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Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis (Review)

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[Intervention Review]

Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis

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ABSTRACT

Background

Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) modalities can reduce oedema and thereby improve vision and prevent further visual loss. These drugs have replaced laser photocoagulation as the standard of care for people with DMO.

Objectives

The 2014 update of this review found high-quality evidence of benefit with antiangiogenic therapy with anti-VEGF modalities, compared to laser photocoagulation, for the treatment of DMO.The objective of this updated review is to compare the effectiveness and safety of the different anti-VEGF drugs in preserving and improving vision and quality of life using network meta-analysis methods.

Search methods

We searched various electronic databases on 26 April 2017.

Selection criteria

We included randomised controlled trials (RCTs) that compared any anti-angiogenic drug with an anti-VEGF mechanism of action versus another anti-VEGF drug, another treatment, sham or no treatment in people with DMO.

Data collection and analysis

We used standard Cochrane methods for pair-wise meta-analysis and we augmented this evidence using network meta-analysis methods. We focused on the relative efficacy and safety of the three most commonly used drugs as interventions of direct interest for practice: aflibercept and ranibizumab, used on-label; and off-label bevacizumab.

We collected data on three efficacy outcomes (gain of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters; mean change in best-corrected visual acuity (BCVA); mean change in central retinal thickness (CRT)), three safety outcomes (all severe systemic adverse events (SSAEs); all-cause death; arterial thromboembolic events) and quality of life.

We used Stata '*network*' meta-analysis package for all analyses. We investigated the risk of bias of mixed comparisons based on the variance contribution of each study, having assigned an overall risk of bias to each study.

Main results

Twenty-four studies included 6007 participants with DMO and moderate vision loss, of which two studies randomised 265 eyes of 230 participants and one was a cross-over study on 56 participants (62 eyes) that was treated as a parallel-arm trial. Data were collected on drugs of direct interest from three studies on aflibercept (975 eyes), eight studies on bevacizumab (515 eyes), and 14 studies on ranibizumab (1518 eyes). As treatments of indirect interest or legacy treatment we included three studies on pegaptanib (541 eyes), five studies on ranibizumab plus prompt laser (557 eyes), one study on ranibizumab plus deferred laser (188 eyes), 13 studies on laser photocoagulation (936 eyes) and six studies on sham treatment (793 eyes).

Aflibercept, bevacizumab and ranibizumab were all more effective than laser for improving vision by 3 or more lines after one year (high-certainty evidence). Approximately one in 10 people improve vision with laser, and about three in 10 people improve with anti-VEGF treatment: risk ratio (RR) versus laser 3.66 (95% confidence interval (CI) 2.79 to 4.79) for aflibercept; RR 2.47 (95% CI 1.81 to 3.37) for bevacizumab; RR 2.76 (95% CI 2.12 to 3.59) for ranibizumab. On average there was no change in visual acuity (VA) with laser after one year, compared with a gain of 1 or 2 lines with anti-VEGF treatment: laser versus aflibercept mean difference (MD) −0.20 (95% CI −0.22 to −0.17) logMAR; versus bevacizumab MD −0.12 (95% CI −0.15 to −0.09) logMAR; versus ranibizumab MD −0.12 (95% CI −0.14 to −0.10) logMAR. The certainty of the evidence was high for the comparison of aflibercept and ranibizumab with laser and moderate for bevacizumab comparison with laser due to inconsistency between the indirect and direct evidence.

People receiving ranibizumab were less likely to gain 3 or more lines of VA at one year compared with aflibercept: RR 0.75 (95% CI 0.60 to 0.94), moderate-certainty evidence. For every 1000 people treated with aflibercept, 92 fewer would gain 3 or more lines of VA at one year if treated with ranibizumab (22 to 148 fewer). On average people receiving ranibizumab had worse VA at one year (MD 0.08 logMAR units, 95% CI 0.05 to 0.11), moderate-certainty evidence; and higher CRT (MD 39 µm, 95% CI 2 µm to 76 µm; low-certainty evidence). Ranibizumab and bevacizumab were comparable with respect to aflibercept and did not differ in terms of VA: RR of gain of 3 or more lines of VA at one year 1.11 (95% CI 0.87 to 1.43), moderate-certainty evidence, and difference in change in VA was 0.00 (95% CI −0.02 to 0.03) logMAR, moderate-certainty evidence. CRT reduction favoured ranibizumab by −29 µm (95% CI −58 µm to −1 µm, low-certainty evidence). There was no evidence of overall statistical inconsistency in our analyses.

The previous version of this review found moderate-certainty evidence of good safety of antiangiogenic drugs versus control. This update used data at the longest available follow-up (one or two years) and found that aflibercept, ranibizumab and bevacizumab do not differ regarding systemic serious adverse events (SSAEs) (moderate- or high-certainty evidence). However, risk of bias was variable, loop inconsistency could be found and estimates were not precise enough on relative safety regarding less frequent events such as arterial thromboembolic events or death (low- or very low-certainty evidence).

Two-year data were available and reported in only four RCTs in this review. Most industry-sponsored studies were open-label after one year. One large publicly-funded study compared the three drugs at two years and found no difference.

Authors' conclusions

Anti-VEGF drugs are effective at improving vision in people with DMO with three to four in every 10 people likely to experience an improvement of 3 or more lines VA at one year. There is moderate-certainty evidence that aflibercept confers some advantage over ranibizumab and bevacizumab in people with DMO at one year in visual and anatomic terms. Relative effects among anti-VEGF drugs at two years are less well known, since most studies were short term. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often under-treated and under-monitored.

We found no signals of differences in overall safety between the three antiangiogenic drugs that are currently available to treat DMO, but our estimates are imprecise for cardiovascular events and death.

PLAIN LANGUAGE SUMMARY

Anti-vascular endothelial growth factor (anti-VEGF) drugs for diabetic macular oedema

What is the aim of this review?

The aim of this Cochrane Review was to find out which is the best type of anti-VEGF drug for diabetic macular oedema (DMO). Cochrane researchers collected and analysed all relevant studies to answer this question and found 24 studies.

Key messages

Anti-VEGF drugs given by injection into the eye improve vision in people with diabetic macular oedema as compared to no average improvement with laser photocoagulation. One of these drugs, aflibercept, probably works slightly better after one year. There did not appear to be important harms from any of these drugs.

What was studied in the review?

The light-sensitive tissue at the back of the eye is known as the retina. The central area of the retina is called the macula. People with diabetes can develop problems in the retina, known as retinopathy. Some people with diabetic retinopathy can also develop oedema (swelling or thickening) at the macula. DMO is a common complication of diabetic retinopathy and can lead to visual loss.

One type of treatment for DMO is anti-VEGF. This drug is given by means of an injection into the eye. It can reduce the swelling at the back of the eye and prevent visual loss. There are three main types of anti-VEGF drugs in use: aflibercept (Eyelea^{TM}), bevacizumab (Avastin) and ranibizumab (Lucentis^{TM}). Only aflibercept and ranibizumab have received marketing authorisation for the treatment of DMO. All three drugs are used to prevent visual loss and improve vision. They do this by slowing down the growth of new blood vessels and thereby reducing the swelling at the back of the eye. They may have adverse effects, particularly related to effects on blood vessels in the rest of the body. These effects may include stroke and heart attack.

What are the main results of the review?

Cochrane researchers found 24 relevant studies. Fourteen of these studies were industry-sponsored studies from USA, Europe or Asia. Ten studies were independent of industry funding and were from USA, Europe, Middle East and South America.

These studies investigated ranibizumab, bevacizumab and aflibercept. These anti-VEGF drugs were compared with no treatment, placebo treatment, laser treatment, or each other. The drugs were given every month, every two months, as needed or 'treat and extend', which means that the time period between treatments is extended if the condition has stabilised. Decisions about re-treating were based on visual acuity or by looking at the back of the eye.

The review reveals the following results.

• All three anti-VEGF drugs prevent visual loss and improve vision in people with DMO (high-certainty evidence).

• People receiving ranibizumab were probably slightly less likely to improve vision compared with aflibercept at one year after the start of treatment (moderate-certainty evidence). Approximately three in 10 people improve vision by 3 or more lines with ranibizumab and one in 10 additional people can achieve this with aflibercept.

• People receiving ranibizumab and bevacizumab probably have a similar visual outcome at one year after the start of treatment (moderate-certainty evidence).

• Aflibercept, ranibizumab and bevacizumab are similar for common and serious systemic harms (such as any disease leading to hospitalisation, disability or death) (moderate- or high-certainty evidence) but is less certain for arterial thromboembolic events (mainly stroke, myocardial infarction and vascular death) and death of any cause (very low-certainty evidence).

How up to date is this review?

Cochrane researchers searched for studies that had been published up to 26 April 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antiangiogenic therapy versus control

Patient or population: people with diabetic macular oedema
Settings: ophthalmology clinics
Interventions: laser photocoagulation, aflibercept, bevacizumab, ranibizumab

Outcomes	Assumed risk*	Corresponding risk and relative risk** (95% CI) , mixed evidence			Certainty of evidence and reason for downgrading
	Laser photocoagulation	Aflibercept	Bevacizumab	Ranibizumab	
Gain 3+ lines of visual acuity at 1 year	**100 per 1000**	**366 per 1000** (279 to 479) **RR: 3.66 (2.79 to 4.79)**	**247 per 1000** (181 to 337) **RR: 2.47 (1.81 to 3.37)**	**276 per 1000** (212 to 359) **RR: 2.76 (2.12 to 3.59)**	⊕⊕⊕⊕ high
Visual acuity change at 1 year Measured on the logMAR scale, range −0.3 to 1. 3. Higher values represent worse visual acuity.	On average visual acuity improved by **−0.01 logMAR** units in the laser group between the start of treatment and 1 year (effectively no change)	Average change in visual acuity was **−0.20 (−0.22 to −0.17) logMAR units better** with aflibercept compared with laser photocoagulation	Average change in visual acuity was **−0.12 (−0.15 to −0.09) logMAR units better** with bevacizumab compared with laser photocoagulation	Average change in visual acuity was **−0.12 (−0.14 to −0.10) logMAR units better** with ranibizumab compared with laser photocoagulation	⊕⊕⊕⊕ high for aflibercept and ranibizumab ⊕⊕⊕ moderate for bevacizumab (−1 for inconsistency of indirect versus direct evidence)
Central retinal thickness μm (CRT) change at 1 year The aim of treatment is to reduce central retinal thickness so thinner is better.	On average CRT changed by **−64 μm** in the laser group between the start of treatment and 1 year (became thinner)	Average change in CRT was **−114 (−147 to −81) μm more (thinner) with aflibercept** compared with laser photocoagulation	Average change in CRT was **−46 (−78 to −14) μm more (thinner)**with bevacizumab compared with laser photocoagulation	Average change in CRT was **−75 (−100 to −50) μm more (thinner)** with ranibizumab compared with laser photocoagulation	⊕⊕⊕⊕ high
Quality of life: NEI-VFQ composite score at 6 to 12 months An improvement by 5 units is clinically significant.	On average the composite score improved by +2 units in the laser group between the start of treatment and 6 to 12 months			Average change in composite score was 5.14 (2.96 to 7.32) with ranibizumab compared with laser photocoagulation	⊕⊕⊕ moderate (−1 for risk of bias)

All serious systemic adverse events at 1 to 2 years	**200 per 1000**	**196 per 1000** (166 to 232) **RR: 0.98 (0.83 to 1.16)**	**186 per 1000** (146 to 238) **RR: 0.93 (0.73 to 1.19)**	**194 per 1000** (160 to 234) **RR: 0.97 (0.80 to 1.17)**	⊕⊕⊕⊕ high
Arterial thromboembolic events at 1 to 2 years	**45 per 1000**	**38 per 1000** (16 to 94) **RR: 0.88 (0.37 to 2.13)**	**41 per 1000** (15 to 117) **RR: 0.94 (0.33 to 2.66)**	**48 per 1000** (23 to 101) **RR: 1.09 (0.52 to 2.29)**	⊕⊕ low (−2 for imprecise estimates)
Death at 1 to 2 years	**20 per 1000**	**20 per 1000** (7 to 61) **RR: 1.01 (0.34 to 3.03) a**	**32 per 1000** (9 to 114) **RR: 1.61 (0.45 to 5.69)**	**18 per 1000** (8 to 40) **RR: 0.90 (0.40 to 2.01)**	⊕⊕ low for bevacizumab and aflibercept (−2 for imprecise estimates) ⊕ very low for aflibercept (additional −1 direct evidence inconsistent, higher risk)

The **assumed risk** in the laser group was estimated as the row sum of the events divided by the row sum of the participants (eyes) for dichotomous variables, and as the (unweighted) median change of visual acuity or central retina thickness
The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** The risk ratio was estimated from mixed (direct and indirect) comparisons.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

BACKGROUND

Description of the condition

Diabetic retinopathy (DR) is the most frequent and severe ocular complication of diabetes mellitus (DM) and the leading cause of blindness in the working age population in developed countries (Frank 2004; Klein 1984; Tranos 2004).

Diabetic macular oedema (DMO) is the swelling of the retina resulting from the exudation and accumulation of extracellular fluid and proteins in the macula (Ciulla 2003), due to the breakdown of the blood-retina barrier with an increase in vascular permeability (Antcliff 1999). About a third of people with diabetes have DR and one in 10 is affected by DMO (Yau 2012). The prevalence of DMO increases with diabetes duration, haemoglobin A1c, and blood pressure levels and is higher in people with type 1 compared with type 2 diabetes (Yau 2012).

Intraretinal fluid accumulation results in significant reduction in visual acuity that may be reversible in the short term, but prolonged oedema can cause irreversible damage resulting in permanent visual loss. Blurred vision represents the most common clinical symptom of DMO. Other symptoms can include metamorphopsia (distortion of visual image), floaters, changes in contrast sensitivity, photophobia (visual intolerance to light), changes in colour vision and scotomas (a localised defect of the visual field).

During the last decades, the clinical gold standard to detect macular oedema has been fundus examination with contact lens, but non-contact lenses can also be used for this purpose with good sensitivity. Optical coherence tomography (OCT) has progressively been used as an objective and reproducible tool to measure retinal thickness and has been suggested to be the new gold standard for diagnosing DMO (Olson 2013; Ontario HTA 2009). The most severe form of DMO is CSMO, which was defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) as: retinal oedema within 500 µm of the centre of the fovea; hard exudates within 500 µm of the centre of the fovea, if associated with adjacent retinal thickening (which may be outside the 500 µm limit); and one disc area of retinal oedema (1500 µm) or larger, any part of which is within one disc diameter of the centre of the fovea (ETDRS 1985). Since its introduction, OCT was found to be in good agreement with the clinical gold standard (slit-lamp examination with a contact lens) for detecting the presence of macular oedema and was found to be potentially more sensitive in cases of mild foveal thickening (Brown 2004). A simple OCT-based classification of DMO is often used as centre-involving or non-centre-involving DMO (Browning 2008).

Description of the intervention

Antiangiogenic therapy has been believed a standard of care for treatment of DMO and has largely replaced laser photocoagulation (Jampol 2014), than which it was proven to be more effective (Virgili 2014). Anti-vascular endothelial growth factor (anti-VEGF) treatments inhibit VEGF angiogenic activity, binding to VEGF protein and thus preventing its receptor activation or interaction. These drugs were originally hypothesised as an alternative adjunctive treatment for DMO (Cunningham 2005), following evidence that VEGF-A plays a key role in the occurrence of increased vascular permeability in ocular diseases such as DMO (Aiello 2005).

Grid or focal laser photocoagulation could not be used in all patients with DMO; thus, either laser or sham procedures were current practice comparators in initial studies on the efficacy of antiangiogenic drugs for DMO (Macugen 2005; RESOLVE 2010; RESTORE 2011; Soheilian 2007), and only recently have directly comparative RCTs been conducted (DRCRnet 2015).

Safety of intravitreal antiangiogenic therapy is acceptable; endophthalmitis, the major adverse event (< 1/1000 injections) is related to the surgical injection procedure, rather than the drug itself. These drugs were shown not to increase systemic adverse events such as arterial thromboembolic events, but differences between drugs are not well known (Virgili 2014).

Another therapeutic option for DMO treatment is represented by steroids, administered as intravitreal injections or sustained release implants in order to obtain high local concentrations, maximising their anti-inflammatory, angiostatic and anti-permeability effects while minimising systemic toxicity (Ciulla 2004; Haller 2010; Kuppermann 2010). However, intravitreal steroids may cause cataract and ocular hypertension and the visual outcome is dependent on the lens status or the need for cataract surgery after about one year (Haller 2010; Campochiaro 2010). Currently, some investigators think intravitreal steroids are preferred in patients with anti-VEGF resistant and chronic DMO (Hussain 2015), as an alternative to switching between anti-VEGF drugs. This is also consistent with the EU label of the only approved dexamethasone intravitreal implant in Europe: "Ozurdex is indicated for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy" (accessed on EMA on 4 December 2016). For ranibizumab, the EU label prescribes a 0.5 mg dosage, and that "treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters" (accessed on EMA on 4 December 2016). In the USA, ranibizumab "0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days)" (accessed on FDA on 4 December 2016).

Aflibercept has been approved in the USA, as accessed on FDA on 4 December 2016, and "the recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)". The EU label is similar (accessed on EMA on 4 December 2016).
Bevacizumab is widely used off-label although its use has been questioned based on regulatory or safety issues (Banfi 2013), but is still key for treating chorioretinal vascular disease in low- and middle-income countries thanks to its low cost (Stewart 2016).

How the intervention might work

VEGF plays a key role in the occurrence of increased vascular permeability in ocular diseases such as DMO (Aiello 2005). Anti-VEGF agents inhibit VEGF angiogenic activity, binding to VEGF protein thus preventing its receptor activation and interaction.

Why it is important to do this review

DMO results in a significant burden of low vision and blindness, thus the extent of the existing evidence base for the effectiveness and safety of these agents needs to be assessed and updated. There is a continuing clinical need to establish evidence-based recommendations regarding anti-VEGF agents.

OBJECTIVES

The 2014 update of this review found high-quality evidence of benefit with antiangiogenic therapy with anti-VEGF modalities, compared to laser photocoagulation, for the treatment of DMO. As was concluded in the previous version (Virgili 2014), the objective of this updated review is to compare the effectiveness and safety of the different anti-VEGF drugs in preserving and improving vision and quality of life using network meta-analysis methods.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

People with DMO for whom anti-VEGF treatment is indicated. We expected to include most of the studies also included in Virgili 2014.

Types of interventions

Any antiangiogenic drug with anti-VEGF modalities compared with another drug with anti-VEGF modalities, laser treatment, sham treatment or no treatment. The reasons for selecting treatments of direct and indirect treatment have been discussed in the Description of the intervention section. As explained above, we remark that steroids may be compared with anti-VEGF drugs but this needs a different approach, specifically patient subgroups and timing, and their inclusion could lead to violation of similarity in a review aiming to compare different anti-VEGF drugs such as this.
Regarding drug dose and monitoring/retreatment regimen, in efficacy analyses we included schemes that are either on-label or commonly used in clinical practice, such as the PRN regimen, as presented in the Description of the intervention section. Particularly, both 0.3 mg and 0.5 mg ranibizumab dose are included as available in studies. These two ranibizumab doses were merged into one group in our NMA since studies suggest no difference between them when used monthly (Heier 2016). Regarding aflibercept, we selected the bi-monthly retreatment regimen since this is the approved label in the USA. We used all available data regardless of safety and dose for safety analyses as previously done in Moja 2014.

