National Institute for Health and Care Excellence

Final

Diabetic retinopathy

[I] Evidence review for effectiveness of treatments before, during or after cataract surgery for managing non-proliferative diabetic retinopathy, proliferative diabetic retinopathy or diabetic macular oedema

NICE guideline NG242

Evidence reviews underpinning recommendations 1.2.1 and 1.2.2, and research recommendations 10 and 11 in the NICE guideline

August 2024

Final

These evidence reviews were developed by NICE

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1 Evidence review for treatments before, during or after cataract surgery

1.1 Review question

In people who are about to undergo or who have undergone cataract surgery, what is the effectiveness of treatments (before, during or after surgery) for managing:

- **non-proliferative diabetic retinopathy**
- **proliferative diabetic retinopathy**
- **diabetic macular oedema?**

1.1.1 Introduction

It is currently unclear which treatments are most effective at managing non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, or diabetic macular oedema when people have cataract surgery. The aim of this review is to assess evidence in this area to determine which is the most effective treatment and whether the effectiveness of treatment differs depending on whether it is given before, during or after cataract surgery.

This evidence review informs 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 Effectiveness of treatments before, during or after cataract surgery for managing non-proliferative diabetic retinopathy, proliferative diabetic retinopathy or diabetic macular oedema.

Population	People diagnosed with: • non-proliferative diabetic retinopathy • proliferative diabetic retinopathy • diabetic macular oedema who are about to undergo or who have undergone cataract surgery
Intervention	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids (before during or after cataract surgery) including subconjunctival steroids (dexamethasone and triamcinolone)
Comparator	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids • No treatment/placebo

	• Studies comparing treatments before during or after cataract surgery will be included.

Outcomes	**Primary:**
	• 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 to or of proliferative diabetic retinopathy or macular oedema
	
	Secondary:
	• Success of cataract surgery
	• Rates of additional intervention
	• Adverse events (Raised intraocular pressure, Intraocular infection, Intraocular Inflammation)
	• Quality of life
	• Peripheral vision, assessed using visual field measurements
	
	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

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.

An initial database search found 2787 references, all of which were screened at title and abstract. 62 records were ordered for full text screening, of which 52 were excluded and 10 papers (from 9 RCTs) were included in the review. One of the RCTs reported results for 2 of the population groups as part of a subgroup analysis (people with non-proliferative diabetic retinopathy and people with non-proliferative diabetic retinopathy with diabetic macular oedema). The protocol specified that observational studies would be included for comparisons where RCT evidence was not available. However, for the comparisons where there was no RCT evidence, no observational studies met the inclusion criteria. Therefore, only RCT evidence was included in the review. 70 additional studies were identified in the re-run searches, but none met the inclusion criteria for this review.

Of the 3 populations identified in the protocol, evidence was available for people with non-proliferative diabetic retinopathy, and people with non-proliferative diabetic retinopathy with diabetic macula oedema. None of the evidence for people with proliferative diabetic

retinopathy met the inclusion criteria for this review. Evidence was available for the following comparisons:

People with non-proliferative diabetic retinopathy

- Anti-VEGFs vs control (During surgery – 3 RCTs)
- Steroids vs control (During surgery – 2 RCTs)

People with non-proliferative diabetic retinopathy with diabetic macula oedema

- Anti-VEGFs vs control (During surgery – 1 RCT, After surgery – 1 RCT)
- Steroids vs control (During surgery – 1 RCT)
- Anti-VEGFs vs steroids (During surgery – 2 papers from 1 RCT)
- Steroids before vs after surgery (1 RCT)

1.1.4.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Table of included studies: People with non-proliferative diabetic retinopathy

Study	Longest Follow-up time	Population	Intervention	Comparator	Outcomes
Anti-VEGFs vs control: During surgery					
Song 2020 (PROMISE) USA n=30 eyes	90 days	Type 1 or type 2 diabetes and non-proliferative diabetic retinopathy or inactive proliferative diabetic retinopathy without clinically significant macular oedema	Cataract surgery with 2 mg intravitreal aflibercept injection	Cataract surgery with sham injection	• Best corrected visual acuity • Progression to macular oedema • Adverse events (number of ocular treatment-related adverse events)
Chae 2014 Korea n=80 eyes	6 months	People aged over 18 years with type 1 or type 2 diabetes and non-proliferative diabetic retinopathy or stable diabetic retinopathy	Cataract surgery with 0.5 mg ranibizumab injection	Cataract surgery with sham injection	• Best corrected visual acuity • Progression to macular oedema
Fard 2011 Iran n=61 eyes	6 months	People with diabetes and moderate or severe non-proliferative diabetic retinopathy	Cataract surgery with 1.25 mg bevacizumab injection	Cataract surgery alone (control)	• Best corrected visual acuity • Progression of diabetic retinopathy • Adverse events (number of ocular

Study	Longest Follow-up time	Population	Intervention	Comparator	Outcomes
					treatment-related adverse events)
Steroids vs control: During surgery					
Gupta 2021 India n=151 eyes (subgroup from main analysis)	12 weeks	People aged greater than 30 years with type 2 diabetes and mild/moderate/severe non-proliferative diabetic retinopathy, with or without diabetic macular oedema	Cataract surgery with 0.7 mg dexamethasone drug delivery system via injection	Cataract surgery alone (control)	• Rates of additional intervention (number needing rescue treatments)
Ahmadabadi 2010 Iran n=41 eyes	6 months	People with type 2 diabetes and moderate non-proliferative diabetic retinopathy	Cataract surgery with 2 mg triamcinolone injection	Cataract surgery alone (control)	• Best corrected visual acuity • Progression of severe non-proliferative diabetic retinopathy • Progression of macular oedema • Adverse events (number with raised intra-ocular pressure)

Table 3: Table of included studies: People with non-proliferative diabetic retinopathy with diabetic macular oedema

Study	Longest Follow-up time	Population	Intervention	Comparator	Outcomes
Anti-VEGFs vs control: During surgery					
Takamura 2009 Japan n=42 eyes	3 months	People with type 2 diabetes Non proliferative diabetic retinopathy with diabetic macular oedema	Cataract surgery with 1.25 mg bevacizumab injection	Cataract surgery alone (control)	Adverse events: • Number with increased intraocular pressure • Number with intraocular inflammation

Study	Longest Follow-up time	Population	Intervention	Comparator	Outcomes
Lagzagorta-Aresti 2009 Spain n=26 eyes	6 months	People with type 2 diabetes with moderate non-proliferative diabetic retinopathy associated with diffuse macular oedema affecting the foveal center	Cataract surgery with bevacizumab injection (dose not reported)	Cataract surgery with saline solution injection	• Best corrected visual acuity
Steroids vs control: Pre-surgery vs post-surgery					
Barone 2022 Italy n=40 eyes	20 weeks	People with non-proliferative diabetic retinopathy and clinically significant naïve macular oedema	Cataract surgery with 0.7 mg dexamethasone implant administered preoperatively	Cataract surgery with 0.7 mg dexamethasone implant administered postoperatively	• Best corrected visual acuity
Steroids vs control: During surgery					
Gupta 2021 India n=151 eyes (subgroup from main analysis)	12 weeks	People aged greater than 30 years with type 2 diabetes and mild/moderate/severe non-proliferative diabetic retinopathy, with or without diabetic macular oedema	Cataract surgery with 0.7 mg dexamethasone drug delivery system via injection	Cataract surgery alone (control)	• Rates of additional intervention (number needing rescue treatments)
Anti-VEGFs vs steroids: During surgery					
Kandasamy 2019 (DIMECat) Australia n=65 eyes from 62 people	6 months	People aged over 18 years with diabetes and clinically significant macular oedema	Cataract surgery with 1.25 mg bevacizumab injection	Cataract surgery with 4 mg triamcinolone injection	• Best corrected visual acuity • Rates of additional intervention (number of additional treatments) • Adverse events (raised intraocular pressure)
Sasongko 2020 (DIMECat)	As for Kandasamy 2019				• Progression

See Appendix D for full evidence tables

1.1.6 Summary of the effectiveness evidence

Effectiveness evidence was interpreted as, a mean difference less than 0 favours the intervention (anti-VEGF treatment) and a mean difference greater than 0 favours the control arm (placebo). If the confidence interval crosses the line of no effect (0) this would be interpreted as could not distinguish an effect between both treatments.

Table 4: Anti-VEGF agents vs control in people with non-proliferative diabetic retinopathy

Outcome	Number of studies	Sample size	Effect estimate	Quality	Interpretation of effect
Best corrected visual acuity measured with logMAR (change from baseline)	2	137	MD -0.07 (-0.14, -0.00)	low	Effect favouring anti-VEGFs
Best corrected visual acuity measured with ETDRS (change from baseline)	1	30	MD 1.36 (-4.20, 6.92)	high	Could not differentiate
Progression to a higher grade of diabetic retinopathy or to diabetic macular oedema	3	166	RR 0.60 (0.29, 1.23)	moderate	Could not differentiate
Number of ocular treatments related adverse events	2	91	RR 0.91 (0.57, 1.45)	high	Could not differentiate

Table 5: Intravitreal steroids vs control in people with non-proliferative diabetic retinopathy

Outcome	Number of studies	Sample size	Effect estimate	Quality	Interpretation of effect
Best corrected visual acuity measured with logMAR (change from baseline)	1	41	MD -0.02 (-0.08, 0.04)	moderate	Could not differentiate
Progression to macular oedema or Severe non-proliferative diabetic retinopathy					
Subgroup: macular oedema	1	41	RR 0.12 (0.01, 2.03)	moderate	Could not differentiate
Subgroup: severe non-proliferative diabetic retinopathy	1	41	RR 0.26 (0.03, 2.15)	moderate	Could not differentiate
Rates of additional intervention (number who needed rescue treatments)	1	21	RR 1.00 (0.24, 4.20)	high	Could not differentiate
Adverse events (raised intraocular pressure: increase >21 mm hg)	1	42	RR 7.00 (0.38, 127.69)	moderate	Could not differentiate

Table 6: Anti-VEGF agents vs control in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Outcome	Number of studies	Sample size	Effect estimate	Quality	Interpretation of effect
Best corrected visual acuity measured with Snellen (change from baseline)	1	26	MD 0.23 (0.08, 0.38)	moderate	Effect favouring anti-VEGFs

Table 7: Intravitreal steroids pre-surgery vs post-surgery in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Outcome	Number of studies	Sample size	Effect estimate	Quality	Interpretation of effect
Best corrected visual acuity measured with logMAR (change from baseline)	1	40	MD -0.04 (-0.13, 0.05)	low	Could not differentiate

Table 8: Intravitreal steroids vs control in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Outcome	Number of studies	Sample size	Effect estimate	Quality	Interpretation of effect
Rates of additional intervention (number who needed rescue treatments)	1	151	RR 0.82 (0.57, 1.17)	high	Could not differentiate

Table 9: Anti-VEGF agents vs intravitreal steroids in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Outcome	Number of studies	Sample size	Effect estimate	Quality	Interpretation of effect
Best corrected visual acuity measured with letters (change from baseline)	1	61	MD -5.50 (-13.07, 2.07)	high	Could not differentiate
Progression to a higher grade of diabetic retinopathy					
Subgroup: 1-step progression	1	61	RR 1.18 (0.26, 5.38)	high	Could not differentiate
Subgroup: 2-step progression	1	61	RR 0.39 (0.02, 9.23)	high	Could not differentiate
Rates of additional intervention (number who needed retreatments)	1	65	RR 2.36 (1.19, 4.67)	high	Effect favouring intravitreal steroids
Adverse events (number of people with raised intraocular pressure: increase >21 mm hg)	1	65	RR 0.82 (0.20, 3.39)	high	Could not differentiate

See Appendix F for full GRADE and tables and Appendix E for forest plots.

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, 671 of the studies could confidently be excluded for this review question. One study was excluded following the full-text review. No relevant health economic studies were included.

1.1.7.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

See the health economic study selection flow chart presented in Appendix G.

1.1.8 Summary of included economic evidence.

No relevant health economic studies were identified to be included.

1.1.9 Economic model

Original health economic modelling was not conducted for this review question.

1.1.10 Unit costs

Costs associated with treatment are present in Table 11 below. It should be noted that aflibercept, ranibizumab and bevacizumab are recommended by NICE only if the manufacturer provides them with the agreed confidential patient access scheme discount.

Table 10: List prices of treatment alongside cataract surgery

Resource	Unit costs	Source
Aflibercept 4.0mg/0.1ml	£816.00	BNF (accessed 13/02/23)
Ranibizumab 2.3mg/0.23ml	£551.00	BNF (accessed 13/02/23)
Ranibizumab biosimilar (Ongavia) 2.3mg/0.23ml	£523.45	BNF (accessed 13/02/23)
Bevacizumab* 1.25mg	£50.00	Poku et al (2012) cited in NICE TA824
Dexamethasone 700 microgram	£870.00	BNF (accessed 13/02/23)

**Bevacizumab is only available in a 100mg per 4ml vial at a list price of £242.66, and for intravitreal use must be reconstituted into a 1.25mg dose in an aseptic pharmacy.*

1.1.11 Evidence statements

No relevant health economic studies were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

Both visual acuity and progression to proliferative diabetic retinopathy or macular oedema were considered important for decision making as these are the outcomes that result in the need for additional treatment and can lead to loss of vision for patients. Adverse events associated with treatment were also considered important. The committee also highlighted the importance of peripheral vision, as impairment of peripheral vision can have significant consequences, especially when it comes to activities like driving. However, no studies included in the review reported on peripheral vision outcomes. The committee wanted to consider quality of life outcomes but this was not reported in any of the studies.

The committee were also interested in information on success of cataract surgery and rates of additional intervention, but no evidence was reported for these outcomes. However, they did not think these were as important to decision-making as the vision- and progression-related outcomes.

1.1.12.2 The quality of the evidence

The evidence for the outcomes ranged from low- to high-quality, with most being moderate quality. All studies were considered fully applicable to the review. Evidence was available for

people who only had non-proliferative diabetic retinopathy and people who had non-proliferative diabetic retinopathy with diabetic macular oedema. No evidence was available for people with proliferative diabetic retinopathy. The protocol specified that where no RCT evidence was available for a comparison, observational evidence would be considered instead. However, none of the observational evidence that was available for these comparisons met the inclusion criteria for the review.

The studies reported on a number of different interventions, and each study only reported a small number of outcomes. This meant that there was limited meta-analysis, with much of the evidence instead being based on single study results. This, and the small sample sizes in most of the studies, made it difficult to draw strong conclusions from the results. The committee expected more studies to report on ocular adverse events, particularly with the use of steroids. They thought that the low numbers of adverse events may be due to the way these were recorded by the studies, rather than a lack of adverse events associated with treatment. In addition, the committee discussed how the studies were not powered to show the benefits of adjuvant treatments. This made it difficult to be certain of the true effect of different interventions.

Most studies considered interventions during surgery. Only one study compared the effects of delivering an intervention before or after cataract surgery. As a result, the committee could not make any recommendations on the timing of interventions relative to cataract surgery.

The evidence considered the use of anti-VEGFs and of steroids, but there was no evidence for the use of laser photocoagulation before, during or after cataract surgery. The committee discussed how the lack of evidence for laser photocoagulation before cataract surgery is likely to be because the presence of a cataract generally means that the laser would not be able to target the correct areas of the retina, and so this is not common in clinical practice.

Given the limited evidence base, the small sample sizes, and the reliance on single studies for some comparisons, the committee decided they could not make recommendations on the most effective intervention for any of the populations. Instead, they decided that the limitations of the existing evidence meant that research recommendations were needed (see Appendix K). This will help to ensure that people with diabetic retinopathy or diabetic macular oedema receive the most effective treatments in future.

1.1.11.2 Imprecision and clinical importance of effects.

The reliance on single study results for many outcomes and the small number of eyes included in some of the studies resulted in wide confidence intervals which crossed the line of no effect for much of the evidence. This made it difficult for the committee to be certain of the true effect of different interventions. It emphasises the need for more comprehensive studies with larger sample sizes to obtain more precise estimates of treatment effects.

Most of the evidence could not differentiate between different interventions, but the committee thought that this was partly due to the limited evidence base, supporting the need for the research recommendations. There was evidence that visual acuity improved with anti-VEGFs compared to control for people with non-proliferative retinopathy and for people with non-proliferative retinopathy with diabetic macular oedema. However, the committee highlighted that the difference for people with non-proliferative retinopathy was not clinically meaningful. Although the result for people with non-proliferative retinopathy with macular oedema was clinically meaningful, it was based off the result of a single study with a small sample size, which did not report the dose used for bevacizumab. It was therefore difficult to make any recommendations from this result.

1.1.12.3 Benefits and harms.

The limited number of studies, small sample sizes and wide confidence intervals made it difficult for the committee to be confident of the benefits and harms of each treatment. There

was some evidence that anti-VEGFs improved visual acuity compared to control for people with non-proliferative diabetic retinopathy with macular oedema. However, no information was provided on the other outcomes, including adverse events. This made it difficult to be certain of the effectiveness of anti-VEGFs for this group.

There was no clear difference in effectiveness between the use of steroids and either control or anti-VEGFs. One study showed that steroids can result in a reduced number of treatments, but this was not accompanied by improvements in visual acuity. The committee also discussed the lack of evidence for adverse events, and the limited number of adverse events when they were reported. The committee thought this was likely to be related to how the studies reported the events, rather than a lack of events, as steroids are commonly associated with a higher rate of adverse events. As a result, the committee did not think they could make recommendations on the use of either anti-VEGFs or steroids for people who have non-proliferative diabetic retinopathy with diabetic macular oedema.

The committee emphasised that their decision to not make recommendations is not due to a perceived lack of effectiveness of different interventions, but due to the limited amount of evidence. For this reason, they made research recommendations for people with non-proliferative diabetic retinopathy and for people with diabetic macular oedema (see Appendix K). The committee thought these were important research topics, as preventing, or slowing, progression will reduce the number of additional treatments that people may otherwise need if they develop proliferative diabetic retinopathy or have further progression of their macular oedema. It will also reduce the number of people who develop more serious outcomes, such as vision loss, which is a major concern to people who have retinopathy. In addition to benefits to patients, an understanding of the most effective treatments will reduce the resources needed to treat people who have progressed.

The committee were aware of recommendations about managing complications associated with cataract surgery in the NICE cataracts guideline about the use of steroids and NSAIDs to manage complications relating to cystoid macular oedema. These recommendations are related to people who are at increased risk of cystoid macular oedema following cataract surgery, including those with diabetes. The committee thought that this information was relevant to the diabetic retinopathy guideline and were not aware of any major changes to the evidence base since the cataract guideline was published. The population that informed the recommendations in the cataract's guideline included a subgroup specifically for people with diabetic retinopathy, and so the committee decided that this was relevant to the diabetic retinopathy guideline and should be highlighted in the recommendations.

1.1.12.4 Cost-effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost-effectiveness of treatments before, during or after cataract surgery for managing non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema. The committee felt more evidence was required to be able to make recommendations on the effectiveness and cost-effectiveness of treatments before, during and after surgery in people with moderate to severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, or diabetic macular oedema. As such, the committee proposed recommendations for future research to ensure no unnecessary resource impact is made without any clinical evidence.

