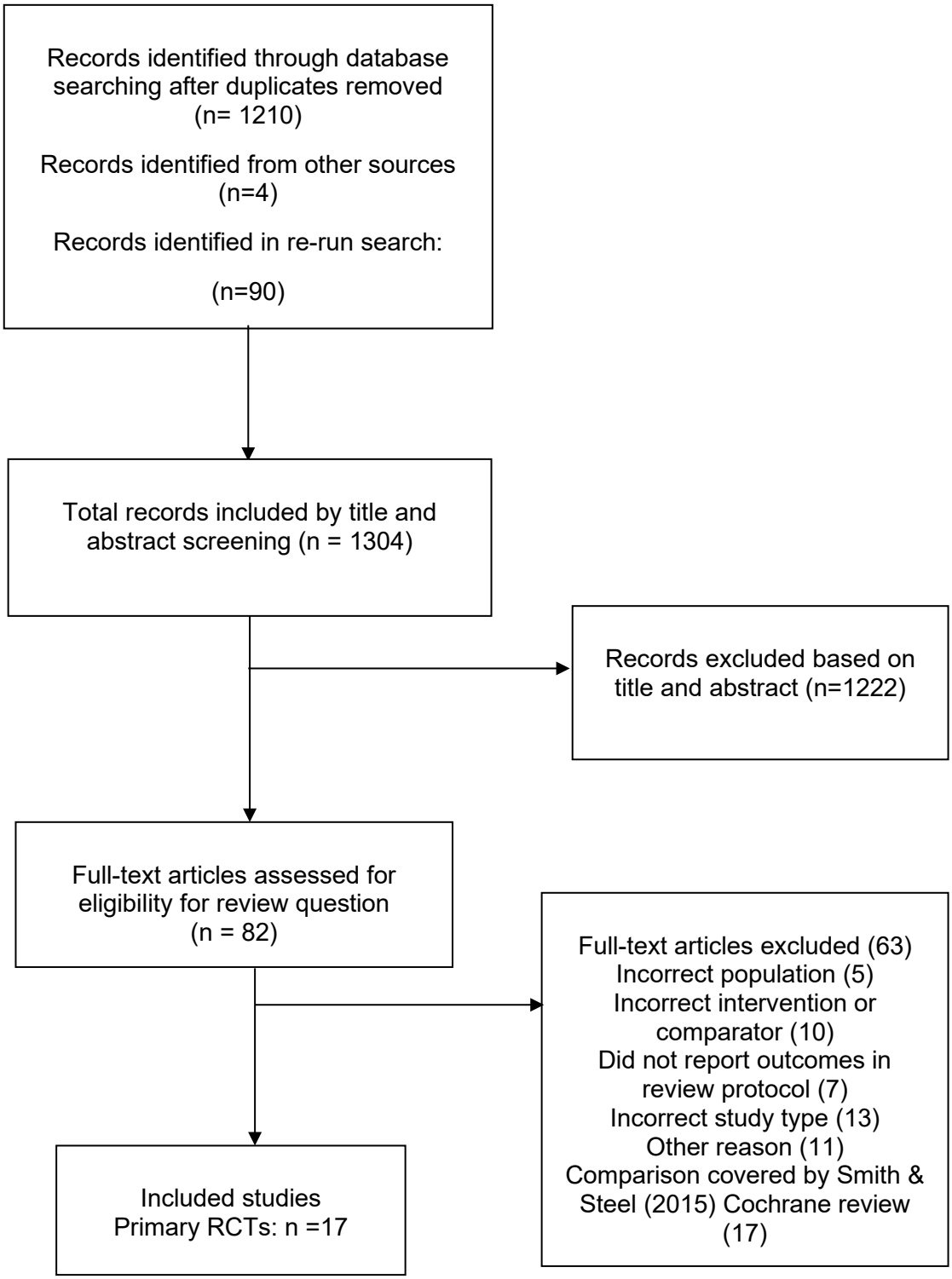
Cohort studies:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 563
4 or/1-3 563
5 exp Cohort Studies/ 0
6 (cohort adj (study or studies)).tw. 9207
7 (cohort adj (analy* or regist*)).tw. 349
8 (follow up adj (study or studies)).tw. 607
9 longitudinal.tw. 6722
10 prospective.tw. 12241
11 retrospective.tw. 18324
12 or/5-11 37987
13 4 and 12 147
14 limit 13 to english language 147

Database: NHS Economic Evaluation Database

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82
3 ((diabet* adj4 (retin* or eye* or macular*))) 216
4 #1 OR #2 OR #3 245
5 * IN NHSEED FROM 2012 TO 2022 4897
6 #4 AND #5 19

Appendix C – Effectiveness evidence study selection



Appendix D – Evidence tables

Altun, 2021

Bibliographic Reference	Altun, Ahmet; Kanar, Hatice Selen; Aki, Suat Fazil; Arsan, Aysu; Hacisalihoglu, Aynur; Effectiveness and Safety of Coadministration of Intravitreal Dexamethasone Implant and Silicone Oil Endotamponade for Proliferative Diabetic Retinopathy with Tractional Diabetic Macular Edema.; Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics; 2021; vol. 37 (no. 2); 131-137

Study details

Study location	Istanbul
Study setting	Clinic of Ophthalmology, Kartal Dr. Lutfi Kirdar Training and Research Hospital and Clinic of Ophthalmology, Fatih Sultan Mehmet Training and Research Hospital,
Study dates	January 2019 and February 2020
Sources of funding	The author has no financial or non-financial relationships, ownership, or commercial interests
Inclusion criteria	eyes with PDR and vitreomacular traction syndrome
Exclusion criteria	• Cases with intense vitreous haemorrhage, macular ischemia, retinal detachment • previous macular laser treatment • non-tractional DME • type I diabetes mellitus • glaucoma, amblyopia, corneal pathology, and uveitis • patients with glycosylated serum haemoglobin A1c greater than 10%
Intervention(s)	Intravitreal ranibizumab (IVR) injection was applied to all eyes 3 days before a 23-gauge PPV. During the PPV operation, panretinal photocoagulation (PRP) was applied to missed areas, fibrovascular membranes were dissected, internal limiting membrane (ILM) was peeled, and 1000 centistoke silicone oil endotamponade was implanted to all the eyes. While the eyes were filled with air, the IVD implant was placed on the inferior retina and then silicone oil endotamponade was injected. Silicone endotamponade was removed from all eyes 3 months later
Comparator	PPV with no additional procedures were applied to eyes in control group. panretinal photocoagulation was completed to the missed areas during PPV
Best corrected visual acuity	Reported

Study arms
PPV + IVD + PRP (N = 26)
PPV + PRP (N = 26)

Study-level characteristics

Characteristic	Study (N = 52)
% Female Sample size	n = 26
PPV + IVD + PRP Mean age (SD) Mean (SD)	54.23 (4.51)
PPV + PRP Mean age (SD) Mean (SD)	55.58 (4.4)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (incomplete reporting)
Overall bias and Directness	Overall Directness	Directly applicable

Antoszyk, 2020

Bibliographic Reference	Antoszyk, Andrew N; Glassman, Adam R; Beaulieu, Wesley T; Jampol, Lee M; Jhaveri, Chirag D; Punjabi, Omar S; Salehi-Had, Hani; Wells, John A 3rd; Maguire, Maureen G; Stockdale, Cynthia R; Martin, Daniel F; Sun, Jennifer K; DRCR Retina, Network; Effect of Intravitreous Aflibercept vs Vitrectomy With Panretinal Photocoagulation on Visual Acuity in Patients With Vitreous Hemorrhage From Proliferative Diabetic Retinopathy: A Randomized Clinical Trial.; JAMA; 2020; vol. 324 (no. 23); 2383-2395

Study details

Trial registration number and/or trial name	NCT02858076
Study type	Parallel-group randomised controlled trial (RCT)
Study location	Thirty-nine sites in USA and Canada
Study setting	Hospital/Clinic
Study dates	11/2016 to 12/2017
Sources of funding	Cooperative agreement EY14231 from the National Eye Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, and the US Department of Health and Human Services. Regeneron Pharmaceuticals Inc provided anti-VEGF for study and funds to DRCR Retina Network to offset study's clinical site costs.
Inclusion criteria	Only one eye from each participant was enrolled. Participants were included if they had:

	• Diagnosis of Type 1 or Type 2 diabetes Eyes were included if they had: • Vitreous haemorrhage (VH) from proliferative diabetic retinopathy causing vision impairment (BCVA≤78 [Snellen equivalent 20/32 or worse] with at least light perception) that investigator deemed intervention indicated
Exclusion criteria	Eyes were excluded if they had known: • Center-involved diabetic macular oedema • Retinal detachment from fibrosis or scar tissue pulling on retina (i.e. traction) that were involving or threatening macula • Rhegmatogenous retinal detachment • Neovascular glaucoma • Prior vitrectomy Participants were also excluded if they received panretinal photocoagulation or intravitreal anti-VEGF ≤2-mo before onset of VH
Intervention(s)	PPV performed on assigned eye within 2 weeks of randomisation with 23-gauge (or smaller) instrument. Panretinal photocoagulation performed intraoperatively. Intraviteral aflibercept was permitted before PPV but not intraoperatively nor within 4 weeks after it. After this time, recurrent vitreous haemorrhage (VH) treated with 2 monthly aflibercept injections and additional injections every 4 weeks at discretion of investigators. Repeat PPV permitted if VH failed to clear after 2 aflibercept injections.
Comparator	Assigned eyes received intravitreal aflibercept injection at baseline and weeks 4, 8 and 12. Injections deferred at week 16 if complete fundus could be viewed and neovascularization absent. Injections given at week 24 unless eye stabilised (defined as 2 consecutive visits with size/density of vitreous haemorrhage [VH] and neovascularization clinically unchanged since last visit). PPV permitted at week 16 if persistent VH causing vision impairment following 2 monthly injections. Care during and after PPV same as PPV + PRP group.
Outcomes	Best corrected visual acuity Retinal detachment Adverse events

Study arms
PPV + PRP (N = 105) Pars plana vitrectomy and panretinal photocoagulation
Intravitreal aflibercept (N = 100) Intravitreal anti-VEGF

Study-level characteristics

Characteristic	Study (N = 205)
% Female Custom value	40

Characteristic	Study (N = 205)
Mean age (SD) Mean (SD)	57 (11)
% vitreous haemorrhage Custom value	100
% with tractional retinal detachment Custom value	0

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Avitabile, 2011

Bibliographic Reference	Avitabile, Teresio; Bonfiglio, Vincenza; Castiglione, Francesco; Castaing, Marine; Contarino, Fabio; Mistretta, Antonio; Severe proliferative diabetic retinopathy treated with vitrectomy or panretinal photocoagulation: a monocenter randomized controlled clinical trial.; Canadian journal of ophthalmology. Journal canadien d'ophtalmologie; 2011; vol. 46 (no. 4); 345-51

Study details

Trial registration number and/or trial name	NCT01115257
Study type	Parallel-group randomised controlled trial (RCT)
Study location	Santa Marta Hospital, Catania University, Catania, Italy
Study setting	Hospital
Study dates	10/2001 to 10/2006
Sources of funding	Reports no proprietary or commercial interest in any materials discussed in article
Inclusion criteria	eyes with advanced PDR, some with TRD not involving macula, which were treated The definition of severe PDR included eyes with extensive, active neovascular and fibrovascular proliferation that was graded using the Modified Airlie House Classification. The minimum required to meet the definition of severe PDR was active retinal neovascularization on or within 1 disc diameter of the optic disc and/or new vessels elsewhere and the presence of fibrovascular proliferation with or without TRD not involving macula.

Exclusion criteria	Eyes were excluded if they had • Fibrovascular tractional detachment involving macula, • Combined tractional and rhegmatogenous retinal detachment, • History of uveitis or trauma, • Received previous vitrectomy, • Ocular hypertension or neovascular glaucoma, or • Received photocoagulation ≤3 months prior to enrolment
Intervention(s)	PPV performed using 20-gauge, with combination of delamination and segmentation of gliotic tractional membranes using bimanual technique. One experienced surgeon in vitreoretinal surgery (T.A.) conducted all vitrectomies. Further internal limiting membrane peeling in macular area in all included eyes performed. Silicone oil or gas tamponade used in eyes with long-standing tractional retinal detachment, as deemed necessary by surgeon, or in eyes in which retinal break occurred during vitrectomy. Focal or grid laser treatment performed during follow-up visit after surgery if persistent CSME detected by fluorangiography and OCT.
Comparator	Extensive, full subconfluent panretinal photocoagulation (PRP) performed using 532-nm Nd:YAG laser in line with ETDRS guidelines. Repeat PRP and focal or grid macular laser treatment performed at time of initial PRP or during FU period.
Outcomes	Best corrected visual acuity

Study arms
PPV-ilm Photocoagulation (N = 90) Pars plana vitrectomy (PPV), membrane and internal limited membrane peeling (-ilm), panretinal photocoagulation, and focal or grid macular laser

Photocoagulation (N = 90) Panretinal photocoagulation and focal or grid macular laser

Study-level characteristics

Characteristic	Study (N = 180)
% Female Sample size	n = 83 ; % = 46
Mean age (SD) Custom value	54.2 (21-79)
% diabetic macular edema Custom value	90%
% vitreous haemorrhage Custom value	97.8
% with tractional retinal detachment Sample size	n = 126 ; % = 70

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Blankenship, 1991

Bibliographic Reference	Blankenship, G W; Evaluation of a single intravitreal injection of dexamethasone phosphate in vitrectomy surgery for diabetic retinopathy complications.; Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie; 1991; vol. 229 (no. 1); 62-5

Study details

Trial registration number and/or trial name	Not reported
Study type	Parallel group randomised controlled trial (RCT)
Study location	Miami, Florida and University Park, Pennsylvania, USA
Study setting	Departments of Ophthalmology, University of Miami School of Medicine and College of Medicine, Penn State University
Study dates	Not reported
Sources of funding	Partly supported by: Patients and contributors of the Departments of Ophthalmology, School of Medicine, University of Miami and College of Medicine, Penn State University; Research to Prevent Blindness, Inc., New York City; Pennsylvania Lions Vision and Research Center; and the Breen Green Diabetic Retinopathy Fund, Miami, Florida
Inclusion criteria	Eyes were included if they had • Loss of vision due to dense, non-clearing vitreous haemorrhage or retinal detachment secondary to diabetic retinopathy complications
Exclusion criteria	Not reported
Intervention(s)	Three-port, closed-system PPV performed to remove haediaopacities and anterior-to-posterior vitreous traction and to minimize retinal traction by epiretinal membrane removal or segmentation. Hemostasis obtained by transvitreal bipolar diathermy or endolaser photocoagulation, which was also used to create chorioretinal adhesions around retinal breaks and to minimize previously unphotocoagulated, ischemic midperipheral and peripheral retina. Intravitreal dexamethasone 0.8 mg received at end of surgery.
Comparator	PPV as described above without dexamethasone
Outcomes	Best corrected visual acuity

	Adverse events

Study arms
PPV + ICS (N = 27) Pars plana vitrectomy + intravitreal corticosteroid (dexamethasone)

PPV (N = 30)

Study-level characteristics

Characteristic	Study (N = 63)
% Female Sample size	n = 27
PPV + IVD group Mean age (SD) Custom value	23 to 76 years (mean, 54 years).
PPV group Mean age (SD) Custom value	22 to 75 years (mean, 51 years).
non-clearing vitreous haemorrhage, in PPV + IVD group Custom value	19 (70%)
non-clearing vitreous haemorrhage in PPV group Custom value	14 (47%)
% with tractional retinal detachment in PPV + IVD group Custom value	8 (30%)
% with tractional retinal detachment in PPV group Custom value	12 (40%)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (high loss to follow up)
Overall bias and Directness	Overall Directness	Directly applicable

Doi, 2012

Bibliographic Reference	Doi, Norihito; Sakamoto, Taiji; Sonoda, Yasushi; Yasuda, Miho; Yonemoto, Koji; Arimura, Noboru; Uchino, Eisuke; Ishibashi, Tatsuro; Comparative study of vitrectomy versus intravitreous triamcinolone for diabetic macular edema on randomized paired-eyes.; Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie; 2012; vol. 250 (no. 1); 71-8

Study details

Study type	Within-person randomised controlled trial
Study location	Japan
Study setting	Imamura Hospital and Kagoshima University Hospital
Study dates	Between July 2006 and December 2008
Sources of funding	1. Supported in part by a Grant from the Research Committee on Chorioretinal Degeneration and Optic Atrophy 2. Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of the Japanese Government
Inclusion criteria	• Those with bilateral diffuse DME (CMT; 300 μm <) determined by optical coherence tomography • without a history of retinal diseases except diabetic retinopathy (DR) • Those with BCVA between 0.2 and 1.0 of a logarithm of the minimum angle of the resolution chart (logMAR) • those aged 20 years or older
Exclusion criteria	• Eyes with signs of vitreo-macular traction on biomicroscopy or OCT • eyes with apparent posterior vitreous detachment • eyes with active proliferative DR, • eyes with known history of glaucoma • eyes with optic nerve atrophy • eyes with a history of photocoagulation within 3 months • eyes with a history of vitrectomy • eyes with a history of intravitreous or periocular injection of drugs, • eyes with significant cataract that prevents preoperative OCT evaluation. • Patients with HbA1c 10% or higher, a history of hemo-dialysis, or diastolic blood pressure of more than 100 mmHg
Intervention(s)	Surgery consisted of standard 20-gauge three-port PPV with endophotocoagulation. Triamcinlone acetonide (TA) was not used during or after surgery. No eyes underwent photocoagulation of the macular area during surgery. The posterior hyaloid was separated from the optic disc in eyes with no posterior vitreous detachment. No eyes underwent internal limiting membrane peeling. S
Comparator	eye was treated with IVTA (4 mg)
Outcomes	Best corrected visual acuity

Study arms
PPV group (N = 20)
IVTA group (N = 20)

Study-level characteristics

Characteristic	Study (N = 20)
% Female Sample size	n = 7

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Faghihi, 2008

Bibliographic Reference	**Faghihi, H.; Taheri, A.; Farahvash, M.S.; Esfahani, M.R.; Rajabi, M.T.; Intravitreal triamcinolone acetonide injection at the end of vitrectomy for diabetic vitreous hemorrhage a randomized, clinical trial; Retina; 2008; vol. 28 (no. 9); 1241-1246**

Study details

Study location	Tehran, Iran.
Study setting	From the Department of Ophthalmology, School of Medicine, Medical Sciences, Tehran University
Study dates	not reported
Sources of funding	Authors declare no financial support or relationships that may pose conflict of interest.
Inclusion criteria	eyes with diabetic non-clearing VH that had indication for pars plana vitrectomy (PPV)
Exclusion criteria	• patients with previous ocular surgery (except cataract surgery), intravitreal silicone oil or SF6 gas injection, • history of ocular trauma, • history of any type of glaucoma or ocular hypertension, • history of other ocular diseases except cataract such as uveitis, age-related macular degeneration • one eyed patients (no light perception or non-operable of the fellow eye), • tractional retinal detachment (detected by B-scan) • uncontrolled diabetes
Intervention(s)	The techniques of PPV were standardized using three port pars plana sclerotomies, removing the vitreous up to the vitreous base, delamination and segmentation of membranes, removing the posterior vitreous surface, and performing panretinal endolaser photocoagulation of the retina. Surgeons maintained intraocular pressure (IOP) between 20 to 30 mmHg

	at the end of surgery intervention group received an intravitreal injection of 4 mg triamcinolone at the end of the operation
Comparator	PPV only not received IVT
Outcomes	Best corrected visual acuity

Study arms
PPV + IVT (N = 38)
PPV (N = 34)

Study-level characteristics

Characteristic	**Study (N = 72)**
% Female Sample size	n = 47
Mean age (SD) Mean (SD)	54.9 (9.9)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	**Question**	**Answer**
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Freyler, 1980

Bibliographic Reference	Freyler, H.; Klemen, U.; Prskavec, F.; Egerer, I.; Treatment of advanced proliferative diabetic retinopathy: photocoagulation or vitrectomy?; Metabolic Ophthalmology; 1980; vol. 4 (no. 3); 129-132

Study details

Study type	Parallel group randomised controlled trial (RCT)
Study location	USA
Study setting	not reported
Study dates	not reported
Sources of funding	not reported
Inclusion criteria	• insulin dependent juvenile type of diabetes • between 12-26 years • asymmetrical proliferative diabetic retinopathy in both eyes (stage 3 according to classification of Zweng) • extensive glial and fibrous strands
Exclusion criteria	Not reported

Intervention(s)	underwent panretinal photocoagulation with xenon-are as well as argon laser, in all cases one eye underwent PPV
Comparator	underwent panretinal photocoagulation with xenon-are as well as argon laser
Best corrected visual acuity	Reported

Study arms
PPV + PRP (N = 12)
PRP (N = 12)

Study-level characteristics

Characteristic	Study (N = 28)
Mean age (SD)	12-26 Average 16 years

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High – unclear blinding and randomisation
Overall bias and Directness	Overall Directness	Directly applicable

Jorge, 2021

Bibliographic Reference	Jorge, D.M.; Tavares Neto, J.E.S.; Poli-Neto, O.B.; Scott, I.U.; Jorge, R.; Intravitreal bevacizumab (IVB) versus IVB in combination with pars plana vitrectomy for vitreous hemorrhage secondary to proliferative diabetic retinopathy: a randomized clinical trial; International Journal of Retina and Vitreous; 2021; vol. 7 (no. 1); 35