Types of outcome measures

Primary outcomes

Best-corrected visual acuity (BCVA) expressed as the proportion of participants with at least 15 ETDRS letters (3 ETDRS lines or 0.3 logMAR) of improvement in BCVA from baseline to 12 months.

Secondary outcomes

- Mean change in BCVA from baseline to 12 months, measured using ETDRS charts.
- Mean change in central retinal thickness (CRT), from baseline to 12 months, measured using optical coherence tomography (OCT).
- Mean change in quality of life from baseline to 12 months, measured using a validated instrument.

Measurements at varying lengths of follow-up were pooled at annual intervals, plus or minus six months, the primary analysis being that at 12 months. The time point closer to 12 months, or the

latest time point in the window frame in the case of symmetry, was chosen where multiple time points were available.

Adverse events

The following adverse events were considered.

- All-cause mortality.
- Arterial thromboembolic events (ATC 1994).
- Systemic serious adverse events (SSAEs).

Adverse events were analysed at the longest available follow-up time (Moja 2014).

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 26 April 2017.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 3) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 26 April 2017) (Appendix 1);
- MEDLINE Ovid (1946 to 26 April 2017) (Appendix 2);
- Embase Ovid (1980 to 26 April 2017) (Appendix 3);
- LILACS (Latin American and Caribbean Health Science Information database (1982 to 26 April 2017) (Appendix 4);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 26 April 2017) (Appendix 5);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 26 April 2017) (Appendix 6);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 26 April 2017) (Appendix 7).

Searching other resources

We handsearched the reference lists of the included trials for other possible trials. We accessed the Novartis Clinical Trials database (www.novctrd.com/ctrdWebApp/clinicaltrialrepository/public/main.jsp) on 28 May 2014 and checked all trials indexed under the headings: Ophthalmic Disorders and ranibizumab.

Data collection and analysis

Selection of studies

Two review authors independently selected the studies for inclusion. The titles and abstracts of all reports identified by the electronic searches and handsearching were examined by the review authors. We classified the abstracts as (a) definitely include, (b) unsure and (c) definitely exclude. We obtained and re-assessed full-text copies of those classified as either (a) definitely include or (b) unsure. Having reviewed the full-text copies, we classified the studies as (1) included, (2) awaiting assessment and (3) excluded. Studies identified by both review authors as 'excluded' were excluded and documented in the review. Studies identified as 'included' were included and assessed for methodological quality. The review authors were unmasked to the report authors, institutions and trial results during this assessment. Disagreements between the two review authors were resolved by a third review author.

Data extraction and management

Two review authors independently extracted the data for the primary and secondary outcomes onto paper data extraction forms developed by the Cochrane Eyes and Vision Group. A pilot test of this form was carried out using a small number of studies. We resolved discrepancies by discussion. One review author entered all data into Review Manager 5 (Review Manager 5 2014). The entered data were checked by a second author. In case standard deviations were not available in the publication, and could not be obtained from the authors, these were imputed from standard deviations of other studies with the same comparison.

Assessment of risk of bias in included studies

Two review authors independently assessed the included trials for bias according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). The following parameters were assessed: sequence generation; allocation concealment; masking (blinding) of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting. We evaluated these parameters for each outcome measure or class of outcome measure. We classified each parameter as low risk of bias, high risk of bias or unclear.

If the information available in the published trial reports was inadequate to assess methodological quality, we contacted the trial authors for clarification. We had planned that if they did not respond within six months we would assess the trial based on the available information. However, in the latest update of this review we assessed the trial had the authors not responded within one month.

We followed Salanti 2014 to assess the risk of bias of mixed evidence (mixed evidence not defined previously).

1. Summary risk of bias for each trial: we considered all domains but gave more importance to allocation concealment and masking of outcome assessor.

2. Summary risk of bias for the mixed evidence: based on the percentage contribution of each direct comparison to each network estimate using the contribution plot (Chaimani 2013). We finally integrated the risk of bias of a given comparison with the assessment of transitivity, or similarity of the characteristics of the studies. We expected the transitivity assumption would hold as long as treatment comparisons were not related to:

- acute versus chronic DMO, defined using the cut-off of three or more years of duration;
- average severity of DMO using OCT CRT of 400 micrometres as a cut-off;
- treatment regimen, such as monthly versus less than monthly and number of injections in the first year;
- drug dose for ranibizumab, since this is commercially available in two doses (0.3 mg in the USA, 0.5 mg otherwise);
- whether the trial was industry sponsored.

Measures of treatment effect

Data analysis followed the guidelines set out in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). For dichotomous outcomes, we calculated a summary risk ratio (RR). For continuous outcome, we calculated the mean difference (MD). We planned to calculate a standardised mean difference (SMD) had different scales been used to measure the same continuous outcome.

We did not use ranking measures in this review, since our main interest was to compare only three drugs: aflibercept, bevacizumab and ranibizumab.

Unit of analysis issues

The unit of randomisation was the eye of individual participants. We included one cross-over study comparing ranibizumab and bevacizumab and treated this as a parallel arm study (Wiley 2016), which equals to assume a moderate (0.5) correlation within-person. However, relative drug safety is impossible to assess with a paired design.

We accepted studies presenting systemic adverse events as the unit of analyses, i.e. when an individual suffers from more than one severe adverse event in the study.

Dealing with missing data

Where data were missing due to dropping out of participants, we conducted a primary analysis based on participants with complete data (available case analysis). Following the guidance available in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), we considered that missing outcome data are missing at random if the reasons for loss to follow-up are documented and judged to be unrelated to outcome in both study arms.

Assessment of reporting biases

To investigate small-study bias at the network level we employed the comparison-adjusted funnel plot, which is an adaptation of the funnel plot. We subtracted from each study-specific effect size the mean of meta-analysis of the study-specific comparison and plotted it against the study's standard error (Chaimani 2013).

Data synthesis

Methods for direct treatment comparisons

If there was no substantial statistical heterogeneity, and if there was no clinical heterogeneity between the trials, we combined the results in a meta-analysis using a random-effects model. A fixed-effect model was used if the number of trials was three or less. In the case of substantial statistical heterogeneity (that is I^2 value more than 50%) or clinical heterogeneity, we combined the results in a meta-analysis using a random-effects model if the individual trial results were all consistent in the direction of the effect (that is the RR or MD and confidence intervals largely fall on one side of the null line); when the individual trial results were inconsistent in the direction of the effect, we did not combine study results but presented a narrative or tabulated summary of each study.

Methods for indirect and mixed comparisons

We performed network meta-analysis using the methodology of the multivariate meta-analysis model where different treatment comparisons are treated as different outcomes (Salanti 2012). For this analysis, we used the '*network*' suite of commands available in STATA (StataCorp, 2011; Stata Statistical Software: Release 14. College Station, TX) (White 2015).

We presented mixed effects as RRs or MDs against laser photocoagulation as a single comparison. We prepared league tables presenting mixed comparisons in the inferior-left part and direct comparisons in the superior-right part of the table in order to allow for the inspection of both types of evidence. The same information was presented graphically. We also presented the contribution of direct and indirect evidence to mixed evidence using contribution plots (Chaimani 2013).

Assessment of statistical heterogeneity

In standard pairwise meta-analyses, we estimated heterogeneity variances for each direct comparison. We assessed statistically the presence of heterogeneity within each pairwise comparison using the I^2 statistic (Higgins 2011b). The I^2 statistic measures the percentage of variability that cannot be attributed to random error. In network meta-analysis, we assumed a common estimate for the heterogeneity variance across the different comparisons. The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the network meta-analysis models.

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally, we used the node-splitting approach (Dias 2010). We assumed a common heterogeneity estimate within each loop.

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network, we used the 'design-by-treatment' model using the 'network' command in STATA (White 2015). This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, we judged the presence of inconsistency from any source in the entire network based on a Chi² test.

'Summary of findings' table and GRADE assessment

We prepared one 'Summary of findings' table for each relevant comparison, including all seven outcomes in a table (GRADEpro 2014). As originally intended, the primary analysis was conducted at 12 months. Relevant comparisons were identified to answer the question of which antiangiogenic drug is most effective among on-label (aflibercept, ranibizumab) and off-label (bevacizumab) drugs that are currently available. Because most of the available evidence is around ranibizumab, we reported on the comparison of aflibercept and bevacizumab with ranibizumab. Analyses conducted at 24 months were presented textually because a network meta-analysis was not feasible.

We graded the certainty of the evidence for mixed estimates as explained above. We started from the premise that RCTs provide high-certainty evidence and downgraded for each GRADE parameter to get an overall certainty for each outcome as high, moderate, low or very low (Higgins 2014; Salanti 2014; Schünemann 2011). We estimated the absolute risk in the control group from the data in the included studies as the raw proportion with event for dichotomous outcomes and the median value for continuous outcomes.

Sensitivity and subgroup analyses

We had not planned sensitivity analyses but we decided post-hoc to conduct one excluding studies which were assessed as being at overall high or unclear risk of bias. Moreover, we acknowledge that DRCRnet 2015 emphasised that the differences in absolute benefit between aflibercept, bevacizumab and ranibizumab at one year were dependent on baseline visual acuity, but when we considered this post hoc subgroup analysis we did not find enough study data to conduct such meta-regression analyses.

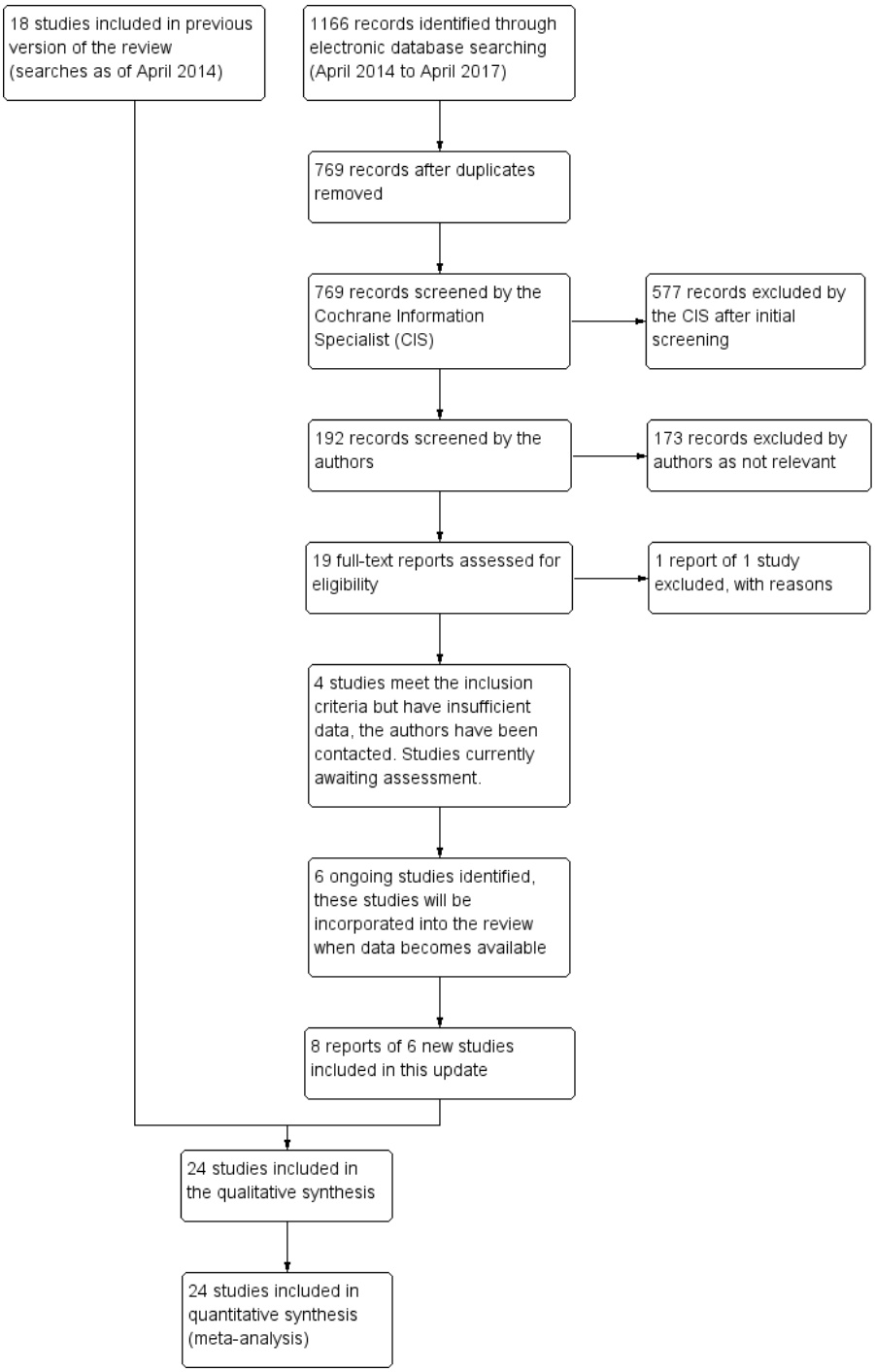
RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies and Characteristics of studies awaiting classification.

The previous version of this review included 18 trials. Update searches run in April 2017 yielded a further 1166 records (Figure 1). After 397 duplicates were removed, the Cochrane Information Specialist screened the remaining 769 records and removed 577 references that were not relevant to the scope of the review. We screened the remaining 192 references and obtained 19 full-text reports for further assessment. We identified eight reports of six new trials for inclusion in the review (DRCRnet 2015, Ishibashi 2014, Lopez-Galvez 2014, REVEAL 2015, Turkoglu 2015, Wiley 2016). A further four trials were deemed eligible but did not provide sufficient data for analysis (Chen 2016; Huang 2016; Jovanovic 2015; Fouda 2017. We have contacted these authors to ask for further information and will assess these studies if we receive additional data. We excluded one study (NCT02985619 (BEVATAAC)) and have identified six new ongoing studies and will assess these for inclusion in the review when data becomes available (NCT02194634;NCT02259088; NCT02348918; NCT02645734; NCT02699450; NCT02712008).

Figure 1. Study flow diagram.



Included studies

We included a total of 24 studies in this updated systematic review and network meta-analysis. BOLT 2010, DA VINCI 2011, Ishibashi 2014, Korobelnik 2014, Macugen 2005, Macugen 2011, READ2 2009, RELATION 2012, RESOLVE 2010, RESPOND 2013, RESTORE 2011, and RISE-RIDE were industry-sponsored, multicentre RCTs conducted in the USA or Europe, whereas REVEAL 2015 was industry-sponsored but conducted in Asia. Ahmadieh 2008, Azad 2012, Ekinci 2014, LUCIDATE 2014, Nepomuceno 2013, Soheilian 2007, and Turkoglu 2015 were independent studies conducted in Brazil, India, Iran, Turkey, and the UK, five of which included bevacizumab. DRCRnet 2010, DRCRnet 2015, Wiley 2016 were publicly-sponsored studies, mainly by the US National Eye Institute, and conducted in the USA or UK. DRCRnet 2015 was the only large parallel-arm study that compared all commercially available drugs (aflibercept, bevacizumab, ranibizumab) and was a large publicly-funded trial comparing aflibercept, bevacizumab and ranibizumab with monthly monitoring and treatment as needed (PRN). Wiley 2016 was a cross-over trial comparing the same three drugs. Lopez-Galvez 2014 was an open-label trial comparing ranibizumab with laser; it was conducted in Spain and results were available only in abstract form.

Only six trials maintained the randomisation scheme at two years' follow-up (BOLT 2010; DRCRnet 2010; DRCRnet 2015; Macugen 2011; READ2 2009; RISE-RIDE). Two industry-sponsored trials used randomisation up to two years (Macugen 2011; RISE-RIDE), while three others obtained follow-up data but allowed anti-VEGF treatment in the control arm after one year (Korobelnik 2014; RESOLVE 2010; RESTORE 2011).

We did not extract data on comparisons of antiangiogenic therapy with triamcinolone and other intravitreal steroids, which were study arms in Ahmadieh 2008, Azad 2012, DRCRnet 2010 and Soheilian 2007, for reasons presented above and also because this comparison is the subject of another Cochrane Review (Grover 2008). Standard deviations of change in CRT were imputed from other studies in REVEAL 2015.

Types of participants

Trials included participants with DMO diagnosed clinically, and often these trials used OCT for confirming macular centre involvement. Baseline visual acuity of participants was generally between 20/200 and 20/40. Most trials required a three- to six-month interval from previous central or peripheral laser, and a few small studies required that participants had not received previous antiangiogenic treatment.

Types of interventions

Eleven studies assessed ranibizumab (DRCRnet 2010; Lopez-Galvez 2014; LUCIDATE 2014; READ2 2009; RELATION 2012; RESOLVE 2010; RESPOND 2013; RESTORE 2011; REVEAL 2015; RISE-RIDE; Turkoglu 2015), six investigated bevacizumab (Ahmadieh 2008; Azad 2012; BOLT 2010; Ekinci 2014; Nepomuceno 2013; Soheilian 2007), two pegaptanib (Macugen 2005; Macugen 2011), and three aflibercept (DA VINCI 2011; and two studies conducted in the USA and Europe using the same protocol, which we will refer to as a single study (Korobelnik 2014). DRCRnet 2015 and Wiley 2016 were the only studies comparing ranibizumab, bevacizumab or aflibercept directly. The drug dose was the same in most studies (0.5 mg ranibizumab, 1.25 mg bevacizumab, 0.3 mg pegaptanib, 2 mg aflibercept) except for RESOLVE 2010 where dose adjustment was allowed for ranibizumab, and also RISE-RIDE, DRCRnet 2015 and Wiley 2016 where 0.3 mg ranibizumab was also delivered.

Anti-VEGF treatment regimens were monthly in RISE-RIDE, in one arm of Korobelnik 2014 and in Wiley 2016. Monthly, bimonthly and 'as needed' or pro re nata (PRN) regimens were adopted in four arms of DA VINCI 2011, and we selected PRN for efficacy data extraction because this is current practice with other anti-VEGF drugs. Ahmadieh 2008 was a short-term study which delivered only the first three injections. Most other studies adopted three initial injections followed by various maintenance regimens. Two studies on aflibercept, reported in Korobelnik 2014 (VISTA and VIVID), compared laser photocoagulation with both monthly injections (2q4) and a regimen of five initial monthly injections followed by bimonthly injections (2q8) followed by a 'treat-and-extend' regimen in year two.

PRN retreatment criteria were based on: visual acuity only in Nepomuceno 2013 and REVEAL 2015; OCT only in BOLT 2010, Macugen 2011 and READ2 2009; OCT and visual acuity in Azad 2012, DRCRnet 2010, DRCRnet 2015, Ekinci 2014, RESOLVE 2010 and in the PRN arm of DA VINCI 2011; inclusion of clinical examination or at the examiners' discretion in Macugen 2005, RESTORE 2011 and Soheilian 2007. They were unclear in Lopez-Galvez 2014, RELATION 2012 and RESPOND 2013.