To ensure people with diabetes who are having cataract surgery are treated correctly, the committee felt it was important the surgeon undertaking the surgery should be aware of their current diabetic eye disease status. The committee did not anticipate this would have any resource impact because it is simply ensuring information is being shared correctly rather than requiring any additional resources for treatment or monitoring.

The committee discussed that anti-VEGFs should be considered as temporary treatment for people who have proliferative diabetic retinopathy and for whom PRP is not suitable because they need cataract surgery. Whilst there was very limited evidence for this recommendation,

the committee did not expect there to be a large resource impact because anti-VEGFs would only be expected to be used for short term treatment such as 1 to 2 injections to prevent progression whilst waiting for cataract treatment. The committee felt that the resources saved by reduced progression whilst waiting for cataract surgery would offset the increase in short term costs associated with anti-VEGF treatments. The committee anticipated that the resource impact would be further managed if either bevacizumab or the cheapest available anti-VEGF which is licensed for the treatment of proliferative diabetic retinopathy such as biosimilars were to be the preferred treatment option, because there was limited evidence for differences in clinical effectiveness between the anti-VEGF treatments.

1.1.12.5 Other factors the committee took into account

There was no evidence on the use of different services, such as independent centres, for cataract surgery. The committee discussed how many people are now treated for cataracts in independent centres, rather than by NHS services. They thought it was important to highlight that, in their experience, the use of these centres can lead to complications for some people. This is because these people's current retinopathy status is not always identified before cataract surgery. Without this information, surgery may not always be tailored to a person's eye condition, or they may not be given the most effective post-operative medication or follow-up care. The committee therefore decided to recommend that surgeons who are performing cataract surgery should obtain information about a person's retinopathy status prior to surgery. They noted that this information can be identified from a number of sources, such as the NHS diabetic eye screening programme, the Hospital Eye Services medical retina clinic or by examination of the retina.

1.1.13 Recommendations supported by this evidence review.

This evidence review supports recommendations 1.2.1 to 1.2.2 and the research recommendations for people with moderate to severe non-proliferative diabetic retinopathy, who are about to undergo or who have undergone cataract surgery and people with diabetic macular oedema, who are about to undergo or who have undergone cataract surgery.

1.1.14 References – included studies

1.1.14.1 Effectiveness

Ahmadabadi, Hooshang Faghihi, Mohammadi, Massood, Beheshtnejad, Hooshang et al. (2010) Effect of intravitreal triamcinolone acetonide injection on central macular thickness in diabetic patients having phacoemulsification. Journal of cataract and refractive surgery 36(6): 917-22

Barone, Antonio, Russo, Vincenzo, Maggiore, Giulia et al. (2022) Dexamethasone intravitreal implant in patients with cataract and naive diabetic macular edema. European journal of ophthalmology 32(1): 364-371

Chae, Ju Byung, Joe, Soo Geun, Yang, Sung Jae et al. (2014) Effect of combined cataract surgery and ranibizumab injection in postoperative macular edema in nonproliferative diabetic retinopathy. Retina (Philadelphia, Pa.) 34(1): 149-56

Fard, Masoud Aghsaei; Yazdanei Abyane, Alireza; Malihi, Mehrdad (2011) Prophylactic intravitreal bevacizumab for diabetic macular edema (thickening) after cataract surgery: prospective randomized study. European journal of ophthalmology 21(3): 276-81

Gupta, Parul Chawla, Ram, Jagat, Kumar, M Praveen et al. (2021) Effect of sustained-release long-acting intravitreal dexamethasone implant in patients of non-proliferative diabetic retinopathy undergoing phacoemulsification: A randomized controlled trial. Indian journal of ophthalmology 69(11): 3263-3272

Kandasamy, Rathika, Constantinou, Marios, Rogers, Sophie L et al. (2019) Prospective randomised clinical trial of intravitreal bevacizumab versus triamcinolone in eyes with diabetic macular oedema undergoing cataract surgery: 6-month results. The British journal of ophthalmology 103(12): 1753-1758

Lanzagorta-Aresti, Aitor, Palacios-Pozo, Elena, Menezo Rozalen, Jose Luis et al. (2009) Prevention of vision loss after cataract surgery in diabetic macular edema with intravitreal bevacizumab: a pilot study. Retina (Philadelphia, Pa.) 29(4): 530-5

Sasongko, Muhammad B, Rogers, Sophie, Constantinou, Marios et al. (2020) Diabetic retinopathy progression 6 months post-cataract surgery with intravitreous bevacizumab vs triamcinolone: A secondary analysis of the DiMECAT trial. Clinical & experimental ophthalmology 48(6): 793-801

Song, Weilin, Conti, Thais F, Gans, Richard et al. (2020) Prevention of Macular Edema in Patients With Diabetic Retinopathy Undergoing Cataract Surgery: The PROMISE Trial. Ophthalmic surgery, lasers & imaging retina 51(3): 170-178

Takamura, Yoshihiro; Kubo, Eri; Akagi, Yoshio (2009) Analysis of the effect of intravitreal bevacizumab injection on diabetic macular edema after cataract surgery. Ophthalmology 116(6): 1151-7

1.1.14.2 Economic

No economic studies were included. The following unit cost references have been included.

National Institute for Health and Care Excellence (NICE). BNF. 2019. Available from: https://bnf.nice.org.uk/drug/

National Institute for Health and Care Excellence (NICE). TA824 Dexamethasone intravitreal implant for treating diabetic macular oedema. 2022. Available from https://www.nice.org.uk/guidance/ta824

1.1.14.3 Other

Poku E, Rathbone J, Everson-Hock E, Essat M, Wong R, Pandor A, Wailoo AJ. (2012) Bevacizumab in eye conditions: Issues related to quality, use, efficacy and safety. NICE Decision Support Unit Report.

Appendices

Appendix A – Review protocols

What is the effectiveness of treatments before, during or after cataract surgery for managing:

1. **non-proliferative diabetic retinopathy**
2. **proliferative diabetic retinopathy**
3. **diabetic macular oedema?**

ID	Field	Content
1.	Review title	In people who are about to undergo or who have undergone cataract surgery, what is the effectiveness of treatments (before, during or after surgery) for managing: • non-proliferative diabetic retinopathy • proliferative diabetic retinopathy • diabetic macular oedema?
2.	Review question	In people who are about to undergo or who have undergone cataract surgery, what is the effectiveness of treatments (before, during or after surgery) for managing: • non-proliferative diabetic retinopathy • proliferative diabetic retinopathy • diabetic macular oedema?

3.	Objective	To determine the effectiveness of treatments listed below (before, during or after cataract surgery) for managing: people diagnosed with non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema who are about to undergo or who have undergone cataract surgery. The aim is to inform recommendations for which treatments are most effective in combination with cataract surgery
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 • 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 and observational filters will be applied • 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.
5.	Condition or domain being studied	Diabetic retinopathy
6.	Population	Inclusion: People diagnosed with: • non-proliferative diabetic retinopathy

		• proliferative diabetic retinopathy • diabetic macular oedema who are about to undergo or who have undergone cataract surgery
7.	Intervention	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids (before during or after cataract surgery) including subconjunctival steroids (dexamethasone and triamcinolone)
8.	Comparators	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids • No treatment/placebo • Studies comparing treatments before during or after cataract surgery will be included.
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Comparative observational studies with a concurrent control group and adjustment for confounding factors (for example age, severity of retinopathy at baseline, severity of macular oedema at baseline) to ensure comparable intervention and comparator groups, only for comparisons where RCTs are not available

10.	Other exclusion criteria	Trials that were not reported in English
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 corrected 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 to or of proliferative diabetic retinopathy or macular oedema,

13.	Secondary outcomes (important outcomes)	• Success of cataract surgery • Rates of additional intervention • Adverse events (Raised intraocular pressure, Intraocular infection, Intraocular Inflammation) • Quality of life measured using a validated tool (the overall score as well as mental health domain scores will be reported separately) • Peripheral vision, assessed using visual field measurements 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. This review will use of the priority screening functionality within the EPPI-reviewer software. 50% of the database will be screened. Following this point, if 5% of the database is screened without finding an include based on title and abstract screening, screening will be stopped, and the remaining records excluded. These stopping criteria are considered appropriate based on the experience of the team, given this topic is a well defined clinical area with clear inclusion and exclusion criteria. As additional measure, the full database will be searched if there are a very small number of included studies (<30). 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. 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.
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. Risk of bias in comparative observational studies will be assessed using the ROBINS-I checklist.
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.
17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women • Non-proliferative retinopathy, proliferative retinopathy, diabetic macular oedema

		If data is available (and assuming if a study has not already adjusted for these factors) a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80) • Socioeconomic status • Severity of non-proliferative retinopathy (moderate, severe and very severe), severity of proliferative retinopathy (low vs high risk), Severity of diabetic macular oedema (centre involving vs non-centre involving)
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ 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		
		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 • Syed MohiuddinHannah Lomax • 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 • 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, macular oedema, cataract surgery
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 November 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.

Observational studies

The terms used for observational studies are standard NICE practice that have been developed in house.

Clinical search strategies

Database	Date searched	Database Platform	Database segment or version
Cochrane Central Register of Controlled Trials (CENTRAL)	01-Nov-2022	Wiley	02/11/2022
Cochrane Database of Systematic Reviews (CDSR)	01-Nov-2022	Wiley	02/11/2022
Embase	01-Nov-2022	Ovid	<1974 to 2022 October 24>
Epistemonikos	Not searched	Not searched	Not searched
HTA	01-Nov-2022	CRD	02/11/2022
INAHTA	01-Nov-2022	INAHTA	02/11/2022
MEDLINE	01-Nov-2022	Ovid	<1946 to November 01, 2022>
MEDLINE-in-Process	01-Nov-2022	Ovid	<1946 to November 01, 2022>
MEDLINE ePub Ahead-of-Print	01-Nov-2022	Ovid	<November 01, 2022>

Database: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)
#1 MeSH descriptor: [Diabetic Retinopathy] this term only 1583 #2 MeSH descriptor: [Macular Edema] this term only 1286 #3 (diabet* near/6 (retin* or eye* or macular* or maculopath*)):ti,ab,kw 5690 #4 {or #1-#3} 6135 #5 MeSH descriptor: [Cataract] explode all trees 1654 #6 MeSH descriptor: [Cataract Extraction] explode all trees 2876 #7 (cataract*):ti,ab,kw 8698 #8 ((pha?oemulsif* or phaco or phako)):ti,ab,kw 3482 #9 (((lens* or capsul*) near/4 (opaci* or cloud*))):ti,ab,kw 826 #10 ((lensectom* or capsulorhexis or capsulorrhexis)):ti,ab,kw 459 #11 ((lens* near/4 (extract* or aspirat* or operat* or remov* or surg* or excis* or emulsif*))):ti,ab,kw 1749 #12 MeSH descriptor: [Lenses, Intraocular] this term only 1027

#13 MeSH descriptor: [Lens Implantation, Intraocular] this term only 1269
#14 (((lens* near/4 (intraocul* or implant*)) or IOL*)):ti,ab,kw 4454
#15 {or #5 - #14} 1595254
#16 MeSH descriptor: [Laser Coagulation] this term only 600
#17 (photocoagulat* or thermocoagulat* or argon or diode or micropulse):ti,ab,kw 5066
#18 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) near/4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)):ti,ab,kw 21160
#19 ((focal or grid) near/3 laser*):ti,ab,kw 344
#20 PRP:ti,ab,kw 2944
#21 {or #16-#20} 25493
#22 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees 1497
#23 MeSH descriptor: [Receptors, Vascular Endothelial Growth Factor] explode all trees 452
#24 (anti near/2 VEGF*):ti,ab,kw 1542
#25 (anti-VEGF* or antiVEGF*):ti,ab,kw 1519
#26 ((anti-vascular or antivascular) near/2 endothelial growth factor*):ti,ab,kw 660
#27 (((vascular endothelial near/2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) near/2 (trap* or inhibit* or antagonist*)):ti,ab,kw 6665
#28 (vascular proliferation near/4 inhibit*):ti,ab,kw 94
#29 (endothelial near/2 growth near/2 factor*):ti,ab,kw 4655
#30 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees 1387
#31 MeSH descriptor: [Angiogenesis Inducing Agents] this term only 51
#32 MeSH descriptor: [Vascular Endothelial Growth Factor A] this term only 1408
#33 Aflibercept*:ti,ab,kw 1039
#34 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 250
#35 MeSH descriptor: [Bevacizumab] this term only 2260
#36 Bevacizumab*:ti,ab,kw 7099
#37 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865):ti,ab,kw 932
#38 (IVB near/2 inject*):ti,ab,kw 84
#39 MeSH descriptor: [Ranibizumab] this term only 972
#40 Ranibizumab*:ti,ab,kw 2201
#41 (Lucentis or rhuFab):ti,ab,kw 448
#42 (IVR near/2 inject*):ti,ab,kw 31
#43 (Faricimab or Vabysmo):ti,ab,kw 40
#44 (Pegaptanib* or macugen*):ti,ab,kw 181
#45 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 82
#46 MeSH descriptor: [Sunitinib] this term only 353
#47 (Sunitinib or Sutent):ti,ab,kw 1348
#48 MeSH descriptor: [Sorafenib] this term only 540
#49 (Sorafenib or Nexavar):ti,ab,kw 2038
#50 MeSH descriptor: [Axitinib] this term only 112
#51 (Axitinib or Inlyta):ti,ab,kw 373
#52 (Pazopanib or Votrient):ti,ab,kw 612
#53 {or #22-#52} 21264
#54 MeSH descriptor: [Intravitreal Injections] this term only 987
#55 (Intravitreal* near/2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)):ti,ab,kw 3204
#56 MeSH descriptor: [Dexamethasone] this term only 5128
#57 MeSH descriptor: [Fluocinolone Acetonide] this term only 351

#58 MeSH descriptor: [Triamcinolone Acetonide] this term only 1203
#59 (Triamcinolone acetonide):ti,ab,kw 2447
#60 (Dexamethasone* or kenalog or kenacort or retisert* or adcortyl*):ti,ab,kw 14293
#61 ((fluocinolone* or triamcinolone*) near/2 acetonide*):ti,ab,kw 2918
#62 Iluvien*:ti,ab,kw 16
#63 {or #54-#62} 19635
#64 #21 or #53 or #63 61854
#65 #4 and #15 5319
#66 #64 and #65 2886
#67 "conference":pt or (clinicaltrials or trialsearch):so 650308
#68 #66 not #67 1849

Database: Embase

1 Diabetic Retinopathy/ 41265
2 Macular Edema/ 6461
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 46417
4 or/1-3 63229
5 exp Cataract/ 53925
6 exp Cataract Extraction/ 41974
7 cataract*.tw. 57629
8 (pha?oemulsif* or phaco or phako).tw. 12433
9 ((lens* or capsul*) adj4 (opaci* or cloud*)).tw. 6072
10 (lensectom* or capsulorhexis or capsulorrhexis).tw. 2719
11 (lens* adj4 (extract* or aspirat* or operat* or remov* or surg* or excis* or emulsif*)).tw. 8887
12 Lenses, Intraocular/ 18322
13 Lens Implantation, Intraocular/ 11236
14 ((lens* adj4 (intraocul* or implant*)) or IOL*).tw. 25185
15 or/5-14 100414
16 exp vasculotropin/ 153565
17 exp vasculotropin receptor/ 12738
18 (anti adj2 VEGF*).tw. 14684
19 (anti-VEGF* or antiVEGF*).tw. 14320
20 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 6719
21 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 16549
22 (vascular proliferation adj4 inhibit*).tw. 43
23 (endothelial adj2 growth adj2 factor*).tw. 87581
24 angiogenesis/ or angiogenesis inhibitor/ or angiogenic factor/ or endothelial cell growth factor/ 160671
25 aflibercept/ 8180
26 Aflibercept*.tw. 4510
27 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 1635
28 Bevacizumab/ 69201
29 Bevacizumab*.tw. 34333
30 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 10692

31 (IVB adj2 inject*).tw. 385
32 Ranibizumab/ 11786
33 Ranibizumab*.tw. 6990
34 (Lucentis or "rhuFab V2").tw. 3071
35 (IVR adj2 inject*).tw. 191
36 faricimab/ 162
37 (Faricimab or Vabysmo).tw. 83
38 pegaptanib/ 2416
39 (Pegaptanib* or macugen*).tw. 1572
40 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 1245
41 Sunitinib/ 26145
42 (Sunitinib or Sutent).tw. 13984
43 Sorafenib/ 35200
44 (Sorafenib or Nexavar).tw. 20545
45 Axitinib/ 6497
46 (Axitinib or Inlyta).tw. 2665
47 pazopanib/ 9903
48 (Pazopanib or Votrient).tw. 4469
49 or/16-48 378763
50 Laser Coagulation/ 16942
51 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 50545
52 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 123168
53 PRP.tw. 22491
54 ((focal or grid) adj3 laser*).tw. 1372
55 or/50-54 190336
56 intravitreal drug administration/ 5908
57 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 17882
58 Triamcinolone Acetonide/ 12579
59 Triamcinolone acetonide.tw. 4950
60 Dexamethasone/ 143647
61 (Dexamethasone* or kenalog or kenacort or retisert* or adcortyl*).tw. 72130
62 Fluocinolone Acetonide/ 2038
63 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 5651
64 Iluvien*.tw. 385
65 or/56-64 180829
66 49 or 55 or 65 720108
67 4 and 15 7033
68 66 and 67 2673
69 Nonhuman/ not Human/ 3799611
70 68 not 69 2634
71 limit 70 to english language 2423
72 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5096733
73 71 not 72 1990
74 random:.tw. 1715758
75 placebo:.mp. 426219
76 double-blind:.tw. 189473
77 or/74-76 1920566
78 Clinical study/ 110061

79	Case control study/	190046
80	Family study/	22987
81	Longitudinal study/	173480
82	Retrospective study/	1305405
83	comparative study/	763091
84	Prospective study/	785730
85	Randomized controlled trials/	237488
86	84 not 85	776187
87	Cohort analysis/	907688
88	cohort analy$.tw.	17130
89	(Cohort adj (study or studies)).tw.	413983
90	(Case control$ adj (study or studies)).tw.	153436
91	(follow up adj (study or studies)).tw.	56715
92	(observational adj (study or studies)).tw.	228011
93	(epidemiologic$ adj (study or studies)).tw.	101357
94	(cross sectional adj (study or studies)).tw.	302383
95	case series.tw.	134597
96	prospective.tw.	970156
97	retrospective.tw.	1110929
98	or/78-83,86-97	4599098
99	73 and 77	409
100	73 and 98	837

Database: Health Technology Assessment (HTA)