Study details

Trial registration number and/or trial name	Registered in Plataforma Brasil, CAAE number 927354.7.0000.5440
Study type	Parallel-group randomised controlled trial (RCT)
Study location	Ribeirao Preto, Brazil
Study setting	Hospital
Study dates	01/2019 to 12/2019
Sources of funding	Funding received from RAEPA and CNPq
Inclusion criteria	• Patient≥18 years-old • Vitreous haemorrhage duration>3-mo • Visual acuity worse than 20/40 in study eye • Informed written consent

Exclusion criteria	• Intraocular surgery ≤past 3-mo • Previous PPV • Acute ocular infection • Associated traction retinal detachment • Clinically uncontrolled glaucoma • Severe recent ocular trauma • Use of anticoagulant medications (except aspirin) • Glycosylated haemoglobin>13% • Any condition that would affect documentation or follow-up • Participation in another clinical study ≤past 30 days
Intervention(s)	Single injection 0.06 ml bevacizumab (1.5 mg) 7 days before PPV, followed by phacoemulsification with intraocular lens implantation (if phakic) and 23-gauge PPV with endolaser panretinal photocoagulation. Standard post-PPV moxifloxacin drops for 1 week and dexamethasone drops for 1 week with progressive reduction for 1 month
Comparator	Total of 3 intravitreal injections of 0.06 ml (1.5 mg) bevacizumab (Avastin®) administered at 8-week intervals. 0.5% moxifloxacin eyedrops 3 days before injection to 1 week after
Outcomes	Best corrected visual acuity Retinal detachment Adverse events

Study arms
PPV + Anti-VEGF (N = 35) Pars plana vitrectomy and intravitreal bevacizumab
Anti-VEGF (N = 38) Intravitreal bevacizumab

Study-level characteristics

Characteristic	**Study (N = 73)**
% Female Custom value	51
Mean age (SD) Mean (SD)	63.85 (9.82)
% vitreous haemorrhage Custom value	100
% with tractional retinal detachment Custom value	0

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	**Question**	**Answer**
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kumar, 2007

Bibliographic Reference	Kumar, Atul; Sinha, Subijay; Azad, Rajvardhan; Sharma, Yog Raj; Vohra, Rajpal; Comparative evaluation of vitrectomy and dye-enhanced ILM peel with grid laser in diffuse diabetic macular edema.; Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie; 2007; vol. 245 (no. 3); 360-8

Study details

Study location	India
Study setting	Vohra Vitreous-Retina Service, Dr. Rajendra Prasad Centre for Ophthalmic Sciences,
Study dates	not reported
Sources of funding	not reported
Inclusion criteria	Patients with diffuse macular oedema, best corrected visual acuity ≤6/60, HbA1c ≤ 7.5 mg/dl were included
Exclusion criteria	Eyes that had the following features were excluded: (i) only focal macular oedema attributable to focal leaks from micro aneurysm, (ii) the presence of any other macular pathology like ARMD or any vascular occlusive diseases affecting macula, (iii) optic disc pathology due to chronic glaucoma, (iv) those that had undergone previous vitreoretinal surgery, (v) those that underwent cataract surgery within the past 12 months, (vi) those previously treated with PRP within 12 months and grid laser within 6 months, (vii) those with evidence of vitreomacular traction, and (viii) angiographic evidence of widening or irregularity of the foveal avascular zone suggestive of ischaemic maculopathy. Patients with uncontrolled diabetes, hypertension and chronic renal failure were also excluded from the study.
Intervention(s)	In the first group of 12 eyes, PPV with ILM removal was performed and will subsequently be known as the ILM group. ILM peel involved a 3-port pars plana vitrectomy, PVD induction by active suction (200 mm hg), and 0.3% trypan blue (Membrane Blue, D.O.R.C. Intl., The Netherlands) dye injection for staining the ILM was carried out under air. None of the eyes had pre operative PVD which necessitated PVD induction in all the eyes. The dye was kept for 5–7 minutes and then aspirated using a soft tipped cannula. The intra vitreal air was exchanged with fluid and ILM forceps (D.O.R.C Intl.) used to peel off the ILM. None of the eyes received intravitreal or periocular triamcinolone injection during or after surgery
Comparator	The laser group of 12 eyes was treated with modified grid laser photocoagulation (sparing the papillo-macular bundle) with frequency doubled argon green laser (532 nm), The majority of patients in both

	groups had received some form of focal/grid macular laser photocoagulation previously
Outcomes	Best corrected visual acuity

Study arms
Modified MGP Group (N = 12) modified grid laser photocoagulation

ILM group (N = 12) pars plana vitrectomy (PPV) and dye enhanced peeling of the internal limiting membrane (ILM)

Study-level characteristics

Characteristic	Study (N = 24)
% Female Sample size	n = 3
ILM group mean age (SD) Mean (SD)	57.25 (8.99)
Modified MGP Group mean age (SD) Mean (SD)	57.33 (6.84)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Limon, 2022

Bibliographic Reference	Limon, Utku; Sezgin Akcay, Betul Ilkay; Efficacy of Intravitreal Dexamethasone After Combined Phacoemulsification and Pars Plana Vitrectomy for Diabetic Tractional Retinal Detachments.; Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics; 2022; vol. 38 (no. 2); 176-182

Study details

Study type	Parallel group randomised controlled trial (RCT)
Study location	Turkey
Study setting	not reported
Study dates	not reported
Sources of funding	No funding was received for this article
Inclusion criteria	• Patients with type 2 diabetes mellitus • Patients >49 years old • Patients with treatment-naive macula-off TRD (Grade-C) secondary to PDR with coexisting grade 3 and 4 cataracts • Minimum of 6 months of follow-up after surgery.

Exclusion criteria	• Other causes of TRD except PDR • Patients with rhegmatogenous retinal detachment or exudative retinal detachment • Previous treatment with macular laser or panretinal laser photocoagulation, intravitreal corticosteroids, and intravitreal anti-VEGFs • The presence of corneal pathology, uveitis, glaucoma, age-related macular degeneration, and macular scar • Previous vitreoretinal surgery • Patients with retina or iris neovascularization at baseline • Patients with uncontrolled diabetes (glycosylated haemoglobin [HbA1c] >12%).
Intervention(s)	Group-1 comprised patients who underwent simultaneous silicone tamponade and intravitreal dexamethasone after combined phacoemulsification and PPV. In all patients, 360 panretinal laser photocoagulation was performed with indentation under the liquid perfluorocarbon after the retina was attached. Intravitreal bevacizumab was administered to all eyes 4 days before PPV in both groups.
Comparator	Group-2 contained patients who received only silicone tamponade after combined phacoemulsification and PPV. In all patients, 360 panretinal laser photocoagulation was performed with indentation under the liquid perfluorocarbon after the retina was attached.
Outcomes	Best corrected visual acuity Adverse events (intraocular pressure and intraoperative bleeding)

Study arms
PPV (N = 21)
PPV + IVD (N = 22)

Study-level characteristics

Characteristic	Study (N = 43)
% Female Sample size	n = 15
PPV + IVD group Mean age (SD) Mean (SD)	56.67 (4.13)
PPV group Mean age (SD) Mean (SD)	59.82 (6.21)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Patel, 2006

Bibliographic Reference	Patel, J I; Hykin, P G; Schadt, M; Luong, V; Bunce, C; Fitzke, F; Gregor, Z J; Diabetic macular oedema: pilot randomised trial of pars plana vitrectomy vs macular argon photocoagulation.; Eye (London, England); 2006; vol. 20 (no. 8); 873-81

Study details

Study location	UK
Study setting	Moorfields Eye Hospital, London
Study dates	not reported
Sources of funding	Financial disclosure: None
Inclusion criteria	Inclusion criteria were (i) persistent CSME involving the foveal centre for less than 2 years, (ii) previous treatment with macular laser, and (iii) ETDRS vision score of 65–35 (equivalent Snellen visual acuity 6/15 to 6/60).
Exclusion criteria	Exclusion criteria were: (i) posterior vitreous detachment diagnosed by the presence of a Weiss ring, (ii) macular traction as evidenced by retinal striae involving the foveal centre or the taut vitreous face syndrome, (iii) macular ischaemia as defined by an enlarged foveolar avascular zone (foveolar avascular zone (FAZ)41000 mm) or significant perifoveal capillary loss on FFA, and (iv) coexistent ocular disease.
Intervention(s)	Patients randomised to PPV underwent standard three-port vitrectomy with elevation and the removal of the posterior vitreous cortex without peeling of the internal limiting membrane (ILM). Fluid–SF6 gas Fluid–SF6 gas exchange was performed if retinal breaks were found on the 3601 examinations of the peripheral retina prior to the conclusion of the operation. Such breaks were treated with laser photocoagulation or cryotherapy. Subconjunctival injection of Bethamethasone and Cefuroxime was given at the conclusion of the operation. Patients were treated with topical Atropine 1%, Dexamethasone and Chloramphenicol for 3 weeks after the operation.
Comparator	Patients randomised to laser underwent standard ETDRS argon photocoagulation
Outcomes	Best corrected visual acuity

Study arms

PPV (N = 10) Patients randomised to PPV underwent standard three-port vitrectomy with elevation and the removal of the posterior vitreous cortex without peeling of the internal limiting membrane (ILM)

Laser photocoagulation (N = 10) Patients randomised to laser underwent standard ETDRS argon photocoagulation

Study-level characteristics

Characteristic	Study (N = 20)
% Female Sample size	n = 11
PPV Mean age (SD) Range	61 to 74
Laser photocoagulation Mean age (SD) Range	50 to 71

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Saeed, 2013

Bibliographic Reference	Saeed, A.M.; Combined vitrectomy and intravitreal injection versus combined laser and injection for treatment of intractable diffuse diabetic macular edema; Clinical Ophthalmology; 2013; vol. 7; 283-297

Study details

Study location	Egypt
Study setting	Benha University Hospital
Study dates	November 2010 to July 2012
Sources of funding	Not reported
Inclusion criteria	• All patients had been diagnosed with intractable diffuse diabetic macular oedema, which was defined as biomicroscopically, angiographically, and tomographically confirmed diffuse diabetic macular oedema • Macular oedema did not respond to or recurred after IVTA and/or macular focal laser photocoagulation. • Central foveal thickness had to be greater than 300 μm
Exclusion criteria	• presence of vitreomacular traction, active neovascularization of proliferative diabetic retinopathy • an enlarged foveal avascular zone on fluorescein angiography, neurosensory detachment on optical coherence tomography • treatment for diabetic macular oedema within the previous 3 months • previous vitreoretinal surgery, other major ocular surgery (including cataract extraction, scleral buckle, or other intraocular surgery) within the previous 6 months

	• YAG capsulotomy performed within the 2 months prior to enrolment • other macular pathology (eg, age-related macular degeneration, retinal vascular occlusive diseases, combined optic neuropathy • glaucoma including neovascular glaucoma, vitreous haemorrhage)
Intervention(s)	Pars plana vitrectomy with removal of the posterior hyaloid was performed, and at the end of the procedure, IVTA 0.1 mL (40 mg/mL) and bevacizumab 1.25 mg were injected.
Comparator	Macular grid laser photocoagulation was performed 2 weeks after the same intravitreal injection combination as used in group 1.
Outcomes	Best corrected visual acuity Adverse events (intraocular pressure)

Study arms
PPV-hy + IVTA + IVB (N = 15) Pars plana vitrectomy with removal of the posterior hyaloid, IVTA and IV bevacizumab

IVTA + IVB + MGP (N = 15) Macular grid laser plus IVTA and IV bevacizumab

Study-level characteristics

Characteristic	Study (N = 30)
% Female Sample size	n = 15 ; % = 50

Arm-level characteristics

Characteristic	PPV-hy + IVTA + IVB (N = 15)	IVTA + IVB + MGP (N = 15)
Mean age (SD) Mean (SD)	54 (8.6)	57 (7.5)

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Stolba, 2005

Bibliographic Reference	Stolba, Ulrike; Binder, Susanne; Gruber, Diego; Krebs, Ilse; Aggermann, Tina; Neumaier, Beatrix; Vitrectomy for persistent diffuse diabetic macular edema.; American journal of ophthalmology; 2005; vol. 140 (no. 2); 295-301

Study details

Trial registration number and/or trial name	Not reported
Study type	Parallel group randomised controlled trial (RCT)
Study location	USA
Study setting	Not reported
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Participants included if they had: • History of diffuse macular oedema for minimum of 6 and maximum of 18 months. • Grid laser photocoagulation performed ≥4-mo earlier • Documented attached posterior hyaloid either with B-scan ultrasound examination or presence of a preretinal membrane shown with optical coherence tomography • No or only mild cataract, less than NO3NC3C3P3 according to the Lens Opacities Classification System III (LOCS III) charts
Exclusion criteria	Participants excluded if they had: • >3 laser treatments in macula or other pre-treatments before enrolment • Long-term treatment with diuretics • HbA1c>8.0 • Participants also excluded if they were receiving haemodialysis or were unable to return for follow-up examinations Eyes excluded if they had • Ischemic maculopathy • Proliferative changes with indication for panretinal laser coagulation, optic atrophy or advanced glaucoma • Lens opacification more than NO3NC3C3P3 according to the LOCS III charts,
Intervention(s)	A standard three-port vitrectomy combined with removal of the posterior hyaloid. The internal limiting membrane (ILM) was stained with 0.1 ml of a 0.125% indocyanine green (ICG) solution for 30 seconds and removed with an end-gripping forceps. In patients who had mild cataract and who were older than 60 years, phacoemulsification of the lens with posterior chamber lens implantation performed as a combined procedure. Surgery

	performed under general anaesthesia by one of two surgeons. Postop topical antibiotic and anti-inflammatory therapy administered three times daily over 4 weeks.
Comparator	Participants in this group did not receive any treatment. Postop topical antibiotic and anti-inflammatory therapy administered three times daily over 4 weeks.
Outcomes	Best corrected visual acuity Adverse events

Study arms
PPV (N = 25) PPV = Pars plana vitrectomy
No treatment (N = 31) Participants did not receive any treatment

Study-level characteristics

Characteristic	**Study (N = 56)**
% Female Sample size	n = 39 ; % = 69.7
Mean age (SD) Range	28 to 74
vitrectomy group Mean age (SD) Mean (SD)	62.7 (*empty data*)
no treatment group Mean age (SD) Mean (SD)	63.9 (*empty data*)
% diabetic macular oedema Custom value	100

Critical appraisal – GDT Crit App – Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	**Question**	**Answer**
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Takamura, 2018

Bibliographic Reference	Takamura, Yoshihiro; Shimura, Masahiko; Katome, Takashi; Someya, Hideaki; Sugimoto, Masahiko; Hirano, Takao; Sakamoto, Taiji; Gozawa, Makoto; Matsumura, Takehiro; Inatani, Masaru; writing committee of Japan-Clinical Retina Research Team, (J-CREST); Effect of intravitreal triamcinolone acetonide injection at the end of vitrectomy for vitreous haemorrhage related to proliferative diabetic retinopathy.; The British journal of ophthalmology; 2018; vol. 102 (no. 10); 1351-1357

Study details

Study location	Japan
Study setting	seven clinical centres
Inclusion criteria	Patients with type 2 diabetes who required vitrectomy for VH were eligible for this study.
Exclusion criteria	• history of injection of anti-VEGF drugs and steroids and retinal photocoagulation within 3 months before surgery • active intraocular inflammation or infection in either eye • uncontrolled glaucoma in either eye, • retinal detachment • history of stroke • systolic blood pressure (BP) >160mm Hg or diastolic BP >100mm Hg or untreated hypertension
Intervention(s)	In the IVTA+VIT group, a standard four-port PPV was performed by using 25-gauge microincision procedure. 0.1mL (4mg) was injected into the vitreous cavity through a 30-gauge needle at the end of the surgery. During the vitrectomy, all patients received photocoagulation using a laser system if DME was noticed during vitrectomy, the internal limiting membrane (ILM) peeling were carried out
Comparator	a standard four-port PPV was performed by using 25-gauge microincision procedure. During the vitrectomy, all patients received photocoagulation using a laser system if DME was noticed during vitrectomy, the internal limiting membrane (ILM) peeling were carried out
Outcomes	Best corrected visual acuity Adverse events

Study arms
PPV + IVTA (N = 42)
PPV (N = 42)

Study-level characteristics

Characteristic	**Study (N = 84)**
% Female Sample size	n = 39
PPV + IVTA group Mean age (SD) Mean (SD)	66.9 (8.5)

Characteristic	Study (N = 84)
PPV group Mean age (SD) Mean (SD)	67.3 (8.2)
% vitreous haemorrhage Sample size	n = 84 ; % = 100

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate unclear blinding
Overall bias and Directness	Overall Directness	Directly applicable

Thomas, 2005

Bibliographic Reference	Thomas, D; Bunce, C; Moorman, C; Laidlaw, D A H; A randomised controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema.; The British journal of ophthalmology; 2005; vol. 89 (no. 1); 81-6

Study details

Trial registration number and/or trial name	Not reported. Ethical approval obtained before study from Guy's and St Thomas' research ethics committee (EC00/004)
Study type	Parallel-group randomised controlled trial (RCT)
Study location	UK
Study setting	Hospital
Study dates	Not reported, 18-mo recruitment period.
Sources of funding	Funding from the GKTT Special Trustees Fund, the Weinstock Foundation, and a Lilly Diabetes Grant
Inclusion criteria	• Confirmed diagnosis of diabetes mellitus • Clinical and angiographic evidence of diffuse or diffuse and focal macular oedema in an eye which had already received ≥1 argon laser treatment at least previous 3-mo • Visual acuity of 0.30 logMAR (Snellen equivalent 6/12 or 20/40) or worse • Able and willing to give informed consent and participate in the trial assessment protocol.
Exclusion criteria	• Co-existing eye disease liable to affect visual outcome (including axial or capsular lens opacity, glaucoma, amblyopia and non-diabetic macular disease) • Ischaemic maculopathy • Active proliferative diabetic retinopathy • Vitreous haemorrhage • Biomicroscopic evidence of macular traction including epiretinal membrane, vitreoretinal traction arising from proliferative

	retinopathy, and a thickened, taut, and glistening premacular posterior hyaloid without evidence of retinal striae • Clinically-evident posterior vitreous detachment • Uncontrolled hypertension (BP>140/95 mm Hg) • Severe renal impairment as determined by the need to undergo renal replacement therapy
Intervention(s)	Standard three-port PPV with induction of posterior vitreous detachment, then 0.5 mg/ml indocyanine green assisted removal of internal limiting membrane. All surgeries performed by same surgeon. When both eyes of participant met entry criteria, the eye with the acuity nearest to 0.60 logMAR (6/24 or 20/80 Snellen, 0.25 decimal Snellen) was selected as study eye, with other eye receiving standard care. Assessed at 12-mo post-randomisation and attended for clinical review at months 3,6 and 9 post-treatment.
Comparator	Further argon laser Macular Grid Photocoagulation treatment to areas of areas of angiographically-confirmed leakage. All treatments by one surgeon using the ETDRS protocol. Assessed at 12-mo post-randomisation and attended for clinical review at months 3,6 and 9 post-treatment.
Outcomes	Best corrected visual acuity Adverse events

Study arms
PPV-ilm (N = 19) Pars plana vitrectomy with removal of internal limiting membrane

MGLP (N = 21) Macular Grid Laser Photocoagulation

Study-level characteristics

Characteristic	Study (N = 40)
% Female Custom value	35

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Yanyali, 2006

Bibliographic Reference	Yanyali, A; Horozoglu, F; Celik, E; Ercalik, Y; Nohutcu, A F; Pars plana vitrectomy and removal of the internal limiting membrane in diabetic macular edema unresponsive to grid laser photocoagulation.; European journal of ophthalmology; 2006; vol. 16 (no. 4); 573-81

Study details

Trial registration number and/or trial name	Not reported
Study type	Within-person randomised controlled trial
Study location	Istanbul, Turkey
Study setting	Haydarpasa Numune Education and Research Hospital
Study dates	03/2002 to 12/2004
Sources of funding	Not reported
Inclusion criteria	Patients with • Diagnosis of bilateral diabetic macula oedema • Prior grid laser photocoagulation (GLP) treatment • Persistent diabetic macular oedema bilaterally 6-mo post-GLP treatment
Exclusion criteria	Eyes that met any of these criteria: • Unilateral macular oedema • Had GLP treatment ≤past 6-mo • Only treated with focal LP • Panretinal photocoagulation ≤past 12-mo • Had vitreoretinal surgery • Cataract surgery ≤past12-mo • Traction retinal detachment, active neovascularization • Media opacity such as cataract or vitreous haemorrhage • Evidence of vitreomacular traction (taut and thickened posterior hyaloid or epiretinal membrane)
Intervention(s)	Standard three-port PPV performed by one surgeon. Posterior vitreous detachment achieved with silicone-tipped cannula by active aspiration, continued 360° peripherally. ILM stained with 0.1% (1 mg/mL) indocyanine green (ICG) under intravitreal air and peeled from macula using intravitreal forceps. Subconjunctival injections of dexamethasone (2 mg) and gentamicin (4 mg) administered at end of surgery. Postop examinations at days 1 and 3, months 1, 3 and 6, and every subsequent 6-mo.
Comparator	No treatment was given to this group.
Outcomes	Best corrected visual acuity Adverse events

Study arms
PPV-ilm (N = 10) Pars plana vitrectomy with removal of internal limiting membrane
No treatment (N = 10)