Types of outcomes

The data structure of our efficacy and safety outcomes can be seen in Table 1 where the sum of cases for each outcome is shown.

Studies awaiting assessment

Several trials were included as ongoing in the previous version of this review. We checked the completion status

on the study trial register and tried to contact the authors, but were not able to obtain additional information (NCT00387582; NCT00997191 (IBeTA); NCT01445899 (MATISSE); NCT01565148 (IDEAL)).

Two Chinese trials (Chen 2016, 72 participants; Huang 2016, 78 participants) compared ranibizumab plus laser or, respectively, ranibizumab to grid laser. These trials provided baseline and final CRT data at six months as well as the proportion with visual improvement, but the improvement cut-off was unclear, as was the measurement tool.

Jovanovic 2015 included 72 participants (120 eyes) randomised to either bevacizumab (one or more injections with or without macular laser photocoagulation depending on results after four to six weeks) or macular laser alone to treat DMO. However, results were not provided at desired fixed follow-up times by each randomisation group.

Fouda 2017 included 42 participants (70 eyes) randomised to aflibercept or ranibizumab and treated with three initial injections and then PRN. The authors did not find any significant difference between the two drugs in terms of BCVA, but used decimal rather than logMAR visual acuity and we could not use these data in analyses (authors contacted). The authors reported no difference regarding CRT and a smaller but statistically significant number of injections with aflibercept versus ranibizumab.

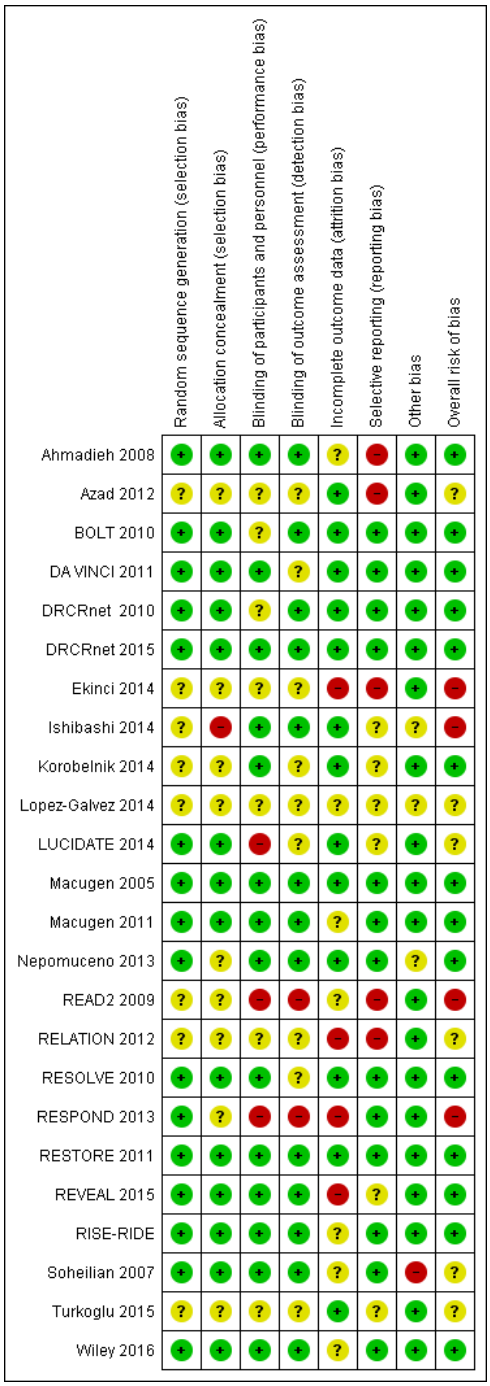
Excluded studies

See 'Characteristics of excluded studies' table for the list of exclusions with reasons.

Risk of bias in included studies

See 'Risk of bias in included studies'; Figure 2.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Sequence generation was judged at low risk of bias in 12 studies and was unclear in nine (Azad 2012; Ekinci 2014; Lopez-Galvez 2014; Ishibashi 2014; Korobelnik 2014; READ2 2009; RELATION 2012; RESPOND 2013; Turkoglu 2015). Method for allocation concealment was also unclear in these studies, as they were in Nepomuceno 2013. Allocation concealment was judged at high risk of bias in Ishibashi 2014.

Blinding

Masking of participants and outcome assessors was obtained in 14 and 12 trials respectively, and was unclear in seven and nine trials respectively. LUCIDATE 2014, READ2 2009 and RESPOND 2013 were unmasked.

Incomplete outcome data

Eleven trials were judged at low risk of attrition bias (Azad 2012; BOLT 2010; DA VINCI 2011; DRCRnet 2010; DRCRnet 2015; Korobelnik 2014; LUCIDATE 2014; Macugen 2005; Nepomuceno 2013; RESOLVE 2010; RESTORE 2011); and eight trials were judged at unclear risk of bias in which some participants were missing but reasons for missingness were not fully reported (Ahmadieh 2008; Ishibashi 2014; Macugen 2011; READ2 2009; RISE-RIDE; Soheilian 2007; Turkoglu 2015; Wiley 2016). Five trials were judged at high risk of attrition bias: Ekinci 2014 excluded 15 participants after randomisation due to ocular and systemic complications; Lopez-Galvez 2014 lost about 20% of participants in each arm and did not report the reasons; RELATION 2012, RESPOND 2013 and REVEAL 2015 lost many more participants in the laser arm than in the ranibizumab arms.

Selective reporting

Table 1 shows the reporting of all outcomes across 24 trials. Reporting was almost complete for mean VA change at one year (21 studies, 4489 complete cases). Mean CRT change was available in 16 studies (3491 cases). Gain of 3 or more VA lines was reported at one year in 17 studies (4031 cases). SSAEs at one or two years were reported from 18 studies (4229 cases). ATC thromboembolic events were reported in 15 (3718 cases) and death in 17 (4455 cases).

Other potential sources of bias

The baseline visual acuity was not balanced in Soheilian 2007; the visual acuity was around 20/100 in the bevacizumab and bevacizumab-triamcinolone arms and 20/70 in the laser arm, suggesting that milder CSMO was included in the laser arm. The trial investigators adjusted for baseline values in the analyses, which also took into account the within-participant correlation (150 eyes of 129 participants, 16% of participants with both eyes in the analyses). However, we could not take within-participant correlation into account when analysing dichotomous visual acuity.

Three studies included both eyes of some participants in analyses: Ahmadieh 2008 14 out of 101 participants; Nepomuceno 2013 15 out of 48 participants; Wiley 2016 6 out of 56 participants.

RELATION 2012 was terminated early when ranibizumab was approved for DMO in Germany. Early termination was unlikely to be associated with treatment effect.

Effects of interventions

See: **Summary of findings for the main comparison** Antiangiogenic therapy versus control; **Summary of findings 2** Ranibizumab versus aflibercept for diabetic macular oedema; **Summary of findings 3** Ranibizumab versus bevacizumab for diabetic macular oedema

Antiangiogenic drugs versus laser photocoagulation or control: efficacy and safety

Summary of findings for the main comparison presents the evidence on the comparison of each drug with laser photocoagulation (efficacy at one year) or control (laser photocoagulation or sham at the longest available follow-up of one or two years).

Efficacy at one year

As found in the previous version of this review based on direct meta-analyses (Virgili 2014), there was high-certainty of evidence of benefit for aflibercept, bevacizumab and ranibizumab compared to laser photocoagulation at one year. Specifically, aflibercept, bevacizumab and ranibizumab were all more effective than laser for improving vision by 3 or more lines after one year, since about one in 10 people improve vision with laser, and about three in 10 people improve with anti-VEGF treatment: risk ratio (RR) versus laser was 3.66 (95% CI 2.79 to 4.79) for aflibercept; 2.47 (95% CI 1.81 to 3.37) for bevacizumab; and 2.76 (95% CI 2.12 to 3.59) for ranibizumab. Regarding change of mean BCVA, on average there was no change with laser after one year, compared with a gain of 1 or 2 lines with anti-VEGF treatment: laser versus aflibercept mean difference (MD) −0.20 (95% CI −0.22 to −0.17) logMAR; versus bevacizumab −0.12 (95% CI −0.15 to −0.09) logMAR; versus ranibizumab −0.12 (95% CI −0.14 to −0.10) logMAR (negative logMAR in favour of anti-VEGF group).

The certainty of evidence was moderate for bevacizumab versus laser regarding mean BCVA change due to inconsistency of direct and indirect evidence.

Safety at the longest available follow-up

This network meta-analysis confirms that aflibercept, bevacizumab and ranibizumab do not increase the risk of all SSAEs compared to laser photocoagulation or sham at one year. We considered this evidence of high-certainty. (Summary of findings for the main comparison), Of notice, SSAEs are a generic indicator of harm, mostly including hospitalisation or death for any cause and unrelated to antiangiogenic effect.

Regarding 'Antiplatelet Trialists Collaboration arterial thromboembolic events' and all-cause death, no statistically significant difference was found between any anti-VEGF drug and control, but the certainty of the evidence was generally low due to imprecision (large 95% CIs).

Quality of life

Only RESTORE 2011, RESPOND 2013 and Turkoglu 2015 presented quality of life data for ranibizumab versus laser photocoagulation at six to 12 months (3 studies, 412 participants). Ranibizumab improved NEI-VFQ composite score by 5.14 units (95% CI 2.96 to 7.32) compared to laser (Summary of findings for the main comparison). The certainty of the evidence was moderate due to risk of bias issues (RESPOND 2013 was unmasked and Turkoglu 2015 was unclear for most items).

Macugen 2011 obtained QOL data at two years and we did not include these data since pegaptanib was not of direct interest and sham, rather than laser, was the comparator. RISE-RIDE obtained QOL data at two years and was not included since sham, rather than laser, was the control group.

Ranibizumab versus aflibercept and bevacizumab

Efficacy at one year

Table 2 presents the number of studies (participants/eyes) in all treatment arms of the network for the efficacy outcomes at one year. Figure 3 presents the corresponding networks' structure. As seen, more data was available for ranibizumab, alone or combined with laser, with respect to aflibercept and bevacizumab. Figure 4, Figure 5 and Figure 6 present forest plots with effects for each study, estimates from direct pairwise meta-analysis and mixed estimate from the network meta-analysis. Summary of findings 2 and Summary of findings 3 present comparisons of ranibizumab versus aflibercept and bevacizumab.

Figure 3. Network structure for efficacy outcomes at 1 year

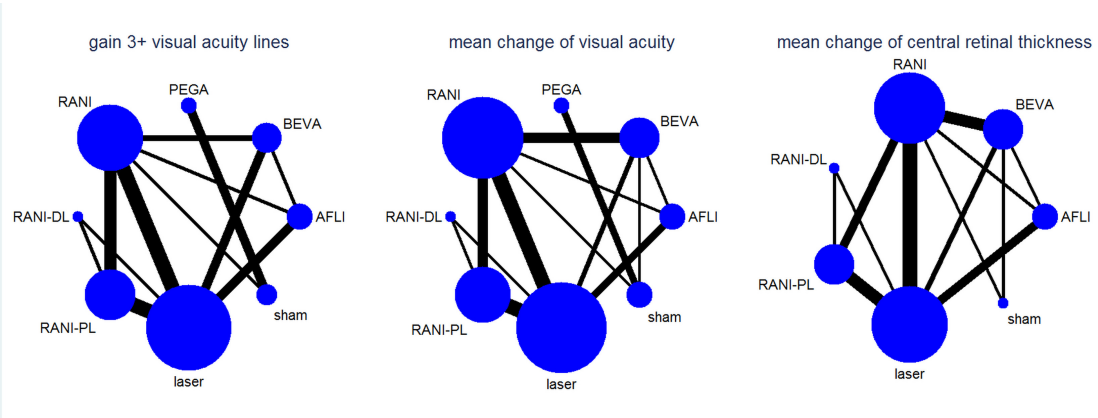


Figure 4. All direct and mixed comparisons: gain of 3 or more lines of visual acuity at 1 year

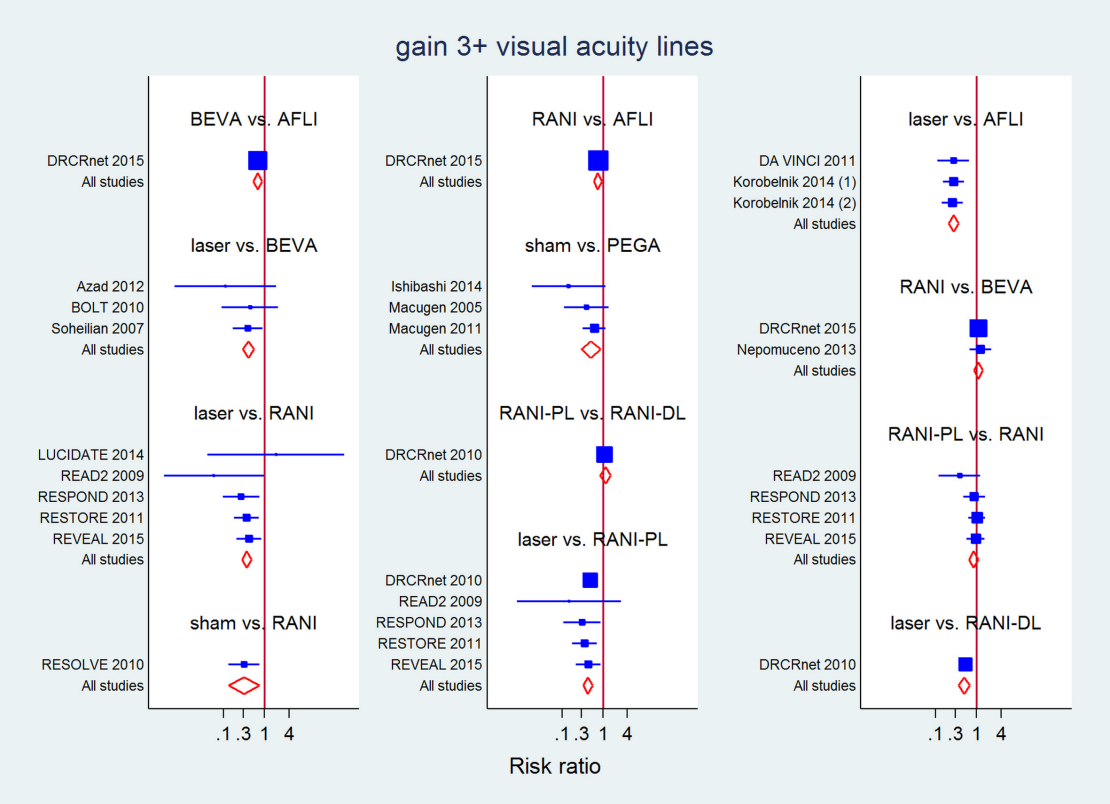


Figure 5. All direct and mixed comparisons: mean change in visual acuity at 1 year

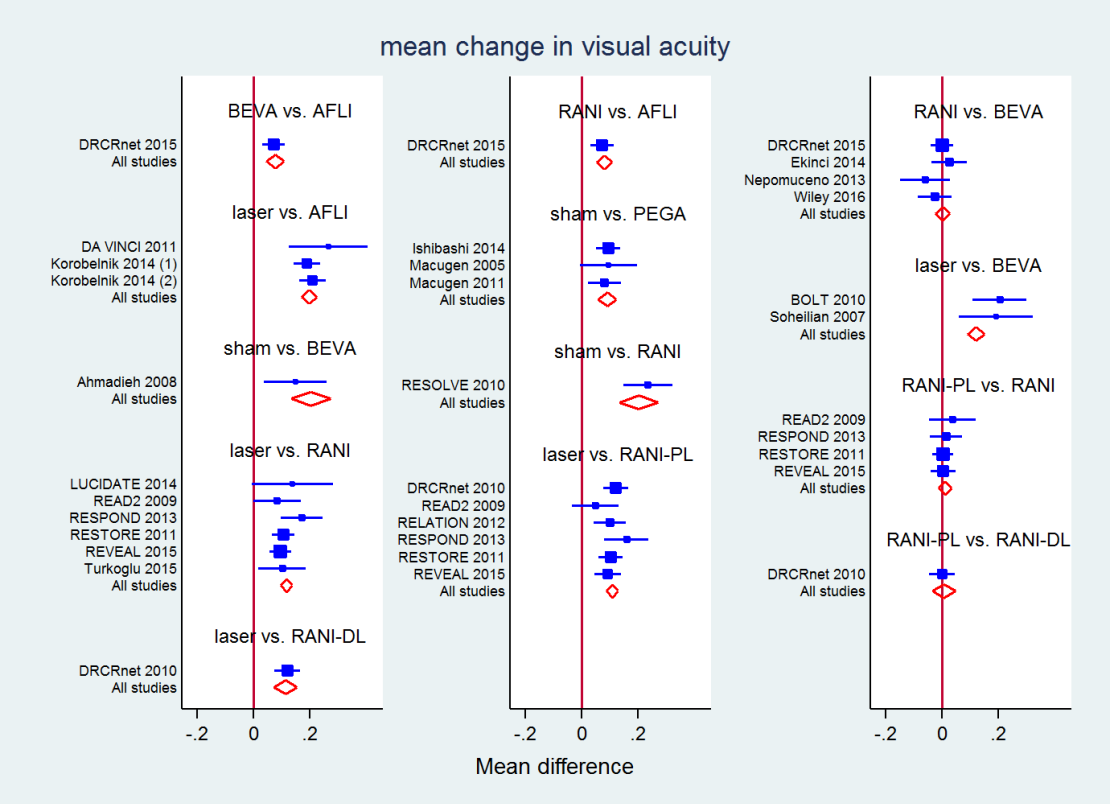
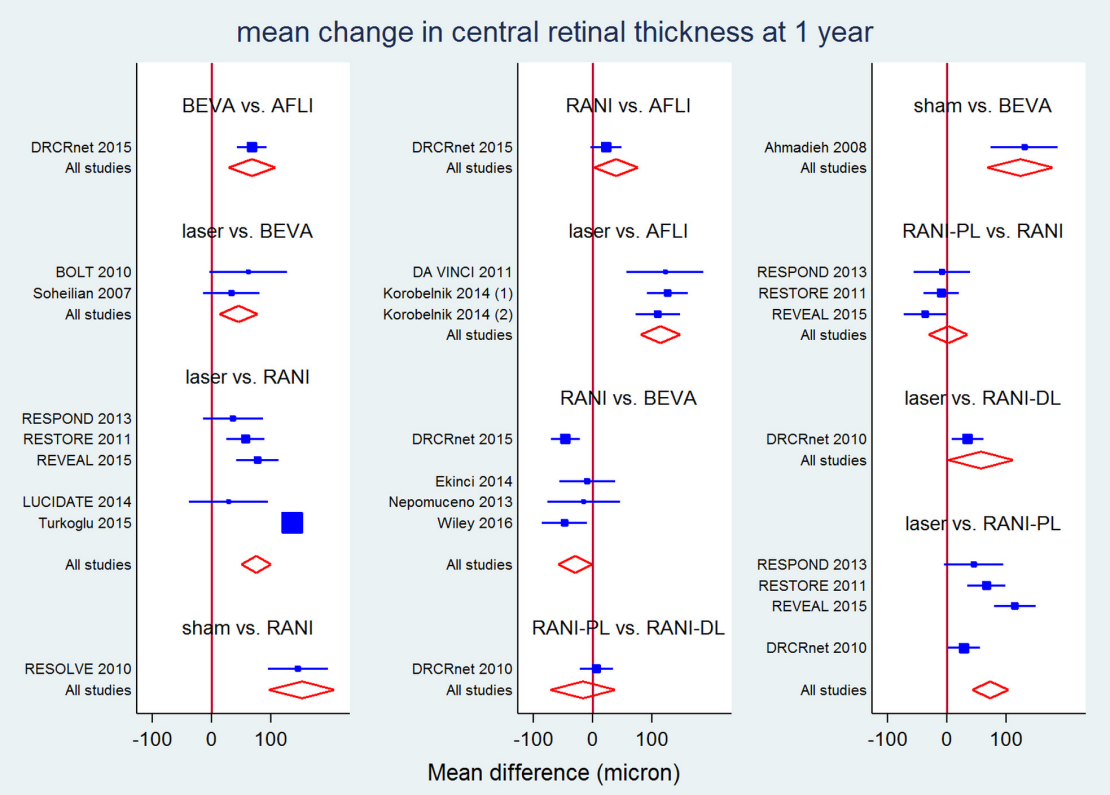