1	MeSH DESCRIPTOR Diabetic Retinopathy IN HTA	29
2	MeSH DESCRIPTOR Macular Edema IN HTA	25
3	((diabet* adj6 (retin* or eye* or macular* or maculopath*)))	225
4	#1 OR #2 OR #3	232
5	MeSH DESCRIPTOR Cataract Extraction EXPLODE ALL TREES IN HTA	29
6	MeSH DESCRIPTOR Cataract EXPLODE ALL TREES IN HTA	23
7	MeSH DESCRIPTOR Lenses, Intraocular IN HTA	20
8	MeSH DESCRIPTOR Lens Implantation, Intraocular IN HTA	11
9	(((lens* adj4 (intraocul* or implant*)) or IOL*)) IN HTA	29
10	(cataract*) IN HTA	69
11	((pha?oemulsif* or phaco or phako)) IN HTA	7
12	(((lens* or capsul*) adj4 (opaci* or cloud*))) IN HTA	3
13	((lensectom* or capsulorhexis or capsulorrhexis)) IN HTA	1
14	((lens* adj4 (extract* or aspirat* or operat* or remov* or surg* or excis* or emulsif*))) IN HTA	11

15	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	85
16	#4 AND #15	5

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

(Diabetic Retinopathy)[mh] OR (Macular Edema)[mh] OR ((diabet* AND (retin* or eye* or macular* or maculopath*)))

AND

(lens* AND IOL*) OR (lens* AND (intraocul* or implant*)) OR (lens* AND (extract* or aspirat* or operat* or remov* or surg* or excis* or emulsif*) OR (lens* or capsul* AND opaci* or cloud*) OR (cataract* or pha?oemulsif* or phaco or phako or lensectom* or capsulorhexis or capsulorrhexis) OR ("Lens Implantation, Intraocular"[mh]) OR ("Lenses, Intraocular"[mh]) OR ("Cataract Extraction"[mhe]) OR ("Cataract"[mhe])

Database: Ovid MEDLINE(R)

1 Diabetic Retinopathy/ 28544
2 Macular Edema/ 8601
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 33037
4 or/1-3 43317
5 exp Cataract/ 31960
6 exp Cataract Extraction/ 36530
7 cataract*.tw. 55209
8 (pha?oemulsif* or phaco or phako).tw. 9035
9 ((lens* or capsul*) adj4 (opaci* or cloud*)).tw. 5513
10 (lensectom* or capsulorhexis or capsulorrhexis).tw. 2513
11 (lens* adj4 (extract* or aspirat* or operat* or remov* or surg* or excis* or emulsif*)).tw. 8551
12 Lenses, Intraocular/ 16060
13 Lens Implantation, Intraocular/ 12935
14 ((lens* adj4 (intraocul* or implant*)) or IOL*).tw. 21593
15 or/5-14 85338
16 exp Vascular Endothelial Growth Factors/ 62460
17 exp Receptors, Vascular Endothelial Growth Factor/ 17875
18 (anti adj2 VEGF*).tw. 7136
19 (anti-VEGF* or antiVEGF*).tw. 6896
20 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 4302
21 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 9417
22 (vascular proliferation adj4 inhibit*).tw. 28
23 (endothelial adj2 growth adj2 factor*).tw. 61681

24 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 113872
25 Aflibercept*.tw. 2081
26 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 232
27 Bevacizumab/ 13693
28 Bevacizumab*.tw. 15408
29 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 1374
30 (IVB adj2 inject*).tw. 236
31 Ranibizumab/ 4538
32 Ranibizumab*.tw. 3779
33 (Lucentis or "rhuFab V2").tw. 360
34 (IVR adj2 inject*).tw. 107
35 (Faricimab or Vabysmo).tw. 37
36 (Pegaptanib* or macugen*).tw. 457
37 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 118
38 Sunitinib/ 4056
39 (Sunitinib or Sutent).tw. 5389
40 Sorafenib/ 6022
41 (Sorafenib or Nexavar).tw. 8042
42 Axitinib/ 685
43 (Axitinib or Inlyta).tw. 971
44 (Pazopanib or Votrient).tw. 1592
45 or/16-44 151069
46 Laser Coagulation/ 8123
47 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 36465
48 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 96754
49 PRP.tw. 15560
50 ((focal or grid) adj3 laser*).tw. 859
51 or/46-50 141026
52 Intravitreal Injections/ 9416
53 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 11478
54 Triamcinolone Acetonide/ 6067
55 Triamcinolone acetonide.tw. 4318
56 Dexamethasone/ 54906
57 (Dexamethasone* or kenalog or kenacort or retisert* or adcortyl*).tw. 57461
58 Fluocinolone Acetonide/ 1443
59 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 4949
60 Iluvien*.tw. 55
61 or/52-60 94419
62 45 or 51 or 61 369793
63 4 and 15 4265
64 62 and 63 1077
65 Animals/ not Humans/ 5027206
66 64 not 65 1061
67 limit 66 to english language 957
68 randomized controlled trial.pt. 579626
69 randomi?ed.mp. 937060

70 placebo.mp. 220162
71 or/68-70 993483
72 Observational Studies as Topic/ 8218
73 Observational Study/ 133928
74 Epidemiologic Studies/ 9190
75 exp Case-Control Studies/ 1365399
76 exp Cohort Studies/ 2411045
77 Cross-Sectional Studies/ 444754
78 Controlled Before-After Studies/ 706
79 Historically Controlled Study/ 222
80 Interrupted Time Series Analysis/ 1707
81 Comparative Study.pt. 1911688
82 case control$.tw. 133766
83 case series.tw. 77835
84 (cohort adj (study or studies)).tw. 250081
85 cohort analy$.tw. 9494
86 (follow up adj (study or studies)).tw. 50312
87 (observational adj (study or studies)).tw. 123270
88 longitudinal.tw. 259849
89 prospective.tw. 600309
90 retrospective.tw. 590024
91 cross sectional.tw. 390472
92 or/72-91 4997391
93 67 and 71 199
94 67 and 92 555
95 93 or 94 754

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. 6
4 or/1-3 6
5 exp Cataract/ 0
6 exp Cataract Extraction/ 0
7 cataract*.tw. 15
8 (pha?oemulsif* or phaco or phako).tw. 4
9 ((lens* or capsul*) adj4 (opaci* or cloud*)).tw. 1
10 (lensectom* or capsulorhexis or capsulorrhexis).tw. 1
11 (lens* adj4 (extract* or aspirat* or operat* or remov* or surg* or excis* or emulsif*)).tw. 3
12 Lenses, Intraocular/ 0
13 Lens Implantation, Intraocular/ 0
14 ((lens* adj4 (intraocul* or implant*)) or IOL*).tw. 12
15 or/5-14 25
16 exp Vascular Endothelial Growth Factors/ 0
17 exp Receptors, Vascular Endothelial Growth Factor/ 0
18 (anti adj2 VEGF*).tw. 1
19 (anti-VEGF* or antiVEGF*).tw. 1

20 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 2
21 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 1
22 (vascular proliferation adj4 inhibit*).tw. 0
23 (endothelial adj2 growth adj2 factor*).tw. 11
24 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 0
25 Aflibercept*.tw. 1
26 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 0
27 Bevacizumab/ 0
28 Bevacizumab*.tw. 6
29 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 0
30 (IVB adj2 inject*).tw. 0
31 Ranibizumab/ 0
32 Ranibizumab*.tw. 1
33 (Lucentis or "rhuFab V2").tw. 0
34 (IVR adj2 inject*).tw. 0
35 (Faricimab or Vabysmo).tw. 0
36 (Pegaptanib* or macugen*).tw. 0
37 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 0
38 Sunitinib/ 0
39 (Sunitinib or Sutent).tw. 0
40 Sorafenib/ 0
41 (Sorafenib or Nexavar).tw. 2
42 Axitinib/ 0
43 (Axitinib or Inlyta).tw. 0
44 (Pazopanib or Votrient).tw. 0
45 or/16-44 20
46 Laser Coagulation/ 0
47 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 0
48 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 28
49 PRP.tw. 9
50 ((focal or grid) adj3 laser*).tw. 0
51 or/46-50 36
52 Intravitreal Injections/ 0
53 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 2
54 Triamcinolone Acetonide/ 0
55 Triamcinolone acetonide.tw. 0
56 Dexamethasone/ 0
57 (Dexamethasone* or kenalog or kenacort or retisert* or adcortyl*).tw. 5
58 Fluocinolone Acetonide/ 0
59 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 0
60 Iluvien*.tw. 0
61 or/52-60 6
62 45 or 51 or 61 59
63 4 and 15 0
64 62 and 63 0

65 Animals/ not Humans/ 0
66 64 not 65 0
67 limit 66 to english language 0
68 randomized controlled trial.pt. 0
69 randomi?ed.mp. 170
70 placebo.mp. 29
71 or/68-70 173
72 Observational Studies as Topic/ 0
73 Observational Study/ 0
74 Epidemiologic Studies/ 0
75 exp Case-Control Studies/ 0
76 exp Cohort Studies/ 0
77 Cross-Sectional Studies/ 0
78 Controlled Before-After Studies/ 0
79 Historically Controlled Study/ 0
80 Interrupted Time Series Analysis/ 0
81 Comparative Study.pt. 0
82 case control$.tw. 23
83 case series.tw. 23
84 (cohort adj (study or studies)).tw. 79
85 cohort analy$.tw. 4
86 (follow up adj (study or studies)).tw. 4
87 (observational adj (study or studies)).tw. 34
88 longitudinal.tw. 67
89 prospective.tw. 102
90 retrospective.tw. 153
91 cross sectional.tw. 128
92 or/72-91 473
93 67 and 71 0
94 67 and 92 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. 497
4 or/1-3 497
5 exp Cataract/ 0
6 exp Cataract Extraction/ 0
7 cataract*.tw. 707
8 (pha?oemulsif* or phaco or phako).tw. 102
9 ((lens* or capsul*) adj4 (opaci* or cloud*)).tw. 46
10 (lensectom* or capsulorhexis or capsulorrhexis).tw. 25
11 (lens* adj4 (extract* or aspirat* or operat* or remov* or surg* or excis* or emulsif*)).tw. 98
12 Lenses, Intraocular/ 0

13 Lens Implantation, Intraocular/ 0
14 ((lens* adj4 (intraocul* or implant*)) or IOL*).tw. 311
15 or/5-14 955
16 exp Vascular Endothelial Growth Factors/ 0
17 exp Receptors, Vascular Endothelial Growth Factor/ 0
18 (anti adj2 VEGF*).tw. 176
19 (anti-VEGF* or antiVEGF*).tw. 175
20 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 120
21 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 131
22 (vascular proliferation adj4 inhibit*).tw. 0
23 (endothelial adj2 growth adj2 factor*).tw. 633
24 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 0
25 Aflibercept*.tw. 84
26 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 7
27 Bevacizumab/ 0
28 Bevacizumab*.tw. 273
29 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 13
30 (IVB adj2 inject*).tw. 0
31 Ranibizumab/ 0
32 Ranibizumab*.tw. 86
33 (Lucentis or "rhuFab V2").tw. 3
34 (IVR adj2 inject*).tw. 1
35 (Faricimab or Vabysmo).tw. 2
36 (Pegaptanib* or macugen*).tw. 9
37 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 0
38 Sunitinib/ 0
39 (Sunitinib or Sutent).tw. 59
40 Sorafenib/ 0
41 (Sorafenib or Nexavar).tw. 110
42 Axitinib/ 0
43 (Axitinib or Inlyta).tw. 35
44 (Pazopanib or Votrient).tw. 31
45 or/16-44 1151
46 Laser Coagulation/ 0
47 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 658
48 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 1521
49 PRP.tw. 177
50 ((focal or grid) adj3 laser*).tw. 8
51 or/46-50 2220
52 Intravitreal Injections/ 0
53 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 240
54 Triamcinolone Acetonide/ 0
55 Triamcinolone acetonide.tw. 46
56 Dexamethasone/ 0
57 (Dexamethasone* or kenalog or kenacort or retisert* or adcortyl*).tw. 515

58	Fluocinolone Acetonide/	0
59	((fluocinolone* or triamcinolone*) adj2 acetonide*).tw.	64
60	Iluvien*.tw.	6
61	or/52-60	779
62	45 or 51 or 61	3909
63	4 and 15	46
64	62 and 63	16
65	Animals/ not Humans/	0
66	64 not 65	16
67	limit 66 to english language	16
68	randomized controlled trial.pt.	1
69	randomi?ed.mp.	12632
70	placebo.mp.	2622
71	or/68-70	13448
72	Observational Studies as Topic/	0
73	Observational Study/	2
74	Epidemiologic Studies/	0
75	exp Case-Control Studies/	0
76	exp Cohort Studies/	0
77	Cross-Sectional Studies/	0
78	Controlled Before-After Studies/	0
79	Historically Controlled Study/	0
80	Interrupted Time Series Analysis/	0
81	Comparative Study.pt.	0
82	case control$.tw.	2196
83	case series.tw.	2266
84	(cohort adj (study or studies)).tw.	8615
85	cohort analy$.tw.	303
86	(follow up adj (study or studies)).tw.	529
87	(observational adj (study or studies)).tw.	3955
88	longitudinal.tw.	6587
89	prospective.tw.	11197
90	retrospective.tw.	16984
91	cross sectional.tw.	10489
92	or/72-91	47863
93	67 and 71	6
94	67 and 92	8

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. Update searches were run in Feb 2023.

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/5-133358085
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: 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:

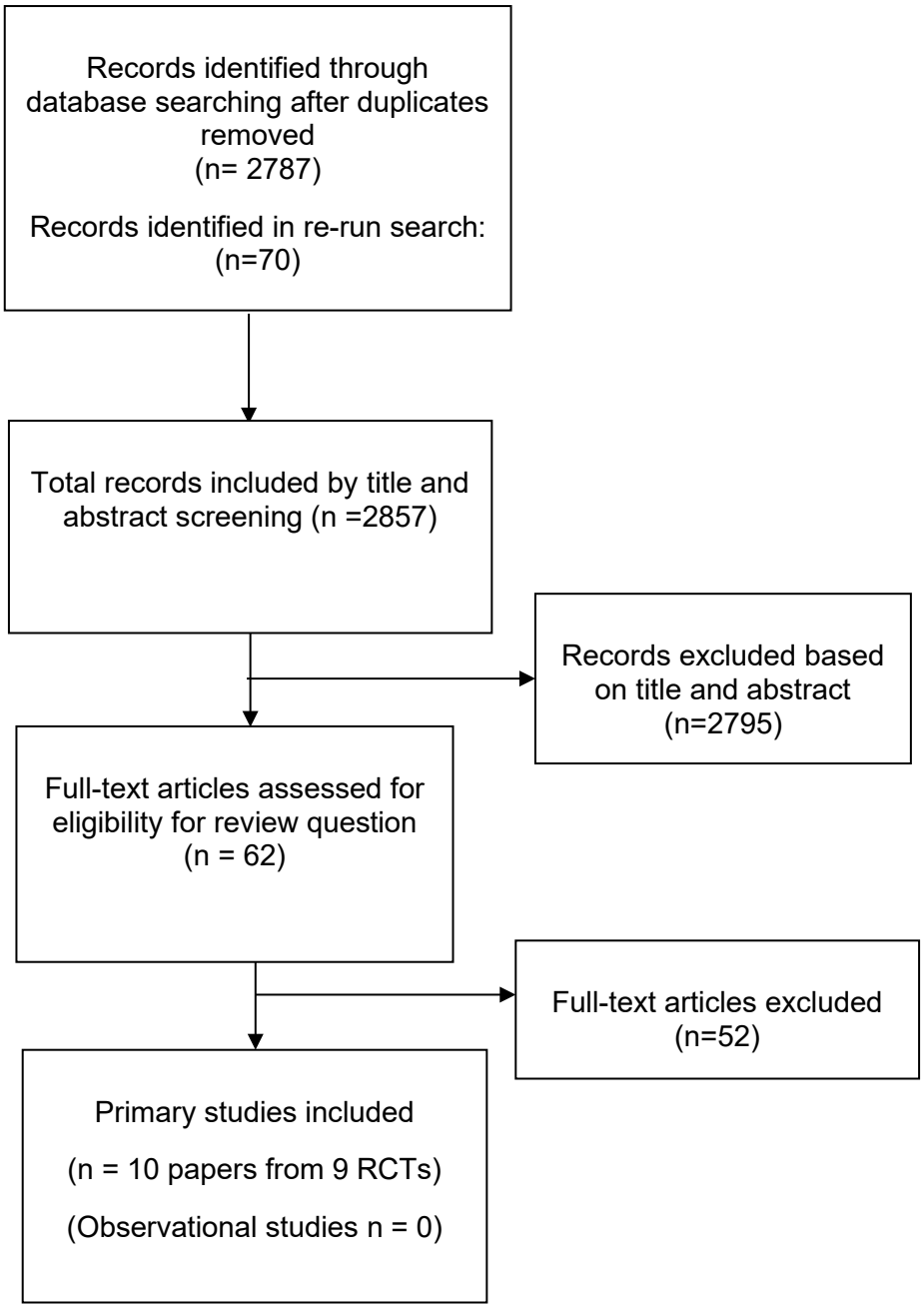
1	Diabetic Retinopathy/	0
2	Macular Edema/	0
3	(diabet* adj4 (retin* or eye* or macular*)).tw.	563
4	or/1-3	563
5	exp Cohort Studies/	0

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 – Effectiveness evidence

Ahmadabadi, 2010

Bibliographic Reference	Ahmadabadi, Hooshang Faghihi; Mohammadi, Massood; Beheshtnejad, Hooshang; Mirshahi, Ahmad; Effect of intravitreal triamcinolone acetonide injection on central macular thickness in diabetic patients having phacoemulsification.; Journal of cataract and refractive surgery; 2010; vol. 36 (no. 6); 917-22

Study details

Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Farabi Eye Hospital, Tehran University of Medical Sciences
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Included participants Patients with type 2 diabetes and moderate non-proliferative diabetic retinopathy who were candidates for surgery for visually significant cataract.
Exclusion criteria	Excluded participants Exclusion criteria were previous intraocular surgery; history of uveitis, glaucoma, or ocular hypertension; media opacity other than cataract; retinal or choroidal disease other than diabetes that could affect retinal thickness; current presence or history of clinically significant macular edema (CSME), history of retinal laser procedures; and intraoperative complications (eg, vitreous loss, iris manipulation).
Intervention(s)	The same surgery as the control arm, with the addition of an injection of 2 mg of triamcinolone acetonide (0.05 mL) 3.5 mm posterior to the inferotemporal limbus; the injection was given with a 27-gauge needle at the end of surgery. Postoperatively, both groups were prescribed ciprofloxacin 0.3% eyedrops 4 times a day and betamethasone 0.1% eyedrops 6 times a day for 1 week. After 1 week, the betamethasone was tapered over 4 weeks.
Comparator	Control: standard cataract extraction was performed under peribulbar anesthesia though a 3.2 mm temporal clear corneal incision, after which an intraocular lens (IOL) (AcrySof MA60AC, Alcon, Inc.) was implanted in the bag. Postoperatively, both groups were prescribed ciprofloxacin 0.3% eyedrops 4 times a day and betamethasone 0.1% eyedrops 6 times a day for 1 week. After 1 week, the betamethasone was tapered over 4 weeks.
Outcome measures	BCVA Change in logMAR from baseline

	intraocular pressure (IOP) Number of people with an increase greater than 21 mm Hg DR progression Incidence of Macular Edema CDVA Progression to severe non-proliferative diabetic retinopathy
Number of participants	41 eyes from 41 people
Duration of follow-up	1 , 3, and 6 months postoperatively.
Loss to follow-up	Not reported
Methods of analysis	A 2 sample t test was used to compare the means of the parametric data. The chi-square test was used for categorical data. The CDVA readings were converted to logMAR values for statistical analysis.