Study-level characteristics

Characteristic	Study (N = 20)
% Female Custom value	60
Mean age (SD) Range	51 to 71
Mean age (SD) Mean (SD)	61.5 (6)
% diabetic macular oedema Custom value	100
% vitreous haemorrhage Custom value	0
% with tractional retinal detachment Custom value	0

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Yanyali, 2005

Bibliographic Reference	Yanyali, Ates; Nohutcu, Ahmet F; Horozoglu, Fatih; Celik, Erkan; Modified grid laser photocoagulation versus pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema.; American journal of ophthalmology; 2005; vol. 139 (no. 5); 795-801

Study details

Trial registration number and/or trial name	Not reported
Study type	Within-person randomised controlled trial
Study location	Istanbul, Turkey
Study setting	Haydarpasa Numune Education and Research Hospital
Study dates	05/2002 to 04/2004

Sources of funding	Not reported
Inclusion criteria	• Diagnosis of bilateral diabetic macular oedema (defined as retinal thickening of ≥2 disk areas involving foveal avascular zone with or without cystoid changes attributable to diffuse leakage from dilated retinal capillaries, retinal pigment epithelium, and ischemic retina • Diastolic blood pressure<100 mm Hg • Glycosylated haemoglobin ≤10 mg/dl
Exclusion criteria	Eyes that met any of these criteria: • Unilateral macular oedema • Focal macular oedema attributable to focal leaks from microaneurysms • Previous macular laser photocoagulation • Panretinal photocoagulation ≤past 12-mo • Had vitreoretinal surgery • Cataract surgery ≤past12-mo • Traction retinal detachment • Active neovascularization • Media opacity such as cataract or vitreous haemorrhage • Angiographic evidence of widening or irregularity of foveal avascular zone • >6 clock-hours of macular capillary nonperfusion in fluorescein angiography • Evidence of vitreomacular traction Patients that met any of these criteria: • Chronic renal failure maintained on renal dialysis
Intervention(s)	Standard three-port pars plana vitrectomy (PPV) with internal limiting membrane peeling (ILMP). Posterior vitreous detachment achieved with silicone-tipped cannula by active aspiration then continued 360° peripherally. ILM (stained with 0.1% [1 mg/ml] indocyanine green under intravitreal air) peeled from macula using intravitreal forceps. Subconjunctival gentamicin injection performed at end of surgery. No eyes received periocular corticosteroid injection at time of surgery. Participants examined postop at days 1 and 3, 1 week, 1-mo, 6-mo, and every 6-mo after. Trial explained to participants and informed consent obtained.
Comparator	Modified Grid Argon (green 514 nm) Laser Photocoagulation (GLP) performed under topical anaesthesia by same surgeon using Ultima 20000 SE Coherent. One-hundred micron spot applied to 2-3 rows around parafoveal region up to/including edge of foveal avascular zone, placing lesions approximately 100m apart. Two-hundred micron spots then applied throughout all areas of leakage seen on fluorescein angiogram, placing the lesions approximately 200 m apart. In areas of obvious focal leakage, additional 200-m spots were "confluently applied". Average settings included 50 to 100 100-m spots at 75 to 100 mW and 200 to 500200-m spots at 100 to 200 mW. Recent fluorescein angiogram

	used as guide during treatment session. No supplemental treatment provided. Participants examined postop at days 1 and 3, 1 week, 1-mo, 6-mo, and every 6-mo after. Trial explained to participants and informed consent obtained.
Outcomes	Best corrected visual acuity

Study arms
PPV-ilm (N = 12) Pars plana vitrectomy with removal of internal limiting membrane

Modified GLP (N = 12) Modified Grid Laser Photocoagulation

Study-level characteristics

Characteristic	Study (N = 24)
% Female Nominal	58
Mean age (SD) Mean (SD)	64.4 (8.4)
% diabetic macular edema Nominal	100
% vitreous haemorrhage Nominal	0
% with tractional retinal detachment Nominal	0

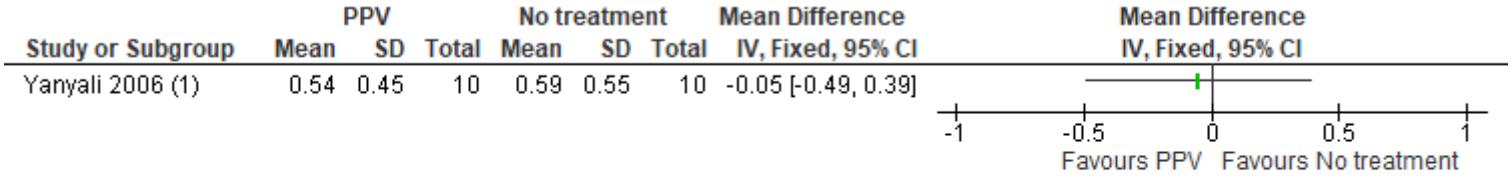
Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

Pars plana vitrectomy (PPV) vs no treatment (population with diabetic macular oedema)

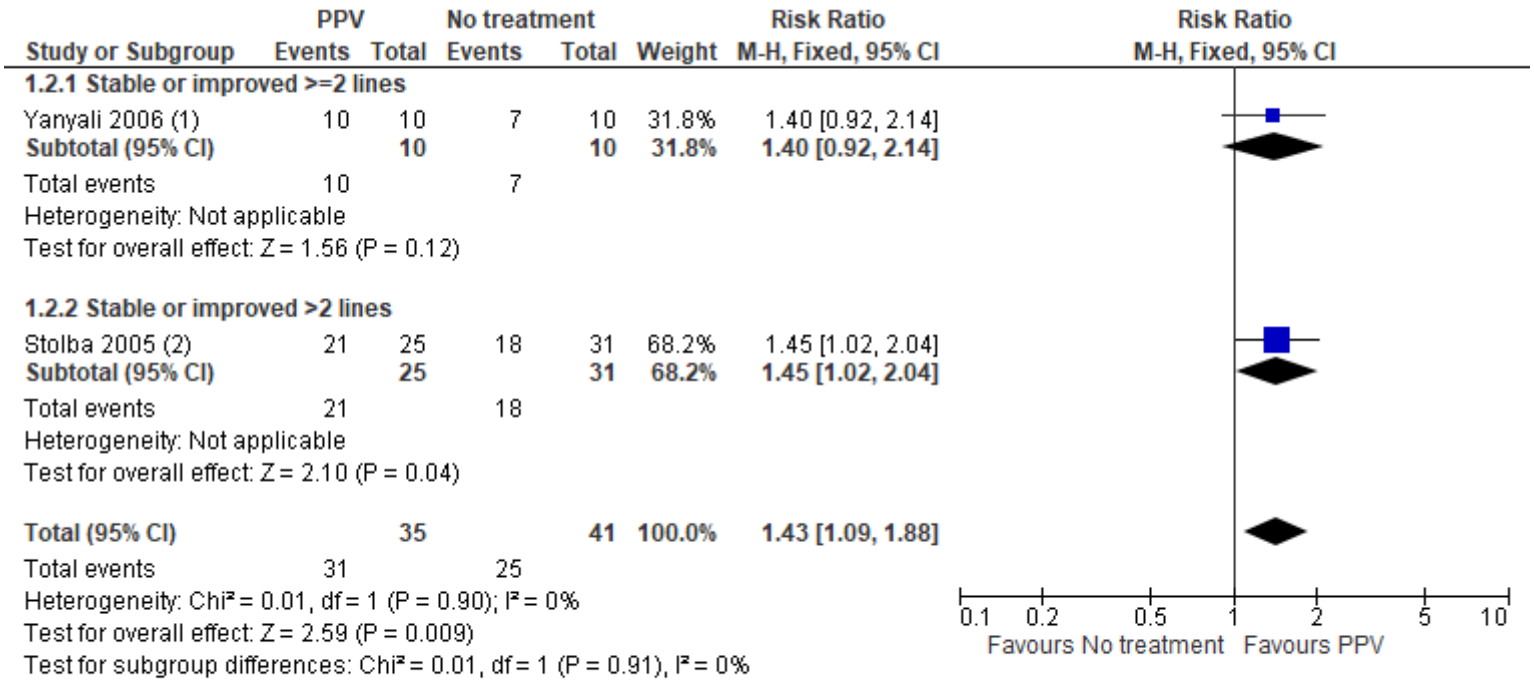
Figure 1. Best corrected visual acuity (MD less than 0 favours PPV)



Footnotes

(1) Snellen LogMAr at 12-mo FU. PPV group included removal of internal limiting membrane.

Figure 2. Improvement in visual acuity (RR greater than 1 favours PPV)

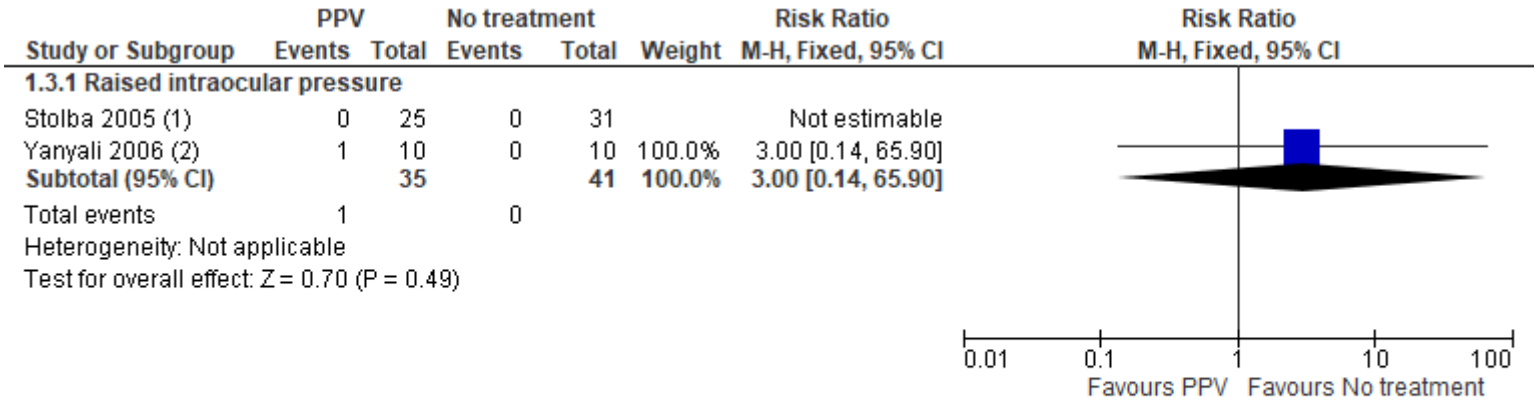


Footnotes

(1) Snellen at 12-mo FU. PPV group included removal of internal limiting membrane.

(2) ETDRS at 6-mo FU. PPV group included removal of both posterior hyaloid and internal limiting membrane. PPV: Improved=13,...

Figure 3. Adverse events during follow up (RR less than 1 favours PPV)



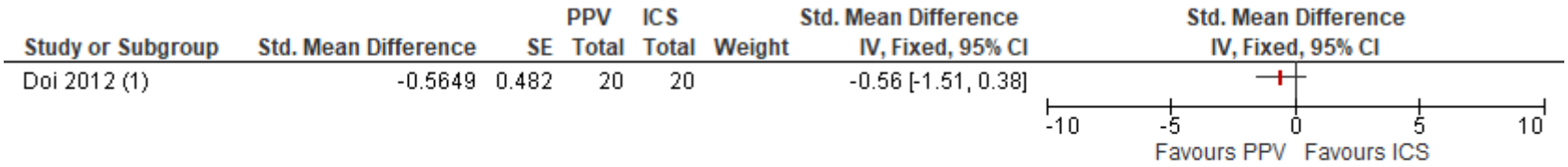
Footnotes

(1) 6-mo FU. PPV group included removal of both posterior hyaloid and internal limiting membrane.

(2) 12-mo FU. Reports transient increase in intraocular pressure. PPV group included removal of internal limiting membrane.

Pars plana vitrectomy (PPV) vs intravitreal corticosteroids

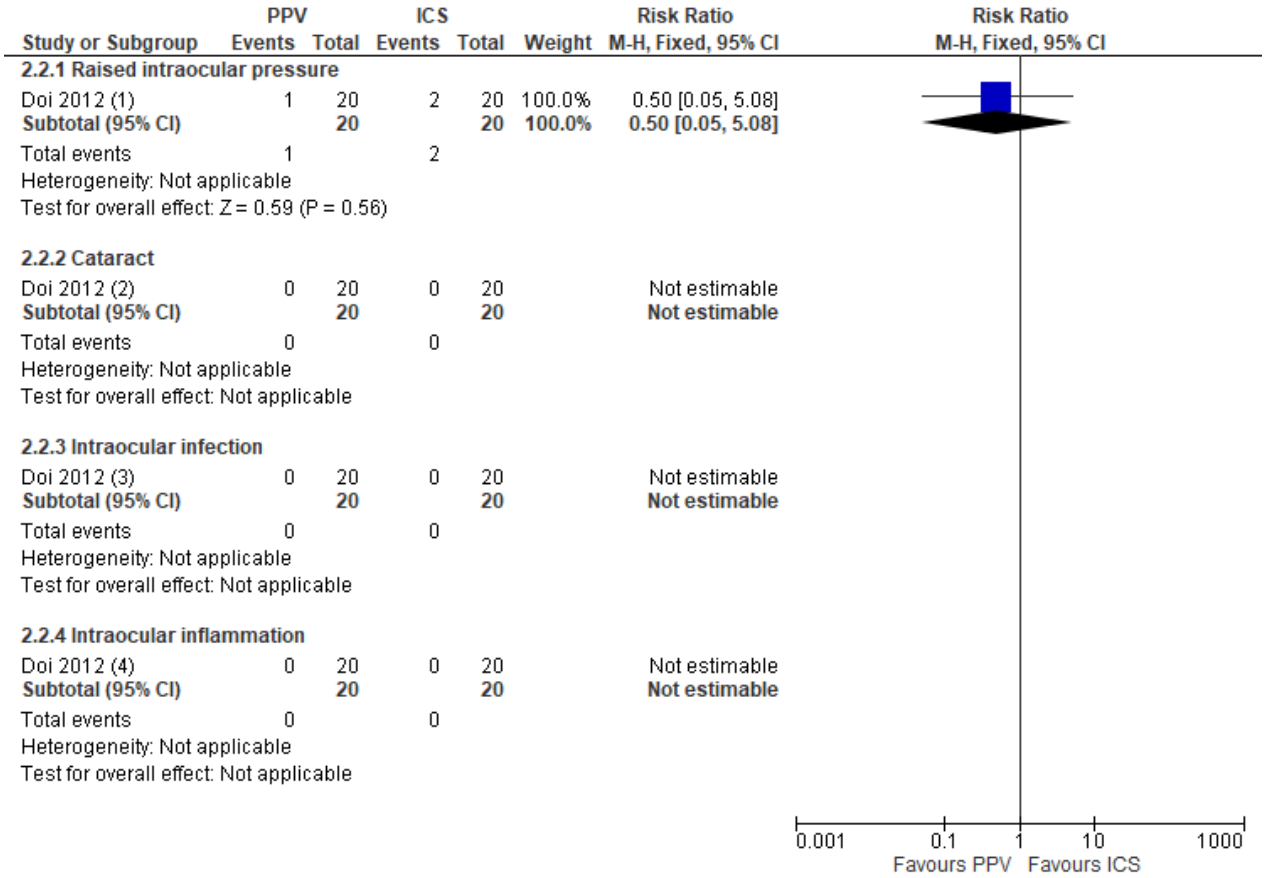
Figure 4. Best corrected visual acuity (SMD less than 0 favours PPV)



Footnotes

(1) 12-mo FU. Data converted to SMD from reported p-value of 0.082; SE calculated from 95%Ci and significant difference P<0.0125.

Figure 5. Adverse events during follow up (RR less than 1 favours PPV)



Footnotes

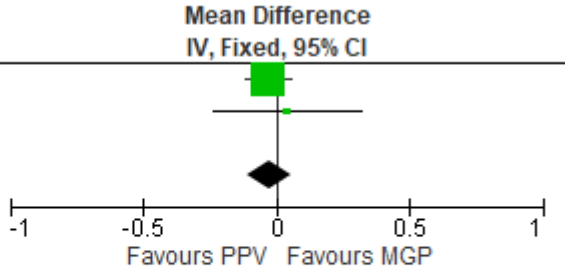
(1) 12-mo FU. Standard 20-gauge three-port PPV with endophotocoagulation. Particpants in ICS group received 4mg IVTA.
(2) See above footnote.
(3) See above footnote. Reports no other complications related to either intervention.
(4) See above footnote.Reports no other complications related to either intervention.

Pars plana vitrectomy (PPV) vs Macular grid laser photocoagulation (population with diabetic macular oedema)

Figure 6. Best corrected visual acuity – treatment naïve (MD less than 0 favours PPV)

	PPV			MGP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Kumar 2007 (1)	0.932	0.117	12	0.965	0.1	12	91.1%	-0.03 [-0.12, 0.05]
Yanyali 2005 (2)	0.53	0.41	12	0.49	0.27	12	8.9%	0.04 [-0.24, 0.32]
Total (95% CI)			**24**			**24**	**100.0%**	**-0.03 [-0.11, 0.06]**

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)

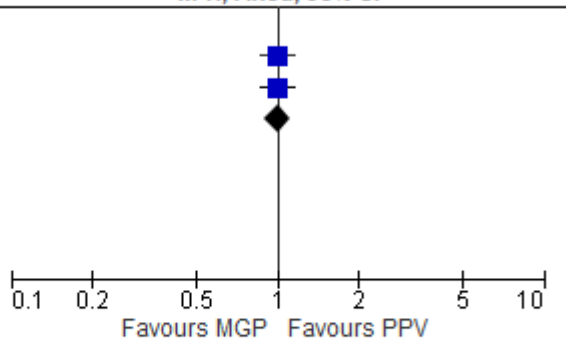


Footnotes
(1) ETDRS logMAR at 6-mo FU. PPV group includes removal of internal limiting membrane. Modified grid laser photocoagulation sparing...
(2) Snellen logMAR at 6-mo FU. PPV group included posterior vitreous detachment and removal of internal limiting membrane.

Figure 7. Best corrected visual acuity – treatment naïve (RR greater than 1 favours PPV)

	PPV		MGP			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
3.2.1 Stable or improved >=2 lines						
Kumar 2007 (1)	12	12	12	12	50.0%	1.00 [0.86, 1.17]
Yanyali 2005 (2)	12	12	12	12	50.0%	1.00 [0.86, 1.17]
Subtotal (95% CI)		**24**		**24**	**100.0%**	**1.00 [0.90, 1.11]**
Total events	24		24			

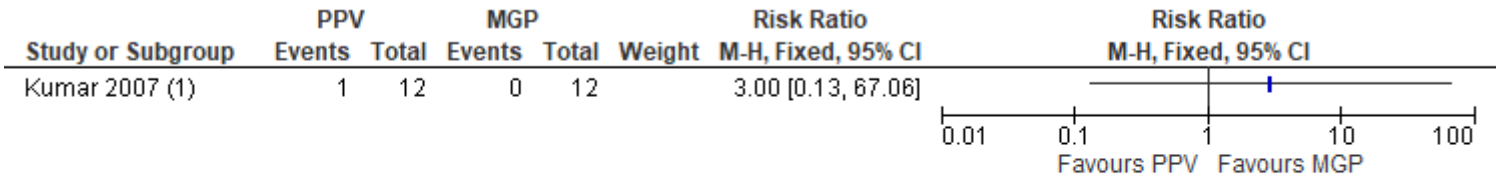
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



Test for subgroup differences: Not applicable

Footnotes
(1) Snellen lines at 6-mo FU. PPV: Improved=3, Stable=9; MGP: Improved=1, Stable=11. PPV group includes removal of internal...
(2) Snellen lines at 6-mo FU. PPV: Improved=6, Stable=6; MGP: Improved=3, Stable=9. PPV group included posterior vitreous...

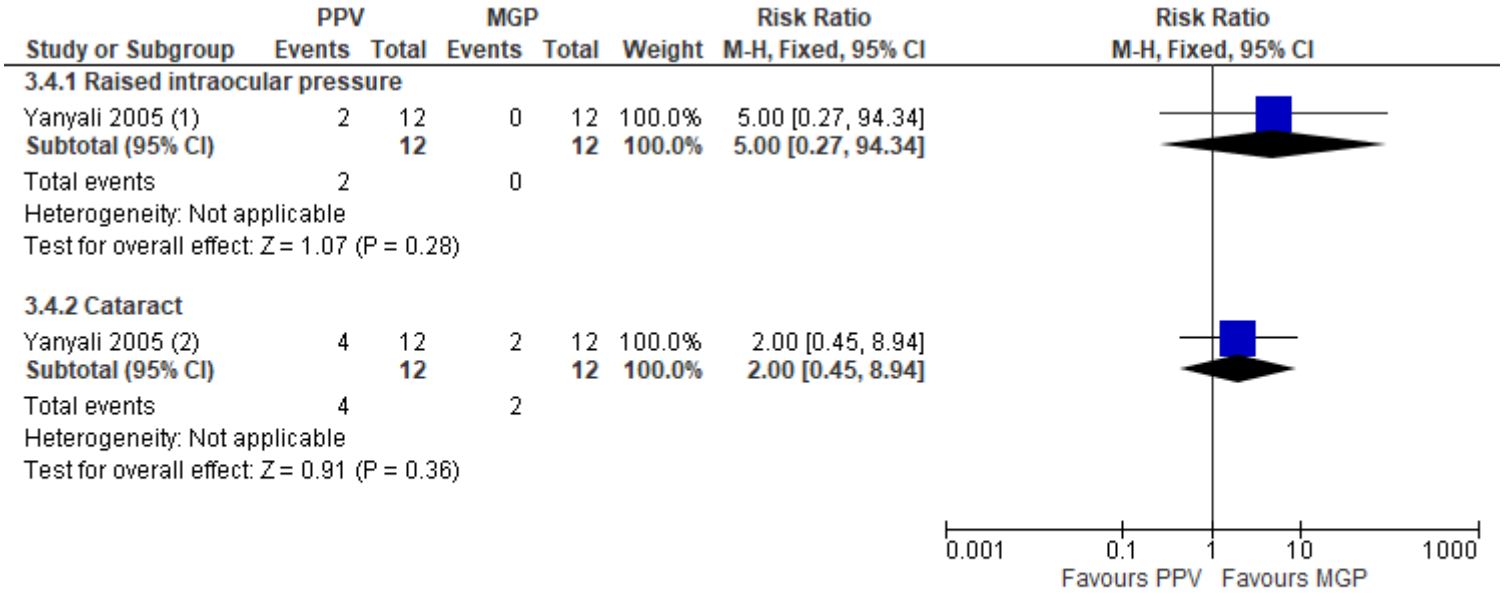
Figure 8. Retinal detachment – treatment naïve (RR less than 1 favours PPV)



Footnotes

(1) 6-mo FU. Reported as rhegmatogenous retinal detachment. PPV group includes removal of internal limiting membrane. Modified...