Figure 6. All direct and mixed comparisons: mean change in central retinal thickness at 1 year (micron)



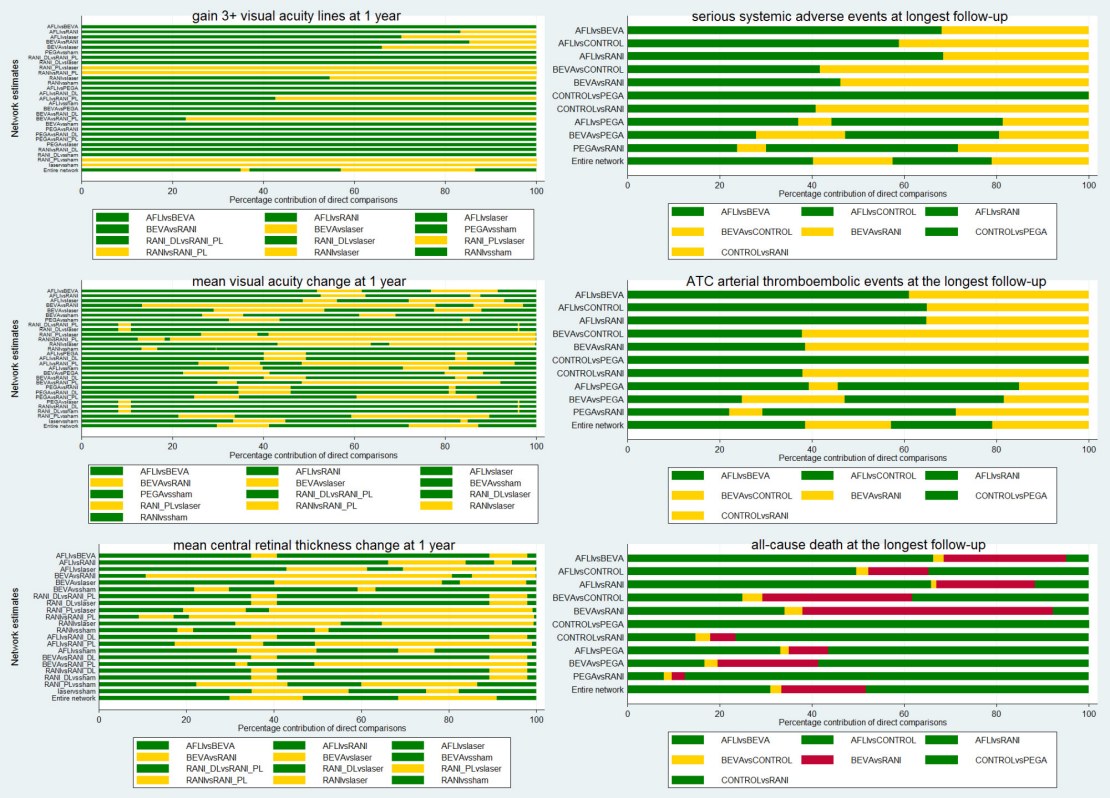
Comparing the available drugs as monotherapy, all efficacy outcomes significantly favoured aflibercept over ranibizumab and bevacizumab (Table 3; Table 4; Table 5). Compared with ranibizumab and bevacizumab, aflibercept increased the chances of gaining 3 or more lines (17 studies, 4031 eyes) by about 30%, since the RR for gain was 0.75 (95% CI 0.60 to 0.94) and 0.68 (95% CI 0.53 to 0.86) versus ranibizumab and bevacizumab, respectively. The corresponding figures for mean BCVA change (21 studies, 2689 eyes) were a difference of 0.08 (95% CI 0.05 to 0.11) logMAR and 0.08 (95% CI 0.05 to 0.11) logMAR and were 38.90 (95% CI 2.27 to 75.52) micron and 68.32 (95% CI 28.69 to 107.96) micron for CRT change (16 studies, 3491 eyes), all favouring aflibercept.

Ranibizumab and bevacizumab did not differ in term of functional outcomes: RR of gain 1.11 (95% CI 0.87 to 1.43) and difference in mean VA change 0.00 (95% CI −0.02 to 0.03) logMAR. However, CRT reduction favoured ranibizumab by −29.4 (95% CI −58.2 to −0.70) micron.

There was no evidence of overall statistical inconsistency in our efficacy analyses (Table 3; Table 4; Table 5). We found evidence of statistical inconsistency in one comparison (bevacizumab versus laser) for mean BCVA change and in the loop connecting ranibizumab, ranibizumab plus prompt laser and laser for mean CRT change, where two direct meta-analyses also showed high heterogeneity in the same loop.

Mean risk of bias was low for mixed and direct comparisons among aflibercept, bevacizumab and ranibizumab for all efficacy outcomes, except for the comparison between bevacizumab and ranibizumab regarding mean BCVA change and mean CRT change, which were judged at unclear risk of bias (Figure 7).

Figure 7. Contribution plot of mean overall study risk of bias to pairwise network estimates. Legends show the risk of bias of each direct comparison.



We had not pre-planned any subgroup analyses and were unable to obtain data to carry out post hoc subgroup analyses by baseline BCVA. DRCRnet 2015, the only large study comparing the three drugs, found that aflibercept was superior to bevacizumab and ranibizumab for participants with lower vision (69 ETDRS letter or less or approximately 20/50 or 0.4 logMAR or worse), whereas differences between the three drugs were unimportant for participants with better vision.

Efficacy at two years

Three publicly funded studies (BOLT 2010; DRCRnet 2010; DRCRnet 2015) and two industry-sponsored studies (Macugen 2011; RISE-RIDE) provided data at two years. There was only one study for each comparison, making data unsuitable for a network meta-analysis.

Only DRCRnet 2015 (complete cases: aflibercept n = 201, bevacizumab n = 185, ranibizumab n = 191) compared different antiangiogenic drugs, and found no VA differences between ranibizumab 0.3 mg and aflibercept (gain 3+ VA lines, RR 0.94, 95% CI 0.73 to 1.22; difference in mean VA change 0.01, 95% CI −0.04 to 0.06). Ranibizumab and bevacizumab did not differ in terms of gain of 3 or more VA lines (RR 0.94, 95% CI 0.72 to 1.24) but the difference in mean VA change favoured ranibizumab (mean difference −0.05, 95% CI −0.09 to 0.00), although it was not precisely estimated. Although effects on CRT favoured aflibercept over ranibizumab and ranibizumab over bevacizumab, none was statistically significant: mean difference −22 micron (95% CI −50 to 6 micron) and −23 micron (95% CI −52 to 6 micron) respectively.

We were unable to obtain data allowing subgroup analyses by baseline BCVA. DRCRnet 2015 found that such subgroup differences were attenuated at two years.

Safety at the longest available follow-up

Table 6 presents the number of studies (participants/eyes) in the network for safety outcomes at the longest available follow-up, and Figure 8 presents the corresponding network structure. Figure 9, Figure 10 and Figure 11 present forest plots for each study as well as their direct meta-analysis and mixed estimates from the

Figure 8. Network structure for safety outcomes at 1 year

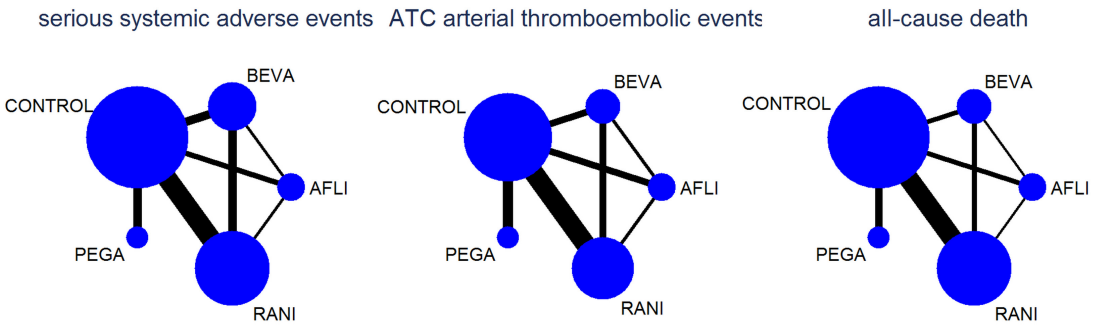


Figure 9. All direct and mixed comparisons: serious systemic adverse events at the longest available follow-up (1 or 2 years)

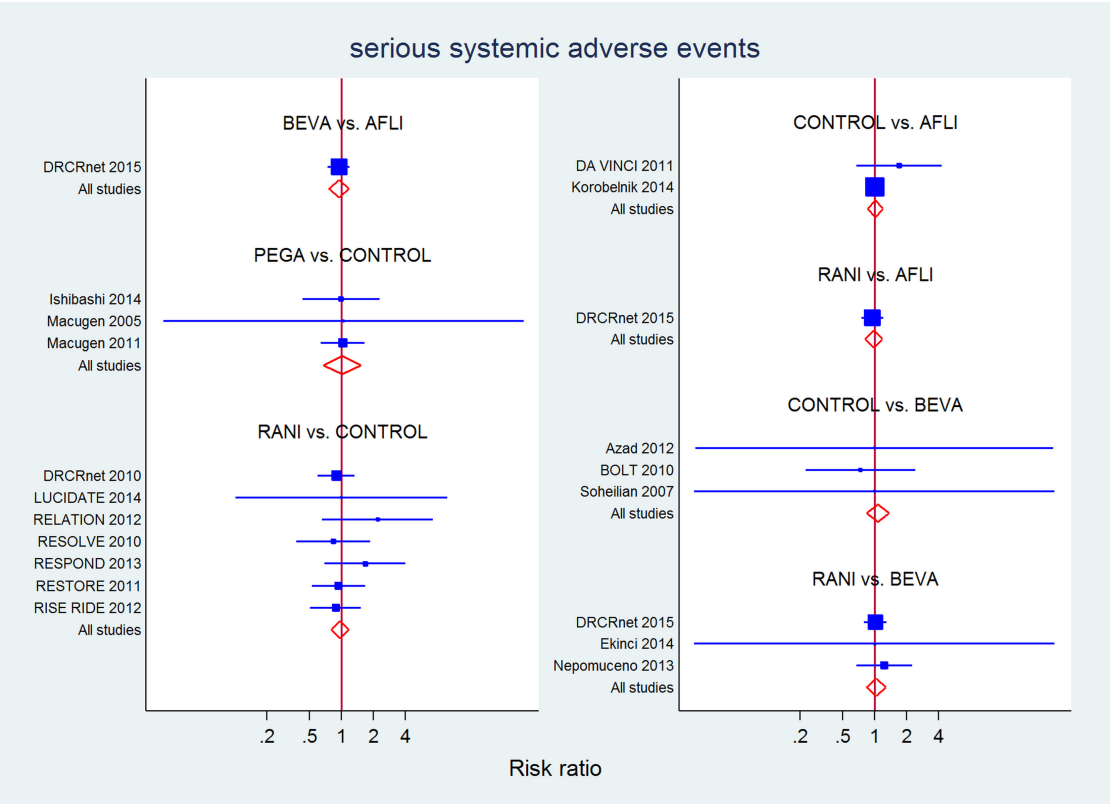


Figure 10. All direct and mixed comparisons: arterial thromboembolic events at the longest available follow-up (1 or 2 years)

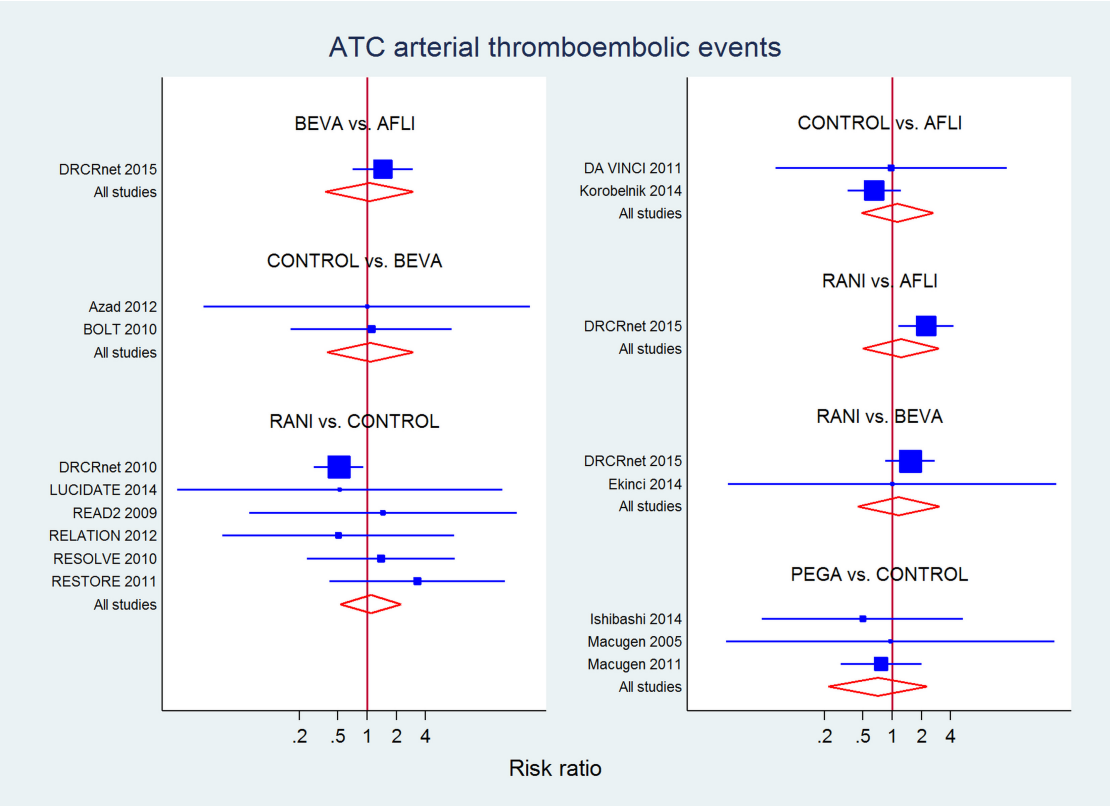
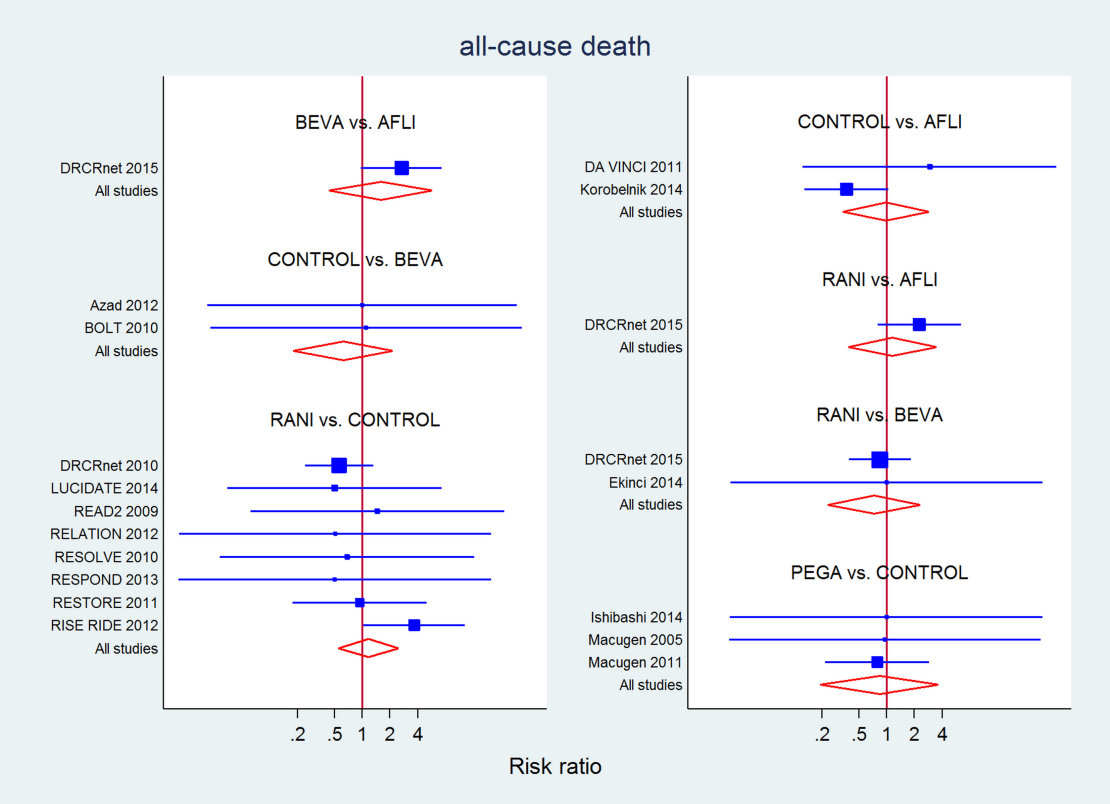


Figure 11. All direct and mixed comparisons: all-cause death at the longest available follow-up (1 or 2 years)



Two-year data were available and reported in only four RCTs in this review. Most industry-sponsored studies were open-label after one year. Differently from efficacy analyses at one year, our safety analyses included data from RISE-RIDE on ranibizumab with monthly treatments up to two years, as well as data from the monthly treatment arm (2q4) of Korobelnik 2014, which became PRN in the second year.

Though no analysis suggested a difference among drugs for any safety outcome, only estimates for SSAEs (18 studies, 4229 eyes) reached sufficient precision to exclude very large differences among drugs. Overall, no difference was detected in mixed evidence estimates for any drug compared to laser or sham. Moreover, RR 95% CI width excluded differences of 20% to 30% or more between aflibercept, bevacizumab and ranibizumab, while estimates for pegaptanib were less precise (Table 7). No overall (P = 0.86) or loop-specific inconsistency was detected.