Study arms

Intervention arm (N = 20)

intravitreal injection of triamcinolone acetonide (TCA) 2 mg (0.05 mL) at the end of phacoemulsification (20 eyes)

Control arm (N = 21)

Standard cataract surgery with routine phacoemulsification (21 eyes)

Characteristics

Arm-level characteristics

Characteristic	Intervention arm (N = 20)	Control arm (N = 21)
Age (years) Mean (SD)	63 (10.54)	62 (10.96)
Duration of diabetes (years) Mean (SD)	12.05 (8.04)	10.86 (5.22)
CDVA (LogMAR) Corrected distance visual acuity Mean (SD)	0.18 (0.12)	0.19 (0.12)

Characteristic	Intervention arm (N = 20)	Control arm (N = 21)
HbAc1 (%) Mean (SD)	8.89 (0.7)	9.5 (1.57)
CPT (mm) central point thickness Mean (SD)	176.35 (34.39)	170.05 (30.89)
IOP (mm Hg) (intraocular pressure) Mean (SD)	16.35 (2.52)	16.86 (2.52)

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 *(Limited information on participant or assessor blinding and what was done with missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

Barone, 2022

Bibliographic Reference	Barone, Antonio; Russo, Vincenzo; Maggiore, Giulia; Loiodice, Marco Sabino; Stella, Andrea; Bux, Anna Valeria; Iaculli, Cristiana; Dexamethasone intravitreal implant in patients with cataract and naive diabetic macular edema.; European journal of ophthalmology; 2022; vol. 32 (no. 1); 364-371

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Department of Ophthalmology, University of Foggia, Foggia, Italy
Study dates	Not reported
Sources of funding	The author(s) received no financial support for the research, authorship, and/or publication of this article.
Inclusion criteria	Included participants Inclusion criteria were: glycated hemoglobin ⩽9%,controlled blood pressure (⩽130/80 mmHg), lens opacity (nuclear color and opalescence, cortical or posterior subcapsular lens opacity >3) according to the Lens Opacities Classification System III system,13 nonproliferative diabetic retinopathy and clinically significant naïve macular edema central macular thickness (CMT) >300

	microns, tomographic features of nontractional diabetic macular edema, cystoid pattern, and retinal detachment pattern as described by Koleva-Georgieva
Exclusion criteria	Excluded participants Exclusion criteria included: any treatment of diabetic macular edema with intravitreal anti-VEGF or any type of intravitreal corticosteroid before surgery, presence of treated or untreated proliferative diabetic retinopathy, mature cataract which can obscure the fundus exploration, history of ocular hypertension or glaucomaand presence of associated conditions, such as uveitis, retinal vein occlusion, and neovascular glaucoma, that could worsen macular edema. Patients who experienced intraoperative complications, such as posterior capsular tear or vitreous loss, and patients with a history of ocular surgery, inflammation, active or suspected ocular or periocular infections, were also excluded.
Intervention(s)	Patients were treated with intravitreal dexamethasone implant 0.7 mg (IDI) administered preoperative. Patients underwent phaco surgery 29.2 ± 1.6 days after implant. IDI was performed under sterile protocol, which included the use of 5% povidone-iodine solution, topical anesthesia, eyelid-speculum application, intravitreal injection of 0.7 mg dexamethasone implant via pars plana in the infero-temporal quadrant at 4 mm from the limbus, followed by post-injection topical antibiotic (moxifloxacin eye drops) one drop four times a day for 1 week. All patients underwent a standard uncomplicated phacoemulsification using a 2.5 mm clear cornea tunnel with posterior chamber intraocular lens (IOL) implantation under topical anesthesia, after surgery, chloramphenicol-betamethasone eye drops association, and indomethacin 0.1% eye drops one drop, four times a day for 2 weeks were prescribed.
Comparator	All patients underwent a standard uncomplicated phacoemulsification using a 2.5 mm clear cornea tunnel with posterior chamber intraocular lens (IOL) implantation under topical anesthesia, after surgery, chloramphenicol-betamethasone eye drops association, and indomethacin 0.1% eye drops one drop, four times a day for 2 weeks were prescribed. IDI was performed under sterile protocol, which included the use of 5% povidone-iodine solution, topical anesthesia, eyelid-speculum application, intravitreal injection of 0.7 mg dexamethasone implant via pars plana in the infero-temporal quadrant at 4 mm from the limbus, followed by post-injection topical antibiotic (moxifloxacin eye drops) one drop four times a day for 1 week.
Outcome measures	BCVA Change in LogMAR from baseline
Number of participants	40 eyes of 40 consecutive patients
Duration of follow-up	20 weeks
Loss to follow-up	0 reported
Methods of analysis	Paired *t* test was used for statistical analysis. A *p*-value <0.05 was considered statistically significant.

Study arms

Dexamethasone preoperative implant (N = 20)

0.7 mg Dexamethasone intravitreal implant (IDI) administered preoperatively (20 eyes)

Dexamethasone postoperative implant (N = 20)

0.7 mg Dexamethasone intravitreal implant administered immediately after cataract surgery (20 eyes)

Characteristics

Arm-level characteristics

Characteristic	Dexamethasone preoperative implant (N = 20)	Dexamethasone postoperative implant (N = 20)
Age (years) Mean (SD)	67.05 (4.46)	66.5 (5.19)
ETDRS (logMar) (Early Treatment of Diabetic Retinopathy Study (ETDRS) letters chart) Mean (SD)	0.75 (0.18)	0.74 (0.14)
CMT (microns) central macular thickness Mean (SD)	502 (85.24)	514.16 (93.18)
IOP (mmHg) intraocular pressure Mean (SD)	14.95 (1.5)	15.25 (1.37)

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 *(Lack of information on participant/investigator blinding. Unclear how many people were randomised, so difficult to determine if the numbers analysed are the same as the numbers randomised (missing outcome data))*
Overall bias and Directness	Overall Directness	Directly applicable

Chae, 2014

Bibliographic Reference	Chae, Ju Byung; Joe, Soo Geun; Yang, Sung Jae; Lee, Joo Yong; Sung, Kyung Rim; Kim, Jae Yong; Kim, June-Gone; Yoon, Young Hee; Effect of combined cataract surgery and ranibizumab injection in postoperative macular edema in nonproliferative diabetic retinopathy.; Retina (Philadelphia, Pa.); 2014; vol. 34 (no. 1); 149-56

Study details

Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	Asan Medical Center, Seoul, Korea
Study dates	May 2008 – December 2010
Sources of funding	Research grant from Novartis (2008-0221)
Inclusion criteria	Included participants The inclusion criteria were 1) patients with diabetes aged older than 18 years (Type 1 diabetes mellitus or Type 2 diabetes mellitus); 2) patients with nonproliferative diabetic retinopathy (NPDR), as defined by the Early Treatment Diabetic Retinopathy Study, or patients with stable DR, who had completed panretinal photocoagulation (PRP) at least 3 months earlier; 3) patients with visually significant cataract with bestcoRRected visual acuity (BCVA) under 20/30, as determined using the Snellen acuity chart; and 4) patients with central subfield thickness (CST) that was ,300 mm, as determined by spectral domain optical coherence tomography (SD OCT) (CiRRus HD-OCT; Carl Zeiss Meditec, Dublin, CA).
Exclusion criteria	Excluded participants The exclusion criteria were 1) active intraocular inflammation in either eye, 2) need for intraocular surgery within the next 12 months, 3) intractable glaucoma, 4) intraocular surgery within the previous 3 months, 5) any kind of intravitreal drug injection within the previous 3 months, 6) retinal laser treatment of diabetic ME within the previous 3 months, 7) conditions (e.g., chronic ME, anatomical macular problem, and severe macular infarction) that the investigators believed are associated with a low probability of visual acuity restoration, 8) prescription of warfarin or heparin within the previous 1 month, 9) inability to take mydriatic drugs, 10) expected poor compliance, 11) pregnancy or breastfeeding, and 12) any known history of adverse reactions to anti-VEGF drugs.
Intervention(s)	Phacoemulsification and intraocular lens implantation combined with ranibizumab injection at the conclusion of cataract surgery (0.05 mL of a solution containing 0.5 mg of ranibizumab) Mydriasis was performed by treatment with Mydrin P (Santen, Osaka, Japan). Phacoemulsification was performed under topical anesthesia with topical anesthetics (Alcain; Alcon Laboratories, Fort Worth, TX) by four surgeons (Y.H.Y., J.-G.K., J.Y.K., and K.R.S.). Phacoemulsification was performed with a phaco-machine (Infiniti; Alcon Laboratories). After phacoemulsification, a foldable intraocular lens (Acrysof MA60AC; Alcon Laboratories) was implanted in the capsular bag. At the conclusion of cataract surgery in the ranibizumab injection

	group, 0.05 mL of a solution containing 0.5 mg of ranibizumab was injected intravitreally at the sclera from 3 mm posterior to the limbus. Of the 76 patients, 46 received panretinal PRP at least 3 months before the study. In the ranibizumab injection group, 24 of the 39 patients received PRP.
Comparator	Phacoemulsification and intraocular lens implantation combined with sham injection at the conclusion of cataract surgery. In the sham group, the needle tip was only touched to the conjunctiva surface. In the sham injection group, 22 of the 37 patients received PRP
Outcome measures	BCVA central macular thickness (CMT) total macular volume (TMV) Macular edema
Number of participants	The study included 80 eyes of 80 patients. Using a table of random numbers, 40 patients received the ranibizumab injection and the other 40 patients received a sham injection
Duration of follow-up	After cataract surgery, postoperative examinations were performed at 1 week, 1, 3, and 6 months later. A complete ophthalmic examination and SD OCT values.
Loss to follow-up	Four patients were dropped from the study due to screening failure. Another five patients withdrew their consent during the study in the absence of an adverse event: consequently, 1 ranibizumabinjected patient and 1 sham patient were only followed for 3 months, whereas another 2 ranibizumab-injected patient and 1 sham patients were only followed for 1 month and 1 week after surgery, respectively. Thus, 39 patients who underwent combined phacoemulsification and intravitreal ranibizumab injection and 37 patients who received phacoemulsification and a sham injection only were followed for 6 months.
Methods of analysis	The ranibizumab injection and sham groups were compared in terms of change in BCVA, CST, and TMV after cataract surgery using independent t test. The two groups were compared in terms of PME occurrence rate using chi-square test. A P , 0.05 was considered to indicate statistical significance.
Additional comments	Clinically meaningful PME was defined according to Kim et al,3 albeit with a modification. Kim et al defined PME as a .30% increase in CST relative to the initial screening CST, as assessed by time domain (TD) OCT. In the present study, PME was defined as a .60 mm increase in CST relative to the screening CST value, as assessed by SD OCT. This is because a .30% increase relative to normal CST in TD OCT is approximately equivalent to a .60 mm increase. The safety of ranibizumab injection was evaluated at every follow-up. If there was a serious problem that could affect visual acuity, further treatments that were specific for each situation were performed. All patients had Type 2 diabetes mellitus; none had Type 1 diabetes mellitus.

Study arms

Ranibizumab injection (N = 39)

Phacoemulsification with ranibizumab injection at the conclusion of cataract surgery (0.05 mL of a solution containing 0.5 mg of ranibizumab) (39 eyes)

Sham injection (N = 37)

Phacoemulsification with sham injection at the conclusion of cataract surgery (37 eyes)

Characteristics

Arm-level characteristics

Characteristic	Ranibizumab injection (N = 39)	Sham injection (N = 37)
Age (years) Mean (SD)	62.9 (9.42)	67.2 (8.29)
Males (number) Nominal	21	20
Visual acuity logMAR Mean (SD)	0.5 (0.25)	0.52 (0.25)
CST (µm) (central subfield thickness) Mean (SD)	256 (26.91)	253 (35.69)

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 *(Lack of information on participant/investigator/assessor blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

Fard, 2011

Bibliographic Reference	Fard, Masoud Aghsaei; Yazdanei Abyane, Alireza; Malihi, Mehrdad; Prophylactic intravitreal bevacizumab for diabetic macular edema (thickening) after cataract surgery: prospective randomized study.; European journal of ophthalmology; 2011; vol. 21 (no. 3); 276-81

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Farabi Eye Hospital
Study dates	July 2006 – February 2009
Sources of funding	Study supported by a grant from Tehran University of Medical Sciences.
Inclusion criteria	Included participants Inclusion criteria included diabetic patients with preexisting moderate or severe nonproliferative diabetic retinopathy (as defined by the 4-2-1 rule) scheduled for cataract surgery. This group of patients has been shown to have a high risk of development of ME (5). Only patients with preoperative visual acuity 20/50 or worse and preoperative optical coherence tomography (OCT) showing less than 200 μm central macular thickness were included.
Exclusion criteria	Excluded participants Macular ischemia (by evaluation of previous fluorescein angiograms),vitreomacular traction, macular hole, prior laser photocoagulation in the study eye, macular thickening on OCT, prior intraocular surgery, and history of uveitis, glaucoma, trauma, or age-related macular degeneration
Intervention(s)	Phacoemulsification with intraocular lens implantation (using the same procedure as the control group) with 1.25 mg of intravitreal bevacizumab (IVB) at the end of cataract surgery
Comparator	Standardized procedure of phacoemulsification with intraocular lens (IOL) implantation alone (control group). This included topical anaesthesia, clear corneal incision, capsuloRRhexis, phacoemulsification, and intraocular lens placement in capsular bag
Outcome measures	BCVA Change in logMAR from baseline DR progression Number with progression of diabetic retinopathy Adverse events

	Number of treatment-related ocular adverse events
Number of participants	61 eyes from 61 people
Duration of follow-up	6 months
Loss to follow-up	61 patients completed 6 months of follow-up (0 loss to follow up in intervention group, 2 lost in control group). No one received second intravitreal injection of bevacizumab
Methods of analysis	A 2-sample t test was used to compare the means of the parametric data, and chi-square test was used for categorical data. Sample size was calculated to provide 80% power to detect a 0.13-logMAR difference in mean acuity between the 2 treatment groups with α = 0.05 and a standard deviation of visual acuity of 0.2 based on previously published data with some modifications.

Study arms

Bevacizumab injection (N = 31)

Phacoemulsification with intraocular lens implantation with 1.25 mg intravitreal bevacizumab at the end of surgery (31 eyes)

Control (N = 30)

Phacoemulsification with intraocular lens implantation alone (30 eyes)

Characteristics

Arm-level characteristics

Characteristic	Intervention arm (N = 31)	Control arm (N = 30)
% Female Nominal	58	50
Mean age (SD) Mean (SD)	62 (5)	60 (4)
Comorbidities Coronary artery disease % Nominal	48	53
Comorbidities Hypertension % Nominal	58	60
Mean HbA1c Mean (SD)	7.1 (0.69)	7.29 (0.72)
DM type 1 % (diabetes mellitus) Nominal	42	43

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

Gupta, 2021

Bibliographic Reference	Gupta, Parul Chawla; Ram, Jagat; Kumar, M Praveen; Agarwal, Aniruddha; Gupta, Vishali; Singh, Ramandeep; Bansal, Reema; Katoch, Deeksha; Dogra, Mangat R; Gupta, Amod; Effect of sustained-release long-acting intravitreal dexamethasone implant in patients of non-proliferative diabetic retinopathy undergoing phacoemulsification: A randomized controlled trial.; Indian journal of ophthalmology; 2021; vol. 69 (no. 11); 3263-3272

Study details

Trial registration number and/or trial name	CTRI/2019/05/019407
Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Lens and Retina clinic of a tertiary care referral institute
Study dates	February 2015 – August 2018
Sources of funding	The study drugs and funding were provided by Allergan India.
Inclusion criteria	Included participants Patients of either gender (age 30 years or more) with type-2 diabetes mellitus and mild/moderate or severe non-proliferative DR (NPDR) with/without DME, along with the presence of cataract requiring surgery.
Exclusion criteria	Excluded participants The presence of any one of the following resulted in exclusion: the presence of proliferative DR; ocular hypertension or glaucoma; neovascular glaucoma, retinal vein occlusions, uveitis; previous administration of any intravitreal/ periocular agents (either as systemic or local administration) over the past 3 months; use of prostaglandin analogues, adrenaline or nicotinic acid or drug which can exacerbate DME; intraocular surgery/pars plana vitrectomy/laser photocoagulation in the last 3 months; and patients with media haze.
Intervention(s)	**Dexamethasone DDS group:** received injection dexamethasone drug delivery system 0.7 mg intraoperatively during phacoemulsification and IOL implantation. Standard phacoemulsification and IOL implantation were undertaken in all patients (eyes) by an experienced surgeon (JR) under peribulbar anesthesia. Both groups of patients received a similar standard of care, including routine care for diabetes. If the investigator considered it necessary, the patients were

	administered rescue interventions for DME. Criteria for interventions included a 100-µm increase in central macular thickness or CMT >350 µm on OCT.
Comparator	**Standard of Care group (SOC):** received phacoemulsification and IOL implantation without injection of dexamethasone DDS.
Outcome measures	Rates of additional intervention Number who needed rescue treatments (reported by subgroups of people with NPDR and DMO, and people with NPDR but without DMO)
Number of participants	151 eyes in 151 people
Duration of follow-up	Patients belonging to both groups had a similar follow-up schedule. Each patient was evaluated at day 1, one week, two weeks, four weeks, and 12 weeks after cataract surgery. The patients were followed up for a duration of 3 months from the time of cataract surgery
Loss to follow-up	5 participants were lost to the intervention arm 5 participants were lost to the control arm
Methods of analysis	Sample size estimation was based on the comparison of repeated measures of OCT at 5 different time points, namely, baseline, week 1, 2, 4, and 12, between SOC and dexamethasone DDS by two-way mixed model ANOVA evaluating for time-treatment interaction. This calculated to the total sample size of 138. Keeping a dropout possibility of 10%, the final sample size was calculated to be 151 patients. Based on the allocation ratio of 1.2:1 between the dexamethasone DDS group and SOC, this would amount to 82 patients in dexamethasone DDS group and 69 patients in SOC group. Intention-to-treat (ITT) analysis was used. The analysis was conducted using R.
Additional comments	Included people with mild, moderate and severe NPDR, with and without DMO. Only 1 outcome was reported by subgroup (number of people who needed rescue treatments – people without DMO and people with DMO)

Study arms

Intervention arm (N = 82)

Phacoemulsification and intraocular lens (IOL) implantation with 0.7 mg intraoperative injection of dexamethasone drug delivery system (DEX) (82 eyes)

Control arm (N = 69)

Phacoemulsification and intraocular lens (IOL) implantation without injection of dexamethasone drug delivery system (DDS) (69 eyes)

Characteristics

Arm-level characteristics

Characteristic	Intervention arm (N = 82)	Control arm (N = 69)
% Female Nominal	45.1	42

Characteristic	Intervention arm (N = 82)	Control arm (N = 69)
Mean age (SD) Mean (SD)	60.6 (7.7)	61.7 (7.5)
Diabetic macular edema % Nominal	33.3	66.7
Mild non-proliferative diabetic retinopathy % Nominal	43.6	56.4