Figure 9. Adverse events during follow up – treatment naïve (RR less than 1 favours PPV)

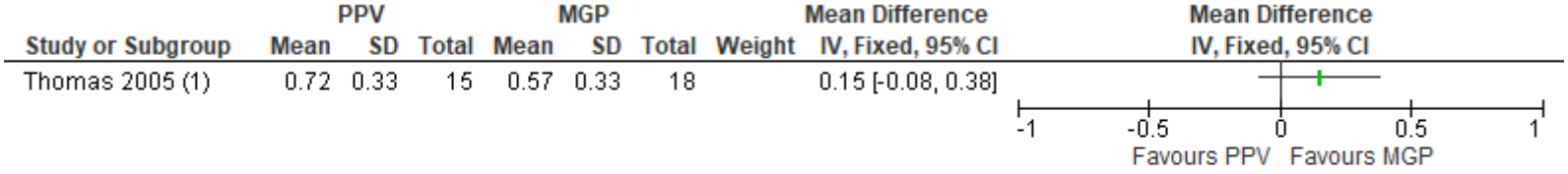


Footnotes

(1) 6-mo FU. PPV group included posterior vitreous detachment and removal of internal limiting membrane. Both events in PPV group...

(2) Reported as progression of nuclear sclerosis. See footnote above.

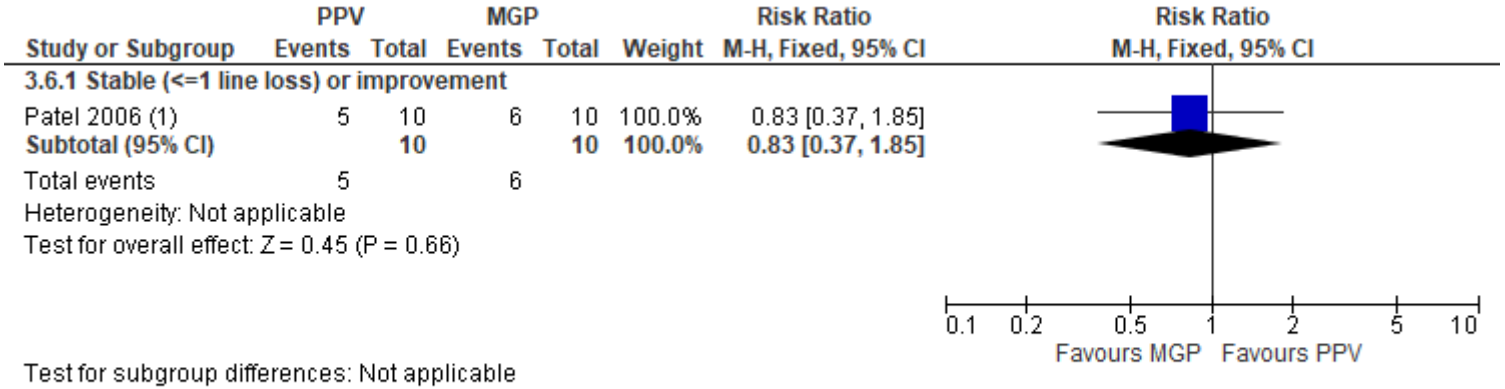
Figure 10. Best corrected visual acuity – recent laser treatment (MD less than 0 favours PPV)



Footnotes

(1) ETDRS logMAR at 12-mo FU. Inclusion criteria for this trial included having received >=1 argon macular grid laser photocoagulation...

Figure 11. Improvement in visual acuity – recent laser treatment (RR greater than 1 favours PPV)

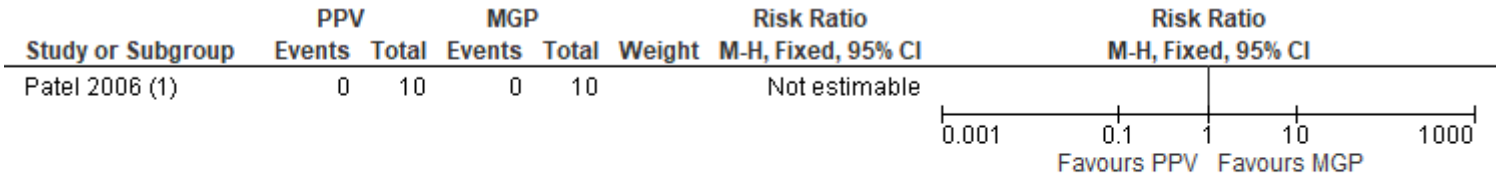


Test for subgroup differences: Not applicable

Footnotes

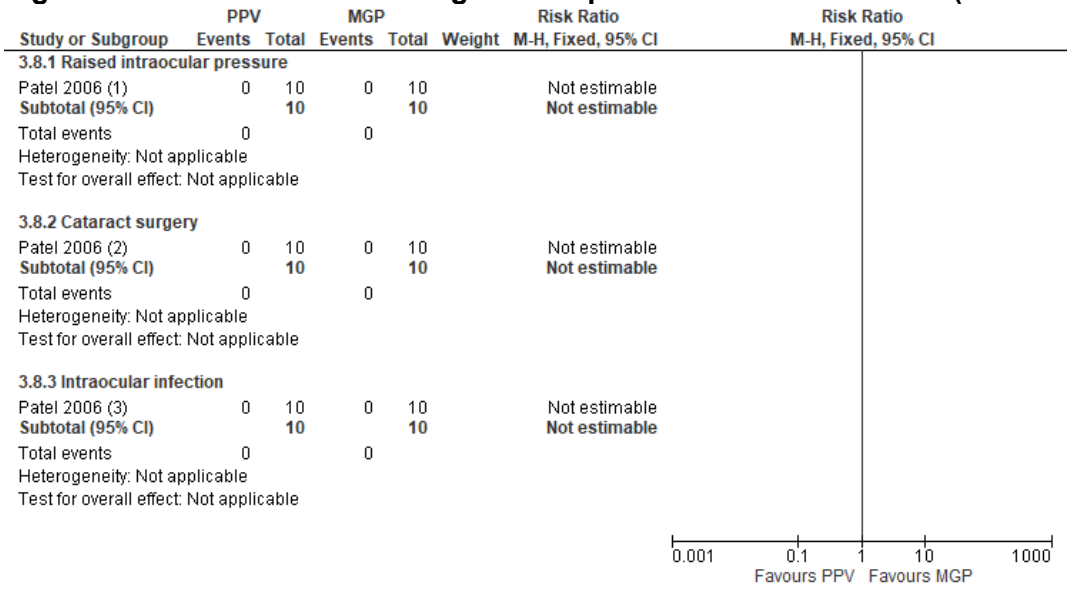
(1) ETDRS at 12-mo FU. PPV group included removal of posterior vitreous cortex.Inclusion criteria for this trial included having...

Figure 12. Retinal detachment – recent laser treatment (RR less than 1 favours PPV)



Footnotes
(1) See previous footnote.

Figure 13. Adverse events during follow up – recent laser treatment (RR less than 1 favours PPV)



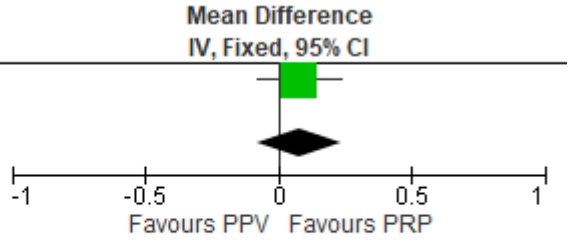
Footnotes
(1) 6-mo FU. Trial reported no complications occurred during FU period. PPV group included removal of posterior vitreous cortex....
(2) See previous footnote.
(3) See previous footnote.

Pars plana vitrectomy (PPV) vs Pan-retinal laser photocoagulation

Figure 14. Best corrected visual acuity (MD less than 0 favours PPV)

Study or Subgroup	PPV Mean	PPV SD	PPV Total	PRP Mean	PRP SD	PRP Total	Weight	Mean Difference IV, Fixed, 95% CI
Avitabile 2012 (1)	1.04	0.59	90	0.96	0.47	90	100.0%	0.08 [-0.08, 0.24]
Total (95% CI)			**90**			**90**	**100.0%**	**0.08 [-0.08, 0.24]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

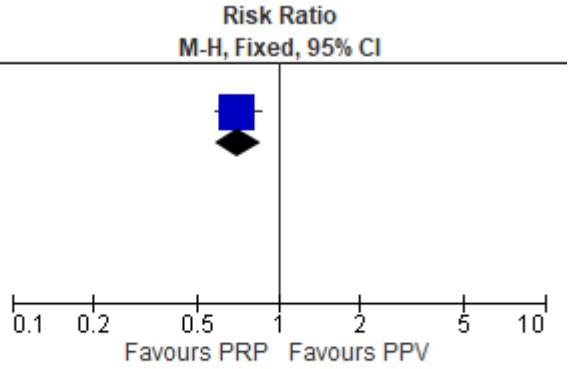


Footnotes
(1) ETDRS logMAR at 12-mo FU. PPV group also had inner limiting membrane removed and received focal or grid laser treatment during FU if...

Figure 15. Improvement in visual acuity (RR greater than 1 favours PPV)

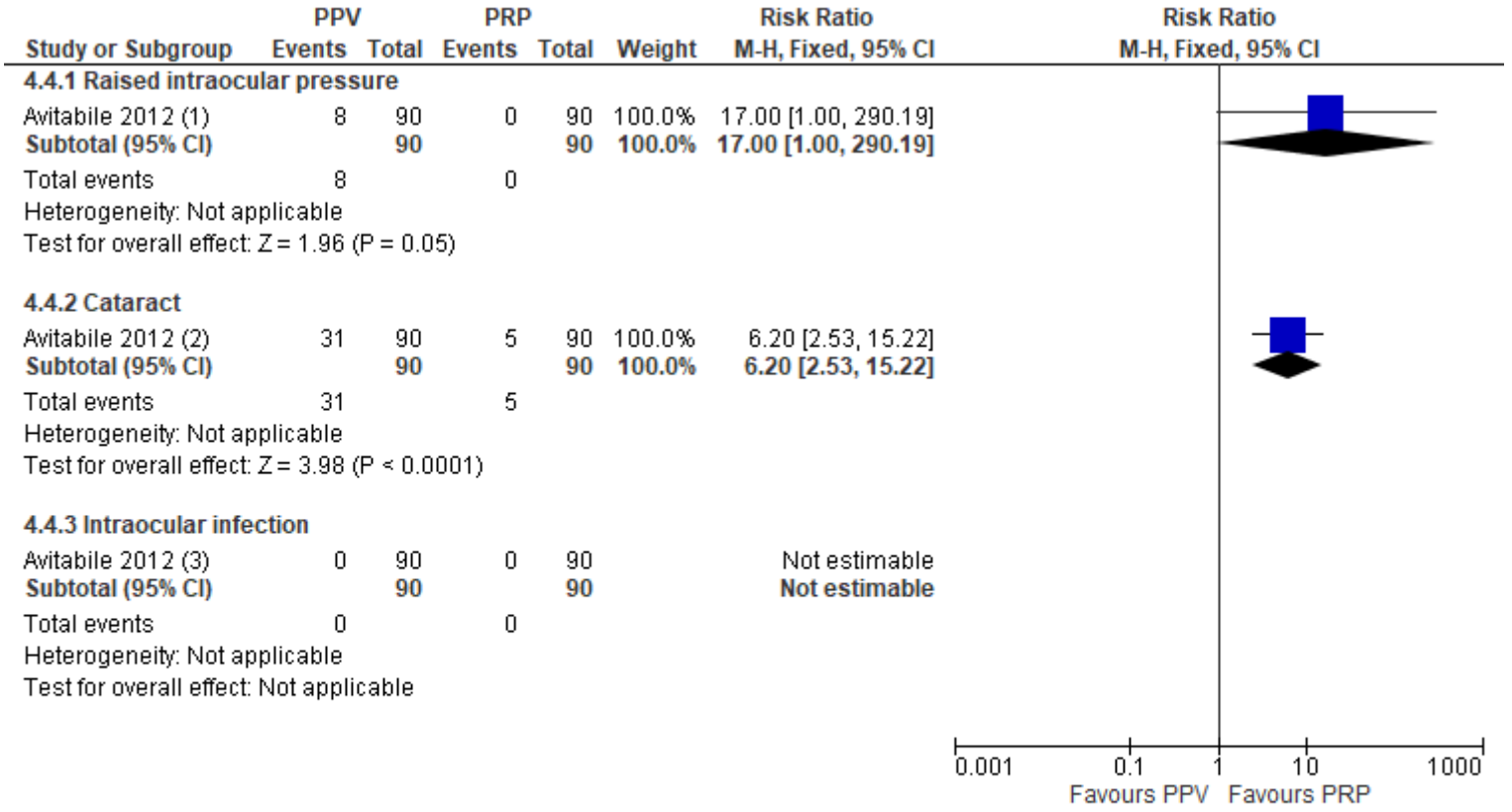
Study or Subgroup	PPV Events	PPV Total	PRP Events	PRP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Stable (<2 lines) or improved (>=2 lines)						
Avitabile 2012 (1)	52	90	74	90	100.0%	0.70 [0.57, 0.86]
Subtotal (95% CI)		**90**		**90**	**100.0%**	**0.70 [0.57, 0.86]**
Total events	52		74			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.44 (P = 0.0006)



Footnotes
(1) ETDRS charts at 12-mo FU. PPV group: Stable=22, Improved=30; PRP group: Stable=42, Improved=32.

Figure 16. Adverse events during follow up (RR less than 1 favours PPV)



Footnotes

(1) Reported as ocular hypertension. PPV group also had inner limiting membrane removed and received focal or grid laser treatment...

(2) See also footnote above.

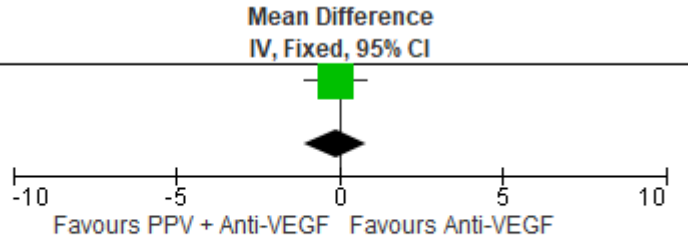
(3) Reported as endophthalmitis. See also footnote above.

Pars plana vitrectomy (PPV) + anti-VEGF vs anti-VEGF

Figure 17. Best corrected visual acuity (MD less than 0 favours PPV + Anti-VEGF)

Study or Subgroup	PPV + Anti-VEGF Mean	SD	Total	Anti-VEGF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jorge 2021 (1)	-0.9629	2.822	35	-0.8543	0.005	35	100.0%	-0.11 [-1.04, 0.83]
Total (95% CI)			**35**			**35**	**100.0%**	**-0.11 [-1.04, 0.83]**

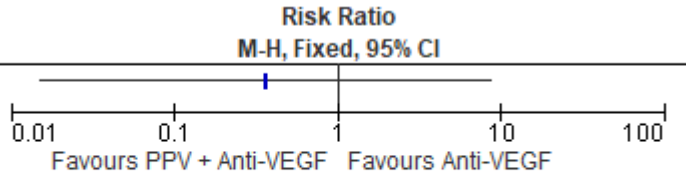
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



Footnotes
(1) 24-weeks FU. ETDRS logMAR change scores (negative score=improvement in BCVA). SEMs converted into SDs.

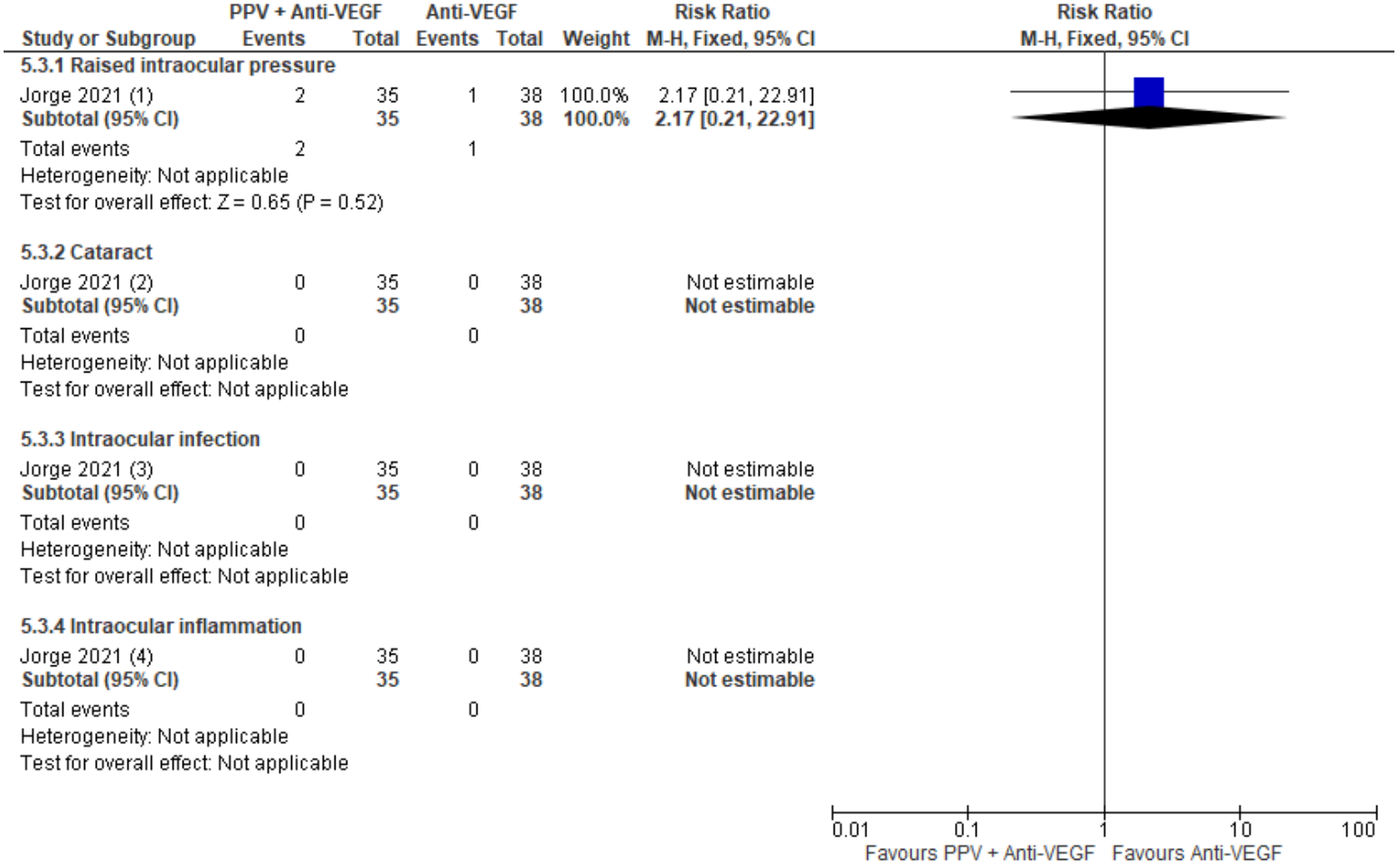
Figure 18. Retinal detachment (RR less than 1 favours PPV + Anti-VEGF)

Study or Subgroup	PPV + Anti-VEGF Events	Total	Anti-VEGF Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jorge 2021 (1)	0	35	1	38		0.36 [0.02, 8.58]



Footnotes
(1) 24-week FU. Reported as tractional retinal detachment.