Fifteen studies (3718 eyes) contributed to this analysis on 'Antiplatelet Trialists Collaboration arterial thromboembolic events' (Table 8). No difference was detected in mixed evidence estimates for any drug compared to laser or sham or between drugs, but estimates were very imprecise. No overall inconsistency was detected (P = 0.19), but direct evidence from DRCRnet 2015 showed increased risk for ranibizumab compared to aflibercept (RR 2.26, 95% CI 1.15 to 4.23) which was larger and inconsistent with indirect evidence (P = 0.002), resulting in mixed evidence showing no difference (RR 1.25, 95% CI 0.50 to 3.05).

Seventeen studies (4455 eyes) contributed to the analysis of 'all-cause mortality' (Table 9). No difference was detected for direct, indirect and mixed evidence estimates for any drug compared to laser or sham or between drugs, but estimates were imprecise.

Mean risk of bias was low for mixed and direct comparisons between aflibercept and ranibizumab and unclear for bevacizumab versus ranibizumab for SSAEs. Regarding ATC arterial thromboembolic events and all-cause death, risk of bias was low for aflibercept versus ranibizumab but it was unclear or high for bevacizumab versus ranibizumab (Figure 7).

Quality of the evidence

See above for the discussion of risk of bias of mixed evidence in pairwise comparisons of interest.

Statistical heterogeneity between studies

When a direct meta-analysis was possible, no heterogeneity of effects was found for the following outcomes: gain of 3 or more BCVA lines, mean BCVA change, SSAEs, ATC arterial thrombembolic events, death. As reported above, there was high heterogeneity in the meta-analysis of change in CRT for the comparisons of ranibizumab with laser (I^2 = 91%) and ranibizumab plus deferred laser versus laser (I^2 = 80%), but not in other two meta-analyses in this network.

Estimates of between-study standard deviation τ in the network meta-analyses suggested little heterogeneity for dichotomous outcomes, except for ATC arterial thrombembolic events when it was moderate (τ = 0.51) . Values for BCVA change and CRT change were 8^{-10} logMAR and 27 micron, respectively. These values mean that heterogeneity was negligible for VA change, but was compatible with a predictive intervals width increased by at least 100 micron for the CRT change.

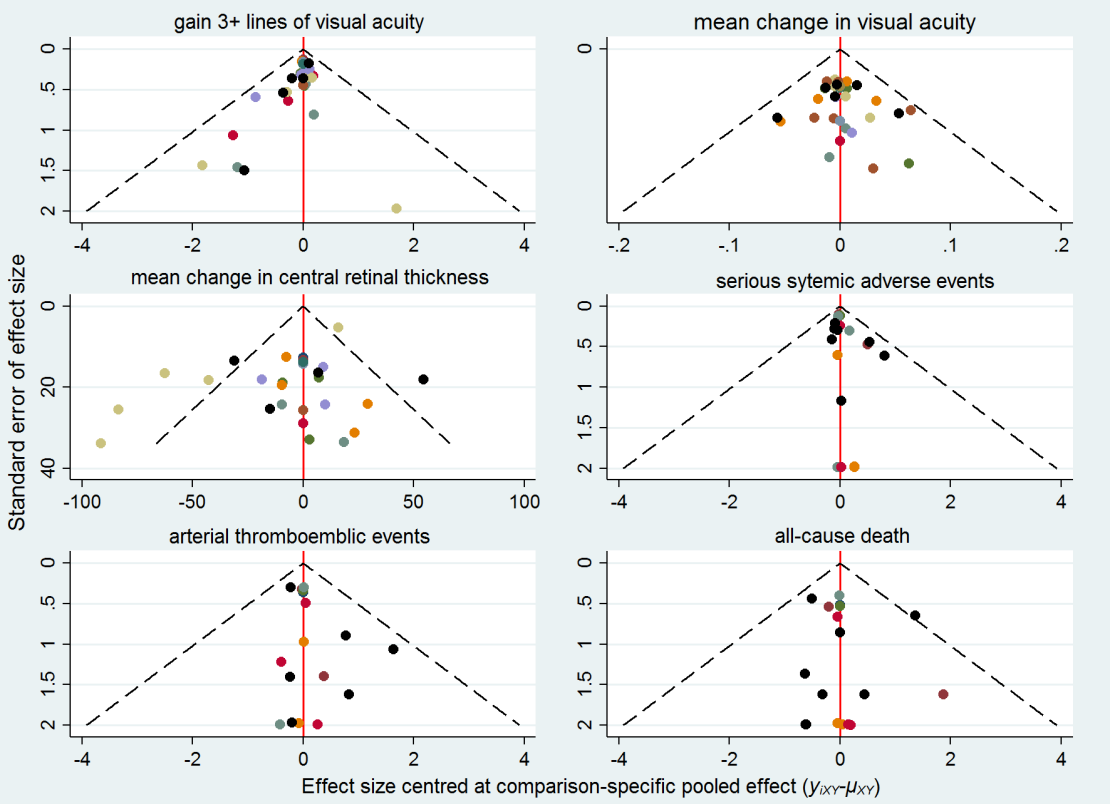
Similarity between studies

Table 10 shows baseline characteristics (BCVA, CRT) and the number of injections across study and treatment arms. Overall, most studies included participants with mean BCVA about 20/60 and CRT between 400 and 500 micron, which we believe sufficiently homogeneous. The number of injections was high compared with current practice (seven to 10 in year one), except for few small studies delivering a low number of injections. No heterogeneity was suspected between studies using 0.3 versus 0.5 mg ranibizumab. In the safety analyses, we included two studies with monthly injections - one arm of Korobelnik 2014 for aflibercept and RISE-RIDE for ranibizumab - and, again, no heterogeneity seemed to arise from lower intensity regimens in other studies. Regarding sponsorship, there were fewer industry-sponsored studies on bevacizumab, but these studies were also smaller than other studies, and the impact of such differences cannot be assessed. Finally, we did not consider the OCT model used in each study as a source of heterogeneity in CRT change since this was balanced between the arms of each study.

Selective reporting

Comparison adjusted funnel plots showed some asymmetry for the outcome 'gain of 3 or more VA lines', but no specific direct comparison seemed to be affected (Figure 12). Instead, asymmetric observations to the left of the non-significance area were seen for the outcome 'mean CRT change at one year' regarding the comparison 'ranibizumab versus laser', which also suffered high heterogeneity.

Figure 12. Comparison-adjusted funnel plot for all outcome measures



Overall quality of evidence for the main comparisons between drugs

Summary of findings 2 and Summary of findings 3 show summary data as well as the overall quality of evidence for the comparisons of interest in this review, based on the data reported above.

Sensitivity analyses on studies at low risk of bias

We conducted analyses of efficacy outcomes after excluding 10 studies at unclear or high risk of bias. These analyses confirmed the findings with all studies.

- Gain of 3 or more BCVA lines: ranibizumab versus aflibercept RR 0.74 (95% CI 0.59 to 0.93); bevacizumab versus ranibizumab RR 0.89 (95% CI 0.69 to 1.15); no overall or comparison-specific inconsistency.
- Mean change in BCVA: ranibizumab versus aflibercept 0.08 (95% CI 0.05 to 0.12) logMAR; bevacizumab versus ranibizumab 0.0 (95% CI 0.2 to −0.03); no overall inconsistency (P = 0.130), some inconsistency for the comparisons of bevacizumab versus laser (P = 0.046) and ranibizumab versus laser (P = 0.043), same direction of effects.
- Mean change in CRT: ranibizumab versus aflibercept 84 (95% CI 43 to 125) micron; bevacizumab versus ranibizumab 16 (95% CI −35 to 67) micron; overall inconsistency was detected (P = 0.012), which was due to the loop ranibizumab plus prompt laser versus ranibizumab plus deferred laser versus laser (P < 0.001 for all comparisons).

Therefore, sensitivity analyses confirmed the results of main analyses.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Ranibizumab versus aflibercept for diabetic macular oedema

Patient or population: people with diabetic macular oedema
Settings: ophthalmology clinics
Interventions: aflibercept, ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI), mixed evidence**	Certainty of the evidence (GRADE)	Reason for downgrading certainty of evidence
	Assumed risk	Corresponding risk			
	Aflibercept	Ranibizumab			
Gain 3+ lines of visual acuity at 1 year	**370 per 1000**	**278 per 1000** (222 to 348)	**RR: 0.75** (0.60 to 0.94)	⊕⊕⊕ moderate	−1 for imprecision as confidence intervals include both clinically important and clinically unimportant effects
Visual acuity change at 1 year Measured on the logMAR scale, range −1.3 to 1.3. Higher values represent worse visual acuity.	On average visual acuity improved by **−0.23 logMAR** units in the aflibercept group between the start of treatment and 1 year	Average change in visual acuity was **0.08 (0.05 to 0.11) logMAR units worse** with ranibizumab compared with aflibercept		⊕⊕⊕ moderate	−1 for imprecision as confidence intervals include both clinically important and clinically unimportant effects
Central retinal thickness μm (CRT) change at 1 year The aim of treatment is to reduce central macular thickness so thinner is better.	On average CRT changed by **−181 μm** in the aflibercept group between the start of treatment and 1 year (became thinner)	Average change in CRT was **39 (2 to 76) μm more (thicker) with ranibizumab** compared with aflibercept		⊕⊕ low	−1 for high heterogeneity in two direct comparisons and large predictive intervals −1 for imprecision
Quality of life at 1 year	No data available.				

All serious systemic adverse events at 1 to 2 years	**345 per 1000**	**338 per 1000** (283 to 411)	**RR 0.98** (0.82 to 1.19)	⊕⊕⊕⊕ high	
Arterial thromboembolic events at 1 to 2 years	**60 per 1000**	**74 per 1000** (29 to 191)	**RR 1.24** (0.48 to 3.19)	⊕ very low	Inconsistency between direct and indirect evidence (−1), and imprecise estimates (−2)
Death at 1 to 2 years	**30 per 1000**	**35 per 1000** (11 to 108)	**RR 1.16** (0.38 to 3.58)	⊕ very low	Inconsistency between direct and indirect evidence (−1), and imprecise estimates (−2)

The **assumed risk** in the aflibercept group was estimated as the row sum of the events divided by the row sum of the participants (eyes) for dichotomous variables, and as the (unweighted) median change of visual acuity or central retina thickness
The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** The risk ratio was estimated from mixed (direct and indirect) comparisons.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

Ranibizumab versus bevacizumab for diabetic macular oedema

Patient or population: people with diabetic macular oedema
Settings: ophthalmology clinics
Interventions: bevacizumab, ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI), mixed evidence**	Certainty of the evidence (GRADE)	Reason for downgrading certainty of evidence
	Assumed risk	Corresponding risk			
	Bevacizumab	Ranibizumab			
Gain 3+ lines of visual acuity at 1 year	**300 per 1000**	**333 per 1000** (261 to 429)	**RR 1.11** (0.87 to 1.43)	⊕⊕⊕ moderate	Imprecise estimate (−1)
Visual acuity change at 1 year Measured on the logMAR scale, range −1.3 to 1. 3. Higher values represent worse visual acuity.	On average visual acuity improved by **−0.19 logMAR units** in the bevacizumab group between the start of treatment and 1 year	Average change in visual acuity was**0.00 (−0.02 to 0.03) logMAR** units (same) with ranibizumab compared with bevacizumab		⊕⊕⊕ moderate	Unclear risk of bias (−1)
Central retinal thickness (CRT) change at 1 year The aim of treatment is to reduce central macular thickness so thinner is better.	On average CRT changed by **−98 μm** in the bevacizumab group between the start of treatment and 1 year (became thinner)	Average change in CRT was **−29 (−58 to −1) μm more (thinner) with ranibizumab** compared with bevacizumab		⊕⊕ low	Unclear risk of bias (−1) Imprecise estimate (−1)
Quality of life at 1 year	No data available				
All serious systemic adverse events at 1 to 2 years	**240 per 1000**	**250 per 1000** (202 to 307)	**RR 1.04** (0.84 to 1.28)	⊕⊕⊕ moderate	Unclear risk of bias (−1)
Arterial thromboembolic events at 1 to 2 years	**60 per 1000**	**70 per 1000** (26 to 189)	**RR 1.17** (0.43 to 3.13)	⊕ very low	Unclear risk of bias (−1) Imprecise estimate (−2)

Death at 1 to 2 years	**40 per 1000**	**29 per 1000** (9 to 95)	**RR 0.73** (0.22 to 2.37)	⊕ very low	High risk of bias (−2) Imprecise estimate (−2)

The **assumed risk** in the bevacizumab group was estimated as the row sum of the events divided by the row sum of the participants (eyes) for dichotomous variables, and as the (unweighted) median change of visual acuity or central retina thickness
The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** The risk ratio was estimated from mixed (direct and indirect) comparisons.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

DISCUSSION

Summary of main results

This review and network meta-analysis confirms the findings of the previous version which found high-certainty evidence that antiangiogenic therapy provides benefit over laser treatment in people with DMO at one year and concluded that further studies should compare different drugs. This update found four studies with direct comparisons between drugs and augmented this evidence with indirect comparisons in a network meta-analysis based on 24 included studies.

At one year, all efficacy outcomes significantly favoured aflibercept over ranibizumab and bevacizumab. Aflibercept increased the chances of gaining 3 or more BCVA lines by about 30%, and conferred an advantage of between half and 1 BCVA line over the other drugs (moderate-certainty of evidence). Ranibizumab and bevacizumab did not differ in terms of functional outcomes (moderate-certainty of evidence), but ranibizumab was more effective in terms of CRT reduction (low-certainty of evidence). There was no evidence of statistical inconsistency in our analyses, except for the comparison between ranibizumab and bevacizumab for mean BCVA change, but the differences between direct and indirect evidence were clinically irrelevant.

The BCVA difference between aflibercept versus ranibizumab or bevacizumab was largely below the threshold of 1 ETDRS line (five letters or 0.1 logMAR) that was used for non-inferiority in trials on DMO (OZDRY 2015, PLACID 2013) and AMD (CATT 2011), suggesting this difference was not clinically relevant.

The previous version of this review found moderate-certainty evidence of good safety of antiangiogenic drugs, including aflibercept, bevacizumab, ranibizumab and pegaptanib, versus control. This update found high-certainty evidence that aflibercept, ranibizumab and bevacizumab do not differ regarding SAEs, excluding RR differences between drugs by more than 25%. However, estimates were imprecise on well-defined hard events such as death or arterial thromboembolic events (very low-certainty evidence).

Two-year data on direct comparisons were available only for one large multicentre publicly funded study showing smaller differences between aflibercept, bevacizumab and ranibizumab as compared to one year (DRCRnet 2015).

Overall completeness and applicability of evidence

This review confirms and enhances the findings of DRCRnet 2015: that aflibercept confers some advantage over bevacizumab and ranibizumab at one year. Two-year data were available and reported in only four RCTs in this review. Most industry sponsored studies were open-label after one year. Thus, long-term outcomes have to be inferred from observational trials.

We could not investigate subgroup effects in this review due to lack of subgroup data. DRCRnet 2015 found the relative benefit with aflibercept versus ranibizumab and bevacizumab is larger when visual acuity is lower than about 20/50, and modest above this level. Moreover, we could not investigate the potential effect of differences in dose and regimen. Nonetheless, our review includes studies with a broad range of characteristics, but without major differences in populations. Particularly, 0.3 mg ranibizumab was used in the direct comparison with aflibercept and bevacizumab in DRCRnet 2015; yet indirect evidence, mostly based on 0.5 mg ranibizumab, was consistent. Regarding treatment frequency: the only study on monthly 0.3 mg ranibizumab was RISE-RIDE for indirect evidence, but this could not be included since one-year data were not available. We excluded the monthly aflibercept treatment arms of Korobelnik 2014 for efficacy outcomes at one year since this is not the registered label.

We would like to remark that this evidence is obtained in clinical trials with high treatment and monitoring standards. A pragmatic RCT would be needed to assess the real-world effectiveness of anti-VEGF treatment for DMO, since it could be dependent on the adequacy of monitoring treatment response, which is also sensitive to resource constraints, as found for AMD (Pagliarini 2014). Moreover, evidence on safety from non-randomised, real-world data was not included in our review. As found for AMD, real-world studies suggest that people with DMO may differ from those in RCTs (Ziemssen 2017). However there is more compelling real-world evidence that patients are under-treated and have less favourable outcomes than in RCTs for AMD (Chong 2016) compared to DMO (Jiang 2015; Patrao 2016).

Quality of the evidence

The quality of evidence has been presented above with reasons for downgrading shown in Summary of findings 2 and Summary of findings 3. Overall, inconsistency was not an issue in our network meta-analyses. We also think that transitivity and generalisablilty, or indirectness according to GRADE (Schünemann 2011), were not a problem since studies included a broad range of people with DMO that resembles those in clinical practice. Minor funnel plot asymmetry was detected only for CRT change and did not involve the treatments of direct interest in this review.

The tight monitoring of participants in RCTs differs from clinical practice, where a lower number of intravitreal injections and under-treatment are common. As for age-related macular degeneration, this may overestimate benefit with anti-VEGF treatment. However, effect differences among drugs may be less biased if similar regimens are compared in RCTs, although this remains presumptive.

Potential biases in the review process

Bevacizumab is an off-label drug for treating DMO in most countries. Because small RCTs using bevacizumab may have been conducted but not published because no difference was found, we could have missed small unpublished studies.

Agreements and disagreements with other studies or reviews

Although we did not systematically search for other reviews on anti-VEGF treatments for DMO, the previous version of this review, which focused on anti-VEGF drugs effects compared to control, reported on other network meta-analyses which were inconclusive (Ford 2012; MEDCAC 2012; Regnier 2014); and included a much smaller set of studies, as did Korobelnik 2015 more recently. Zhang 2016 conducted a network meta-analysis of 21 studies of anti-VEGF drugs versus any control, including studies on intravitreal steroids, such as dexamethasone and triamcinolone, and one retrospective comparative, non-randomised study (Arevalo 2013). The authors concluded that aflibercept was superior to other drugs at 12 months: they found a difference of about 0.04 logMAR (2 ETDRS letters) between aflibercept and ranibizumab as well as between ranibizumab and bevacizumab, but these did not reach statistical significance, as did differences in retinal thickness. Differently from Zhang 2016, we included a larger number of studies on anti-VEGF drugs, but not intravitreal steroids since their benefit profile, as well as their local and systemic harm profile, only partly overlap with that of anti-VEGF drugs and similarity of studies regarding study design and target population would be less likely achieved. Currently, some investigators think intravitreal steroids are preferred in people with anti-VEGF resistant and chronic DMO (Hussain 2015), as an alternative to switching between anti-VEGF drugs. We suggest that a network meta-analysis including both anti-VEGF drugs and steroids is of interest, but a different approach should be used, specifically regarding heterogeneity of effects by time horizon and participants' subgroups.