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	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kandasamy, 2019

Bibliographic Reference	Kandasamy, Rathika; Constantinou, Marios; Rogers, Sophie L; Sandhu, Sukhpal Singh; Wickremasinghe, Sanjeewa; Al-Qureshi, Salmaan; Lim, Lyndell L; Prospective randomised clinical trial of intravitreal bevacizumab versus triamcinolone in eyes with diabetic macular oedema undergoing cataract surgery: 6-month results.; The British journal of ophthalmology; 2019; vol. 103 (no. 12); 1753-1758

Study details

Other publications associated with this study included in review	Sasongko 2020. Sasongko reports on progression outcomes at 6 months. Kandasamy reports on best corrected visual acuity, additional treatments and adverse events at 6 months
Trial registration number and/or trial name	ACTRN12611000888965
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	Hospital
Study dates	June 2012 – August 2017

Sources of funding	This study received funding from the Royal Victorian Eye and Ear Hospital Grants Program 2013–2014 (Melbourne), Diabetes Australia Research Program Grant 2015 (CanbeRRa), Ramaciotti Health Investment Grant 2016 (Sydney) and the Hazel Jean Eastham Bequest (Melbourne). Centre for Eye Research Australia receives operational infrastructure support from the Victorian government.
Inclusion criteria	Included participants People over 18 years of age, with diabetes and clinically significant macular oedema (CSME) involving the fovea in the study eye at baseline, or CSME in the study eye within 24 months of study entry, or microaneurysms at the edge of the foveal avascular zone of the study eye, which are not amenable to treatment with laser (≤500µm from the foveal centre)
Exclusion criteria	Excluded participants Macular oedema from causes other than diabetic retinopathy OR significant angiographic macular ischaemia ConcuRRent ocular inflammation / infection Loss of vision from other causes (e.g. age related macular degeneration, myopic macular degeneration) Intractable glaucoma OR pre-existing glaucomatous visual field defect Previous history of steroid response (Intraocular pressure elevation to more than 35mmHg following steroid treatment) Best corrected visual acuity less than 6/60 in the fellow eye Prior history of adverse reaction/allergy to triamcinolone acetate or anti-vascular endothelial growth factor (VEGF) drugs Previous intravitreal injection of triamcinolone acetate within 10 weeks OR intravitreal injection of anti-VEGF drugs within 3 weeks of study entry Previous macular argon laser photocoagulation within 3 months of study entry Patients requiring systemic steroids for other indications (more than 5mg of prednisolone daily or equivalent) Pregnancy OR breastfeeding Patients with concurrent severe systemic infections/disease (e.g. septicaemia)
Intervention(s)	**Phacoemulsification and intravitreous bevacizumab** All patients underwent standard phacoemulsification with intraocular lens implantation using standard technique under topical or regional anesthesia. The AcrySoft SN60WF (Alcon, Inc, Fort Worth, TX) IOL was used in all cases. This was followed by an intravitreous injection of 1.25 mg bevacizumab (Avastin, Genentech Inc., San Francisco, CA, USA)administered following the surgery using a 30-gauge needle. Prednisolone acetate 1% (Prednefrin Forte, Allergan) and Chloramphenicol 0.5% (Chlorsig, Sigma Pharmaceuticals, Australia) eye drops were prescribed 4 times daily for 1 week, after which the topical steroids only were continued and tapered off within 4 weeks after surgery
Comparator	**Phacoemulsification and intravitreous triamcinolone acetonide** All patients underwent standard phacoemulsification with intraocular lens implantation using standard technique under topical or regional anesthesia. The AcrySoft SN60WF

	(Alcon, Inc, Fort Worth, TX) IOL was used in all cases. This was followed by an intravitreous injection of 4 mg triamcinolone (TA, Triesence; Alcon Pharmaceuticals, Ft. Worth, TX) administered following the surgery using a 27-gauge needle. Prednisolone acetate 1% (Prednefrin Forte, Allergan) and Chloramphenicol 0.5% (Chlorsig, Sigma Pharmaceuticals, Australia) eye drops were prescribed 4 times daily for 1 week, after which the topical steroids only were continued and tapered off within 4 weeks after surgery.
Number of participants	62 participants (65 eyes; 31 eyes randomised to bevacizumab and 34 eyes randomised to triamcinolone acetonide)
Duration of follow-up	1 week post-surgery and monthly thereafter for 12 months
Loss to follow-up	5 eyes were lost to the group receiving phacoemulsification and intravitreous bevacizumab 1 eye was lost to the group receiving phacoemulsification and triamcinolone acetonide
Methods of analysis	Statistical analysis was performed using SPSS software (version 18 for windows; SPSS Inc., Chicago, IL, U.S.A.). Variables are expressed as mean ± standard error of mean. Non-parametric variables were analyzed using Wilcoxon-Mann-Whitney test. P value of less than 0.05 was considered significant.
Additional comments	To better compare the study results with DRCR.net protocols, the authors defined clinically meaningful postoperative macular edema by CMT >300 mm using SD-OCT (Spectralis SD-OCT; Heidelberg engineering; Germany).

Study arms

Intravitreous bevacizumab (N = 28)

Phacoemulsification and 1.25 mg intravitreous bevacizumab (28 eyes)

Intravitreous triamcinolone (N = 33)

Phacoemulsification and 4 mg intravitreous triamcinolone acetonide (33 eyes)

Characteristics

Arm-level characteristics

Characteristic	Intravitreous bevacizumab (N = 28)	Intravitreous triamcinolone (N = 33)
% Female Nominal	36	27
Age (mean, 95% CI) years Mean (95% CI)	70.2 (67.4 to 73)	64.3 (61.1 to 67.5)
HbA1c (%) Median (IQR)	7.5 (7 to 8.6)	7.5 (6.3 to 8.4)

Characteristic	Intravitreous bevacizumab (N = 28)	Intravitreous triamcinolone (N = 33)
Type 1 Sample size	n = 0	n = 1 ; % = 3
Type 2 requiring insulin Sample size	n = 17 ; % = 61	n = 21 ; % = 64
Type 2 not requiring insulin Sample size	n = 11 ; % = 39	n = 11 ; % = 33
BCVA letters Best corrected visual acuity Mean (95% CI)	55.1 (48.7 to 61.4)	50.5 (45.3 to 55.8)
CMT (microns) Central macular thickness Median (IQR)	307.5 (277.5 to 391.5)	316 (282 to 457)
Mild Sample size	n = 1 ; % = 4	n = 6 ; % = 19
Moderate Sample size	n = 13 ; % = 46	n = 11 ; % = 33
Severe Sample size	n = 3 ; % = 11	n = 5 ; % = 15
Panretinal photocoagulation only (inactive proliferative diabetic retinopathy) Sample size	n = 9 ; % = 32	n = 11 ; % = 33
Treated panretinal photocoagulation (active) Sample size	n = 2 ; % = 7	n = 0
Diabetic macular oedema Sample size	n = 22 ; % = 79	n = 26 ; % = 79
Any treatment (triamcinolone, bevacizumab or macular laser) Sample size	n = 15 ; % = 50	n = 20 ; % = 61
Macular laser Sample size	n = 13 ; % = 46	n = 18 ; % = 55
Panretinal photocoagulation laser Sample size	n = 10 ; % = 36	n = 9 ; % = 27
Bevacizumab Sample size	n = 3 ; % = 11	n = 3 ; % = 9

Characteristic	Intravitreous bevacizumab (N = 28)	Intravitreous triamcinolone (N = 33)
Triamcinolone Sample size	n = 1 ; % = 4	n = 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

Lanzagorta-Aresti, 2009

Bibliographic Reference	Lanzagorta-Aresti, Aitor; Palacios-Pozo, Elena; Menezo Rozalen, Jose Luis; Navea-Tejerina, Amparo; Prevention of vision loss after cataract surgery in diabetic macular edema with intravitreal bevacizumab: a pilot study.; Retina (Philadelphia, Pa.); 2009; vol. 29 (no. 4); 530-5

Study details

Study type	Randomised controlled trial (RCT)
Study location	Spain
Study setting	26 consecutive diabetic patients with nonproliferative diabetic retinopathy and macular oedema who were to undergo cataract surgery, and we divided them into two randomized groups to be studied prospectively at the eye centre
Study dates	Not reported
Inclusion criteria	Included participants. We selected consecutive Type II diabetic patients with moderate nonproliferative diabetic retinopathy associated with diffuse macular edema affecting the foveal center who were to undergo cataract surgery at our center.
Exclusion criteria	Excluded participants Patients with other associated ocular diseases capable of causing macular edema, patients who had had previous eye surgery, and patients who had suffered complications during surgery or in the postoperative period were excluded
Intervention(s)	All the patients had been lasered preoperatively with macular grid provided by Pascal Photocoagulator (OptiMedica Corporation, Santa Clara, CA) between 2 and 3 months before surgery (2.3 0.2 months) to standardize prior treatment for DME. The surgical procedure consisted of phacoemulsification with the Alcon Infiniti device plus implantation of a SN60WF Alcon intraocular lens performed without complications by the same surgeon who was also masked. On completion of the surgery and before removing the eye speculum, a volume of 0.05 mL was injected at

	3.5 mm from the limbus with visual control of the needle centered in the eye cavity; Group I received bevacizumab (avastin) via a 30G needle – dose not reported
Comparator	All the patients had been lasered preoperatively with macular grid provided by Pascal Photocoagulator (OptiMedica Corporation, Santa Clara, CA) between 2 and 3 months before surgery (2.3 0.2 months) to standardize prior treatment for DME. The surgical procedure consisted of phacoemulsification with the Alcon Infiniti device plus implantation of a SN60WF Alcon intraocular lens performed without complications by the same surgeon who was also masked. On completion of the surgery and before removing the eye speculum, a volume of 0.05 mL was injected at 3.5 mm from the limbus with visual control of the needle centered in the eye cavity; The control group received balanced saline solution via a 30G needle
Outcome measures	BCVA Change in Snellen ratio from baseline. Converted to LogMAR for this review
Number of participants	26 eyes from 26 people
Duration of follow-up	3 and 6 months
Loss to follow-up	All the patients who achieved the criteria were included for a period of 3 months since the start of the study.
Methods of analysis	Visual acuity and thickness measurements by OTC were statistically studied using the program SPSS v.13.0 (SPSS Inc, Chicago, IL). Visual acuity was converted to logMAR values for statistical analysis, and we use student's t-test for visual acuity and macular thickness
Additional comments	The eye that had less visual acuity was chosen, because it was the first one to have a cataract surgery performed

Study arms

Bevacizumab injection (N = 13)

Phacoemulsification plus implantation of an intraocular lens followed by injection of intravitreal bevacizumab (13 eyes)

Control arm (N = 13)

Phacoemulsification plus implantation of an intraocular lens followed by injection of balanced saline solution (13 eyes)

Characteristics

Arm-level characteristics

Characteristic	Bevacizumab injection (N = 13)	Control arm (N = 13)
BCVA before surgery Best-CoRRected Visual Acuity (Snellen)	0.27 (0.17)	0.24 (0.16)

Characteristic	Bevacizumab injection (N = 13)	Control arm (N = 13)
Mean (SD)		
Central Macular Thickness (OCT) Before surgery (µm) Mean (SD)	282.62 (57.64)	310.38 (82.99)

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 *(Lack of information on patient baseline characteristics and potential missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

Sasongko, 2020

Bibliographic Reference	Sasongko, Muhammad B; Rogers, Sophie; Constantinou, Marios; Sandhu, Sukhpal S; Wickremasinghe, Sanjeewa S; Al-Qureshi, Salmaan; Lim, Lyndell L; Diabetic retinopathy progression 6 months post-cataract surgery with intravitreous bevacizumab vs triamcinolone: A secondary analysis of the DiMECAT trial.; Clinical & experimental ophthalmology; 2020; vol. 48 (no. 6); 793-801

Study details

Secondary publication of another included study- see primary study for details	Secondary publication of the DIMECAT trial (see Kandasamy 2019)
Other publications associated with this study included in review	Kandasamy 2019. Sasongko reports on progression outcomes at 6 months. Kandasamy reports on best corrected visual acuity, additional treatments and adverse events at 6 months
Outcome measures	DR progression Number with 1 step progression and 2 step progression

Study arms

Intravitreous bevacizumab (N = 28)

Phacoemulsification and 1.25 mg intravitreous bevacizumab (28 eyes)

Intravitreous triamcinolone (N = 33)

Phacoemulsification and 4 mg intravitreous triamcinolone acetonide (33 eyes)

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

Song, 2020

Bibliographic Reference	Song, Weilin; Conti, Thais F; Gans, Richard; Conti, Felipe F; Silva, Fabiana Q; Saroj, Namrata; Singh, Rishi P; Prevention of Macular Edema in Patients With Diabetic Retinopathy Undergoing Cataract Surgery: The PROMISE Trial.; Ophthalmic surgery, lasers & imaging retina; 2020; vol. 51 (no. 3); 170-178

Study details

Trial registration number and/or trial name	NCT01988246/The PROMISE Trial
Study type	Randomised controlled trial (RCT)
Study location	Ohio, USA
Study setting	Trial conducted at the Cole Eye Institute, Cleveland, Ohio
Study dates	September 2014 – April 2018
Sources of funding	Supported by a research grant from Regeneron Pharmaceuticals. Dr. Saroj has received personal fees from Aerie, Adverum, Apellis, Regeneron, and RegenxBio; personal fees and other funding from Allegro and SamaCare; and other funding from Prevent outside the submitted work. Dr. Singh has received personal fees from Regeneron Pharmaceuticals, Genentech/Roche, Optos, Alcon/Novartis, Zeiss, and Bausch + Lomb, as well as grants from Apellis, outside the submitted work. The remaining authors report no relevant financial disclosures.
Inclusion criteria	Included participants The study included 30 patients who were 18 years of age or older with diabetes (Type 1 or 2) and nonproliferative DR (NPDR) or inactive proliferative DR (PDR), without clinically significant ME, and requiring cataract extraction by phacoemulsification with planned implantation of a posterior chamber intraocular lens into the capsular bag. All patients had a central subfield macular thickness (CST) of less than 320 µm (evaluated using the CiRRus SD-OCT [Zeiss, Dublin, CA]) in the study eye prior to cataract surgery and BCVA between 20/20 and 20/200

	at time of enrolment into the study. Only one eye was enrolled in the study at a time.
Exclusion criteria	Excluded participants Patients who presented with active PDR or signs of clinically significant vitreomacular traction or epiretinal membrane in the study eye were excluded. Additionally, patients who had a history of retinal detachment, ischemic maculopathy, central or branch retinal vein occlusion, central or branch retinal artery occlusion, exudative AMD, corneal transplants, or chronic or recurrent inflammatory eye disease were excluded. Exclusion criteria based on previous treatment included those who received intraocular or periocular corticosteroids within 3 months of surgery; intravitreal anti-VEGF therapy within 6 months of preoperative baseline visit; systemic corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDS), or anti-VEGF agents within 7 days of surgery; or topical NSAIDs or corticosteroids within 7 days before surgery
Intervention(s)	Enrolled patients were randomised to receive either 2 mg IAI (0.05 mL) or sham in the study eye at the time of surgery (Day 0) post-cataract excision. All patients received standard-of-care (SOC) medications in the study eye during the 90-day follow-up period. The SOC regimen consisted of topical ciprofloxacin hydrochloride four times per day for 1 week and topical prednisolone acetate four times per day in the study eye for 2 weeks following cataract surgery. The study consisted of eight visits: a screening visit (performed within 4 weeks to 2 days before the surgery visit), the cataract surgery (Day 0), and six postoperative follow-up visits (Days 1, 7, 14, 30, 60, and 90).
Comparator	Comparator patients were randomised to receive a sham injection in the study eye at the time of surgery (Day 0) post-cataract excision.
Outcome measures	BCVA Change in ETDRS letters (converted by reviewers to logMAR to allow for meta-analysis) Adverse events Number of ocular treatment-related adverse events Incidence of Macular Edema
Number of participants	30 eyes from 30 people
Duration of follow-up	90 days
Loss to follow-up	1 lost to follow up in control group, 0 lost to follow up in intervention group
Methods of analysis	Mean levels at specific time points were compared between the two groups using two-sample *t*-tests. To estimate changes at BCVA and CST from baseline at 30, 60, and 90 days within groups and compare these changes between groups, linear mixed-effect models were fitted. An autoregressive correlation structure model repeated measures within subject. Estimated change at each time point along with mean differences between groups on these changes were presented with 95% confidence intervals. Models were then adjusted for the baseline measure of each outcome.

Additional comments	

Study arms

Intervention arm (N = 15)

5 mg intravitreal aflibercept (0.05 mL) during cataract surgery (15 eyes)

Control arm (N = 15)

sham injection during cataract surgery (15 eyes)

Characteristics

Arm-level characteristics

Characteristic	Intervention arm (N = 15)	Control arm (N = 15)
% Female Sample size	n = 6 ; % = 40	n = 10 ; % = 66
Average age at screening (Age range) Nominal	66	66
Age range (years) Range	53 to 80	47 to 80
Inital HbA1C Mean (SD)	8.3 (2.64)	8.7 (1.91)
Mild Nominal	5	5
Moderate Nominal	4	5
Severe Nominal	1	1
Inactive PDR Nominal	5	4
ETDRS Scores: Average (Range) Nominal	70.1	69.2

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, 2009

Bibliographic Reference	Takamura, Yoshihiro; Kubo, Eri; Akagi, Yoshio; Analysis of the effect of intravitreal bevacizumab injection on diabetic macular edema after cataract surgery.; Ophthalmology; 2009; vol. 116 (no. 6); 1151-7

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Outpatient department of the University of Fukui
Study dates	June 2007 – May 2008
Sources of funding	Not reported
Inclusion criteria	Included participants Forty-three patients with type 2 diabetes, non-proliferative diabetic retinopathy and DME, whose macular thickness was 300 m determined by OCT testing, and who had significant lens opacity (more than grade 3 for any type of cataract: cortical, nuclear, or posterior subcapsular) by the Lens Opacities Classification System III were recruited for the study.26 Other inclusion criteria were that DME had ocurred 3 to 18 months earlier, macular edema involved the fovea, and best corrected visual acuity (BCVA) was 20/40
Exclusion criteria	Excluded participants Exclusion criteria were a history of ocular surgery and inflammation, the presence of other ocular diseases, and intraoperative complications such as posterior capsule rupture and severe iris damage. Also, eyes with proliferative diabetic retinopathy were excluded. No patients had undergone photocoagulation of the treated eye within the previous 12 months, and none did so during follow-up. There was no previous intravitreal injection, including any VEGF inhibitors or steroid
Intervention(s)	Cataract surgery with intravitreal injection of bevacizumab. The operative techniques included complete continuous curvilinear capsulorhexis and phacoemulsification through a 3.5-mm corneoscleral incision with intracapsular implantation of a foldable acrylic intraocular lens followed by a single intravitreal injection of bevacizumab. Bevacizumab was prepared by the institutional pharmacy as sterile filled and packed tuberculin syringes containing 0.05 mL (1.25 mg) bevacizumab, which was injected intravitreally using a 30-gauge needle. Postoperatively, all patients received similar routine medication, including topical application of diclofenac sodium, an antibacterial agent, and 0.1% prednisolone 3 times daily for 3 months after surgery. None of the patients were treated with neodymium:YAG laser posterior capsulotomy after cataract surgery.
Comparator	Cataract surgery without intravitreal injection of bevacizumab. In the control group, a sham injection was not performed.
Outcome measures	BCVA Change in LogMAR from baseline – insufficient data reported to extract for use in this review Adverse events Number of people with raised intraocular pressure, Number of people with intraocular inflammation

Number of participants	42 eyes in 42 people
Duration of follow-up	1 and 3 months after surgery
Loss to follow-up	One patient dropped out from the study owing to personal reasons; thus, 42 patients with DME participated
Methods of analysis	Significance of differences in age, the duration of diabetic retinopathy, level of hemoglobin A1c, severity of cataract, RT, and VA between the control and bevacizumab groups was analyzed by the unpaired Student *t* test. The RT and VA at 1 day before and 1 or 3 months after surgery were compared using the paired Student *t* test. CoRRelations between postoperative VA and RT or preoperative VA were studied by ordinary least-squares) regression analysis. Differences at *P*0.05 were considered significant
Additional comments	All patients underwent a complete ophthalmologic examination, including visual acuity (VA), slit-lamp biomicroscopy with a 90-D lens, intraocular pressure (IOP) determination, stereoscopic fundus photography, and RT measurement using OCT. The BCVA was examined using the decimal VA system, and was converted to the logarithm of the minimum angle of resolution scale. DME was defined as retinal thickening of 2 disc areas involving some portion of the foveal avascular zone.