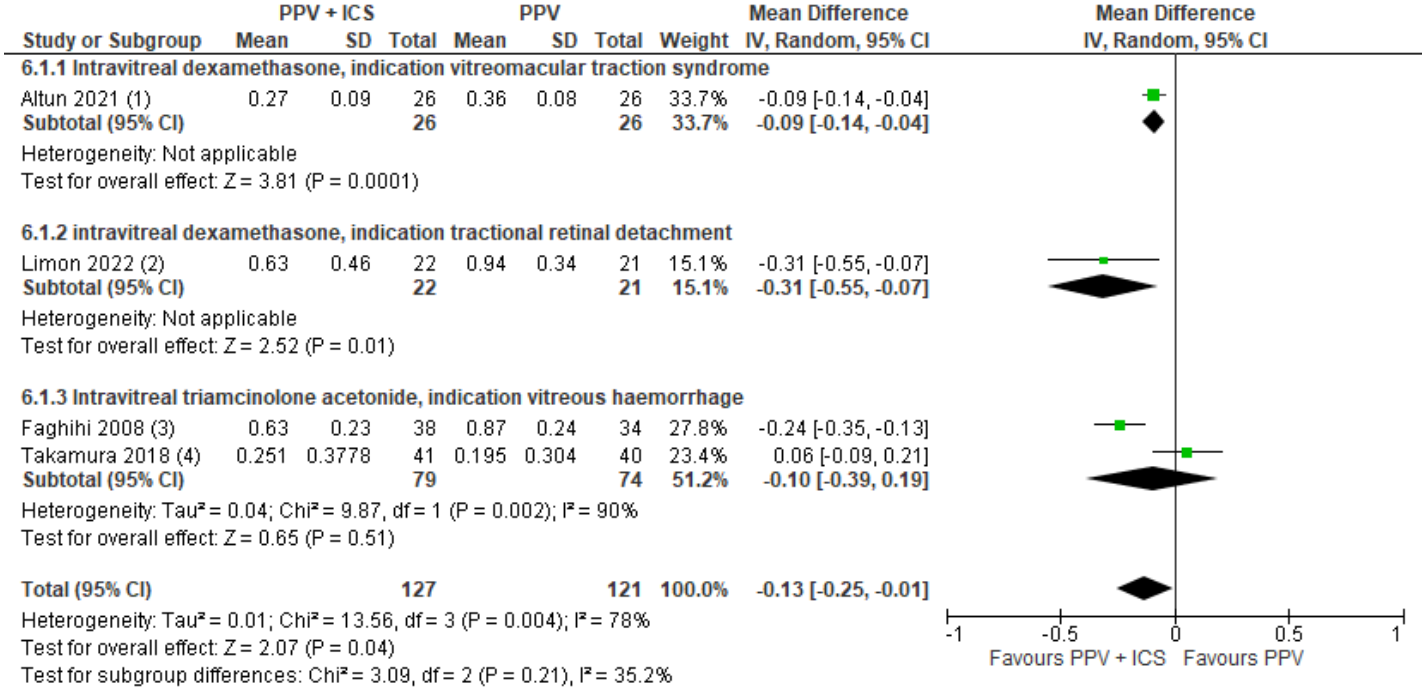
Figure 19. Adverse events during follow up (RR less than 1 favours PPV + Anti-VEGF)



Footnotes
(1) 24-week FU. Defined as IOP>21 mmHg.
(2) 24-week FU. Reported as cataract progression.
(3) 24-week FU. Reported as endophthalmitis.
(4) 24-week FU. Reported as uveitis.

Pars plana vitrectomy (PPV) + intravitreal corticosteroids vs Pars plana vitrectomy (PPV)

Figure 20. Best corrected visual acuity by subgroups of indication for vitrectomy: vitreomacular traction syndrome, indication tractional retinal detachment and by vitreous haemorrhage (MD less than 0 favours PPV + ICS)



Footnotes

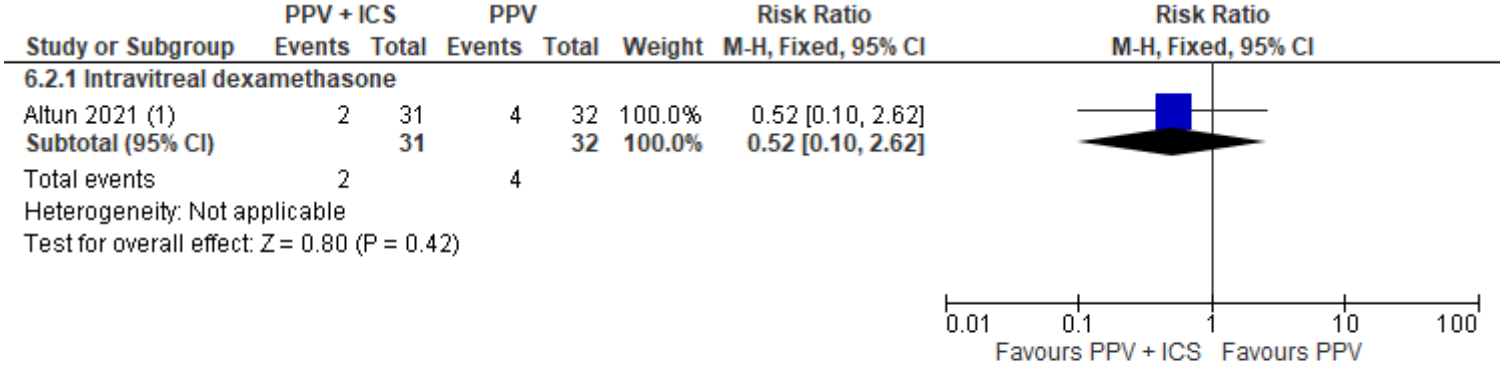
(1) Snellen logMA at 6-mo FU. Intravitreal dexamethasone delivered using Ozurdex implant rather than injection. All participants received panretinal...

(2) ETDRS logMA at 6-mo FU. All participants received 360-degree panretinal photocoagulation with indentation, and also received silicone...

(3) Snellen logMA at 6-mo FU. Four milligram triamcinolone injected at end of surgery. All participants received panretinal photocoagulation and had...

(4) 6-mo FU. SEs converted into SDs. Four milligram triamcinolone injected at end of surgery. All participants received panretinal photocoagulation...

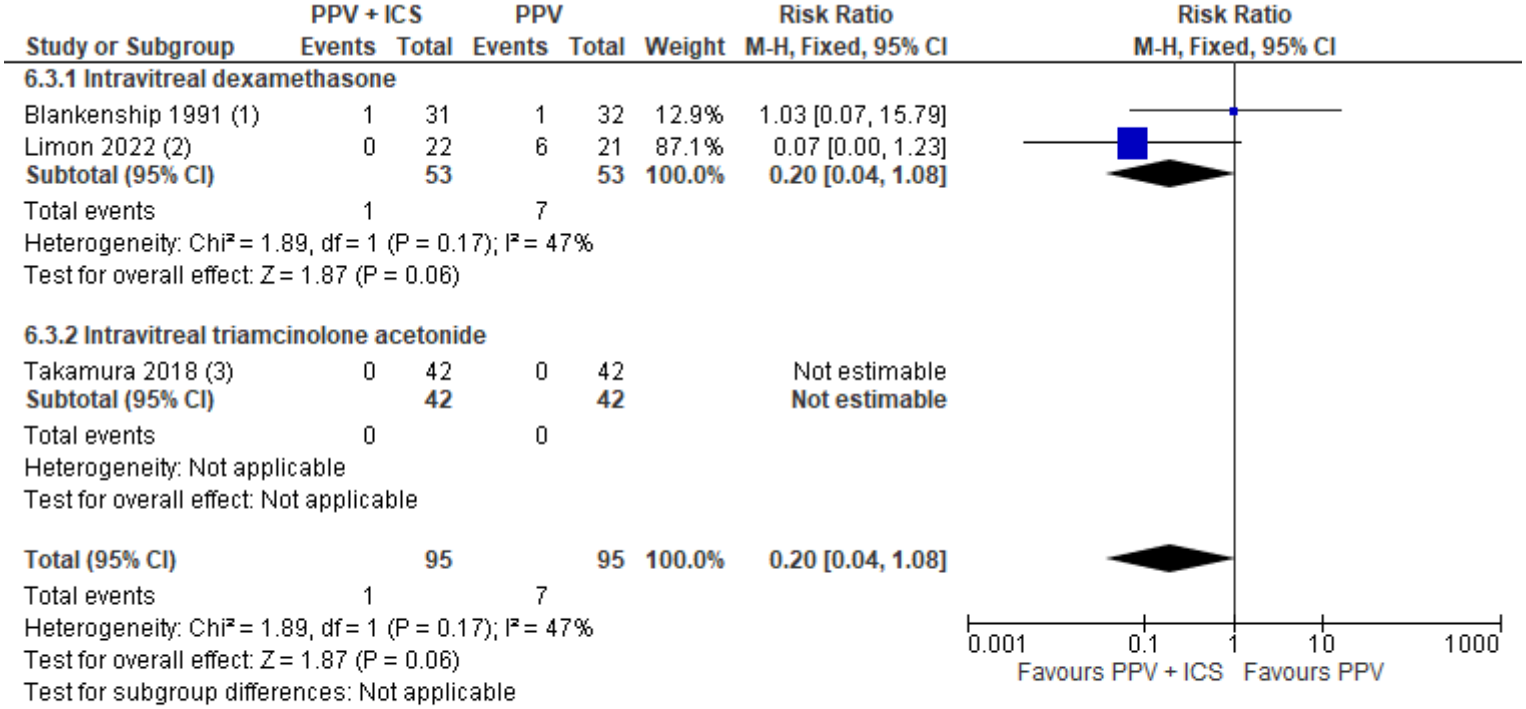
Figure 21. Progression of proliferative retinopathy or diabetic macular oedema (RR less than 1 favours PPV + ICS)



Footnotes

(1) 6-mo FU. Reported as presence of DME. Intravitreal dexamethasone delivered using Ozurdex implant rather than injection. All...

Figure 22. Retinal detachment (RR less than 1 favours PPV + ICS)



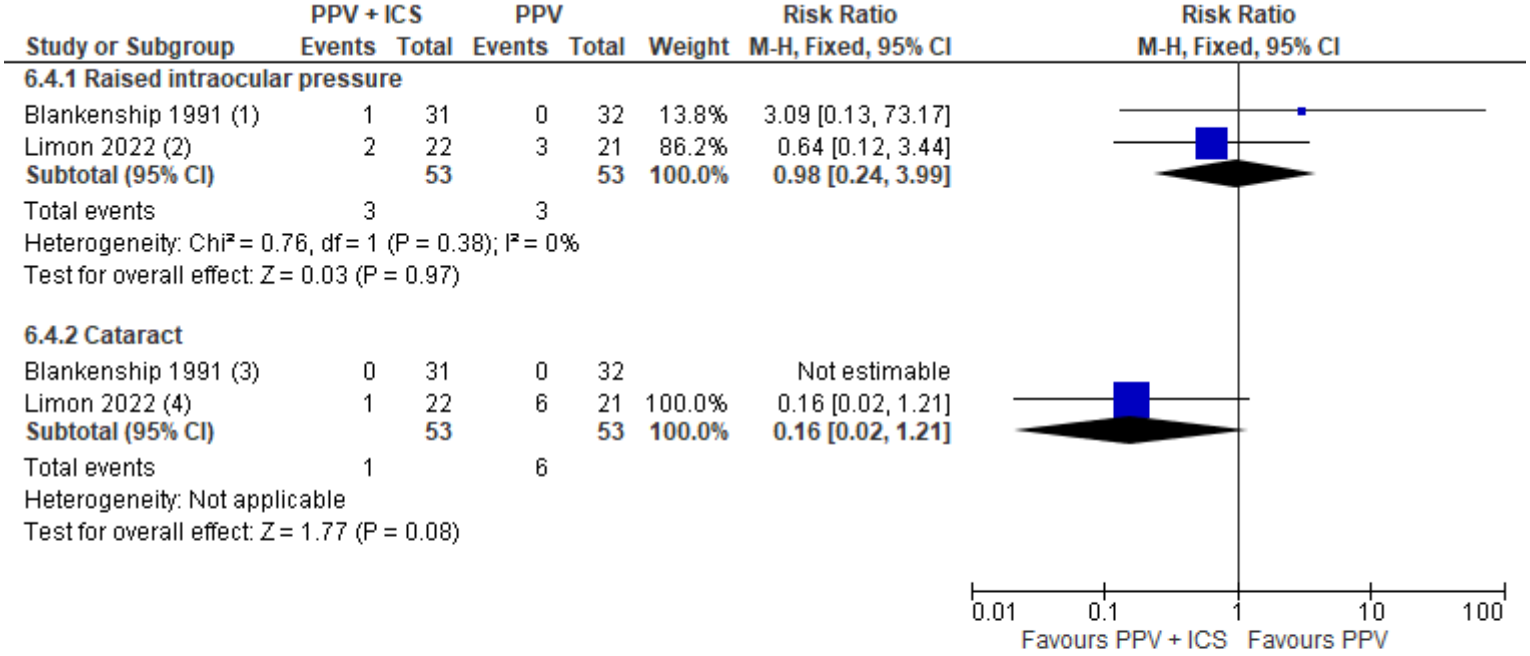
Footnotes

(1) 6-mo FU. Reported as Vitrectomy revisions for intraocular proliferation with retinal detachment. Also reports scleral buckling for...

(2) Reported as retinal re-detachment. All participants received 360-degree panretinal photocoagulation with indentation, and also...

(3) 6-mo FU. Four milligram triamcinolone injected at end of surgery. All participants received panretinal photocoagulation around...

Figure 23. Adverse events during follow up (Intravitreal dexamethasone) (RR less than 1 favours PPV + ICS)



Footnotes

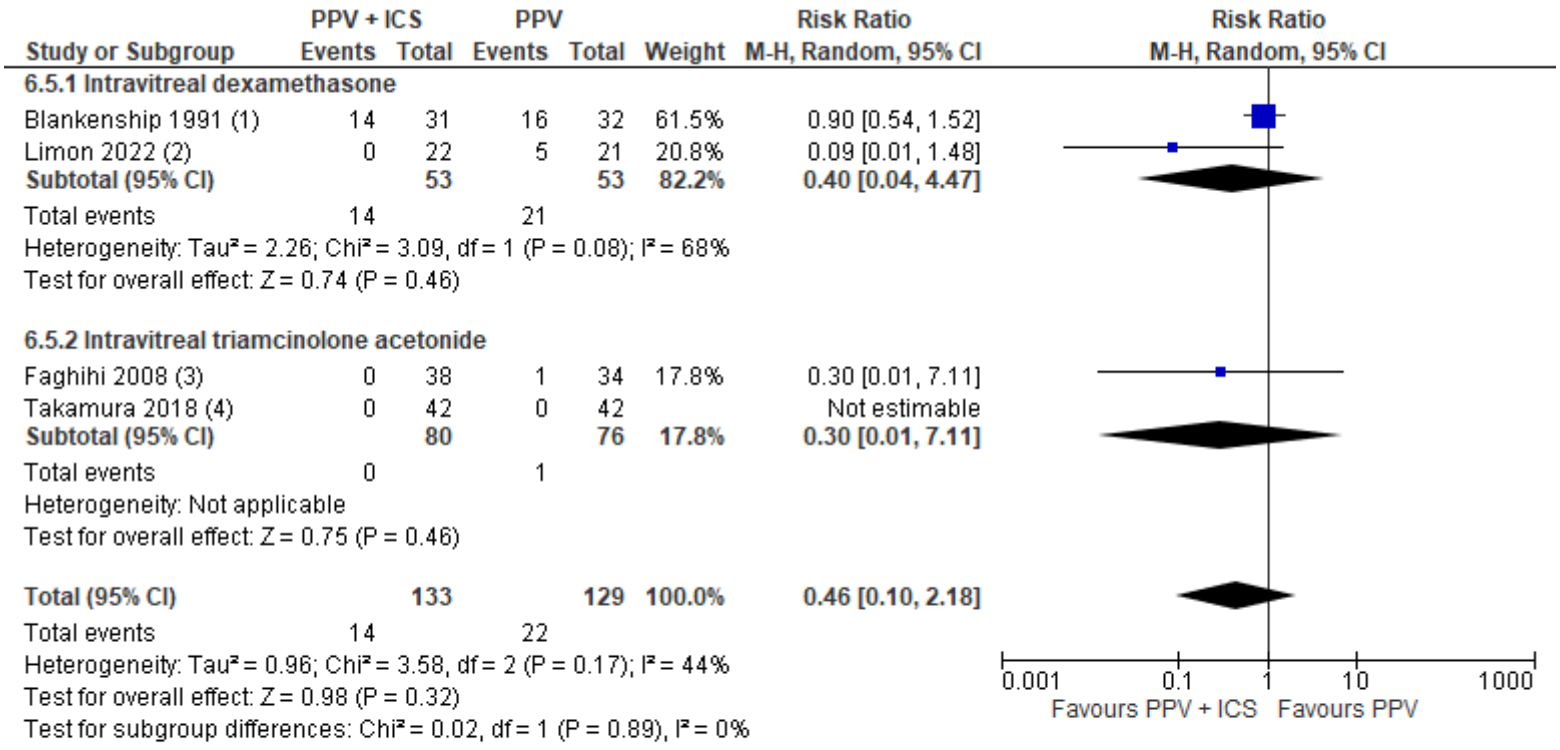
(1) 6-mo FU. Reported as intraocular pressure >30 mmHg. Additional procedures performed if indicated (e.g. lens removal, scleral...

(2) 6-mo FU. All participants received 360-degree panretinal photocoagulation with indentation, and also received silicone tamponade...

(3) 6-mo FU. Additional procedures performed if indicated (e.g. lens removal, scleral buckling).

(4) 6-mo FU. Reported as posterior capsule opacification. All participants received 360-degree panretinal photocoagulation with...

Figure 24. Adverse events during follow up – Intraocular inflammation (RR less than 1 favours PPV + ICS)



Footnotes

(1) 1-week FU. Additional procedures performed if indicated (e.g. lens removal, scleral buckling).

(2) Reported as Anterior Chamber Reaction>+3. Also reports Anterior Chamber Fibrin Exudation (ICS+PPV=0, PPV=8). All participants...

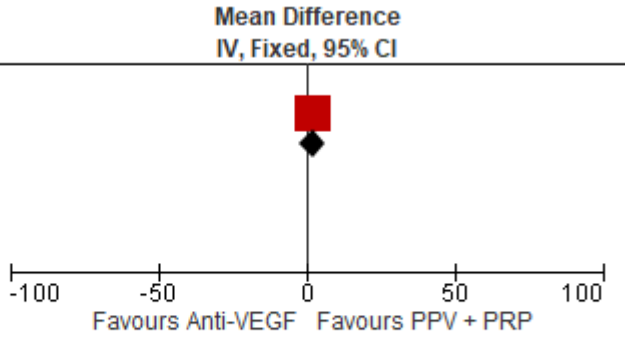
(3) 6-mo FU. Reported as endophthalmitis. All participants received panretinal photocoagulation and had posterior vitreous surface...

(4) 6-mo FU. Four milligram triamcinolone injected at end of surgery. All participants received panretinal photocoagulation around retinal...

Pars plana vitrectomy (PPV) + pan-retinal photocoagulation vs Anti-VEGF

Figure 25. Best corrected visual acuity (MD greater than 0 favours PPV + PRP)

Study or Subgroup	Mean Difference	SE	PPV + PRP Total	Anti-VEGF Total	Weight	Mean Difference IV, Fixed, 95% CI
7.1.1 Intravitreal aflibercept - 2-year FU						
Antoszyk 2020 (1)	2.2	2.296	87	90	100.0%	2.20 [-2.30, 6.70]
Subtotal (95% CI)			**87**	**90**	**100.0%**	**2.20 [-2.30, 6.70]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						

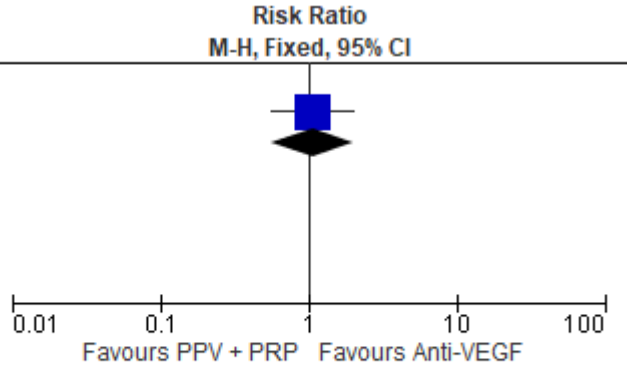


Footnotes

(1) ETDRS chart. Data is mean difference in letter score adjusted for baseline visual acuity and lens status. ETDRS letter score: PPV + PRP=70.0 (sd 24.0),...

Figure 26. Progression of proliferative diabetic retinopathy or diabetic macular oedema (RR less than 1 favours PPV + PRP)

Study or Subgroup	PPV + PRP Events	PPV + PRP Total	Anti-VEGF Events	Anti-VEGF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 Intravitreal aflibercept - 2-years FU						
Antoszyk 2020 (1)	17	105	15	100	100.0%	1.08 [0.57, 2.04]
Subtotal (95% CI)		**105**		**100**	**100.0%**	**1.08 [0.57, 2.04]**
Total events	17		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.81)						



Footnotes

(1) Exclusion criteria for trial was presence of centre-involved DME.