The European Society of Retina Specialists have recently published guidelines on the management of DMO, which cover a broad spectrum of clinical questions ranging from imaging interpretation to diabetes management (EURETINA 2017). These guidelines rely on individual study results, particularly those of DRCRnet 2015 which compared aflibercept, bevacizumab and ranibizumab directly regarding anti-VEGF drug choice. They concluded that "*aflibercept is the drug of choice in DME eyes with baseline BCVA below 69 letters, as it shows superiority to bevacizumab over 2 years and over ranibizumab in the first year of treatment*" and that "*all three medications are equivalent in improving vision in eyes with a baseline BCVA letter score of 69 or more*". Our review does not provide additional evidence regarding the effect of baseline vision on visual outcome, since few studies maintained randomisation beyond one year and subgroup data were not available to conduct a network meta-analysis. Regarding the difference between aflibercept and ranibizumab at one year, EURETINA 2017 stated that "*it remains unclear to which extent the slower effect of ranibizumab seen in Protocol T* [DRCRnet 2015] *compared to aflibercept can be accounted to the lower dose (0.3 mg) of ranibizumab used in this study*". Our review found that the difference between aflibercept and ranibizumab was consistent with indirect evidence based on studies that mostly used ranibizumab 0.5 mg, suggesting no dose effect as previously suggested (Heier 2016).

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-certainty evidence that aflibercept confers some advantage in improving visual function over ranibizumab and bevacizumab in people with DMO at one year. An anatomic benefit was found with ranibizumab over bevacizumab (low-certainty evidence), but there was little difference on functional outcomes (low- and moderate-certainty evidence). Relative effects among anti-VEGF drugs at two years are less well known, since most studies did not maintain randomisation after one year or were short term. A single large publicly-funded trial found no differences in visual outcomes among these drugs at two years. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often under-treated and under-monitored.

We found no signals of differences in safety between the three antiangiogenic drugs that are currently available to treat DMO, particularly for a summary outcome measure such as the sum of all SSAEs (high- or moderate-certainty evidence). However, our estimates were imprecise regarding arterial thromboembolic events and all-cause death (very low-certainty evidence).

Implications for research

Further studies should be directed to effectiveness in real-world use and focus on monitoring and treatment regimens. A network meta-analysis including steroids for DMO is needed, which should take into account different harms as well as account for differences in populations (e.g. regarding pseudophakic patients and chronic DMO). A network meta-analysis of the relative safety of different antiangiogenic drugs could be conducted including people with different diseases.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ahmadieh 2008

Methods	Parallel group RCT People were randomly allocated to treatment but in bilateral cases eyes were randomly allocated to treatment
Participants	Country: Iran Number of people randomised: 101 (115 eyes) Average age: 60 years (range 39 to 74) Sex: 51% women Inclusion criteria: • CSMO unresponsive to previous macular laser photocoagulation (with the last session being more than 3 months prior) Exclusion criteria: • VA ≥ 20/40 • history of cataract surgery within the past 6 months • prior intraocular injection or vitrectomy • glaucoma or ocular hypertension • PDR with high-risk characteristics • vitreous haemorrhage • significant media opacity • presence of traction on the macula • monocular • pregnancy • serum creatinine level ≥ 3 mg/100ml
Interventions	Intervention: • bevacizumab (1.25 mg) n = ? (41 eyes) Comparator: • sham injection n = ? (37 eyes) *"Three consecutive injections were performed at 6-week intervals. Injections were done under sterile conditions with topical anesthesia and insertion of a lid speculum. For the IVB group, 1.25 mg (0.05 cc) bevacizumab (Avastin, made for F. Hoffmann-La Roche Ltd Basel, Switzerland by Genentech Inc., San Francisco, CA, USA) was injected intravitreally with a 30-gauge needle through the superotemporal quadrant."* Page 485 *"In the control group, a needleless syringe was pressed against the conjunctiva and sclera in each session."* Page 485 There was another intervention arm that combined bevacizumab with triamcinolone acetonide, but this is not included in this review (n = 37 eyes)
Outcomes	Primary outcome: • change in CRT *"Central macular thickness was defined by the average thickness of a central macularregion 1,000 ìm in diameter centered on the patient's foveola."* Page 485 Secondary outcomes: • change in BCVA (logMAR)

	• intraocular pressure • cataract progression • intraocular inflammation • any serious adverse event Follow-up: 18 and 24 weeks
Notes	Date study conducted: November 2005 to September 2006 Funding: not reported Conflict of interest: *"The authors have no proprietary interest in this study."* Trial registration: NCT00370422

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"Randomization was performed using a random block permutation method according to a computer-generated randomization list. The block lengths varied randomly. A random allocation sequence was performed by a biostatistician. Details of the series were unknown to the investigators."* Page 485
Allocation concealment (selection bias)	Low risk	*"Randomization was performed using a random block permutation method according to a computer-generated randomization list. The block lengths varied randomly. A random allocation sequence was performed by a biostatistician. Details of the series were unknown to the investigators."* Page 485
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"Subjects were masked to the treatment modality. Visual acuity assessment and OCT were performed by optometrists who were masked to the groups."* Page 485
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No incomplete outcome data were reported, but number of participants at 24 weeks' follow-up was not specied
Selective reporting (reporting bias)	High risk	The study protocol is mentioned. However, dichotomous VA outcomes are not provided

Ahmadieh 2008 (*Continued*)

Other bias	Low risk	28 eyes of 14 participants (14%) with bilateral CSMO were included in the analysis
Overall risk of bias	Low risk	Low risk of bias for most items

Azad 2012

Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: India Number of people randomised: 40 (40 eyes) Average age: 54 years Sex: 42% women Inclusion criteria: • diffuse DMO on FFA refractory to at least two prior sessions of macular laser photocoagulation • CRT > 250 µm on TD-OCT • no evidence of vitreo-retinal traction • good metabolic control (HbA1c < 7.0%) Exclusion criteria: • history of having received prior intraocular, peribulbar or systemic steroids or prior anti-VEGF therapy • uncontrolled diabetes mellitus • diabetic nephropathy • uncontrolled hypertension • history of myocardial infarction, stroke or other thromboembolic • episode • monocular • not available for a follow-up duration of at least 6 months
Interventions	Intervention: • bevacizumab (1.25 mg) n = 20 (20 eyes) Comparator: • macular grid augmentation n = 20 (20 eyes) *"IVB [...] injected via pars plana route in the doses mentioned above by a single experienced investigator using full aseptic precautions. Postinjection, all patients were prescribed topical moxifloxacin 0.5% qid for 5 days. Macular grid laser augmentation was performed by a single experienced examiner according to the modified ETDRS protocol with a spot size of 100 µ, pulse duration of 100 ms, and a power of 50-100 mW titrated to produce mild intensity burns in areas showing diffuse leakage on the FFA in a 'C' shaped zone between 500 and 3000µ from the foveal center sparing the papilla-macular bundle."* Page 167 Another intervention arm evaluated triamcinolone acetonide, but is not included in this review (n = 20 eyes)
Outcomes	Outcomes: • BCVA measured used Snellen chart (mean at follow-up, gain/loss of 3 lines) • CRT assessed using OCT

Azad 2012 (*Continued*)

	• adverse effects (increased IOP, cataract progression, others) Primary outcome: not specified Follow-up: 1, 3 and 6 months
Notes	Date study conducted: not reported Funding: not reported Conflict of interest: not reported Trial registration: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported
Selective reporting (reporting bias)	High risk	VA data and other outcomes incompletely reported
Other bias	Low risk	No other bias identified
Overall risk of bias	Unclear risk	Unclear risk of bias for most items

BOLT 2010

Methods	Parallel group RCT One eye per person; if both eyes were eligible eye with worse VA was selected
Participants	Country: UK Number of people randomised: 80 (80 eyes) Average age: 64 years (range 40 to 86) Sex: 31% women Inclusion criteria: • 18 years or older • diabetes mellitus • BCVA in the study eye between 35 and 69 ETDRS letters at 4 m (Snellen

	equivalent 6/60 or 6/12) • centre-involving CSMO with CRT on OCT of ≥ 270 µm • media clarity, pupillary dilation, and subject co-operation sufficient for adequate fundus imaging • at least 1 prior macular laser therapy • intraocular pressure < 30 mmHg • ability to return for regular study visits • fellow eye ≥ BCVA 3/60 • fellow eye received no anti-VEGF treatment within the past 3 months and there was no expectation of such treatment during the study Exclusion criteria: (for study eye) • macular ischaemia (FAZ ≥ 1000 µm GLD or severe perifoveal intercapillary loss on FFA) • macular oedema due to a cause other than DMO • pre-existing ocular condition that was likely to preclude VA improvement despite resolution of macular oedema • ocular condition that may affect macular oedema or alter VA during the course of the study, any treatment for DMO in the preceding 3 months • PRP within 3 months of enrolment or anticipated 6 months thereafter • PDR except for tufts of new vessels elsewhere < 1 disc in area with no vitreous haemorrhage • HbA1c > 11.0% • medical history of chronic renal failure requiring dialysis or kidney transplantation • BP > 170/100 mmHg • any thromboembolic event within 6 months • unstable angina, or evidence of active ischaemia on electrocardiogram at time of screening • major surgery within 28 days of randomisation or planned during the subsequent 12 months • participation in an investigational drug trial within 30 days of randomisation (or any time during the study) • systemic anti-VEGF or pro-VEGF treatment within 3 months of enrolment • pregnancy, breast feeding, or intention to become pregnant within the study period • intraocular surgery within 3 months of randomisation • aphakia • uncontrolled glaucoma • significant external ocular disease
Interventions	Intervention: • bevacizumab (1.25 mg) n = 42 (42 eyes) Comparator: • macular laser therapy (MLT) n = 38 (38 eyes) *"Bevacizumab (1.25 mg in 0.05 ml) (Avastin; Roche Registration Limited, UK) was prepared by Moorfields Pharmaceuticals (London, UK) as a prefilled syringe containing 0.13 ml. In a designated intravitreal treatment room, under sterile conditions, using topical anesthesia and povidone-iodine 5% into the conjunctival sac and onto the lid margins, and following application of a drape and insertion of a lid speculum, injections were undertaken with a 30-gauge needle through the supra- or infratemporal quadrant, with a drop of ofloxacin placed*

BOLT 2010 (*Continued*)

	in the fornix at the end of the procedure. Patency of the central retinal artery was determined by indirect ophthalmoscopy and VA of hand movements or better. The IOP was checked 30 minutes after the injection, and if the pressure was increased (30 mmHg) appropriate treatment was commenced. After the injection, topical ofloxacin was instilled 4 times per day for 4 days". Page 1080 *"After baseline IVB, patients received 2 further IVB injections (6- and 12-week time points). Subsequent* IVB*injections were guided by an OCT-based retreatment protocol. In brief, if the thinnest recorded central retinal thickness was less than 270 m at 18 weeks, then treatment was continued only if macular thickness was not "stable." If central retinal thickness was greater than 270 m at 18 weeks and subsequent visits, then* IV*B injections were administered until a "stable" macular thickness was attained. "Stable macular thickness" was defined as 3 consecutive visits with the central retinal thickness within 20 m of the patient's thinnest recorded central retinal thickness. Patients could thereby receive a minimum of 3 injections and a maximum of 9 injections in the first 12 months."* Page 1080 *"Modified ETDRS MLT comprised 50 m argon laser spot size, laser applied only greater than 500 m from the edge of the FAZ, with focal treatment aiming to cause mild blanching of the retinal pigment epithelium and not darkening/whitening of microaneurysms. Areas of diffuse leakage or nonperfusion were similarly treated in a grid pattern."* Page 1080
Outcomes	Primary outcome: • mean change in BCVA (EDTRS letters measured at 4 m) Secondary outcomes: • mean CRT and mean change in CRT • gain and loss of 15 and 10 letters of ETDRS • loss of 30 ETDRS letters • retinopathy severity (ETDRS grading) • safety ◦ GLD of the FAZ ◦ area of the FAZ ◦ Retinal Nerve Fibre Layer thickness ◦ other ocular side effects ◦ systemic side effects, including thromboembolic events, BP, and ECG findings Follow-up: 12 and 24 months
Notes	Date study conducted: May 2007 to August 2009 Funding: *"Supported by grants from Moorfields Special Trustees and the National Institute for Health Research UK to the Biomedical Research Center for Ophthalmology based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology."* Conflict of interest: *"The author(s) have no proprietary or commercial interest in any materials discussed in this article"* Trial registration: eudract.ema.europa.eu Identifier: 2007-000847-89

Risk of bias

Bias	Authors' judgement	Support for judgement

BOLT 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	*"Patients were randomised into 2 groups by means of an in-house computerized randomization program. The research investigator was not involved in the randomization process. Patients were stratified for BCVA, with the aim being that both groups would have comparable mean baseline BCVAs."* Page 1080
Allocation concealment (selection bias)	Low risk	The doctor had to phone the Clinical Trial Unit in order to obtain a randomisation from the statistician [personal communication from investigators]
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	*"Although the patient and the study physician were not masked to the therapeutic modality, the study optometrist, OCT technician, photographer, graders performing assessment of the FAZ and ETDRS retinopathy grading, and study statistician were all masked to the patient randomization."* Page 1080
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"Two patients in the laser group did not complete 12 months of follow-up (1 patient moved away, and 1 patient could not be contacted) . They were last reviewed at the 32-week time point,with these data being carried forward and an intention-to-treat analysis undertaken. All 42 patients in the* IVB*group completed the study."* Page 1082
Selective reporting (reporting bias)	Low risk	We could not find a protocol but primary outcomes were stated in the methods and were those routinely used in the field
Other bias	Low risk	No other bias identified
Overall risk of bias	Low risk	Low risk for most items; we considered masking of outcome assessors, though not of participants and physicians, sufficient to ensure unbiased outcome measurement

DA VINCI 2011

Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: USA, Canada and Austria Number of people randomised: 221 (221 eyes) Average age: 64 years (range 40 to 86) Sex: 31% women Inclusion criteria: • 18 years or older • diabetes mellitus • DMO involving the central macula defined as CRT ≥ 250 µm in the central subfield based on Stratus OCT • BCVA letter score at 4 m of 73-24 (Snellen equivalent: 20/40-20/320) measured by the ETDRS protocol • women of childbearing potential were included only if they were willing to not become pregnant and to use a reliable form of birth control during the study period Exclusion criteria: (for study eye) • history of vitreoretinal surgery • PRP or macular laser photocoagulation or use of intraocular or periocular corticosteroids or anti-angiogenic drugs within 3 months of screening • vision decrease due to causes other than DMO • PDR (unless regressed and currently inactive) • ocular inflammation • cataract or other intraocular surgery within 3 months of screening • laser capsulotomy within 2 months of screening • aphakia • spherical equivalent of > −8 dioptres or any concurrent disease that would compromise VA or require medical or surgical intervention during the study period (in either eye) • active iris neovascularisation • vitreous haemorrhage • traction retinal detachment • preretinal fibrosis involving the macula • visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT • history of idiopathic or autoimmune uveitis • structural damage to the center of the macula that is likely to preclude improvement in VA after the resolution of macular oedema • uncontrolled glaucoma or previous filtration surgery • infectious blepharitis, keratitis, scleritis, or conjunctivitis • current treatment for serious systemic infection (systemic) • uncontrolled diabetes mellitus • uncontrolled hypertension • history of cerebral vascular accident or myocardial infarction within 6 months • renal failure requiring dialysis or renal transplant • pregnancy or lactation • history of allergy to fluorescein or povidone iodine

DA VINCI 2011 (*Continued*)

	• only 1 functional eye • ocular condition in the fellow eye with a poorer prognosis than the study eye
Interventions	Intervention: • VEGF Trap-Eye n = 177 (177 eyes) Comparator: • laser photocoagulation n = 44 (44 eyes) *"Patients were randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 treatment regimens in 1 eye only: 0.5 mg VEGF Trap-Eye every 4 weeks (0.5q4); 2 mg VEGF Trap-Eye every 4 weeks (2q4); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then every 8 weeks, (2q8); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then on an as-needed (PRN) basis (2 PRN) ; or macular laser treatment by the modified ETDRS protocol"* Page 1820
Outcomes	Primary outcome: • change in BCVA from baseline to week 24 (ETDRS chart at 4 m) Secondary outcomes: • retinal thickness assessed by OCT • safety and tolerability • change in BCVA from baseline at week 52 • proportion of eyes that gained at least 15 ETDRS letters in BCVA compared with baseline at weeks 24 and 52 • the change in CRT (central subeld on OCT) from baseline to weeks 24 and 52 • number of focal laser treatments given Follow-up: 24 and 52 weeks
Notes	Date study conducted: December 2008 to June 2009 Funding: *"Sponsored by Regeneron Pharmaceuticals, Inc., Tarrytown, New York."* Conflict of interest: *"The author(s) have made the following disclosure (s): Diana V. Do: Genentech (financial support), Regeneron Pharmaceuticals (financial support). Ursula Schmidt-Erfuth: Alcon Labs (consultant, lecturer), Bayer Healthcare (consultant, lecturer), Novartis (consultant, lecturer), Regeneron Pharmaceuticals (lecturer), Pfizer (lecturer). Victor H. Gonzalez: Pfizer (consultant, lecturer), Genentech (lecturer), Eyetech (consultant, lecturer) , Regeneron (lecturer). Carmelina M. Gordon: Allergan (consultant), Regeneron Pharmaceuticals (lecturer), Novartis (consultant, lecturer). Michael Tolentino: Genentech (consultant, lecturer), Eyetech (consultant, lecturer), Regeneron Pharmaceuticals (consultant, lecturer). Alyson J Berliner: Regeneron Pharmaceuticals (employee, equity owner). Robert Vitti: Regeneron Pharmaceuticals (employee, equity owner). Rene Rückert: Bayer Schering Pharma (employee). Rupert Sandbrink: Bayer Schering Pharma (employee). David Stein: Regeneron Pharmaceuticals (employee,equity owner). Ke Yang: Regeneron Pharmaceuticals (employee, equity owner). Karola Beckmann: Bayer Schering Pharma (employee). Jeff S.Heier: Genentech (consultant, lecturer), Regeneron Pharmaceuticals (consultant,lecturer), Fovea (consultant).* Trial registration:NCT00789477

Risk of bias

Bias	Authors' judgement	Support for judgement

DA VINCI 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	*"The randomization was handled by an IVRS vendor. The study statistician at REGENERON provided the randomization plan and reviewed and approved the dummy rand table. Study Data Management at REGENERON tested the randomization function extensively along with the Clinical team."*
Allocation concealment (selection bias)	Low risk	*"Sites called into IVRS to randomize patients and received the randomization number and drug kit assignment at the completion of the call. The site also received a confirmation email. Neither of these contained the actual randomization assignment. The randomization assignments were kept by the IVRS vendor in a secure, access-controlled database and were delivered to REGENERON by the IVRS vendor at the primary endpoint database lock. "*
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"To maintain participant masking, sham injections were performed on visits when an active dose was not given, and a sham laser was given to the VEGF Trap-Eye groups at week 1. Study drug and sham injections and laser and sham laser treatments were performed by an unmasked physician who had no other role in the study except to assess adverse events (AEs) immediately posttreatment. Sham injections followed the active treatment protocol with the exception that no needle was attached to the syringe, and the syringe hub was gently applied to the sclera to mimic an injection. Sham laser consisted of placing a contact lens on the study eye and positioning the patient in front of the laser machine for the approximate duration of a laser treatment."* Page 1820-1
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	*A separate masked physician was assigned to assess adverse events (AEs) and retreatment and rescue criteria and to supervise the masked assessment of efficacy. Every effort was made to ensure that all other study site personnel remained masked to treatment assignment to facilitate an unbiased assessment of efficacy and safety."*