Study arms

Bevacizumab injection (N = 21)

Cataract surgery combined with intravitreal injection of 1.25 mg bevacizumab (21 eyes).

Control (N = 21)

Cataract surgery only (21 eyes)

Characteristics

Arm-level characteristics

Characteristic	Bevacizumab injection (N = 21)	Control (N = 21)
% Female No of events	n = 12 ; % = 57	n = 11 ; % = 52
Age (years) Mean (SD)	67.3 (5.2)	69.1 (5.9)
HbA1c Mean (SD)	7.1 (0.6)	6.8 (0.8)
Cortical cataract Mean (SD)	3.09 (1.14)	3.14 (0.96)
Nuclear cataract Mean (SD)	3.38 (0.87)	3.46 (0.81)
Posterior subcapsular cataract	2.43 (*1.21*)	2.57 (1.21)

Characteristic	Bevacizumab injection (N = 21)	Control (N = 21)
Mean (SD)		
Preoperative visual acuity (logMAR) Mean (SD)	0.9 (0.3)	0.84 (0.4)

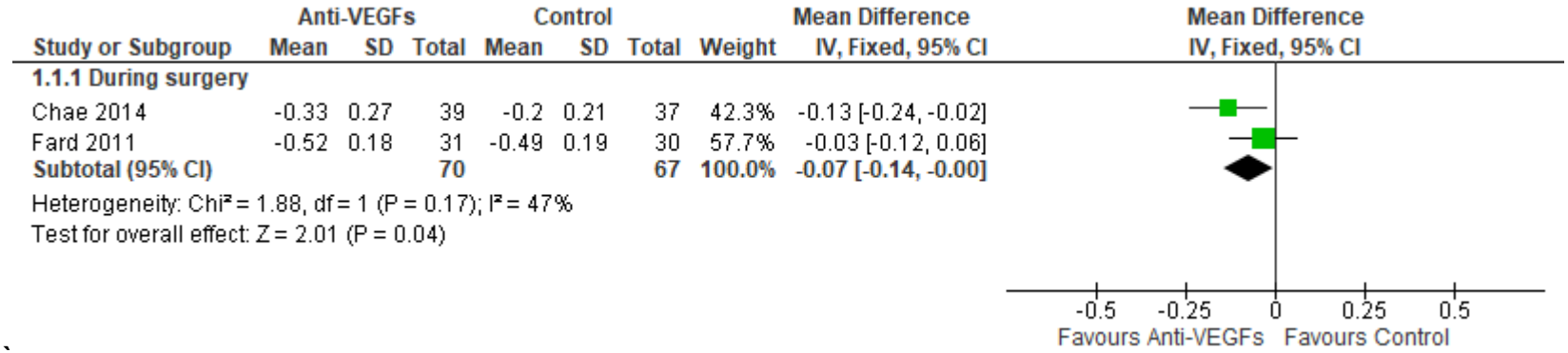
Critical appraisal – GDT Crit App – Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

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

Appendix E – Forest plots

E.1.1 Anti-VEGF agents vs control in people with non-proliferative diabetic retinopathy

Figure 1. Best corrected visual acuity measured with logMAR (change from baseline)



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Change from baseline calculated by reviewer for Fard 2011.

Figure 2. Best corrected visual acuity measured with ETDRS (change from baseline)

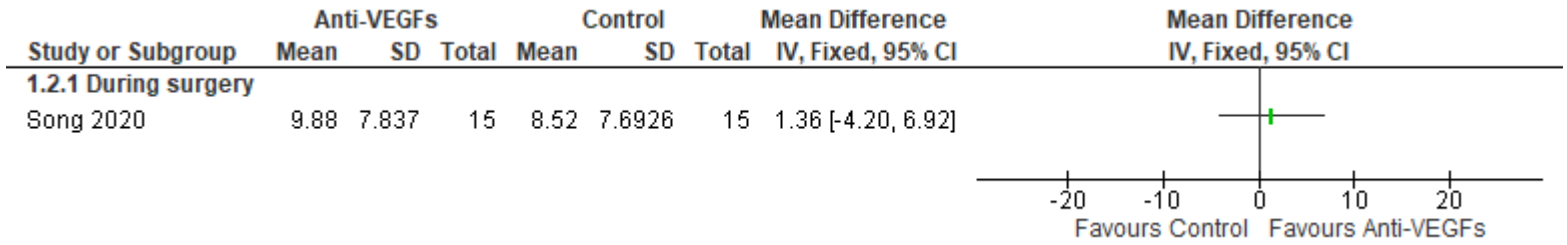


Figure 3. Progression to a higher grade of diabetic retinopathy or to diabetic macular oedema

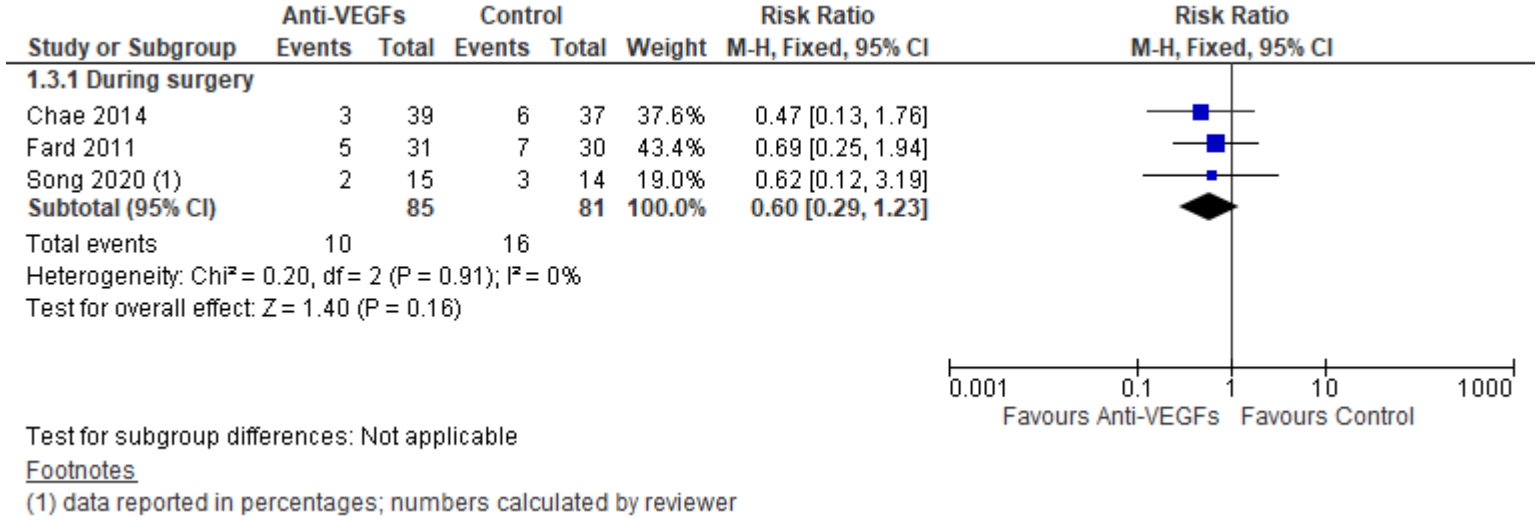
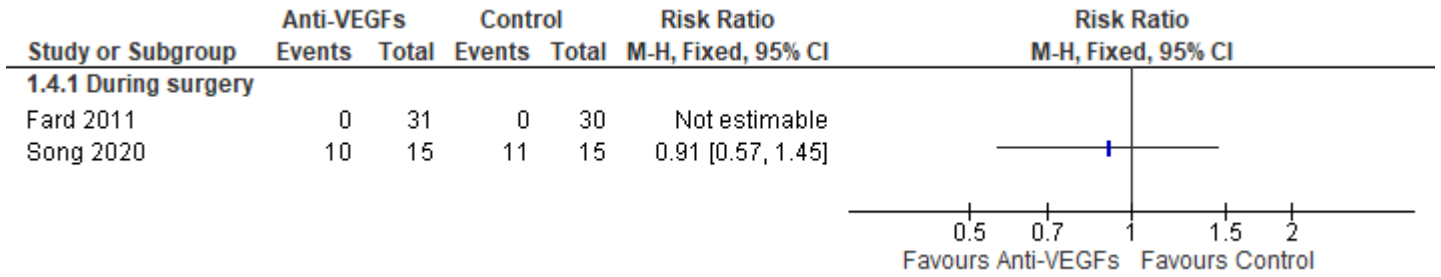
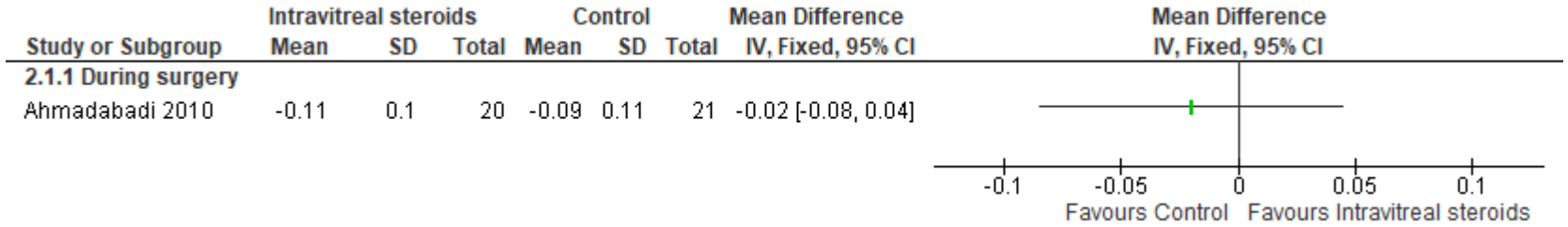


Figure 4. Number of ocular treatment related adverse events



E.1.2 Intravitreal steroids vs control in people with non-proliferative diabetic retinopathy

Figure 5. Best corrected visual acuity measured with logMAR (change from baseline)



Change from baseline calculated by reviewer.

Figure 6. Progression to macular oedema or Severe non-proliferative diabetic retinopathy

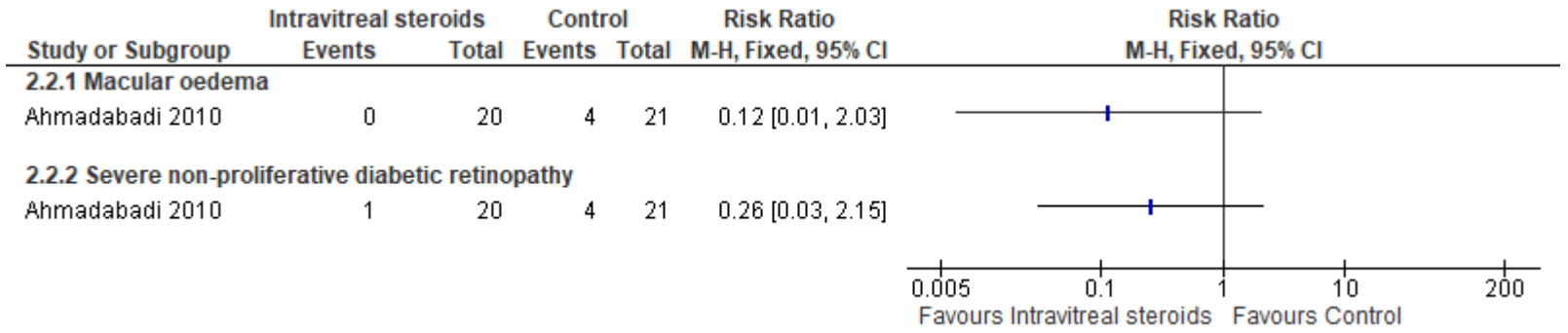


Figure 7. Rates of additional intervention (number who needed rescue treatments)

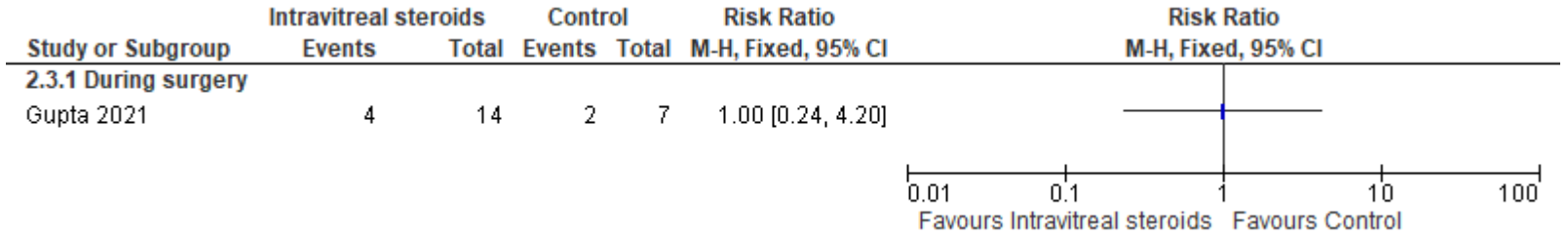
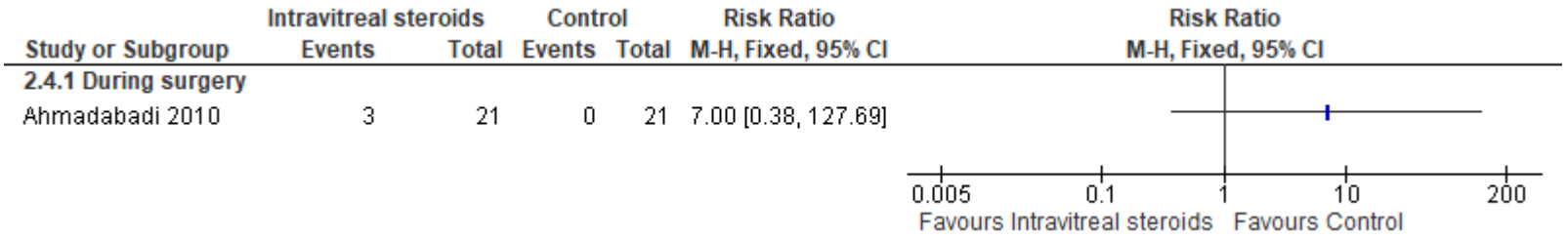
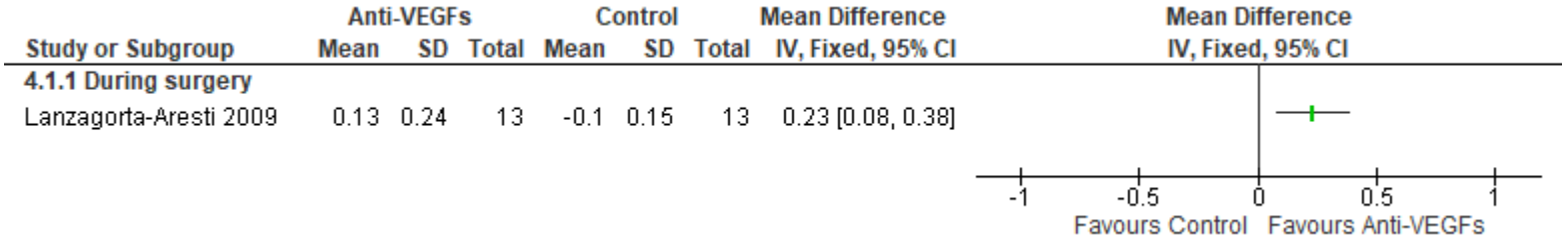


Figure 8. Adverse events (number of people with raised intraocular pressure: increase >21 mm Hg)



E.1.3 Anti-VEGF agents vs control in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Figure 9. Best corrected visual acuity measured with Snellen (change from baseline)



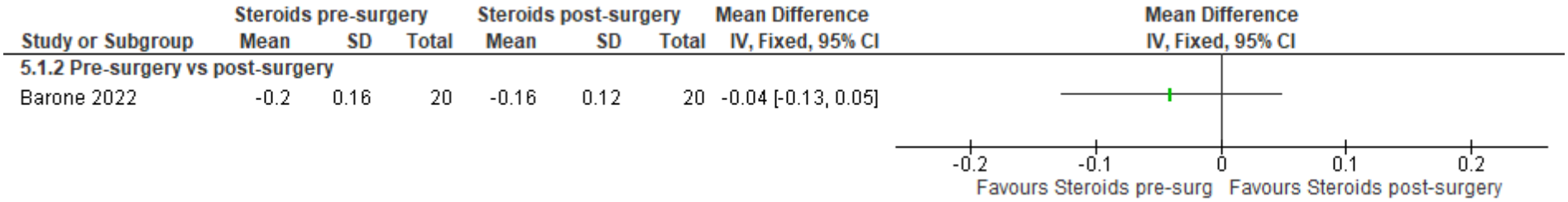
Change from baseline calculated by reviewer.

E.1.4 Anti-VEGF agents vs control in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Takamura 2009 reported that there were no adverse events (severe ocular inflammation; significant increase of IOP) in any of the participating eyes. Therefore, effect estimate could not be calculated.