Figure 27. Retinal detachment – intravitreal aflibercept (RR less than 1 favours PPV + PRP)

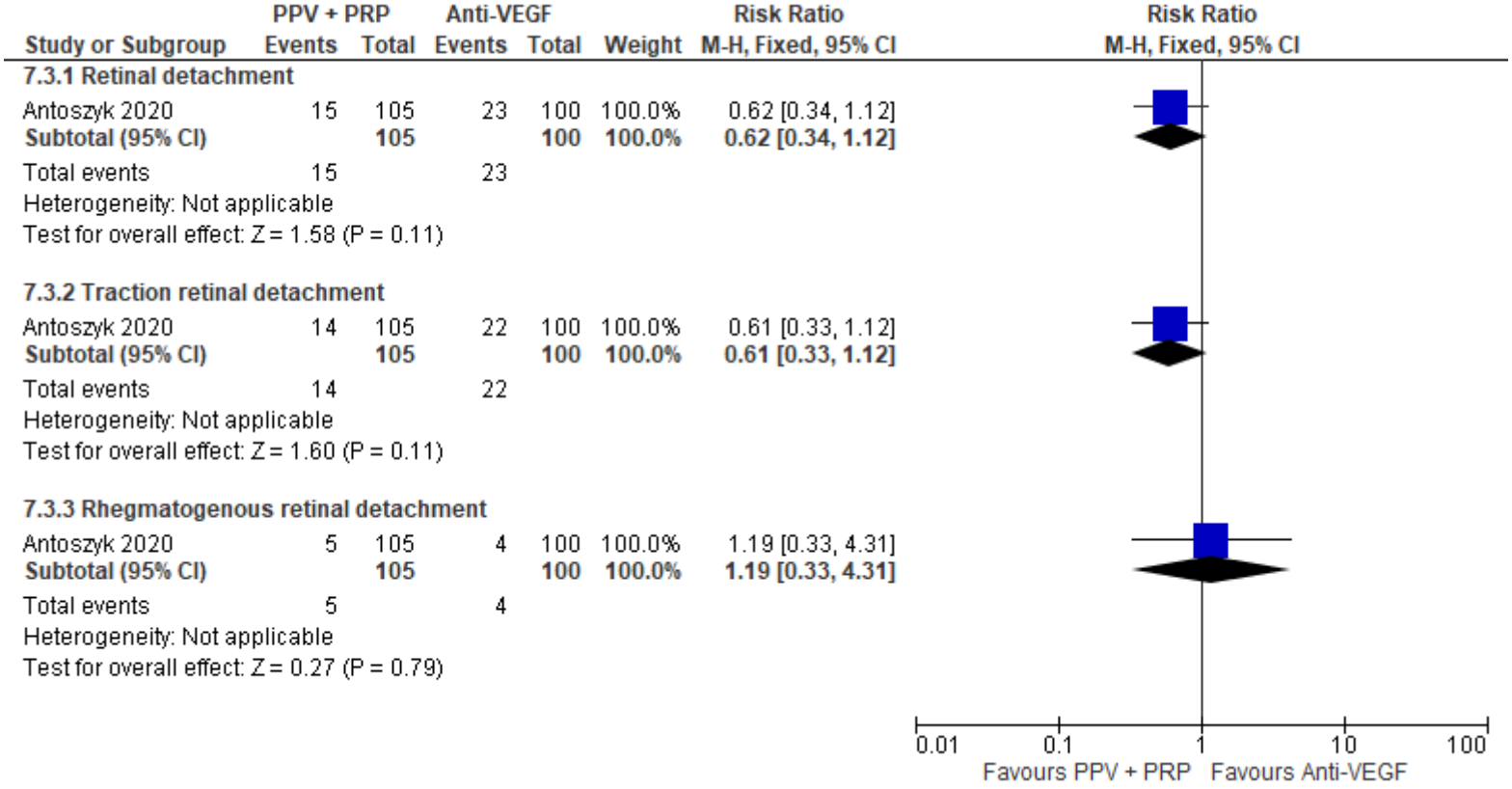
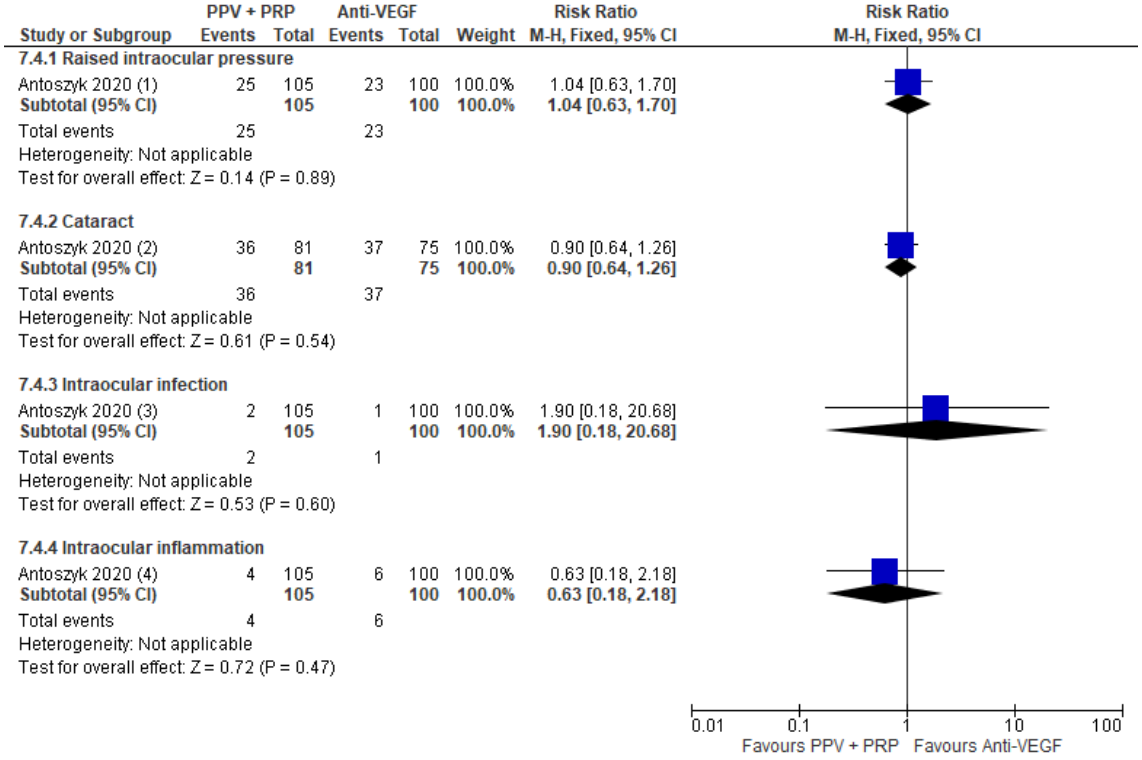


Figure 28. Adverse events during follow up – intravitreal aflibercept (RR less than 1 favours PPV + PRP)



Footnotes

(1) 2-year FU. Data reported for 'adverse intraocular pressure event' (MedDRA definition). Also reports intraocular pressure>=30 mmHg at...

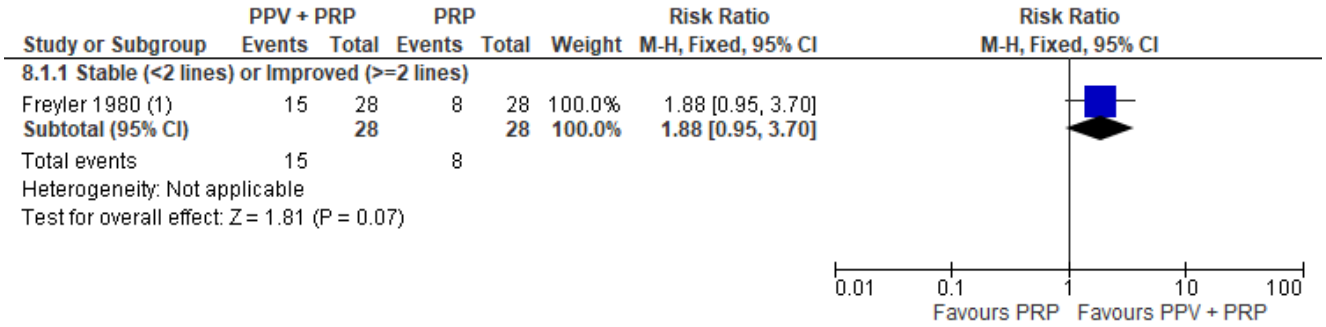
(2) 2-year FU. Data includes number of participants who had at least one event of cataract extraction (PPV + PRP=23, Anti-VEGF=22) or...

(3) 2-year FU. Reported as endophthalmitis.

(4) 2-year FU.

Pars plana vitrectomy (PPV) + pan retinal photocoagulation vs pan-retinal photocoagulation

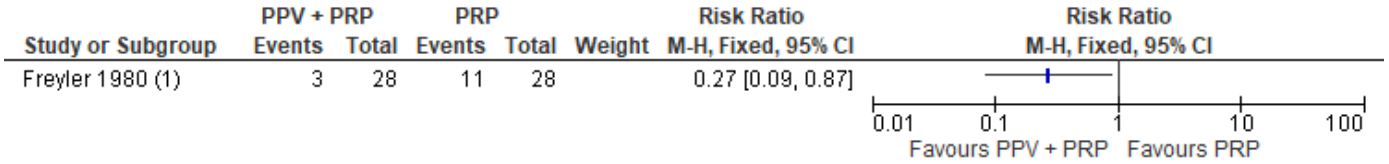
Figure 29. Best corrected visual acuity (RR greater than 1 favours PPV + PRP)



Footnotes

(1) PPV + PRP group: Stable=15, Improved=0, Deterioration=13; PRP group: Stable=8, Improved=0, Deterioration=20. PPV performed...

Figure 30. Retinal detachment (RR less than 1 favours PPV + PRP)



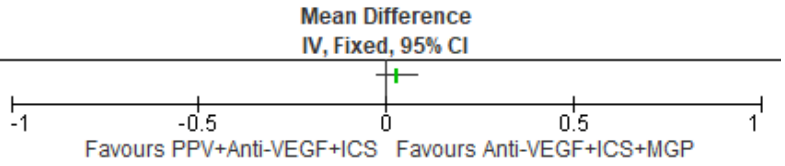
Footnotes

(1) Reported as vitreoretinal retraction. PPV performed 1-15 days before PRP. All participants received PRP with Xenon-arc and Argon...

Pars plana vitrectomy (PPV) + Anti-VEGF + Intravitreal corticosteroid vs Anti-VEGF + Intravitreal corticosteroid + Macular grid photocoagulation (population with diabetic macular oedema)

Figure 31. Best corrected visual acuity (MD less than 0 favours PPV + Anti-VEGF + ICS)

	PPV + Anti-VEGF + ICS			Anti-VEGF + ICS + MGP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saeed 2013 (1)	0.41	0.09	15	0.38	0.06	15		0.03 [-0.02, 0.08]

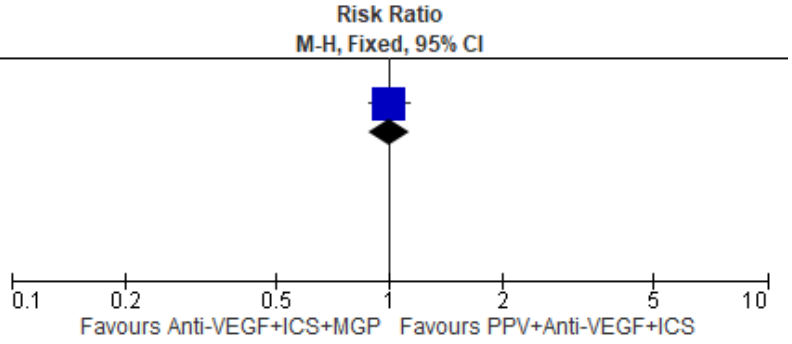


Footnotes

(1) ETDRS logMAR at 12-mo FU. Posterior hyaloid removed during PPV. All participants received IVTA 0.1 mL and 1.25 mg IVB injections at end of procedure. Argon laser...

Figure 32. Improvement in visual acuity (RR greater than 1 favours PPV + Anti-VEGF + ICS)

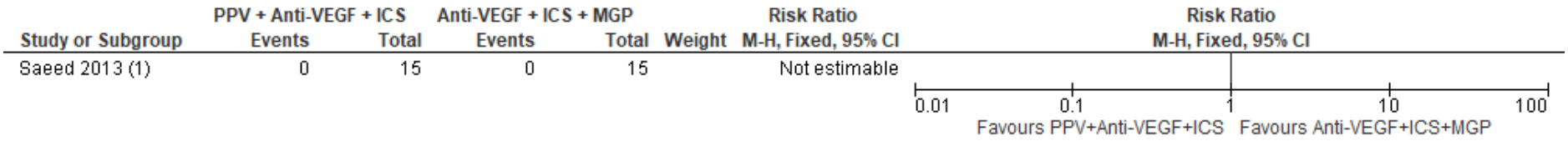
	PPV + Anti-VEGF + ICS		Anti-VEGF + ICS + MGP			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
9.2.1 Stable (<2 lines) or Improved (>=2 lines)						
Saeed 2013 (1)	15	15	15	15	100.0%	1.00 [0.88, 1.13]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**1.00 [0.88, 1.13]**
Total events	15		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						



Footnotes

(1) ETDRS at 12-mo FU. Reports 10 eyes in each group improved>2 lines and 1 eye in PPV + ICS + Anti-VEGF group decreased by 2 lines. Posterior hyaloid removed during PPV. All...

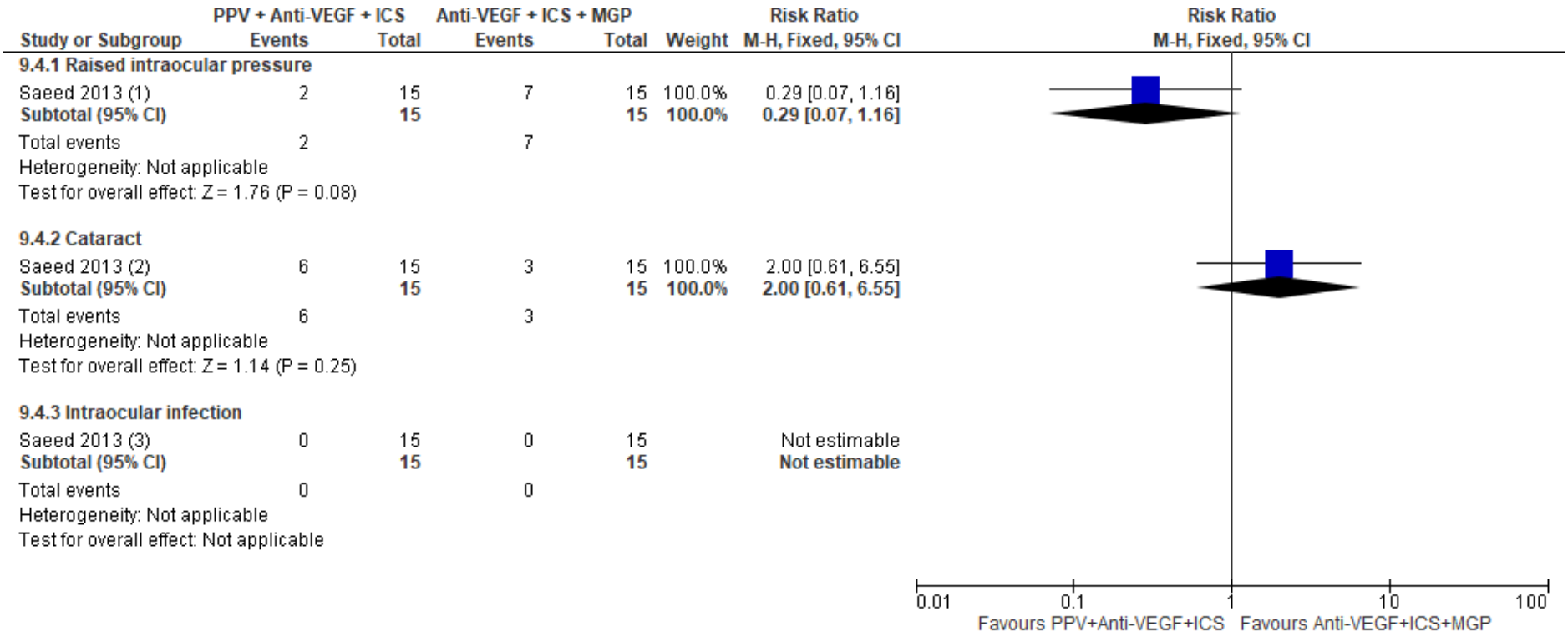
Figure 33. Retinal detachment (RR less than 1 favours PPV + Anti-VEGF + ICS)



Footnotes

(1) 12-mo FU. Posterior hyaloid removed during PPV. All participants received IVTA 0.1 mL and 1.25 mg IVB injections at end of procedure. Argon laser photocoagulation received 2...

Figure 34. Adverse events during follow up (RR less than 1 favours PPV + Anti-VEGF + ICS)



Footnotes

(1) 12-mo FU. Posterior hyaloid removed during PPV. All participants received IVTA 0.1 mL and 1.25 mg IVB injections at end of procedure. Argon laser photocoagulation received 2...

(2) See footnote above.

(3) See footnote above.

Appendix F – GRADE Tables

Table 15. Pars plana vitrectomy (PPV vs No treatment) (population with diabetic macular oedema)

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with no treatment	Risk with PPV					
Best corrected visual acuity at 12-mo FU (MD less than 0 favours PPV)									
1 (Yanyali 2006)	RCT	20	-	-	Mean Difference; -0.05 [-0.49, 0.39]	No serious	N/A	No serious	High
Improvement in visual acuity – overall (RR greater than 1 favours PPV)									
2	RCT	76	610 per 1000	262 more per 1000 (55 more to 537 more)	Risk Ratio: 1.43 [1.09, 1.88]	No serious	No serious	No serious	Moderate
Improvement in visual acuity – Subgroup: Stable or improved >=2 line (RR greater than 1 favours PPV)									
1 (Yanyali 2006)	RCT	20	700 per 1000	280 more per 1000 (56 fewer to 798 more)	Risk Ratio 1.40 [0.92, 2.14]	No serious	N/A	No serious	High
Improvement in visual acuity – Subgroup: Stable or improved >2 lines (RR greater than 1 favours PPV)									
1 (Yanyali 2006)	RCT	56	581 per 1000	261 more Per 1000 (12 more to 604 more)	Risk Ratio 1.45 [1.02, 2.04]	No serious	N/A	No serious	High
Adverse Events during FU (RR less than 1 favours PPV) **Intraocular pressure**									
2	RCT	20	Not estimable[2]	Not estimable[2]	Risk Ratio 3.00 [0.14, 65.90]	No serious	No serious	No serious	High

1 Weighted data from a single study.
Abbreviations: FU, follow up.

Table 16. Pars Plana Vitrectomy vs Intravitreal Corticosteroid (ICS)

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with PPV	Risk with PPV + ICS					
Best correct visual acuity (SMD less than 0 favours PPV)									
1 (Doi 2012)	RCT	106	-	-	Std. Mean Difference -0.56 [-1.51, 0.38]	No serious	N/A	No serious	High
Adverse Events during FU - Intravitreal triamcinolone acetonide (RR less than 1 favours PPV)									
Raised intraocular pressure									
1 (Doi 2012)	RCT	40	100 per 1000	50 fewer per 1000 (95 fewer to 408 more)	Risk Ratio 0.50 [0.05, 5.08]	No serious	N/A	No serious	High
Cataracts									
1 (Doi 2012)	RCT	40	Not estimable[2]	Not estimable[2]	Not estimable[2]	No serious	N/A	No serious	High
Intraocular infection									
1 (Doi 2012)	RCT	40	- Not estimable[2]	Not estimable[2]	Not estimable[2]	No serious	N/A[1]	No serious	High

1 Weighted data from a single study.
2 Zero events reported
Abbreviations: FU, follow up.

Table 17. Pars Plana Vitrectomy (PPV) vs Macular Grid Laser Photocoagulation (MGP) (population with diabetic macular oedema)

Treatment naïve

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with MGP	Risk with PPV					
Best corrected visual acuity (logMAR) - treatment-naïve participants (MD less than 0 favours PPV)									
2	RCT	48	-	-	Mean Difference -0.03 [-0.11, 0.06]	No serious	No serious	No serious	High
Improvement in visual acuity - treatment-naïve participants (Stable or improved >=2 lines) (RR greater than 1 favours PPV)									
2	RCT	48	1000 per 1000	0 more Per 1000 (100 fewer to 110 more)	Risk Ratio 1.00 [0.90, 1.11]	No serious	No serious	No serious	High
Adverse Events during FU - participants who received recent laser treatment									
Retinal detachment									
1(Thomas 2005)	RCT	24	Not estimable[1]	Not estimable[1]	Risk Ratio 3.00 [0.13, 67.06]	No serious	N/A	No serious	High
Raised intraocular pressure - participants who received recent laser treatment									
1(Thomas 2005)	RCT	24	Not estimable[1]	Not estimable[1]	Risk Ratio 5.00 [0.27, 94.34]	No serious	N/A	No serious	High
Cataracts - participants who received recent laser treatment									
1(Thomas 2005)	RCT	24	167 per 1000	167 more per 1000 (92 fewer to 1326 more)	Risk Ratio 2.00 [0.45, 8.94]	No serious	N/A	No serious	High

1 Zero events reported

Table 18. Pars Plana Vitrectomy (PPV) vs Macular Grid Laser Photocoagulation (MGP) (population with diabetic macular oedema) participants who received recent laser treatment