DA VINCI 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	*"Two randomised patients did not receive treatment and 19 patients discontinued the study after receiving at least 1 treatment for the following reasons: lost to follow-up (6 patients), withdrew consent (6 patients), death (3 patients), treatment failures (2 patients) , AE (1 patient), and protocol deviation (1 patient). Discontinuations were evenly distributed among the 5 treatment groups*." Page 1821 Comment: LOCF used
Selective reporting (reporting bias)	Low risk	Primary outcome declared and consistent with our review
Other bias	Low risk	No other bias identified
Overall risk of bias	Low risk	Low risk of bias for most items

DRCRnet 2010

Methods	Parallel group and within-person RCT One or two study eyes per person. If both eyes eligible, right eye randomised first and then left eye assigned to "sham plus prompt laser group". If right eye already assigned to this group then left eye assigned randomly to 1 of the other 3 groups
Participants	Country: USA Number of people randomised: 691 (854 eyes) Average age: 63 years Sex: 44% women Inclusion criteria: • 18 years and older • diabetes (in study eye) • best-corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS Visual Acuity Test) VA letter score 78-24 (20/32-20/320) • definite retinal thickening due to DMO on clinical examination involving the centre of the macula assessed to be the main cause of visual loss • retinal thickness measured on TD-OCT ≥ 250 micron in the central subfield Exclusion criteria: • treatment for DMO within previous 4 months • PRP within the previous 4 months or anticipated need for PRP within the next 6 months • major ocular surgery within the previous 4 months • history of open-angle glaucoma or steroid-induced IOP elevation that required IOP-lowering treatment • IOP ≥ 25 mmHg (participant)

	• systolic BP was 180 mmHg or diastolic BP was 110 mmHg, or if a myocardial infarction, other cardiac event requiring hospitalisation, cerebrovascular accident, transient ischaemic attack, or treatment for acute congestive heart failure occurred within 4 months before randomisation
Interventions	Intervention: • ranibizumab (0.5 mg) and laser photocoagulation n = ? (375 eyes) Comparator: • sham injection and laser photocoagulation n = ? (293 eyes) Ranibizumab group was also randomly allocated to prompt laser photocoagulation (187 eyes) which occurred within 3 to 10 days of the injection and deferred laser photocoagulation (188 eyes) which happened after 24 weeks. All eyes in comparator group were treated within 3 to 10 days of the sham injection Complex retreatment algorithm using web-based, real-time data-entry system (page 1066) There was another intervention arm that combined triamcinolone with prompt laser photocoagulation, but this was not included in this review. n = ? (186 eyes)
Outcomes	Primary outcome: BCVA and safety at 12 months Secondary outcomes: CRT Follow-up: every 4 weeks for 12 months. After 12 months, the trial was unmasked and follow-up continued to 3 years
Notes	Dates participants enrolled: March 2007 to December 2008 Funding: *"Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, and EY018817. The funding organization (National Institutes of Health) participated in oversight of the conduct of the study and review of the manuscript but not directly in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation of the manuscript. Genentech provided the ranibizumab for the study, and Allergan, Inc., provided the triamcinolone for the study. In addition, Genentech and Allergan, Inc., provided funds to the DRCR.net to defray the study's clinical site costs. As described in the DRCR.net Industry Collaboration Guidelines (available at www.drcr.net), the DRCR.net had complete control over the design of the protocol, the ownership of the data, and all editorial content of presentations and publications related to the protocol."* Conflict of interest: "*A complete list of all DRCR.net investigator financial disclosures can be found at www.drcr.net*" Trial registration: NCT00445003

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was computer-generated by the DRCR.net co-ordinating centre *"...study participants with 1 study eye were assigned randomly on the DRCR.net study web-*

DRCRnet 2010 (*Continued*)

		site (using a permuted blocks design stratified by study eye visual acuity)" Page 1065
Allocation concealment (selection bias)	Low risk	Randomisation assignments were obtained through the DRCR.net study website, therefore no study personnel had access to the list or to the next assignment before it was assigned *"study participants with 1 study eye were assigned randomly on the DRCR.net study website (using a permuted blocks design stratified by study eye visual acuity)"* Page 1065
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	*"Study participants in the 3 groups receiving laser were masked to treatment assignment through the primary outcome visit, whereas the ranibizumab deferred laser group was not masked."* Page 1065-6
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Visual acuity examiners and OCT technicians were masked to treatment group assignment before and at the 1-year primary outcome visit."* Page 1066
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants randomised in each group were: 293 laser, 187 ranibizumab + prompt laser, 188 ranibizumab + deferred laser and 186 IVTA + laser. At 1 year complete participants were 274, 171, 178, 176 respectively (91% to 95%) At 2 years complete participants were 211, 136, 139, 142 respectively (72% to 76%) Causes of missing data were balanced across groups
Selective reporting (reporting bias)	Low risk	We could not find a protocol but primary outcomes were stated in the methods and were those routinely used in the field
Other bias	Low risk	No other source of bias identified
Overall risk of bias	Low risk	Low risk of bias for most items

DRCRnet 2015

Methods	Parallel group study *"One eye of each participant was randomly assigned in a 1:1:1 ratio to be injected with aflibercept (at a dose of 2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg). Randomization was performed at the DRCR.net study website, in permuted blocks and with stratification according to study site and visual acuity in the study eye."*
Participants	Country: USA Number of people (eyes) randomised: 660 Average age: 61 years Sex: not reported Inclusion criteria: • 18 years and older • diabetes (in study eye) • best-corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS Visual Acuity Test) VA letter score 78-24 (20/32-20/320) • definite retinal thickening due to DMO on clinical examination involving the centre of the macula assessed to be the main cause of visual loss • retinal thickness measured on TD-OCT ≥ 250 micron in the central subfield Exclusion criteria: • treatment for DMO within previous 4 months • PRP within the previous 4 months or anticipated need for PRP within the next 6 months • major ocular surgery within the previous 4 months • history of open-angle glaucoma or steroid-induced IOP elevation that required IOP-lowering treatment • IOP ≥ 25 mmHg (participant) • systolic BP was 180 mmHg or diastolic BP was 110 mmHg, or if a myocardial infarction, other cardiac event requiring hospitalisation, cerebrovascular accident, transient ischaemic attack, or treatment for acute congestive heart failure occurred within 4 months before randomisation
Interventions	Interventions: • aflibercept 2 mg: 224 eyes • bevacizumab 1.25 mg: 218 eyes • ranibizumab 0.3 mg: 218 eyes Randomisation was stratified by site and visual acuity: ≥ 66 letter score/ ≤ 65 letter score retreatment algorithm: *"In general, an eye will continue to receive an injection if the eye is improving or worsening on OCT or visual acuity. The first time an eye has not improved or worsened, the eye will receive an injection. If the eye has not improved or worsened for at least 2 consecutive 4-week injections and OCT central subfield thickness is <250μ and visual acuity is 20/20 or better, the injection will be deferred."* *"In general, focal/grid laser will be initiated at or after the 24 week visit if 1) the OCT central subfield thickness is ≥250μ or there is edema that is threatening the fovea and 2) the eye has not improved on OCT or visual acuity from the last two consecutive injections."*

DRCRnet 2015 (*Continued*)

Outcomes	Primary outcome: BCVA and safety at 12 months Secondary outcomes: CRT Follow-up: after 12 months the trial was unmasked and follow-up continued to 3 years
Notes	Dates participants enrolled: March 2007 to December 2008 Funding: *"Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, and EY018817. The funding organization (National Institutes of Health) participated in oversight of the conduct of the study and review of the manuscript but not directly in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation of the manuscript. Genentech provided the ranibizumab for the study, and Allergan, Inc., provided the triamcinolone for the study. In addition, Genentech and Allergan, Inc., provided funds to the DRCR.net to defray the study's clinical site costs. As described in the DRCR.net Industry Collaboration Guidelines (available at www.drcr.net), the DRCR.net had complete control over the design of the protocol, the ownership of the data, and all editorial content of presentations and publications related to the protocol."* Conflict of interest: "*A complete list of all DRCR.net investigator financial disclosures can be found at www.drcr.net*" Trial registration: NCT00445003 (Protocol T)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation sequence was computer-generated by the DRCR.net co-ordinating centre *"Randomization was performed at the DRCR.net study website, in permuted blocks and with stratification according to study site and visual acuity in the study eye."* Page 3
Allocation concealment (selection bias)	Low risk	Randomisation assignments were obtained through the DRCR.net study website, therefore no study personnel had access to the list or to the next assignment before it was assigned See above, Page 3
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"Study participants, reading-center graders, and the medical monitor who reviewed all adverse events were unaware of the treatment group assignments. Visual-acuity and OCT technicians were unaware of the treatment-group assignments at the 1-year visit. Investigators and study coordinators were aware of the treatment group assignments."* Page 3

DRCRnet 2015 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Visual-acuity and OCT technicians were unaware of the treatment-group assignments at the 1-year visit."* Page 3
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*The 2-year visit was completed by 90%, 85%, and 88% of the 660 randomised participants (91%, 90%, and 91% excluding deaths) in the aflibercept, bevacizumab, and ranibizumab groups, respectively (Fig S1, available at www.aaojournal.org). There were no substantial differences identified in the baseline characteristics of those who completed and those who did not complete the 2-year visit (Table S1, available at www.aaojournal.org).*"
Selective reporting (reporting bias)	Low risk	Outcomes match those in the Study Protocol available at http://publicfiles.jaeb.org/AntiVEGFCompPrtclv5_03_18_14.pdf
Other bias	Low risk	No other source of bias identified
Overall risk of bias	Low risk	Low risk of bias for most items

Ekinci 2014

Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: Turkey Number of people randomised unclear: 100 (100 eyes) completed follow-up Average age: 67 years (range 50 to 89) Sex: 68% women Inclusion criteria: • clinically significant DMO (CRT > 300 mm), as found through FFA and OCT evaluations and dilate fundus examination, after 1-year follow-up period Exclusion criteria: • participants who received intravitreal treatment at another centre • additional diseases that might have an effect on sight (age related macular degeneration, uveitis, occlusion on the vein root or branch, hereditary macular diseases) • PRP, grid or focal laser photocoagulation application or intraocular surgery within 6 months • participants with acute ocular infection, stroke, myocardial infarction, uncontrolled hypertension, pregnancy, renal failure and cataract formation during the follow-up period were excluded from the study

Ekinci 2014 (*Continued*)

Interventions	Intervention: • bevacizumab (1.25 mg) n = 50 (50 eyes) Comparator: • ranibizumab (0.05 mg) n = 50 (50 eyes) *"Topical anesthetic drops were instilled, and a drape application and blepharostat attachment were applied. Afterward, fornix lavage was applied using diluted povidone iodine. For Group 1, 1.25 mg (0.05 ml) of bevacizumab was injected into the eye that needed treatment, using a 30 gauge needle; for Group 2, 0.05 mg (0.05 cc) of ranibizumab was injected into the vitreous humor through the lower temporal quadrant, 3.5-4 mm behind the limbus. After the treatment, all patients were treated with topical antibiotics four-times a day for 1 week."* Page 140 Bevacizumab and ranibizumab injections were applied, with an interval of 1 month for the first three doses. Retreatment criteria. "*After the third dose of bevacizumab/ranibizumab for patients in Groups 1 and 2, an additional three consecutive bevacizumab/ranibizumab injections were applied if the central macular thickness was greater than 275 μm or if there was an increase in BCVA of at least three letters compared with baseline. After the sixth intravitreal injection, if the central macular thickness was greater than 275 mm or if there was an increase in BCVA of at least two letters, additional intravitreal injections were performed until stable visual acuity was obtained."* Page 140
Outcomes	Outcomes: • BCVA using the Snellen chart • CRT assessed with OCT • IOP assessed with applanation tonometry Primary outcome not specified Follow-up: monthly intervals after treatment to 12 months
Notes	Dates participants enrolled: 2011 to 2014 Funding: not reported Conflict of interest: "*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*" Page 142 Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if participants, care providers or outcome assessors were masked to treatment method

Ekinci 2014 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants, care providers or outcome assessors were masked to treatment method
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion after randomisation: 15 participants excluded *"Patients with acute ocular infection (endophthalmitis after intravitreal injection, n = 3), stroke, myocardial infarction (n = 2), uncontrolled hypertension (n = 4), pregnancy (n = 1), renal failure (n = 1) and cataract formation during follow-up period (n = 4) were excluded from the study."* Page 140
Selective reporting (reporting bias)	High risk	We could not find a protocol and our primary outcomes were not reported
Other bias	Low risk	No other bias identified
Overall risk of bias	High risk	Most items at high or unclear risk of bias

Ishibashi 2014

Methods	Allocation: randomised endpoint classification; safety/efficacy study intervention model; parallel assignment Masking: double-masked
Participants	n = 243; country: Japan 43 recruiting hospitals
Interventions	Drug: pegaptanib sodium (n = 123) Other: sham injection (n = 120) Sex: female 113, male 130 Age: (SD) pegaptanib 65.9 (9.0), sham 66.0 (9.2) years Inclusion criteria: • Participants with macular oedema including central fovea diagnosed by fluorescein angiography • Thickening of the retina ($\geq$ 250 μm) • Corrected VA is 35-68 letters by ETDRS charts Exclusion criteria: • Participants who underwent focal/grid laser within 4 month before study started • Atrophy, scar and fibrosis Including the centre of macula • Underwent any eye surgery within 3 months before study started • Participants with HbA1c 12.5% $\leq$ or with symptoms of uncontrolled diabetes
Outcomes	• Number of participants who experience a $\geq$ 10 letter improvement of VA in ETDRS chart from baseline to week 24 • Change from baseline in VA: double-masked phase (time frame: baseline, weeks 6, 12, 18, and 24); changes in VA were monitored through refraction and BCVA

	measurements using retro-illuminated, modified Ferris-Bailey ETDRS charts • Number of participants underwent focal/grid laser, or vitrectomy: double-masked phase (time frame: up to 24 weeks; included focal laser photocoagulation, grid laser photocoagulation, and vitrectomy • Number of participants who experience a ≥ 10 letter improvement of VA in ETDRS chart from baseline at week 54: open phase (time frame: baseline and week 54); BCVA measurements performed using retro-illuminated, modified Ferris-Bailey ETDRS charts • Change from baseline in VA: open phase (time frame: baseline, weeks 30, 36, 42, 48 and 54); changes in VA were monitored through refraction and BCVA measurements using retro-illuminated, modified Ferris-Bailey ETDRS charts • Number of participants who underwent focal/grid laser, or vitrectomy: open phase (time frame: weeks 24 to 54; included focal laser photocoagulation, grid laser photocoagulation, and vitrectomy
Notes	Completion Date: August 2012 (results also partly available on ClinicalTrials.gov, accessed on 5 December 2013) Sponsor: Pfizer, two authors (Isogawa N, Esaka E) employee of Pfizer Author contact not found

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	High risk	"*Pegaptanib sodium or a syringe of sham was enclosed by aluminium bag, then the aluminium bag was put in a box. These boxes were supplied to each hospitals. These box could maintain masking. However, Pfizer Japan Inc, which requested this drug trial, made the mistake of allowing to open the box for some hospitals during transportation, so it was clear that it was possible not to ensure the masking sufficiently.*" In 71 cases, there was the evidence of opening the box of study drugs In 172 cases, there was no evidence of opening the box. In 50 cases, there was evidence of not opening the box, so it was clear that masking is sufficient
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treating physician and his/her assistants were not masked and other staff (physician who did not directly give the drug, orthoptist, clinical research coordinator,

Ishibashi 2014 (*Continued*)

		nurses, laboratory technician, administrator for study drugs and other staffs) were masked Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: 6 pegaptanib, 4 sham
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information
Overall risk of bias	High risk	Unclear or high risk for most items

Korobelnik 2014

Methods	Parallel group RCT Eyes: 862 eyes from 862 participants. One eye per participant. *"For patients who met eligibility criteria in both eyes, the eye with the worst BCVA was selected as the study eye. If a patient had DME with similar BCVA in both eyes, the eye with the clearest media was selected as the study eye. If the ocular media of the both eyes were similar in clarity, the patient's non-dominant eye (if identifiable) was selected as the study eye. If neither eye is dominant, the right eye was designated as the study eye."* (Appendix 2)
Participants	Country: 54 centres in USA (VISTA study, 446 participants) and 73 centres in Europe, Japan, and Australia (VIVID study, 406 participants) Number of people randomised: 852 (852 eyes) Average age: 63 years Sex: 42% women Inclusion criteria: • adults ≥ 18 years with type 1 or 2 diabetes mellitus • central DMO involvement (defined as retinal thickening involving the 1 mm central (OCT) subfield thickness) • retinal thickness ≥ 300 µm (assessed by OCT) • decrease in vision determined to be primarily the result of DME in the study eye • BCVA ETDRS letter score of 73-24 (20/40-20/320) in the study eye Exclusion criteria: • laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1 • more than 2 previous macular laser treatments in the study eye • previous use of intraocular or periocular corticosteroids in the study eye within 120 days of day 1 • previous treatment with antiangiogenic drugs in either eye (pegaptanib sodium, bevacizumab, ranibizumab etc.) within 90 days of day 1

	• active PDR in the study eye, with the exception of inactive, regressed PDR • uncontrolled diabetes mellitus, as defined by HbA1c > 12% • only 1 functional eye even if that eye is otherwise eligible for the study See paper for details
Interventions	Intervention: • aflibercept 2q4 n = 290 (290 eyes): aflibercept 2 mg every 4 weeks • aflibercept 2q8 n = 286 (286 eyes): aflibercept 2 mg monthly for 5 months, then every 8 weeks Comparator • laser photocoagulation and sham monthly injection = 286 (286 eyes) *"Eyes were randomised in a 1:1:1 ratio to receive either 2 mg IAI every 4 weeks (2q4), 2 mg IAI every 8 weeks after 5 initial monthly doses (from baseline to week 16) with sham injections on non-treatment visits (2q8), or macular laser photocoagulation at baseline and sham injections at every visit (laser control group)"* Page 2
Outcomes	Primary outcome: • change in BCVA from baseline to week 52 (ETDRS chart at 4 m) Secondary outcomes: • proportion of eyes that gained at least 10 ETDRS letters in BCVA at week 52 compared with baseline • proportion of eyes that gained at least 15 ETDRS letters in BCVA compared with baseline • change in CRT (central subfield on OCT) from baseline to week 52 • proportion of eyes with a 2-step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score • change from baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) near activities subscale score • change from baseline in the NEI VFQ-25 distance activities subscale score Follow-up: 52 weeks
Notes	Date study conducted: May 2011 to June 2013 Funding: *"The VISTA and VIVID studies were funded by Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Bayer HealthCare, Berlin, Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript."* Conflict of interest: *"Assistance with the study design and conduct and data analysis was provided by Karen Chu, MS, and Xiaoping Zhu, PhD, Regeneron Pharmaceuticals, Inc. (VISTA), and Jana Sachsinger, PhD, and Christiane Norenberg, MS, Bayer HealthCare (VIVID). Editorial and administrative assistance to the authors was provided by Hadi Moini, PhD, and S. Balachandra Dass, PhD, Regeneron Pharmaceuticals, Inc."* Other conflicts of interest reported in the paper. Trial registration: VISTA NCT01363440, VIVID NCT01331681