E.1.5 Intravitreal steroids pre-surgery vs post-surgery in people with non-proliferative diabetic retinopathy and diabetic macular oedema

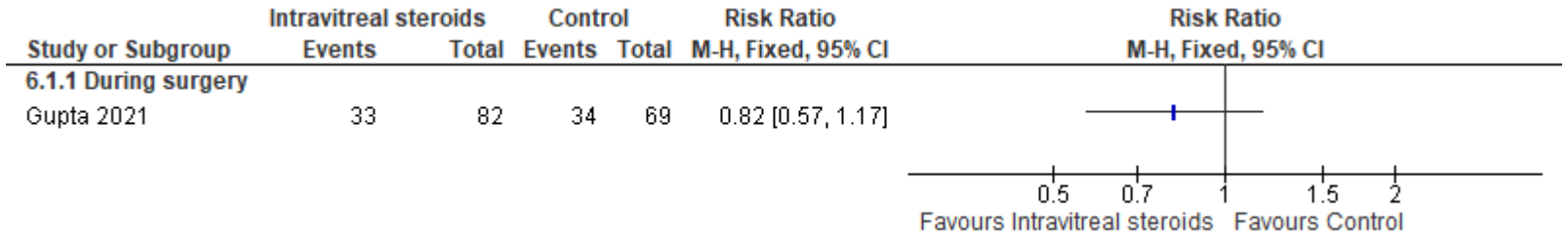
Figure 10. Best corrected visual acuity measured with logMAR (change from baseline)



Change from baseline calculated by reviewer.

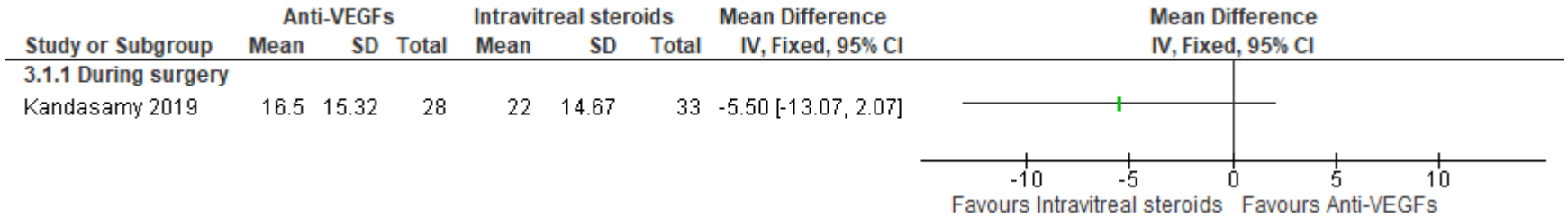
E.1.6 Intravitreal steroids vs control in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Figure 11. Rates of additional intervention (number who needed rescue treatments)



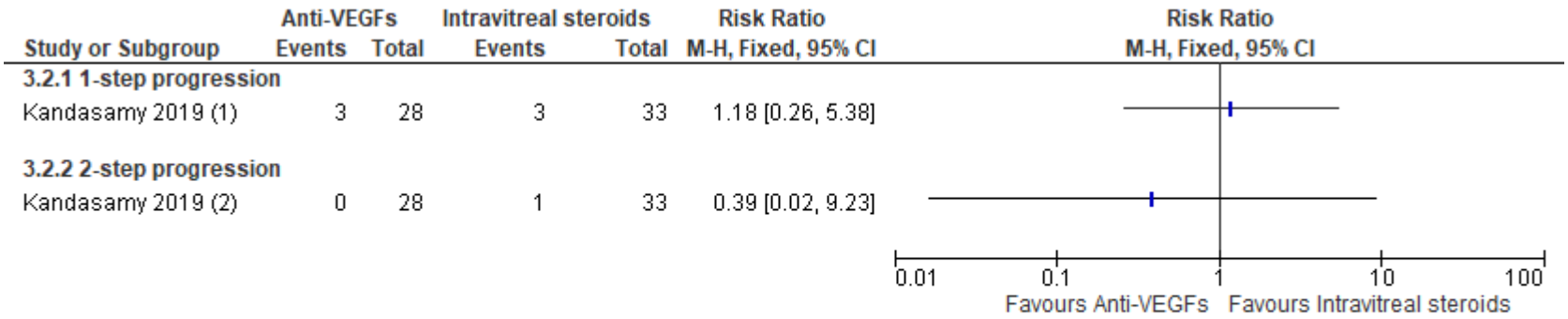
E.1.7 Anti-VEGF agents vs intravitreal steroids in people with non-proliferative diabetic retinopathy and diabetic macular oedema

Figure 12. Best corrected visual acuity measured with letters (change from baseline)



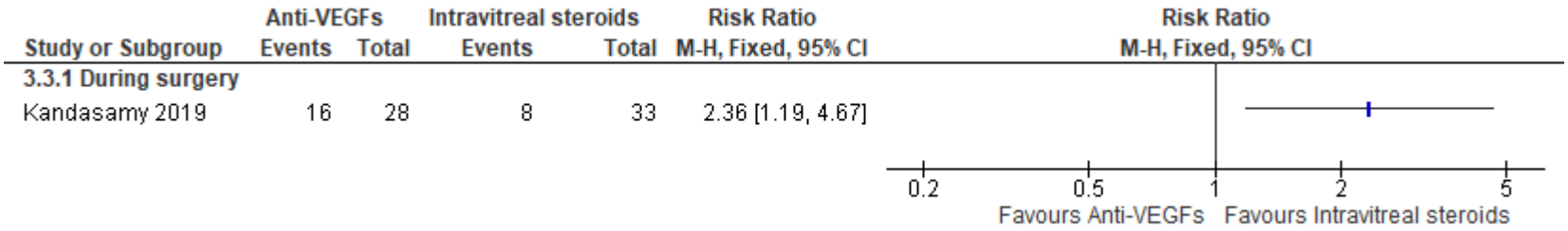
Change from baseline calculated by reviewer.

Figure 13. Progression to a higher grade of diabetic retinopathy



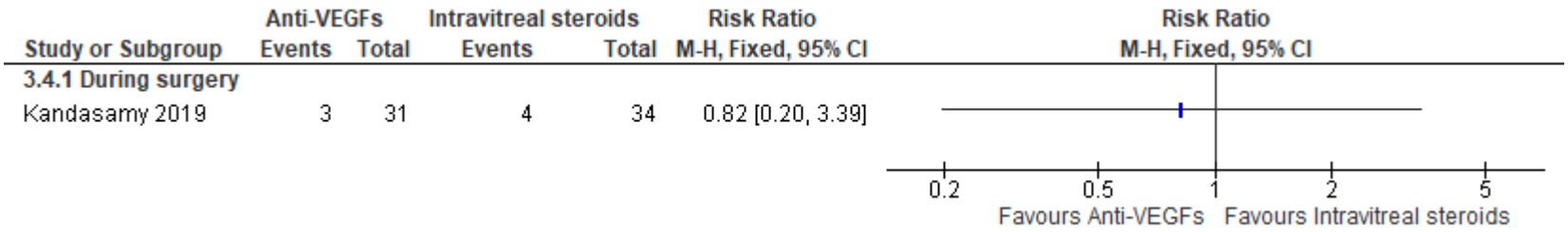
Footnotes
(1) reported by Sasongko 2020
(2) reported by Sasongko 2020

Figure 14. Rates of additional intervention (number who needed retreatments)



Study reported number who did not need retreatments. This has been converted by the reviewer to the number who did need retreatments, for consistency with other retreatment outcomes.

Figure 15. Adverse events (raised intraocular pressure: increase >21 mm Hg)



Appendix F – GRADE tables

F.1.1 Anti-VEGF agents vs control in people with non-proliferative diabetic retinopathy

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Quality
Best corrected visual acuity measured with logMAR (change from baseline): MD less than 0 favours anti-VEGF agents									
Chae 2014 Fard 2011	RCT	137	MD -0.07 (-0.14, -0.00)	-	-	serious[1]	not serious	serious[2]	low
Best corrected visual acuity measured with ETDRS (change from baseline): MD greater than 0 favours anti-VEGF agents									
Song 2020	RCT	30	MD 1.36 (-4.20, 6.92)	-	-	not serious	not serious	NA[3]	high
Progression to a higher grade of diabetic retinopathy or to diabetic macular oedema: RR less than 1 favours anti-VEGF agents									
Chae 2014 Fard 2011 Song 2020	RCT	166	RR 0.60 (0.29, 1.23)	198 per 1000	79 fewer per 1000 (141 fewer to 46 more)	serious[1]	not serious	not serious	moderate
Number of ocular treatments related adverse events: RR less than 1 favours anti-VEGF agents									
Fard 2011 Song 2020	RCT	91	RR 0.91 (0.57, 1.45)	733 per 1000	66 fewer per 1000 (315 fewer to 330 more)	not serious	not serious	not serious	high

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. I2 between 33.3% and 66.7%
3. Only one study so no inconsistency

F.1.2 Intravitreal steroids vs control in people with non-proliferative diabetic retinopathy

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Quality
Best corrected visual acuity measured with logMAR (change from baseline): MD less than 0 favours intravitreal steroids									
Ahmadabadi 2010	RCT	41	MD -0.02 (-0.08, 0.04)	-	-	serious[1]	not serious	NA[2]	moderate
Progression to macular oedema or Severe non-proliferative diabetic retinopathy									
Subgroup: macular oedema: RR less than 1 favours intravitreal steroids									
Ahmadabadi 2010	RCT	41	RR 0.12 (0.01, 2.03)	190 per 1000	167 fewer per 1000(188 fewer to 196 more)	serious[1]	not serious	NA[2]	moderate
Subgroup: severe non-proliferative diabetic retinopathy: RR less than 1 favours intravitreal steroids									
Ahmadabadi 2010	RCT	41	RR 0.26 (0.03, 2.15)	190 per 1000	141 fewer per 1000 (184 fewer to 219 more)	serious[1]	not serious	NA[2]	moderate
Rates of additional intervention (number who needed rescue treatments): RR less than 1 favours intravitreal steroids									
Gupta 2021	RCT	21	RR 1.00 (0.24, 4.20)	286 per 1000	0 more per 1000 (217 fewer to 915 more)	not serious	not serious	NA[2]	high
Adverse events (number of people with raised intraocular pressure: increase >21 mm hg): RR less than 1 favours anti-VEGF agents									
Ahmadabadi 2010	RCT	42	RR 7.00 (0.38, 127.69)	0 per 1000	0 fewer per 1000 (0 more to 0 more)	serious[1]	not serious	NA[2]	moderate

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. Only one study so no inconsistency

F.1.3 Anti-VEGF agents vs control in people with non-proliferative diabetic retinopathy and diabetic macular oedema

No. of studies	Study design	Sample size	Effect size (95 CI)	Risk of bias	Indirectness	Inconsistency	Quality
Best corrected visual acuity measured with Snellen (change from baseline): MD greater than 1 favours anti-VEGFs							
Lanzagorta-Aresti 2009	RCT	26	MD 0.23 (0.08, 0.38)	serious[1]	not serious	NA[2]	moderate

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. Only one study so no inconsistency

F.1.4 Intravitreal steroids pre-surgery vs post-surgery in people with non-proliferative diabetic retinopathy and diabetic macular oedema

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Quality
Best corrected visual acuity measured with logMAR (change from baseline): MD less than 0 favours steroids pre-surgery							
Barone 2022	RCT	40	MD -0.04 (-0.13, 0.05)	very serious[1]	not serious	NA[2]	low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency

F.1.5 Intravitreal steroids vs control in people with non-proliferative diabetic retinopathy and diabetic macular oedema

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Quality
Rates of additional intervention (number who needed rescue treatments): RR greater 1 favour intravitreal steroid									
Gupta 2021	RCT	151	RR 0.82 (0.57, 1.17)	493 per 1000	89 fewer per 1000 (212 fewer to 84 more)	not serious	not serious	NA[1]	high

1. Only one study so no inconsistency

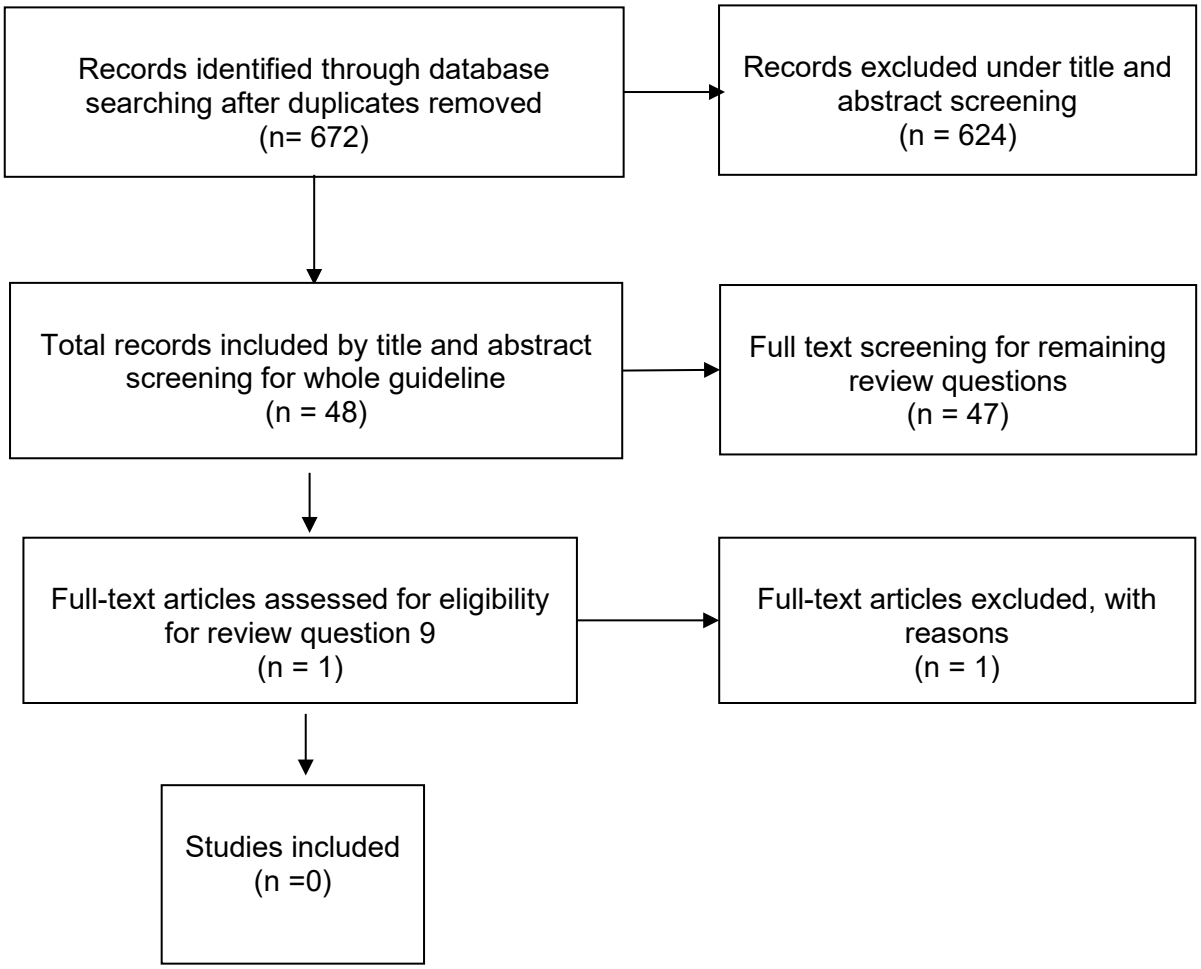
F.1.6 Anti-VEGF agents vs intravitreal steroids in people with non-proliferative diabetic retinopathy and diabetic macular oedema

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Quality
Best corrected visual acuity measured with letters (change from baseline): RR greater than 1 favours anti-VEGF agents									
Kandasamy 2019	RCT	61	MD -5.50 (-13.07, 2.07)	-	-	not serious	not serious	NA[1]	high
Progression to a higher grade of diabetic retinopathy									
Subgroup: 1-step progression: RR less than 1 favours anti-VEGF agents									
Kandasamy 2019	RCT	61	RR 1.18 (0.26, 5.38)	91 per 1000	16 more per 1000 (67 fewer to 399 more)	not serious	not serious	NA[1]	high
Subgroup: 2-step progression: RR less than 1 favours anti-VEGF agents									

Kandasamy 2019	RCT	61	RR 0.39 (0.02, 9.23)	30 per 1000	18 fewer per 100 (29 fewer to 247 more)	not serious	not serious	NA[1]	high
Rates of additional intervention (number who needed retreatments): RR less than 1 favours anti-VEGF agents									
Kandasamy 2019	RCT	65	RR 2.36 (1.19, 4.67)	242 per 1000	329 more per 1000 (46 more to 888 more)	not serious	not serious	NA[1]	high
Adverse events (number of people with raised intraocular pressure: increase >21 mm hg): RR less than 1 favours anti-VEGF agents									
Kandasamy 2019	RCT	65	RR 0.82 (0.20, 3.39)	118per 100	21 fewer per 1000 (94 fewer to 282 more)	not serious	not serious	NA[1]	high

1. Only one study so no inconsistency

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

There are no included studies for this review question.

Appendix I – Health economic model

Original health economic modelling has not been conducted for this review question.