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with MGP	Risk with PPV					
Best corrected visual acuity – participants who received recent laser treatment (MD less than 0 favours PPV)									
1 (Thomas 2005)	RCT	33	-	-	Mean Difference 0.15 [-0.08, 0.38]	No serious	N/A	No serious	High
Improvement in visual acuity - participants who received recent laser treatment (Stable [<=1 line loss] or improvement)									
1(Patel 2006)	RCT	20	600 per 1000	102 fewer per 1000 (378 fewer to 510 more)	Risk Ratio 0.83 [0.37, 1.85]	No serious	N/A	No serious	High
Retinal detachment - participants who received recent laser treatment									
1(Patel 2006)	RCT	20	Not estimable[1]	Not estimable[1]	Not estimable[1]	No serious	N/A	No serious	High
Adverse Events during FU - participants who received recent laser treatment									
Raised intraocular pressure by 6-mo FU									
1(Patel 2006)	RCT	20	Not estimable[1]	Not estimable[1]	Not estimable[1]	No serious	N/A	No serious	High
Cataract surgery - participants who received recent laser treatment									
1(Patel 2006)	RCT	20	Not estimable[1]	Not estimable[1]	Not estimable[1]	No serious	N/A	No serious	High
Intraocular infection- participants who received recent laser treatment									
1(Patel 2006)	RCT	20	Not estimable[1]	Not estimable[1]	Not estimable[1]	No serious	N/A	No serious	High

1. Zero events in 1 or both study arms

Table 19. Pars Plana Vitrectomy (PPV) vs Pan retinal Photocoagulation (PRP)

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with PRP	Risk with PPV					
Best corrected visual acuity (MD less than 0 favours PPV)									
1 (Avitabile 2012)	RCT	180	-	-	Mean Difference 0.08 [-0.08, 0.24]	No serious	N/A	No serious	High
Improvement in visual acuity (Stable [<2 lines] or improved [>=2 lines]) (RR greater than 1 favours PPV)									
1 (Avitabile 2012)	RCT	180	822 per 1000	247 fewer per 1000 (353 fewer to 115 fewer)	Risk Ratio: 0.70 [0.57, 0.8]	No serious	N/A	No serious	High
Adverse Events during FU Retinal detachment (RR less than 1 favours PPV)									
Raised intraocular pressure by 6-mo FU									
1 (Avitabile2012)	RCT	180	Not estimable[2]	Not estimable[2]	Risk Ratio: 17.00 [1.00, 290.19]	No serious	N/A	No serious	High
Cataract surgery									
1 (Avitabile 2012)	RCT	180	56 per 1000	291 more per 1000 (86 more to 796 more)	Risk Ratio: 6.20 [2.53, 15.22]	No serious	N/A	No serious	High
Intraocular infection									
1 (Avitabile 2012)	RCT	180	Not estimable[1]	Not estimable[1]	Not estimable[1]	No serious	N/A	No serious	High

1 Zero events reported
2 Zero events in one study arm
Abbreviations: FU, follow up.

Table 20. Pars Plana Vitrectomy + Anti-VEGF vs Anti-VEGF

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with PRP	Risk with PPV + PRP					
Best corrected visual acuity Stable (<2 lines) or improved (>=2 lines) (MD less than 0 favours PPV + Anti-VEGF)									
1 (Jorge 2021)	RCT	70	-	-	Mean Difference -0.11 [-1.04, 0.83]	Very serious[1]	N/A	No serious	Low
Retinal detachment (RR less than 1 favours PPV + Anti-VEGF)									
1 (Jorge 2021)	RCT	73	26 per 1000	17 fewer Per 1000 (25 fewer to 197 more)	Risk ratio: 0.36 [0.02, 8.58]	Very serious[1]	N/A	No serious	Low
Adverse Events during FU intraocular pressure (RR less than 1 favours PPV + Anti-VEGF)									
1 (Jorge 2021)	RCT	73	26 per 1000	30 more (21 fewer to 570 more)	Risk ratio: 2.17 [0.21, 22.91]	Very serious[1]	N/A	No serious	Low
Adverse Events during FU cataract (RR less than 1 favours PPV + Anti-VEGF)									
1 (Jorge 2021)	RCT	73	Not estimable[2]	Not estimable[2]	Not estimable[2]	Very serious[1]	N/A	No serious	Low
Adverse Events during FU intraocular infection (RR less than 1 favours PPV + Anti-VEGF)									
1 (Jorge 2021)	RCT	73	Not estimable[2]	Not estimable[2]	Not estimable[2]	Very serious[1]	N/A	No serious	Low
Adverse Events during FU intraocular inflammation (RR less than 1 favours PPV + Anti-VEGF)									
1 (Jorge 2021)	RCT	73	Not estimable[2]	Not estimable[2]	Not estimable[2]	Very serious[1]	N/A	No serious	Low

1 Very serious risk of bias due to unclear randomisation, blinding and reporting bias
2 Zero events reported

Table 21: Plana Vitrectomy + Intravitreal corticosteroid (ICS) vs Pars Plana Vitrectomy (PPV)

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with PPV	Risk with PPV + IC					
Best corrected visual acuity – overall (MD less than 0 favours PPV + ICS)									
4	RCT	248	-	-	Mean difference: -0.13 [-0.25, -0.01]	No serious	Very serious[1]	No serious	Low
Best corrected visual acuity - Subgroup: Intravitreal dexamethasone, indication vitreomacular traction syndrome (MD less than 0 favours PPV + ICS)									
1 (Altun 2021)	RCT	52	-	-	Mean difference: -0.09 [-0.14, -0.04]	No serious	N/A	No serious	High
Best corrected visual acuity - Subgroup: Intravitreal dexamethasone, indication tractional retinal detachment (MD less than 0 favours PPV + ICS)									
1 (Limon 2022)	RCT	43	-	-	Mean difference: -0.31 [-0.55, -0.07]	No serious	N/A	No serious	High
Best corrected visual acuity - Subgroup: Intravitreal triamcinolone acetonide, indication vitreous haemorrhage (MD less than 0 favours PPV + ICS)									
2	RCT	153	-	-	Mean difference: -0.10 [-0.39, 0.19]	No serious	Very serious[1]	No serious	Low
Progression of PDR or DMO Presence of DMO at 6-mo FU - Intravitreal dexamethasone (RR less than 1 favours PPV + ICS)									
1 (Altun 2021)	RCT	63	125 per 1000	60 fewer Per 1000 (112 fewer to 203 more)	Risk Ratio: 0.52 [0.10, 2.62]	No serious	N/A	No serious	High

1 Weighted data from studies with high heterogeneity, I^2 > 66% so downgraded by increment of two

Table 22: Pars plana vitrectomy (PPV) + intravitreal corticosteroids vs Pars plana vitrectomy (PPV)

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with ANTI-VEGF	Risk with PPV + ICS					
Retinal detachment - Subgroup: Intravitreal triamcinolone acetonide (RR less than 1 favours PPV + ICS)									
2	RCT	106	132 per 1000	106 fewer per 1000 (127 fewer to 11 more)	Risk ratio 0.20 [0.04,1.08]	No serious	No serious	No serious	High
Retinal detachment - Subgroup: Intravitreal Dexamethasone (RR less than 1 favours PPV + ICS)									
Takamura 2018	RCT	84	-	-	Not estimable[4]	Serious[3]	N/A	No serious	Moderate
Adverse events during follow up (Intravitreal dexamethasone) (RR less than 1 favours PPV + ICS) retinal detachment (RR less than 1 favours PPV + PRP) Raised intraocular pressure (RR less than 1 favours PPV + ICS)									
2	RCT	106	57 per 1000	1 fewer per 1000 (43 fewer to 170 more)	Risk Ratio: 0.98 [0.24,3.99]	No serious	No serious	No serious	High
Cataracts (RR less than 1 favours PPV + ICS)									
2	RCT	106	286 per 1000	240 fewer per 100 (280 fewer to 60 more)	Risk Ratio: 0.16 [0.02,1.21]	No serious	No serious	No serious	High
Adverse events during follow up – Intraocular inflammation (RR less than 1 favours PPV + ICS									
4	RCT	262	171 per 1000	92 fewer per 1000 (154 fewer to 202 more)	Risk Ratio 0.46 [0.10, 2.18]	No serious	Serious[1]	No serious	Moderate
Intraocular inflammation Subgroup: Intravitreal Dexamethasone (RR less than 1 favours PPV + ICS)									
2	RCT	106	396 per 1000	238 fewer per 1000 (380 fewer to 1374 more)	Risk Ratio 0.40 [0.04, 4.47]	No serious	Very Serious[2]	No serious	Low
Intraocular inflammation Subgroup: Intravitreal triamcinolone acetonide (RR less than 1 favours PPV + ICS)									
2	RCT	156	13 per 1000	9 fewer per 1000 (13 fewer to 79 more)	Risk Ratio 0.30 [0.01, 7.11]	No serious	No serious	No serious	High

1 I2> 66% so downgraded by increment of two
2 I2> 33% so downgraded by 1 increment

3 Single study at moderate risk of bias
4 Zero events

Table 23:Pars Plana Vitrectomy + Pan-retinal photocoagulation (PRP) vs Anti-VEGF

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with ANTI-VEGF	Risk with PPV + PRP					
Best corrected visual acuity Intravitreal aflibercept - 2-year FU (MD greater than 0 favours PPV + PRP)									
1 (Antonszyk 2020)	RCT	177	-	-	Mean difference: 2.20 [-2.30, 6.70]	No serious	N/A	No serious	High
Progression of PDR or DMO Subgroup: Intravitreal aflibercept - 2-years FU (RR less than 1 favours PPV + PRP)									
1(Antonszyk 2020)	RCT	205	150 per 1000	12 more per 1000 (64 fewer to 156 more)	Risk ratio 1.08 [0.57, 2.04]	No serious	N/A	No serious	High
Retinal detachment - Intravitreal aflibercept (RR less than 1 favours PPV + PRP)									
1 (Antonszyk 2020)	RCT	205	230 per 1000	87 fewer per 1000 (152 fewer to 28 more)	Risk Ratio :0.62 [0.34, 1.12]	No serious	N/A	No serious	High
Traction retinal detachment (RR less than 1 favours PPV + PRP)									
1 (Antonszyk 2020)	RCT	205	220 per 1000	86 fewer per 1000 (147 fewer to 26 more)	Risk Ratio 0.61 [0.33, 1.12]	No serious	N/A	No serious	High
Rhegmatogenous retinal detachment (RR less than 1 favours PPV + PRP)									
1 (Antonszyk 2020)	RCT	205	40 per 1000	8 more per 1000 (27 fewer to 132 more)	Risk Ratio 1.19 [0.33, 4.31]	No serious	N/A	No serious	High
Adverse Events during FU - Intravitreal aflibercept (RR less than 1 favours PPV + PRP) **Raised intraocular pressure**									

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with ANTI-VEGF	Risk with PPV + PRP					
1 (Antonszyk 2020)	RCT	205	230 per 1000	9 more Per 1000 (85 fewer to 161 more)	Risk Ratio 1.04 [0.63, 1.70]	No serious	N/A	No serious	High
Cataracts (RR less than 1 favours PPV + PRP)									
1 (Antonszyk 2020)	RCT	156	493 per 1000	49 fewer Per 1000 (177 fewer to 128 more)	Risk Ratio 0.90 [0.64, 1.26]	No serious	N/A	No serious	High
Intraocular infection (RR less than 1 favours PPV + PRP)									
1 (Antonszyk 2020)	RCT	205	10 per 1000	9 more Per 1000 (8 fewer to 197 more)	Risk Ratio 1.90 [0.18, 20.68]	No serious	N/A	No serious	High
Intraocular inflammation (RR less than 1 favours PPV + PRP)									
1 (Antonszyk 2020)	RCT	205	60 per 1000	22 fewer per 1000 (49 fewer to 71 more)	Risk Ratio 0.63 [0.18, 2.18	No serious	N/A	No serious	High

Abbreviations: FU, follow up.

Table 24. Pars Plana Vitrectomy (PPV) + Pan-retinal Photocoagulation (PRP) vs PRP

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with PRP	Risk with PPV + PRP					
Improvement in visual acuity Stable (<2 lines) or improved (>=2 lines) (RR greater than 1 favours PPV + PRP)									
1 (Freyler 1980)	RCT	56	286 per 1000	252 more Per 1000 (14 fewer to 772 more)	Risk ratio: 1.88 [0.95, 3.70]	Very serious[1]	N/A	No serious	Low
Retinal detachment (RR less than 1 favours PPV + PRP)									
1 (Freyler 1980)	RCT	56	393 per 1000	287 fewer per 1000 (358 fewer to 51 fewer)	Risk ratio: 0.27 [0.09, 0.87]	Very serious[1]	N/A	No serious	Low

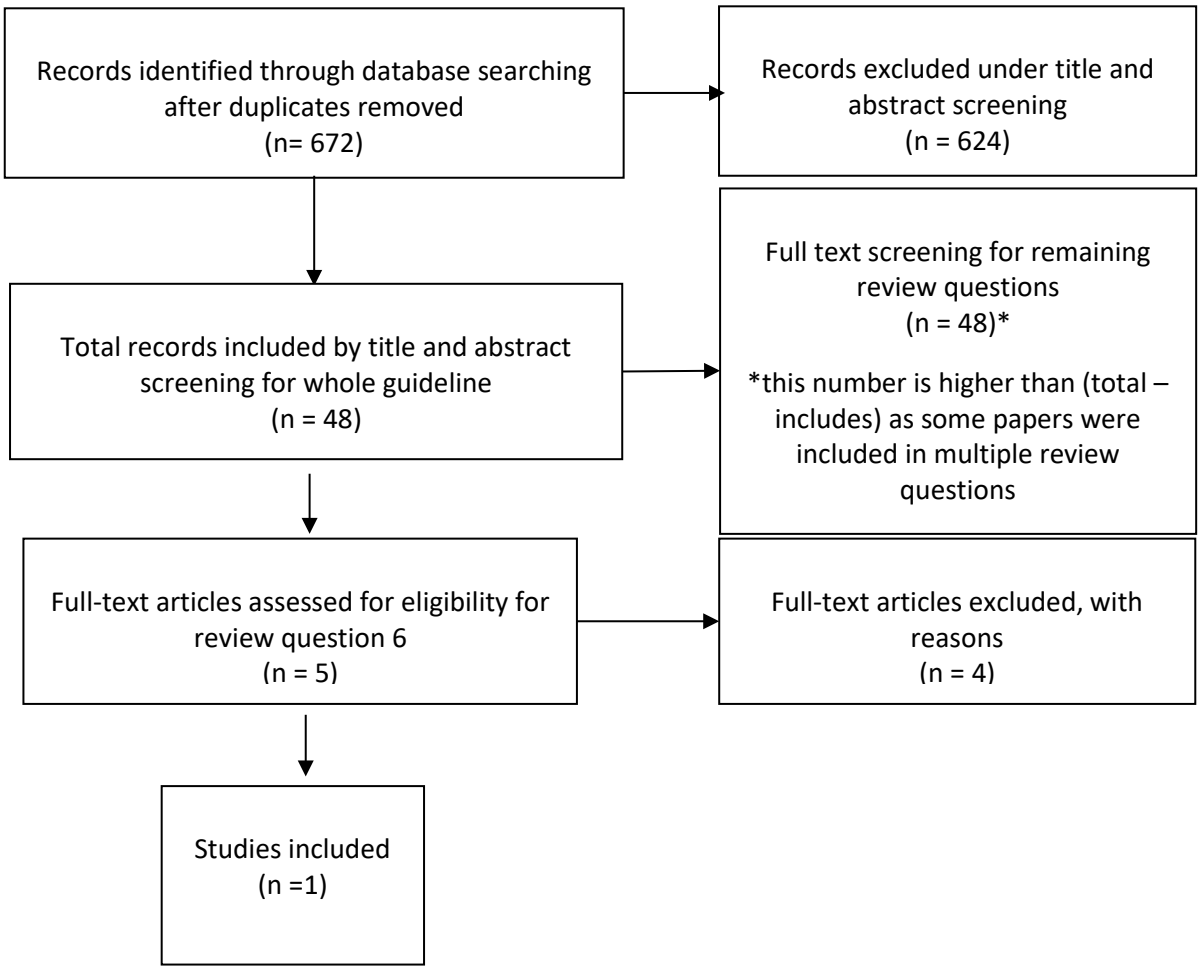
1 Very serious risk of bias due to unclear randomisation, blinding and reporting bias.
2 Weighted data from a single study

Table 25. Pars Plana Vitrectomy (PPV) + Anti-VEGF + Intravitreal corticosteroid (ICS) vs Anti-VEGF + ICS + Macular grid photocoagulation (MGP) (Population with diabetic macular oedema)

No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with MGP+ IC + Anti-VEGF	Risk with PPV + IC + Anti-VEGF					
Best corrected visual acuity (MD less than 0 favours PPV + Anti-VEGF + ICS)									
1 (Saeed 2013)	RCT	30	-	-	Mean Difference 0.03 [-0.02, 0.08]	No serious	N/A	No serious	High
Improvement in visual acuity (Stable [<2 lines] or Improved [>=2 lines]) (RR greater than 1 favours PPV + Anti-VEGF + ICS)									
1 (Saeed 2013)	RCT	30	1000 per 1000	0 more per 1000 (120 fewer to 130 more)	Risk Ratio 1.00 [0.88, 1.13]	No serious	N/A	No serious	High
Retinal detachment (RR less than 1 favours PPV + Anti-VEGF + ICS)									
1 (Saeed 2013)	RCT	30	-	-	Not estimable[1]	No serious	N/A	No serious	High
Adverse Events during FU Raised intraocular pressure (RR less than 1 favours PPV + Anti-VEGF + ICS)									
1 (Saeed 2013)	RCT	30	467 per 1000	332 fewer per 1000 (434 fewer to 75 more)	Risk Ratio 0.29 [0.07, 1.16]	No serious	N/A	No serious	High
Cataracts (RR less than 1 favours PPV + Anti-VEGF + ICS)									
1 (Saeed 2013)	RCT	30	200 per 1000	200 more per 1000 (78 fewer to 1110 more)	Risk Ratio 2.00 [0.61, 6.55]	No serious	N/A	No serious	High
Intraocular infection (RR less than 1 favours PPV + Anti-VEGF + ICS)									
1 (Saeed 2013)	RCT	30	-	-	Not estimable[1]	No serious	N/A	No serious	High

1 Zero events
Abbreviations: FU, follow up.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Table 26: Economic evidence

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Lin et al. (2018)	Cost-utility analysis over both 2 years and lifetime, although cost-utility outcomes were not clearly presented. Modelling methods were not clearly explained.	US Study Perspective Both facility and non-facility based.	Early vitrectomy (PPV) Panretinal photocoagulation (PRP) Intravitreal ranibizumab (IVR)	Patients with proliferative diabetic retinopathy without diabetic macular edema From the DRCR network protocol S trial, mean age 52 years, 44% female, 52% white 25% Hispanic 20% black/African-American	Data on natural history, baseline characteristics and effectiveness were taken from the Protocol S trial report. Cost data was taken from the Centers for Medicare and Medicaid schedules, and resource use from Protocol S. Outcomes data was taken from Protocol S, and utility data from the Diabetic Retinopathy Study for IVR and PRP. Values for PPV were based on investigator estimates and clinical experience. Results were presented for two time horizons; 2 years and lifetime. A 3% discount rate was used for all future costs and QALYs.	Total 2-year cost* PRP: $7,379 IVR: $19,665 PPV: $8,151 Total lifetime cost* PRP: $42,182 IVR: $244,192 PPV: $42,369 The ICERs presented in the were not calculated comparatively. Absolute cost per QALY: PRP: $61,695 IVR: $338,348 PPV: $63,942	A sensitivity analysis was performed in the PPV group while varying the number and frequency of IVR to give the expected cost-utility ranges in which treatments for the PPV group would be expected to be as efficacious as treatments in the IVR group for 2 years and extended over a lifetime. 78% of those in the PPV group would require 10.1 injections of ranibizumab for the cost per QALY to be equivalent with the IVR group in the 2-year period. Other sensitivity analyses were not detailed in the publication.	Supported by a National Institutes of Health Center Core Grant, Research to Prevent Blindness Unrestricted Grant, and the Department of Defense Grant. Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. and by a National Eye Institute Vision Research Core Grant No mention of health inequalities. Limitations: reliance on estimates of outcomes and resource use, difficult to apply this analysis to other countries based on differences in PDR treatment costs. The authors concluded that there is value in considering PPV earlier in the course of treatment for patients with PDR.

PRP, panretinal photocoagulation; IVR, intravitreal ranibizumab; PPV, pars plana vitrectomy.

*These results are from the scenario of the 0.3mg dose of ranibizumab. Scenarios were also run using a 0.5mg dose, and with an assumption that 20/50 BCVA would be maintained. These other scenarios were not considered to be as relevant (dose) or clinically plausible.

Table 27: Economic evaluation checklist

Study identification **Lin et al. (2018) Cost Evaluation of Early Vitrectomy versus Panretinal Photocoagulation and Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	Proliferative diabetic retinopathy
1.2 Are the interventions appropriate for the review question?	Yes	Pars plana vitrectomy vs. ranibizumab vs. panretinal photocoagulation
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US study
1.4 Is the perspective for costs appropriate for the review question?	Partly	US based costs, for both hospital/facility-based and non-facility based care
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% per year
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Unclear	It was not reported where the utility values were sourced from
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Unclear	The modelling was not clearly described in the study, although it stated a decision analysis model was developed and noted that the analysis incorporated costs and utilities over 2 years and was extended to lifetime based on a previously published analysis
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Extrapolated to lifetime
2.3 Are all important and relevant outcomes included?	Yes	Visual outcomes, severe visual loss, quality of life, adverse events

Study identification Lin et al. (2018) Cost Evaluation of Early Vitrectomy versus Panretinal Photocoagulation and Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy		
Category	**Rating**	**Comments**
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	No	The study stated that the values and information used for PPV were derived from the investigators' estimates based on the clinical courses reported for IVR and PRP, tempered by clinical experience.
2.6 Are all important and relevant costs included?	Yes	Treatment costs, follow up visits, professional and hospital fees,
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	CPT (Current Procedural Terminology) codes with reimbursement schedules based on Centers for Medicare and Medicaid Services
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	No	The incremental analysis did not compare treatments, and given the calculation of QALYs was not clearly presented, an incremental analysis could not be calculated from the data shown in the report.
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Sensitivity analysis varying the number and frequency of ranibizumab
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Appendix I – Health economic model

No economic modelling was done for this review question.

Appendix J – Excluded studies

Clinical studies

Study	Reason for exclusion
Abd Elhamid, Ahmed Hosni; Mohamed, Ahmed Abd El Alim; Khattab, Abeer Mohamed (2020) Intravitreal Aflibercept injection with Panretinal photocoagulation versus early Vitrectomy for diabetic vitreous hemorrhage: randomized clinical trial. BMC ophthalmology 20(1): 130	- Comparator in study does not match that specified in protocol
Ahmadieh, Hamid, Shoeibi, Nasser, Entezari, Morteza et al. (2009) Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: a randomized clinical trial. Ophthalmology 116(10): 1943-8	- Comparison covered by Smith & Steel 2015 Cochrane review
Ahn, Jeeyun, Woo, Se Joon, Chung, Hum et al. (2011) The effect of adjunctive intravitreal bevacizumab for preventing postvitrectomy hemorrhage in proliferative diabetic retinopathy. Ophthalmology 118(11): 2218-26	- Comparator in study does not match that specified in protocol
Aleman, Isaac, Castillo Velazquez, Javier, Rush, Sloan W et al. (2019) Ziv-aflibercept versus bevacizumab administration prior to diabetic vitrectomy: a randomised and controlled trial. The British journal of ophthalmology 103(12): 1740-1746	- Comparison covered by Smith & Steel 2015 Cochrane review
Algvere, P; Franzen, G; Wiklund, P (1987) Visual and social benefits of vitreous surgery in diabetics. A long-term follow-up evaluation. Acta ophthalmologica 65(3): 363-8	- Mixed population
Anonymous (1985) Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study report 2. The Diabetic Retinopathy Vitrectomy Study Research Group. Archives of ophthalmology (Chicago, Ill. : 1960) 103(11): 1644-52	- Study does not contain a relevant intervention
Anonymous (1988) Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision. Results of a randomized trial--Diabetic Retinopathy Vitrectomy Study Report 3. The Diabetic Retinopathy Vitrectomy Study Research Group. Ophthalmology 95(10): 1307-20	- Not a peer-reviewed publication
Arevalo, J Fernando, Lasave, Andres F, Kozak, Igor et al. (2019) Preoperative Bevacizumab for Tractional Retinal Detachment in Proliferative Diabetic Retinopathy: A Prospective Randomized Clinical Trial. American journal of ophthalmology 207: 279-287	- Comparison covered by Smith & Steel 2015 Cochrane review

Study	Reason for exclusion
Comyn, O, Wickham, L, Charteris, D G et al. (2017) Ranibizumab pretreatment in diabetic vitrectomy: a pilot randomised controlled trial (the RaDiVit study). Eye (London, England) 31(9): 1253-1258	- Comparison covered by Smith & Steel 2015 Cochrane review
da R Lucena, D, Ribeiro, J A S, Costa, R A et al. (2009) Intraoperative bleeding during vitrectomy for diabetic tractional retinal detachment with versus without preoperative intravitreal bevacizumab (IBeTra study). The British journal of ophthalmology 93(5): 688-91	- No relevant outcomes reported
de Bustros, S, Glaser, B M, Michels, R G et al. (1985) Effect of epsilon-aminocaproic acid on postvitrectomy hemorrhage. Archives of ophthalmology (Chicago, Ill. : 1960) 103(2): 219-21	- Study does not contain a relevant intervention
di Lauro, Raffaello, De Ruggiero, Pio, di Lauro, Raffaella et al. (2010) Intravitreal bevacizumab for surgical treatment of severe proliferative diabetic retinopathy. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 248(6): 785-91	- Comparison covered by Smith & Steel 2015 Cochrane review
Eberhart, Leopold H J, Morin, Astrid M, Hoerle, Steffen et al. (2004) Droperidol and dolasetron alone or in combination for prevention of postoperative nausea and vomiting after vitrectomy. Ophthalmology 111(8): 1569-75	- Mixed population
El-Batarny AM (2008) Intravitreal bevacizumab as an adjunctive therapy before diabetic vitrectomy. Clinical Opthalmology 2(4): 709-716	- Comparison covered by Smith & Steel 2015 Cochrane review
Elwan MM; Ghanem AA; Abousamra WA (2013) Outcome of a Single Intravitreal Bevacizumab Injection on the Visual Acuity and Course of Pars Plana Vitrectomy in Proliferative Diabetic Retinopathy. Current Eye Research	- Comparison covered by Smith & Steel 2015 Cochrane review
Faisal, S.M., Tahir, M.A., Cheema, A.M. et al. (2018) Pars plana vitrectomy in vitreous hemorrhage with or without intravitreal Bevacizumab: A comparative overview. Pakistan Journal of Medical Sciences 34(1): 221-225	- Comparison covered by Smith & Steel 2015 Cochrane review
Farahvash MS, Majidi AR, Roohipoor R et al. (2011) Preoperative injection of intravitreal bevacizumab in dense diabetic vitreous hemorrhage. Retina 31(7)	- Comparison covered by Smith & Steel 2015 Cochrane review

Study	Reason for exclusion
Farahvash, Mohammad-Sadegh, Majidi, Ali Reza, Roohipoor, Ramak et al. (2011) Preoperative injection of intravitreal bevacizumab in dense diabetic vitreous hemorrhage. Retina (Philadelphia, Pa.) 31(7): 1254-60	- Duplicate reference - Data not reported in an extractable format
Figueroa, Marta S; Contreras, Ines; Noval, Susana (2008) Surgical and anatomical outcomes of pars plana vitrectomy for diffuse nontractional diabetic macular edema. Retina (Philadelphia, Pa.) 28(3): 420-6	- Comparator in study does not match that specified in protocol
Fung, W E (1984) The national, prospective, randomized vitrectomy study for chronic aphakic cystoid macular edema. Progress report and comparison between the control and nonrandomized groups. Survey of ophthalmology 28suppl: 569-75	- Does not contain a population of people with PDR
Glassman, Adam R, Beaulieu, Wesley T, Maguire, Maureen G et al. (2021) Visual Acuity, Vitreous Hemorrhage, and Other Ocular Outcomes After Vitrectomy vs Aflibercept for Vitreous Hemorrhage Due to Diabetic Retinopathy: A Secondary Analysis of a Randomized Clinical Trial. JAMA ophthalmology 139(7): 725-733	- Secondary publication of an included study that does not provide any additional relevant information *Post-hoc exploratory analysis of Antonszyk 2020*
Hernandez-Da Mota, Sergio E and Nunez-Solorio, Silvia M (2010) Experience with intravitreal bevacizumab as a preoperative adjunct in 23-G vitrectomy for advanced proliferative diabetic retinopathy. European journal of ophthalmology 20(6): 1047-52	- Comparison covered by Smith & Steel 2015 Cochrane review
Hesse, L; Chofflet, J; Kroll, P (1995) Tissue plasminogen activator as a biochemical adjuvant in vitrectomy for proliferative diabetic vitreoretinopathy. German journal of ophthalmology 4(6): 323-7	- Study does not contain a relevant intervention
Jiang, Tingting, Gu, Junxiang, Zhang, Peijun et al. (2020) The effect of adjunctive intravitreal conbercept at the end of diabetic vitrectomy for the prevention of post-vitrectomy hemorrhage in patients with severe proliferative diabetic retinopathy: a prospective, randomized pilot study. BMC ophthalmology 20(1): 43	- Drug not licensed in UK
Jorge, D.M., Tavares Neto, J.E.S., Poli-Neto, O.B. et al. (2021) Intravitreal bevacizumab (IVB) versus IVB in combination with pars plana vitrectomy for vitreous hemorrhage secondary to proliferative diabetic retinopathy: a randomized clinical trial. International Journal of Retina and Vitreous 7(1): 35	- Comparison covered by Smith & Steel 2015 Cochrane review

Study	Reason for exclusion
Kartasasmita, A.S., Arsih, W., Switania, A. et al. (2017) The effectiveness of continuous intravitreal adrenaline as mydriatic adjuvant on pars plana vitrectomy in diabetic patient, a randomized clinical trial. Revista Mexicana de Oftalmologia 91(5): 229-234	- No relevant outcomes reported
Koutsandrea, C N, Apostolopoulos, M N, Chatzoulis, D Z et al. (2001) Hemostatic effects of SF6 after diabetic vitrectomy for vitreous hemorrhage. Acta ophthalmologica Scandinavica 79(1): 34-8	- Study does not contain a relevant intervention
Kucukevcilioglu, Murat, Koylu, Mehmet Talay, Ayyildiz, Onder et al. (2015) Pars plana vitrectomy versus three intravitreal injections of bevacizumab for nontractional diabetic macular edema: A prospective, randomized comparative study. Indian journal of ophthalmology 63(10): 804-5	- Not a peer-reviewed publication
Kumagai, K., Hangai, M., Ogino, N. et al. (2015) Effect of internal limiting membrane peeling on long-term visual outcomes for diabetic macular edema. Retina 35(7): 1422-1428	- Study does not contain a relevant intervention
Laatikainen, L; Summanen, P; Immonen, I (1987) Effect of tranexamic acid on postvitrectomy haemorrhage in diabetic patients. International ophthalmology 10(3): 153-5	- Study does not contain a relevant intervention
Le Mer, Y, Korobelnik, J F, Morel, C et al. (1999) TPA-assisted vitrectomy for proliferative diabetic retinopathy: results of a double-masked, multicenter trial. Retina (Philadelphia, Pa.) 19(5): 378-82	- Study does not contain a relevant intervention
Lewis, L (1990) Diabetic retinopathy study results reveal combination therapy beneficial. Journal of clinical laser medicine & surgery 8(1): 3-6	- Not a peer-reviewed publication
Li, Bing, Li, Meng-Da, Ye, Jun-Jie et al. (2020) Vascular endothelial growth factor concentration in vitreous humor of patients with severe proliferative diabetic retinopathy after intravitreal injection of conbercept as an adjunctive therapy for vitrectomy. Chinese medical journal: 664-669	- Drug not licensed in UK
Li, Shengguo, Yang, Yan, Zou, Jingling et al. (2022) The efficacy and safety of intravitreal injection of Ranibizumab as pre-treatment for vitrectomy in proliferative diabetic retinopathy with vitreous hemorrhage. BMC ophthalmology 22(1): 63	- Comparison covered by Smith & Steel 2015 Cochrane review

Study	Reason for exclusion
Manabe, Ayumu, Shimada, Hiroyuki, Hattori, Takayuki et al. (2015) RANDOMIZED CONTROLLED STUDY OF INTRAVITREAL BEVACIZUMAB 0.16 MG INJECTED ONE DAY BEFORE SURGERY FOR PROLIFERATIVE DIABETIC RETINOPATHY. Retina (Philadelphia, Pa.) 35(9): 1800-7	- Comparison covered by Smith & Steel 2015 Cochrane review
Modarres, Mehdi, Nazari, Hossein, Falavarjani, Khalil Ghasemi et al. (2009) Intravitreal injection of bevacizumab before vitrectomy for proliferative diabetic retinopathy. European journal of ophthalmology 19(5): 848-52	- Comparison covered by Smith & Steel 2015 Cochrane review
NCT00516464 (2007) Evaluation of Ranibizumab in Proliferative Diabetic Retinopathy (PDR) Requiring Vitrectomy. https://clinicaltrials.gov/show/NCT00516464	- Clinical trial record *No results posted and not updated since 2007. Included in list of ongoing studies in Smith & Steel 2015 Cochrane SR.*
NCT00596297 (2008) Preoperative Bevacizumab for Vitreous Hemorrhage. https://clinicaltrials.gov/show/NCT00596297	- Clinical trial record *No result reported nor associated publications*
NCT00690768 (2008) Pars Plana Vitrectomy (PPV) Versus Preoperative Intravitreal Bevacizumab Plus PPV to Treat Diabetic Tractional Retinal Detachment (IBETRA). https://clinicaltrials.gov/show/NCT00690768	- Clinical trial record *Record for trial reported in da R Lucena 2009.*
NCT00745498 (2008) Pre- and Intra-operative Intravitreal Bevacizumab Injection in Diabetic Vitrectomy. https://clinicaltrials.gov/show/NCT00745498	- Clinical trial record *Results published in https://journals.lww.com/retinajournal/Citation/2006/07000/USE_OF_INTRAVITREAL_BEVACIZUMAB_AS_A_PREOPERATIVE.20.aspx. Not included in search for Smith 2015 Cochrane SR.*
NCT00931125 (2009) Safety and Efficacy of Intravitreal Ranibizumab as a Preoperative Adjunct Treatment Before Vitrectomy Surgery in Proliferative Diabetic Retinopathy (PDR) Compared to Vitrectomy Alone. https://clinicaltrials.gov/show/NCT00931125	- Clinical trial record *Trial active but status unknown, last updated 2013. Included as ongoing study in Smith & Steel 2015 Cochrane SR.*
NCT01201161 (2010) Ranibizumab for Diabetic Traction Retinal Detachment. https://clinicaltrials.gov/show/NCT01201161	- Clinical trial record *No associated publications nor results*
NCT01854593 (2013) Prospective Randomized Controlled Study of Intravitreal Injection of Bevacizumab	- Clinical trial record

Study	Reason for exclusion
for Proliferative Diabetic Retinopathy. https://clinicaltrials.gov/show/NCT01854593	*Record for Manabe 2015 (included in Smith & Steel 2015 Cochrane SR)*
NCT02447185 (2015) 25-G Vitrectomy With Ranibizumab or Triamcinolone Acetonide on PDR in China-Randomized Clinical Trial. https://clinicaltrials.gov/show/NCT02447185	- Clinical trial record *Comparator does not match that specified in protocol*
NCT02858076 (2016) Anti-VEGF vs. Prompt Vitrectomy for VH From PDR. https://clinicaltrials.gov/show/NCT02858076	- Clinical trial record *Record for Antonszyk 2020 and Glassman 2021*
NCT03426540 (2018) Intravitreal Conbercept After Vitrectomy. https://clinicaltrials.gov/show/NCT03426540	- Drug not licensed in UK
NCT04089605 (2019) Ranibizumab vs Dexamethasone Implant in Vitrectomized Eyes With Diabetic Macular Edema. https://clinicaltrials.gov/show/NCT04089605	- Clinical trial record *Comparator does not match that specified in protocol*
NCT05248334 (2022) A Prospective Study of Ranibizumab in the Treatment of Postoperative Recurrent Vitreous Haemorrhage of Diabetic Retinopathy. https://clinicaltrials.gov/show/NCT05248334	- Clinical trial record *Trial still recruiting, comparison is anti-VEGF vs PPV*
NCT05414149 (2022) Efficacy and Safety Comparison of IVR and IVC Before Vitrectomy in Proliferative Diabetic Retinopathy. https://clinicaltrials.gov/show/NCT05414149	- Drug not licensed in UK
Pakzad-Vaezi, Kaivon, Albiani, David A, Kirker, Andrew W et al. (2014) A randomized study comparing the efficacy of bevacizumab and ranibizumab as pre-treatment for pars plana vitrectomy in proliferative diabetic retinopathy. Ophthalmic surgery, lasers & imaging retina 45(6): 521-4	- No relevant outcomes reported
Ren, X., Bu, S., Zhang, X. et al. (2019) Safety and efficacy of intravitreal conbercept injection after vitrectomy for the treatment of proliferative diabetic retinopathy. Eye (Basingstoke) 33(7): 1177-1183	- Drug not licensed in UK
Rezar, S, Sacu, S, Ritter, M et al. (2014) Influence of postoperative oral steroid treatment on retinal sensitivity in patients after macular surgery. A randomized, controlled, clinical trial. Der Ophthalmologe 111(1): 31-36	- Study not reported in English

Study	Reason for exclusion
Rizzo, Stanislao, Genovesi-Ebert, Federica, Di Bartolo, Emanuele et al. (2008) Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR). Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 246(6): 837-42	- Comparison covered by Smith & Steel 2015 Cochrane review
Rush, Ryan B, Del Valle Penella, Agustin, Reinauer, Robert M et al. (2021) INTERNAL LIMITING MEMBRANE PEELING DURING VITRECTOMY FOR DIABETIC VITREOUS HEMORRHAGE: A Randomized Clinical Trial. Retina (Philadelphia, Pa.) 41(5): 1118-1126	- Comparator in study does not match that specified in protocol
Rush, Ryan B, Rush, Sloan W, Reinauer, Robert M et al. (2022) VITRECTOMY FOR DIABETIC COMPLICATIONS: A Pooled Analysis of Randomized Controlled Trials Using Modern Techniques and Equipment. Retina (Philadelphia, Pa.) 42(7): 1292-1301	- Data not reported in an extractable format *Pooled analysis of 4 trials, no relevant data reported.*
Schulze, S; Sekundo, W; Kroll, P (2005) Autologous serum versus hyaluronic acid eye drops for the treatment of corneal erosions after vitrectomy in diabetic patients. A prospective randomized study. Der Ophthalmologe 102(9): 863-868	- Study not reported in English
Sohn, Elliott H, He, Shikun, Kim, Leo A et al. (2012) Angiofibrotic response to vascular endothelial growth factor inhibition in diabetic retinal detachment: report no. 1. Archives of ophthalmology (Chicago, Ill. : 1960) 130(9): 1127-34	- Comparison covered by Smith & Steel 2015 Cochrane review
Su, Long, Ren, Xinjun, Wei, Huiyu et al. (2016) INTRAVITREAL CONBERCEPT (KH902) FOR SURGICAL TREATMENT OF SEVERE PROLIFERATIVE DIABETIC RETINOPATHY. Retina (Philadelphia, Pa.) 36(5): 938-43	- Drug not licensed in UK
Thompson, J.T., Glaser, B.M., Michels, R.G. et al. (1986) The use of intravitreal thrombin to control hemorrhage during vitrectomy. Ophthalmology 93(3): 279-282	- Study does not contain a relevant intervention
Wang, Dong-Yue, Zhao, Xin-Yu, Zhang, Wen-Fei et al. (2020) Perioperative anti-vascular endothelial growth factor agents treatment in patients undergoing vitrectomy for complicated proliferative diabetic retinopathy: a network meta-analysis. Scientific reports 10(1): 18880	- Data not reported in an extractable format *Cui 2018, Gao 2020, Yang 2015 listed and appear relevant but no references for included studies provided in main article nor supplementary information*

Study	Reason for exclusion
Wildan, A.; Winarto; Kristina, T.N. (2019) Aflibercept and bevacizumab injection effects on visual acuity of post vitrectomy diabetic retinopathy. Pakistan Journal of Medical and Health Sciences 13(4): 1214-1218	- Comparison covered by Smith & Steel 2015 Cochrane review
Yamakiri K, Sakamoto T, Noda Y et al. (2007) Reduced Incidence of Intraoperative Complications in a Multicenter Controlled Clinical Trial of Triamcinolone in Vitrectomy. Opthalmology 114(2): 289.e1-296.e1	- Mixed population
Yamakiri, Keita, Sakamoto, Taiji, Noda, Yoshihiro et al. (2008) One-year results of a multicenter controlled clinical trial of triamcinolone in pars plana vitrectomy. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 246(7): 959-66	- Mixed population
Zaman, Y.; Aziz-ur-Rehman; Memon, A.F. (2013) Intravitreal Avastin as an adjunct in patients with proliferative diabetic retinopathy undergoing pars plana vitrectomy. Pakistan Journal of Medical Sciences 29(2)	- Comparison covered by Smith & Steel 2015 Cochrane review
Zhao, H., Li, X., Zhao, X. et al. (2021) Comparative Analysis of the Effects of the Anti-VEGF Drug and Glucocorticoid by Injection before the End of Vitrectomy for Proliferative Diabetic Retinopathy. Evidence-based Complementary and Alternative Medicine 2021: 1285372	- Drug not licensed in UK
Zhou, J., Liu, Z., Chen, M. et al. (2018) Concentrations of VEGF and PlGF Decrease in Eyes After Intravitreal Conbercept Injection. Diabetes Therapy 9(6): 2393-2398	- Drug not licensed in UK

Economic studies

Study	Reason for exclusion
Crijns, H; Casparie, A F; Hendrikse, F (1999) Continuous computer simulation analysis of the cost-effectiveness of screening and treating diabetic retinopathy. International journal of technology assessment in health care 15(1): 198-206	- Exclude - not relevant intervention
Javitt, J C; Canner, J K; Sommer, A (1989) Cost effectiveness of current approaches to the control of retinopathy in type I diabetics. Ophthalmology 96(2): 255-64	- Exclude - not relevant intervention - Exclude - not relevant population

Study	Reason for exclusion
Sharma, S, Hollands, H, Brown, G C et al. (2001) The cost-effectiveness of early vitrectomy for the treatment of vitreous hemorrhage in diabetic retinopathy. Current opinion in ophthalmology 12(3): 230-4	- Exclude - perspective is too different from UK perspective - Exclude - not relevant comparison
Smiddy, William E (2011) Economic considerations of macular edema therapies. Ophthalmology 118(9): 1827-33	- Exclude - serious limitations with model structure, outcome calculation and reporting, and sensitivity analysis