Appendix J – Excluded studies

Clinical evidence

Study	Reason
Agarwal, Aniruddha, Gupta, Vishali, Ram, Jagat et al. (2013) Dexamethasone intravitreal implant during phacoemulsification. Ophthalmology 120(1): 211-5	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with non-proliferative retinopathy, proliferative retinopathy and with or without macular oedema. Results not reported separately*
Akinci, Arsen, Batman, Cosar, Ozkilic, Ersel et al. (2009) Phacoemulsification with intravitreal bevacizumab injection in diabetic patients with macular edema and cataract. Retina (Philadelphia, Pa.) 29(10): 1432-5	- Comparator in study does not match that specified in protocol
Akinci, Arsen, Muftuoglu, Orkun, Altinsoy, Ali et al. (2011) Phacoemulsification with intravitreal bevacizumab and triamcinolone acetonide injection in diabetic patients with clinically significant macular edema and cataract. Retina (Philadelphia, Pa.) 31(4): 755-8	- Comparator in study does not match that specified in protocol
Amana-Rattan, S., Kadhim-Mutasher, M., Farhood, Q. et al. (2022) Posterior subtenon triamcinolone acetonide combined with phacoemulsification for patients with diabetic maculopathy. Revista Mexicana de Oftalmologia 96(3): 108-113	- Comparator in study does not match that specified in protocol
Angkadjaja, Julia, Chu, Joshua, Sierpina, David I et al. (2020) Evaluating the effect of intravitreal triamcinolone-moxifloxacin during cataract surgery on central macular edema in patients with preexisting diabetic retinopathy. Journal of cataract and refractive surgery 46(9): 1253-1259	- Comparator in study does not match that specified in protocol *No comparator group*
Brito, Pedro N, Rosas, Vitor M, Coentrao, Luis M et al. (2015) Evaluation of visual acuity, macular status, and subfoveal choroidal thickness changes after cataract surgery in eyes with diabetic retinopathy. Retina (Philadelphia, Pa.) 35(2): 294-302	- Not a relevant study design *People with NPDR, PDR without MO and DR with MO. Only 1 group was given bevacizumab*
Cheema, Rizwan A, Al-Mubarak, Mahdi M, Amin, Yasir M et al. (2009) Role of combined cataract surgery and intravitreal bevacizumab injection in preventing progression of diabetic retinopathy: prospective randomized study. Journal of cataract and refractive surgery 35(1): 18-25	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with and without diabetic macular oedema. Results not reported separately*
Chen, Chih-Hsin; Liu, Ya-Chi; Wu, Pei-Chang (2009) The combination of intravitreal bevacizumab and phacoemulsification surgery in patients with cataract and coexisting diabetic macular edema. Journal of ocular pharmacology	- RCT with relevant comparison included in this review

Study	Reason
and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 25(1): 83-9	
Chew, E Y, Benson, W E, Remaley, N A et al. (1999) Results after lens extraction in patients with diabetic retinopathy: early treatment diabetic retinopathy study report number 25. Archives of ophthalmology (Chicago, Ill. : 1960) 117(12): 1600-6	- Comparator in study does not match that specified in protocol
Corbelli, Eleonora, Fasce, Francesco, Iuliano, Lorenzo et al. (2020) Cataract surgery with combined versus defeRRed intravitreal dexamethasone implant for diabetic macular edema: long-term outcomes from a real-world setting. Acta diabetologica 57(10): 1193-1201	- Does not include relevant outcomes *doesn't adjust for confounding factors (which is specified in the protocol)*
El-Ghrably, Ibraheem, Steel, David H W, Habib, Maged et al. (2017) Diabetic macular edema outcomes in eyes treated with fluocinolone acetonide 0.2 microg/d intravitreal implant: real-world UK experience. European journal of ophthalmology 27(3): 357-362	- Comparator in study does not match that specified in protocol
Fallico, Matteo, Avitabile, Teresio, Castellino, Niccolo et al. (2021) Intravitreal dexamethasone implant one month before versus concomitant with cataract surgery in patients with diabetic macular oedema: the dexcat study. Acta ophthalmologica 99(1): e74-e80	- Does not include relevant outcomes *doesn't adjust for confounding factors (which is specified in the protocol)*
Fallico, Matteo, Lotery, Andrew, Maugeri, Andrea et al. (2021) Intravitreal dexamethasone implant versus anti-vascular endothelial growth factor therapy combined with cataract surgery in patients with diabetic macular oedema: a systematic review with meta-analysis. Eye (London, England)	- Systematic review used as source of primary studies *Yumusak 2016 added to database*
Fang, T, Liu, F, Shu, H-E et al. (2012) Clinical study of inhibition of triamcinolone acetonide on posterior capsule opacification in diabetic cataract surgery. International eye science 12(9): 1659-1661	- Study not reported in English
Feng, Yifan, Zhu, Senmiao, Skiadaresi, Eirini et al. (2019) PHACOEMULSIFICATION CATARACT SURGERY WITH PROPHYLACTIC INTRAVITREAL BEVACIZUMAB FOR PATIENTS WITH COEXISTING DIABETIC RETINOPATHY: A Meta-Analysis. Retina (Philadelphia, Pa.) 39(9): 1720-1731	- Systematic review used as source of primary studies
Fraser-Bell, S., Kang, H.K., Mitchell, P. et al. (2021) Dexamethasone intravitreal implant in treatment-naive diabetic macular oedema: findings from the prospective, multicentre,	- Comparator in study does not match that specified in protocol

Study	Reason
AUSSIEDEX study. The British journal of ophthalmology	
Fukushima, H, Kato, S, Kaiya, T et al. (2001) Effect of subconjunctival steroid injection on intraocular inflammation and blood glucose level after cataract surgery in diabetic patients. Journal of cataract and refractive surgery 27(9): 1386-91	- Does not include relevant outcomes
Fukushima, H, Kato, S, Kaiya, T et al. (1999) Effect of subconjunctival corticosteroid immediately after cataract surgery in diabetic patients. Japanese journal of clinical ophthalmology 53(13): 2001-2004	- Study not reported in English
Furino, Claudio, Boscia, Francesco, Niro, Alfredo et al. (2021) DIABETIC MACULAR EDEMA AND CATARACT SURGERY: Phacoemulsification Combined With Dexamethasone Intravitreal Implant Compared With Standard Phacoemulsification. Retina (Philadelphia, Pa.) 41(5): 1102-1109	- Does not include relevant outcomes *doesn't adjust for confounding factors (which is specified in the protocol)*
Gallego-Pinazo, Roberto, Dolz-Marco, Rosa, BeRRocal, Maria et al. (2014) Outcomes of cataract surgery in diabetic patients: results of the Pan American Collaborative Retina Study Group. Arquivos brasileiros de oftalmologia 77(6): 355-9	- Does not include a relevant population *Includes people with non-proliferative and proliferative DR. Results not reported separately*
Hu, M (2017) Clinical study on the treatment of PDR with cataract by vitreous cavity injection and intraocular lens implantation. International eye science 17(2): 281-283	- Study not reported in English
Hykin, PG, Dowler, JGF, Sehmi, K et al. (1997) Indirect laser panretinal photocoagulation during phakoemulsification in eyes with proliferative diabetic retinopathy. IOVS 38: arvoabstract3546	- Conference abstract
Javed, M.A., Latif, S., Javaid, R.M.M. et al. (2022) Prophylaxis of Macular Edema with Preoperative Intravitreal Bevacizumab in Patients with Diabetic Retinopathy Undergoing Phacoemulsification. Pakistan Journal of Medical and Health Sciences 16(3): 737-739	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with and without diabetic macular oedema. Results not reported separately*
Khodabandeh, A., Fadaifard, S., Abdollahi, A. et al. (2018) Role of combined phacoemulsification and intravitreal injection of bevacizumab in prevention of postoperative macular edema in non-proliferative diabetic retinopathy. Journal of CuRRent Ophthalmology 30(3): 245-249	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with no diabetic retinopathy and non-proliferative retinopathy. Results not reported separately (most had no retinopathy)*
Kim, Su-Young, Yang, Jiwook, Lee, Young-Chun et al. (2008) Effect of a single intraoperative sub-Tenon injection of	- RCT with relevant comparison included in this review

Study	Reason
triamcinolone acetonide on the progression of diabetic retinopathy and visual outcomes after cataract surgery. Journal of cataract and refractive surgery 34(5): 823-6	*Triamcinolone vs control for people with non-proliferative diabetic retinopathy*
Kwon, Soon Il, Hwang, Duck Jin, Seo, Ji Young et al. (2011) Evaluation of changes of macular thickness in diabetic retinopathy after cataract surgery. Korean journal of ophthalmology : KJO 25(4): 238-42	- Comparator in study does not match that specified in protocol
Li, J-Y, Shao, J, Wang, Y et al. (2013) Clinical observation of macular grid photocoagulation before cataract surgery for diabetes patients with diffuse macular edema. International eye science 13(9): 1887-1889	- Study not reported in English
Lim, Lyndell L, MoRRison, Julie L, Constantinou, Marios et al. (2016) Diabetic Macular Edema at the time of Cataract Surgery trial: a prospective, randomized clinical trial of intravitreous bevacizumab versus triamcinolone in patients with diabetic macular oedema at the time of cataract surgery - preliminary 6 month results. Clinical & experimental ophthalmology 44(4): 233-42	- Relevant study but doesn't report latest timepoint *DIMECat study - pilot results. 6 month results reported in follow-up papers (Kandasamy 2019, Sasongko 2020)*
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	- Study does not contain a relevant intervention
Lin, W-H, Lu, M, Tang, H-Y et al. (2015) Clinical application of Ranibizumab in the therapy of diabetic cataract. International eye science 15(5): 880-882	- Study not reported in English
Minnella, Angelo Maria, Maceroni, Martina, Picardi, Stefano Maria et al. (2020) Combined Intravitreal Dexamethasone Implant and Cataract Surgery in Patients with Diabetic Retinopathy: Effect on Retinal Morphology and Function. Advances in therapy 37(11): 4675-4684	- Not a relevant study design *Observational study that does not include a comparator group*
Moshfeghi, Andrew A, Shapiro, Howard, Lemmon, Linda A et al. (2018) Impact of Cataract Surgery during Treatment with Ranibizumab in Patients with Diabetic Macular Edema. Ophthalmology. Retina 2(2): 86-90	- Comparator in study does not match that specified in protocol
Moshfeghi, Andrew A, Thompson, Desmond, Berliner, Alyson J et al. (2020) Outcomes in Patients with Diabetic Macular Edema Requiring	- Comparator in study does not match that specified in protocol

Study	Reason
Cataract Surgery in VISTA and VIVID Studies. Ophthalmology. Retina 4(5): 481-485	
Ozgur, O.R., Ozkurt, Y., Kulekci, Z. et al. (2016) The combination of phacoemulsification surgery and intravitreal triamcinolone injection in patients with cataract and diabetic macular edema. Saudi Journal of Ophthalmology 30(1): 33-38	- Does not include relevant outcomes *doesn't adjust for confounding factors (which is specified in the protocol)*
Rauen, Paulo I, Ribeiro, Jefferson A S, Almeida, Felipe P P et al. (2012) Intravitreal injection of ranibizumab during cataract surgery in patients with diabetic macular edema. Retina (Philadelphia, Pa.) 32(9): 1799-803	- Comparator in study does not match that specified in protocol
Salehi, Ali, Beni, Afsaneh Naderi, Razmjoo, Hassan et al. (2012) Phacoemulcification with intravitreal bevacizumab injection in patients with cataract and coexisting diabetic retinopathy: prospective randomized study. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 28(3): 212-8	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with non-proliferative and proliferative retinopathy, with and without macular oedema. Separates results by type of retinopathy but not by whether they have macular oedema*
Shi, X., Dong, N., Liang, Y. et al. (2022) 23G Minimally Invasive Vitrectomy Combined with Glaucoma Drainage Valve Implantation and Phacoemulsification Cataract Extraction for Neovascular Glaucoma Secondary to Proliferative Diabetic Retinopathy with Vitreous HemoRRhage. Computational and Mathematical Methods in Medicine 2022: 7393661	- Comparator in study does not match that specified in protocol
StaRR, Matthew R, Mahr, Michael A, Smith, Wendy M et al. (2021) Outcomes of Patients With Active Diabetic Macular Edema at the Time of Cataract Surgery Managed With Intravitreal Anti-Vascular Endothelial Growth Factor Injections. American journal of ophthalmology 229: 194-199	- Comparator in study does not match that specified in protocol
Suto, Chikako; Hori, Sadao; Kato, Satoshi (2008) Management of type 2 diabetics requiring panretinal photocoagulation and cataract surgery. Journal of cataract and refractive surgery 34(6): 1001-6	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with severe non-proliferative retinopathy and early proliferative retinopathy. Results not separated by type of retinopathy*
Suto, Chikako; Kitano, Shigehiko; Hori, Sadao (2011) Optimal timing of cataract surgery and panretinal photocoagulation for diabetic retinopathy. Diabetes care 34(7): e123	- Not a peer-reviewed publication *Letter*
Sze, Amy M, Luk, Fiona O, Yip, TeRRi P et al. (2015) Use of intravitreal dexamethasone implant in patients with cataract and macular	- Not a relevant study design *Case series*

Study	Reason
edema undergoing phacoemulsification. European journal of ophthalmology 25(2): 168-72	
Takata, Clecio, Messias, Andre, Folgosa, Marco S et al. (2010) Intravitreal injection versus subtenon infusion of triamcinolone acetonide during cataract surgery in patients with refractory diabetic macular edema. Retina (Philadelphia, Pa.) 30(4): 562-9	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with non-proliferative and proliferative DR. Results not reported separately*
Tang, B., Wang, X., Luo, Y. et al. (2022) Efficacy and Safety of Intravitreal Injection of Triamcinolone Acetonide and Conbercept for Intraocular Lens after Cataract Surgery. Evidence-based Complementary and Alternative Medicine 2022: 5606343	- Study does not contain a relevant intervention *Conbercept anti-VEGF. Not cuRRently licensed in the UK*
Tang, H-Y, Lu, M, Hong, D-M et al. (2015) Effect and safety of intrachamberal triamcinolone acetonide injection during cataract surgery in diabetic patients. International eye science 15(3): 474-477	- Study not reported in English
Tatsumi, Tomoaki, Oshitari, Toshiyuki, Ando, Takaaki et al. (2019) Comparison of the Efficacy of Sub-Tenon versus Intravitreal Triamcinolone Acetonide Injection during Cataract Surgery for Diabetic Macular Edema. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde 241(1): 17-23	- Not a relevant study design *doesn't adjust for confounding factors (which is specified in the protocol)*
Wahab, Shahid and Ahmed, Jamshed (2010) Management of cataract with macular oedema due to diabetes mellitus type-II and hypertension with grid laser prior to surgery and intra-vitreal bevacizumab (Avastin) peroperatively. JPMA. The Journal of the Pakistan Medical Association 60(10): 836-9	- Not a relevant study design *Observational study that does not include a comparator group*
Wang, J., Liu, Y., Hu, Y. et al. (2021) Clinical Observation of Phacoemulsification Combined with Intravitreal Injection of Conbercept in Cataract Patients with Diabetic Macular Edema. Journal of Ophthalmology 2021: 8849730	- Study does not contain a relevant intervention *Not cuRRently licensed in the UK*
Wielders, Laura H P, Schouten, Jan S A G, Winkens, Bjorn et al. (2018) Randomized controlled European multicenter trial on the prevention of cystoid macular edema after cataract surgery in diabetics: ESCRS PREMED Study Report 2. Journal of cataract and refractive surgery 44(7): 836-847	- Does not include a relevant population *People with cystoid macular oedema* - Mixed population. Outcomes not reported by relevant subgroups *Includes people with no diabetic retinopathy, non-proliferative retinopathy and proliferative retinopathy. Results not reported separately*
Yang, B and Song, Y (2015) Therapeutic effects of phacoemulsification combined with intravitreal	- Study not reported in English

Study	Reason
injection of triamcinolone in treating cataract with diabetic macular edema. International eye science 15(9): 1532-1535	
Yen, Chu-Yu, Yen, Ju-Chuan, Chen, Chun-Chen et al. (2022) Therapeutic effect of cataract surgery with simultaneous intravitreal injection of aflibercept on diabetic macular edema: An observational study. Medicine 101(33): e30115	- Mixed population. Outcomes not reported by relevant subgroups *Includes people with non-proliferative and proliferative DR. Results not reported separately*
Yumusak, E. & Ornek K (2016) Comparison of Perioperative Ranibizumab Injections for Diabetic Macular Edema in Patients Undergoing Cataract Surgery. Journal of Opthalmology	- Does not include relevant outcomes *doesn't adjust for confounding factors (which is specified in the protocol)*
Zhang, W-L; Zhang, W; Shao, Y (2019) Application of Triamcinolone acetonide in cataract surgery with NPDR. International eye science 19(9): 1536-1541	- Study not reported in English

Economic evidence

Title	Reason for exclusion
Simons, R.W.P., Wielders, L.H.P., Nuijts, R.M.M.A. et al. (2021) Economic evaluation of prevention of cystoid macular edema after cataract surgery in diabetic patients: ESCRS PREMED study report 6. Journal of cataract and refractive surgery	- Exclude - not relevant population, non - retinopathy population

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

In people with moderate to severe non-proliferative diabetic retinopathy, who are about to have or who had cataract surgery, what is the effectiveness and cost-effectiveness of treatments (before, during or after surgery)?

K.1.1.1 Why this is important.

It is important to manage a person's diabetic retinopathy if they are also in need of cataract surgery. Without additional treatment, their diabetic retinopathy may progress until the cataract is cleared and they can have additional treatment. It is currently unclear which treatments are most effective at managing non-proliferative diabetic retinopathy when people have cataract surgery.

K.1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	By understanding which treatments are the most effective for people with non-proliferative retinopathy who are having cataract surgery, patients will be able to have the best post-surgery outcomes. This can reduce the risk of them progressing to more severe retinopathy or macular oedema and reduce the number of treatments they may need post-surgery.
Relevance to NICE guidance	There is currently limited evidence for this group of people, making it difficult to be certain which treatments are effective. Additional research will mean that recommendations can be made on this in future guideline updates.
Relevance to the NHS	Many people with severe non-proliferative diabetic retinopathy have cataract surgery but it is currently unclear what the best treatments are for these people. New evidence will help to provide recommendations to ensure that patients are getting the most effective and cost-effective care.
National priorities	Moderate
Current evidence base	5 RCTs - 3 RCTs for anti-VEGFs, 2 RCTs for steroids
Equality considerations	People with different risk factors for progression may respond differently to different treatments. This should be considered when deciding on subgroups.

K.1.1.3 Modified PICO table

Population	People with moderate to severe non-proliferative diabetic retinopathy, who are about to undergo or who have undergone cataract surgery
Intervention	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids (before during or after cataract surgery) including subconjunctival steroids (dexamethasone and triamcinolone)
Comparator	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids • No treatment/placebo Studies comparing treatments before during or after cataract surgery will be included.
Outcomes	• Progression to proliferative diabetic retinopathy • Progression to macular oedema • Change in best corrected visual acuity from baseline • Adverse events (Raised intraocular pressure, Intraocular infection, Intraocular Inflammation) • Quality of life
Study design	RCT (for progression, visual acuity, adverse event and quality of life)
Timeframe	Long-term follow up (2 years)
Additional information	Subgroups should be considered for people who have recognised risk factors for progression of non-proliferative diabetic retinopathy

K.1.2 Research recommendation

In people with diabetic macular oedema, who are about to have or who had cataract surgery, what is the effectiveness and acceptability of treatments (before, during or after surgery)?

K.1.2.1 Why this is important

It is important to manage a person's diabetic macular oedema if they are also in need of cataract surgery. Without additional treatment, their macular oedema may progress until the cataract is cleared and they can have additional treatment. It is currently unclear which treatments are most effective at managing diabetic macular oedema when people have cataract surgery.

K.1.2.2 Rationale for research recommendation

Importance to 'patients' or the population	By understanding which treatments are the most effective for people with diabetic macular oedema who are having cataract surgery, patients will be able to have the best post-surgery outcomes. This can reduce the risk of their oedema progressing and reduce the number of treatments they may need post-surgery.
Relevance to NICE guidance	There is currently limited evidence for this group of people making it difficult to be certain which treatments are effective. Additional research will mean that recommendations can be made on this in future guideline updates.
Relevance to the NHS	Many people with diabetic macular oedema have cataract surgery but it is currently unclear what the best treatments are for these people. New evidence will help to provide recommendations to ensure that patients are getting the most effective and cost-effective care.
National priorities	Moderate
Current evidence base	5 RCTs - 2 RCTs for anti-VEGFs, 2 RCTs for steroids, 1 RCT for anti-VEGFs vs steroids
Equality considerations	People with different risk factors for progression may respond differently to different treatments. This should be considered when deciding on subgroups.

K.1.2.3 Modified PICO table

Population	People with diabetic macular oedema, who are about to undergo or who have undergone cataract surgery
Intervention	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids (before during or after cataract surgery) including subconjunctival steroids (dexamethasone and triamcinolone)
Comparator	• Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids • No treatment/placebo Studies comparing treatments before during or after cataract surgery will be included.
Outcomes	• Progression • Change in best corrected visual acuity from baseline • Adverse events (Raised intraocular pressure, Intraocular infection, Intraocular Inflammation) • Quality of life
Study design	RCT (for progression, visual acuity, adverse event and quality of life)
Timeframe	Long-term follow up (2 years)
Additional information	Subgroups should be considered for people who have recognised risk factors for progression of non-proliferative diabetic retinopathy