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details available

Korobelnik 2014 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"A masked investigator assessed safety and efficacy and decided on the need for laser retreatment and additional treatment."*
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	*"Masked graders at independent central reading centers evaluated OCT images for central retinal thickness (center subfield))"*
Incomplete outcome data (attrition bias) All outcomes	Low risk	About 93% participants completed 52-week follow-up in each arm and causes of loss to follow-up were balanced across arms. Slightly higher loss to follow-up in laser group in VIVID - approx 15% compared to 8% and 11% in aflibercept groups
Selective reporting (reporting bias)	Unclear risk	Some differences between trial registration and final reports
Other bias	Low risk	No other bias identified
Overall risk of bias	Low risk	Though some items could not be fully assessed, we believe randomisation and allocation concealment should be adequate in this multicentre trial aiming at drug registration, as per regulatory requirement

Lopez-Galvez 2014

Methods	Multicentre, randomised, and open-label controlled trial
Participants	Country: Spain Number of people randomised: 83 participants (40 ranibizumab, 43 grid laser) Average age: 63.5 (9.4) years. Sex: 59.8% M Inclusion criteria: • ≥18 years old • diabetes mellitus type 1/2 • altered VA due to DMO. The study eye must have had a BCVA = 78-25 letters, and CRT = 250 μm
Interventions	Participants were randomised to intravitreal injection of ranibizumab (0.5 mg) with 3 loading doses and then PRN treatment or to LP (ratio 1:1)
Outcomes	Primary outcome: • Differences in mean change in best corrected visual acuity (BCVA) of treatment with ranibizumab 0.5 mg versus laser photocoagulation (LP) over 12 months in

	participants with DMO. Secondary outcomes: • % of participants with VA > 73 letters with ranibizumab (0.5 mg) versus laser • Time and mean change in CRT by OCT with ranibizumab (0.5 mg) versus laser • Monitoring and registry of all adverse events, serious adverse events, VA, concomitant medications, ophthalmologic exams (including count of fingers and movement of the hands), IOP, vital constants and analytical parameters
Notes	Sponsor: Novartis Trial Registration: NCT00901186

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information (abstract only; authors contacted but no response yet)
Allocation concealment (selection bias)	Unclear risk	No information (abstract only; authors contacted but no response yet)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information (abstract only; authors contacted but no response yet)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information (abstract only; authors contacted but no response yet)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 and 11 participants lost to follow-up for ranibizumab and laser respectively
Selective reporting (reporting bias)	Unclear risk	No information (abstract only; authors contacted but no response yet)
Other bias	Unclear risk	Insufficient information (abstract only; authors contacted but no response yet)
Overall risk of bias	Unclear risk	Most items at unclear risk

LUCIDATE 2014

Methods	Parallel group RCT One eye per person, unclear how eye selected "*One eye per participant was included to avoid exposure of both eyes to the study drug. If both eyes were eligible, the eye with worse visual acuity became the study eye. Subjects were randomised with 2:1 probability to receive the intervention or standard care (ETDRS macular laser). The randomization list was created using permuted blocks of varying sizes, held by the trial statistician and concealed from the researcher who enrolled, assessed, and allocated treatment to participants.*" (Page 961)
Participants	Country: UK Number of people randomised: 37 (37 eyes) Average age: 66 years Sex: 36% women Inclusion criteria: • adult participants with type 1 or 2 diabetes • BCVA of 55-79 ETDRS letters (Snellen equivalent, 20/30-20/80) resulting from **centre-involving DMO** , with Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) central subfield thickness of 300 mm or more in the study eye Exclusion criteria: • uncontrolled glaucoma • aphakia • cataract precluding fundus photography • external ocular infections • previous anti-VEGF or laser treatment in the preceding 3 months in both eyes • angiographic evidence of macular ischaemia defined as FAZ GLD of > 1000 mm or severe perifoveal capillary loss • other causes for macular oedema, for example after cataract surgery • other causes of visual loss in the study eye; other diseases that may affect the course of macular oedema in the study eye • PDR, either active or treated within the previous 3 months • systemic conditions that precluded trial enrolment included HbA1c > 11.0%; past medical history of chronic renal failure requiring either dialysis or kidney transplantation; BP > 170/100 mmHg; an arteriothrombotic event within 6 months before randomisation, including myocardial infarction, acute congestive heart failure or other cardiac event, and stroke or transient ischaemic attack • planned surgery • pregnancy or breastfeeding
Interventions	Intervention: • ranibizumab (0.5 mg) n = 25 Comparator: • laser photocoagulation n = 12 "*Subjects were randomised with 2:1 probability to receive the intervention or standard care (ETDRS macular laser).*" Page 961. "*Intravitreal injections of ranibizumab (Lucentis, 0.5 mg in 0.05 mL solution for injection; Novartis Pharmaceuticals UK Ltd., Frimley, United Kingdom) at baseline, 4 weeks, and 8 weeks then every 4 weeks as required according to predefined retreatment criteria to a maximum of 12 injections. Retreatment occurred if BCVA was reduced by 5 letters or more from maximum acuity or if OCT central subfield thickness was more than 300 mm. Subjects in the laser arm received ETDRS macular laser at baseline guided by fluorescein angiography, OCT, and clinical examination. Laser retreatment occurred*

	at 12, 24, and 36 weeks if clinically significant macular edema was still present, in accordance with standard clinical practice at the time; this was guided by the most recent fluorescein angiogram, OCT, and clinical examination results" Page 961
Outcomes	Outcomes: • change in ETDRS BCVA • retinal sensitivity • colour vision • electrophysiologic parameters • macular thickness and volume • change in ETDRS severity grade of diabetic retinopathy from fundus photographs Follow-up: 48 weeks
Notes	Date study conducted: November 2010 to July 2011 Sponsor: Moorfields Eye Hospital NHS Foundation Trust Conflict of interest: "*Dr Comyn receives travel support from Novartis. Dr Sivaprasad is a consult for and receives payment for lectures or speaker bureaus and travel support from Novartis, Allergan, and Bayer, and receives payment for development of educational materials from Allergan. Dr Holder is a consultant to Servier. Dr Patel receives grant support from Allergan, Heidelberg United Kingdom, and Topcon United Kingdom and is a consultant to Bayer, Novartis, and Thrombogenics. Dr Hykin is a consultant to and receives grant support from Novartis, Allergan, and Bayer. Drs Comyn, Sivaprasad, Peto, Patel, Egan, Bainbridge, and Hykin have received a proportion of their funding from the Department of Health's National Institute for Health Research Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and University College London, Institute of Ophthalmology. Dr Bainbridge is supported by a National Institute for Health Research Professorship. Supported by an unrestricted research grant from Novartis and the National Institute for Health Research Biomedical Research Centre based at Moorfields Eye Hospital National Health Service Foundation Trust and University College London Institute of Ophthalmology."* Page 970 Trial registration: NCT01223612

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"The randomization list was created using permuted blocks of varying sizes, held by the trial statistician and concealed from the researcher who enrolled, assessed, and allocated treatment to participants."* Page 96
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	High risk	No sham procedure

LUCIDATE 2014 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	*"The microperimetry and electrophysiologic assessors were masked to the patient treatment arm. Evaluation of OCT scans, fundus photographs and fluorescein angiograms was performed by masked Reading Centre graders. The protocol states that the visual acuity assessors were also masked to the patient treatment arm but due to a protocol deviation they had access to the source notes and were potentially unmasked."*
Incomplete outcome data (attrition bias) All outcomes	Low risk	22/25 (88%) of anti-VEGF group compared to 11/12 (92%) laser group followed up
Selective reporting (reporting bias)	Unclear risk	Unclear risk
Other bias	Low risk	No other source of bias identified
Overall risk of bias	Unclear risk	High or unclear risk of bias for nearly half the items

Macugen 2005

Methods	Parallel group RCT One eye per person, chosen by participant and physician. In 81% of cases the eye with the worse VA was chosen
Participants	Country: USA Number of people randomised: 172 (172 eyes) Average age: 62 years (range 27 to 89) Sex: 49% women Inclusion criteria: • 18 years or older • diabetes (study eyes) • macular oedema involving the centre of the macula demonstrated on OCT with corresponding leakage from microaneurysms, retinal telangiectasis, or both on fluorescein angiography • an area of retinal thickening of at least half a disc area involving the central macula as confirmed by graders at an independent fundus photograph and angiogram reading center (University of Wisconsin, Madison, Wisconsin) • clear ocular media and adequate pupillary dilation to permit good stereoscopic fundus photographs (participants) • BCVA letter scores between 68-25 inclusive (approximate Snellen equivalent, 20/50-20/320) in the study eye and at least 35 (20/100 or better) in the fellow eye • IOP ≤ 23 mmHg

	• assessment by the treating ophthalmologist that focal photocoagulation could be deferred safely for 16 weeks • an electrocardiogram that demonstrated no abnormalities judged to be clinically relevant and serological test results that suggested no clinically meaningful haematological, liver, or renal abnormalities • women enrolling in the study were required to be postmenopausal for 12 months before the study, surgically sterile, or not pregnant and on 2 forms of effective contraception Exclusion criteria: • history of PRP or focal photocoagulation • neodymium:yttrium-aluminum-garnet laser or peripheral retinal cryoablation within the previous 6 months • any abnormality thought likely to confound VA assessments or fundus photography, including cataract; vitreoretinal traction within 1 disc diameter of the fovea confirmed either clinically or on OCT • vitreous incarceration in a previous wound or incision • any retinal vein occlusion involving the macula; and atrophy/scarring/fibrosis or hard exudates involving the centre of the macula that would preclude improvement in VA • a history of any intraocular surgery within the previous 12 months, myopia of ≥ 8 dioptres, axial length of ≥ 25 mm, and the likelihood of requiring either scatter (panretinal) photocoagulation within the ensuing 9 months or cataract surgery within 12 months • active ocular or periocular infection • previous therapeutic radiation to the eye, head, or neck • any treatment with an investigational agent for any condition in the 60 days before enrolment. Known serious allergies to fluorescein dye • glycosylated haemoglobin (GHb) levels of ≥ 13% • 3 episodes of severe hypoglycaemia within 3 months of study entry • 2 episodes of ketoacidosis within 1 year of baseline • any episode of ketoacidosis within 3 months of baseline • evidence of severe cardiac disease • clinically significant peripheral vascular disease (previous surgery, amputation, or symptoms of claudication) • uncontrolled hypertension (treated systolic BP 155 or diastolic BP 95), or stroke within the preceding 12 months
Interventions	Intervention: • pegaptanib (0.3 mg, 1 mg, or 3 mg) n = 130 (130 eyes) Comparator: • sham injection n = 42 (42 eyes) *"Intravitreous pegaptanib or sham injections were administered at entry, week 6, and week 12, for a minimum of 3 injections. Thereafter, additional injections were administered every 6 weeks at the discretion of investigators if judged indicated, to a maximum of 6 injections up to week 30. [...] Pegaptanib was formulated for intravitreous injection at 0.3 mg/90 µl, 1 mg/90 µl, and 3 mg/90 µl concentrations in preservative-free phosphate-buffered saline (pH 5-7). Pegaptanib was packaged in sterile, single-use, United States Pharmacopeia type 1 graduated glass 1-ml syringes with preattached 27-gauge needles"* Page 1748

Macugen 2005 (*Continued*)

Outcomes	Outcomes: • BCVA (measured using ETDRS chart) • CRT on OCT • change in retinal thickness derived by comparing measurements at baseline with those at week 36 or nal examination if before week 36 • focal photocoagulation applied at week 12 or later • size of the area of retinal thickness measured by photography • macular capillary leakage and cystoid spaces • adverse events • laboratory test abnormalities Follow-up: 36 weeks
Notes	Dates participants enrolled: not reported, study published 2005 Funding: *"The study was sponsored by Eyetech Pharmaceuticals, Inc., New York, New York, and Pfizer Inc., New York, New York."* Page 1747 Conflict of interest: not reported Trial registration: NCT00040313

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"Patients were allocated [...] by a dynamic minimization procedure using a stochastic treatment allocation algorithm based on the variance method. Randomization was stratified by study site, size of the thickened retina area [...] and baseline VA [...]"*. Page 1748
Allocation concealment (selection bias)	Low risk	*"An independent fundus photograph and angiogram reading center confirmed eligibility and appropriate retinal thickness classification both for study entry and for randomization and stratification using baseline fluorescein angiography and OCT."* Page 1748
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"Study subjects receiving sham or study medication were treated identically in all regards, including ocular antisepsis procedures and subconjunctival anesthetic, except that subjects receiving active treatment had pegaptanib injected into the vitreous, whereas those receiving sham had a needleless syringe pressed against the conjunctiva and sclera. The injection procedure prevented subjects from seeing the syringe and needle, to minimize the risk of unmasking. In all but 3 subjects, injection was administered by a staff member other*

		than the study ophthalmologist responsible for all other aspects of the protocol, to maintain investigator masking." Page 1748
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Study subjects receiving sham or study medication were treated identically in all regards, including ocular antisepsis procedures and subconjunctival anesthetic, except that subjects receiving active treatment had pegaptanib injected into the vitreous, whereas those receiving sham had a needleless syringe pressed against the conjunctiva and sclera. The injection procedure prevented subjects from seeing the syringe and needle, to minimize the risk of unmasking. In all but 3 subjects, injection was administered by a staff member other than the study ophthalmologist responsible for all other aspects of the protocol, to maintain investigator masking. Visual acuity was determined by a separate VA examiner masked to treatment."* Page 1748 *"At baseline and at each study visit thereafter, refraction and VA were determined and OCT was performed by certified examiners masked both to randomization and to findings of the previous measurement."* Page 1749
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nine participants were discontinued from the study before week 36. None in pegaptanib groups 0.3 mg and 1 mg, 3 in pegaptanib 3 mg group (3 mg subgroup: 2 participants by request at weeks 12 and 16 and 1 by other reason at week 1), 6 in sham group (5 participants by request at weeks 6, 11, 18, 30, and 33 and 1 due to death at week 8)
Selective reporting (reporting bias)	Low risk	The study protocol is available and all (primary and secondary) outcomes that are of interest in the study have been reported in the pre-specied way
Other bias	Low risk	No other source of bias identified
Overall risk of bias	Low risk	Low risk of bias for all items

Macugen 2011

Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: Australia, Europe, India, North America, and South America Number of people randomised: 288 (288 eyes) Average age: 62 years (20 to 83) Sex: 43% women Inclusion criteria: • 18 years or older • diabetes • DMO involving the centre of the macula not associated with ischaemia (study eye) • foveal thickness of ≥ 250 μm (centre point thickness measured on OCT) • BCVA with a letter score of 65-35 (20/50-20/200 Snellen equivalents) • IOP ≤ 21 mmHg • clear ocular media and adequate pupillary dilation to allow good quality stereoscopic fundus photography • focal or grid laser photocoagulation could be deferred for 18 weeks in the opinion of the treating ophthalmologist Exclusion criteria: • yttrium-aluminum-garnet laser, peripheral retinal cryoablation, laser retinopexy for retinal tears, or focal or grid photocoagulation within the prior 16 weeks or scatter PRP 6 months before baseline or likely to be needed within 9 months • macular ischaemia if a nonperfusion area of > 1 disc area involving the foveal avascular zone (2 quadrants centred around the FAZ)
Interventions	Intervention: • pegaptanib sodium (0.3 mg) n = 145 (145 eyes) Comparator: • sham injection n = 143 (143 eyes) Participants received pegaptanib 0.3 mg or sham injections every 6 weeks in year 1 (total 9 injections) and could receive focal/grid photocoagulation beginning at week 18. During year 2, participants received injections as often as every 6 weeks according to pre-specified criteria
Outcomes	Primary outcome: • 10-letter (2-line) improvement from baseline at 12 months (ETDRS chart) Secondary outcomes: (at 12 and 24 months unless otherwise specified) • 10-letter improvement from baseline at 24 months • changes from baseline in mean VA • 15-letter (3-line) improvement in VA • change in degree of retinopathy of 2 steps based on the 12-step scale of retinopathy • decrease in retinal thickness at the centre point by 25% and 50% • focal or grid laser • change in NEI VFQ-25 and EQ-5D Follow-up: 12 and 24 months
Notes	Dates participants enrolled: September 2005 to July 2009 Funding: *"Sponsored by Pfizer Inc, New York, New York. The sponsor participated in the*

	design of the study, in the management, analysis, and interpretation of the data, and in the preparation and review of the manuscript." Page 12 Conflict of interest: The authors were employees of Pfizer, the sponsor Trial registration: NCT00605280

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"[...] subjects were centrally allocated to receive either pegaptanib 0.3 mg or sham injections (1:1) using a dynamic minimization procedure stratified by the site, hemoglobin A1c (<7.6% vs >=7.6%), systolic blood pressure (<140 vs >=140 mmHg), diastolic blood pressure (80 vs 80 mmHg), and baseline BCVA (<54 vs >=54 letters); the dynamic minimization used a stochastic treatment allocation algorithm based on the variance method."* Page 3
Allocation concealment (selection bias)	Low risk	*"...subjects were centrally allocated..."* Page 3
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"To maintain masking, the intravitreal procedure was identical between the sham and comparator arms, with the difference lying only in the application of an empty barrel of a needleless syringe in the sham procedure designed to mimic the intravitreal injection."* Page 3
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Throughout the study, BCVA was measured at 4 m by the study refractionist/ophthalmologist, who was masked to the subject's treatment and to the subject's previous visual acuity (VA) assessments"*. Page 3
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At 1 year 116/144 (81%) pegaptanib-treated participants and 114/142 (80%) controls completed the 54-week visit. Adverse events led to discontinuation of 5 treated and 7 control participants At 2 years 66 participants in each group completed the 102 week visit ITT analysis with LOCF was used leading to the analysis of 133 treated and 127 control participants

Macugen 2011 (*Continued*)

Selective reporting (reporting bias)	Low risk	All primary outcomes reported
Other bias	Low risk	No other biases identified
Overall risk of bias	Low risk	Low risk of bias for most items

Nepomuceno 2013

Methods	Parallel group RCT and within-person study People randomised to treatment but two eyes sometimes included. If two eyes included then fellow eye randomised to other treatment
Participants	Country: Brazil Number of people randomised: 48 (63 eyes) Average age 64 years Sex: 55% women (based on eyes included in analyses) Inclusion criteria: • centre-involved DMO defined as a central subfield thickness > 300 mm on Spectral Domain-OCT, despite at least 1 session of macular laser photocoagulation performed at least 3 months previously • BCVA ETDRS measurement between 0.3 logMAR (Snellen equivalent: 20/40) and 1.6 logMAR (Snellen equivalent: 20/800) Exclusion criteria: • vitreomacular traction on SD-OCT • PDR needing PRP or anticipated to need PRP in the next 12 months • macular capillary dropout on fluorescein angiography • history of glaucoma or ocular hypertension (defined as an intraocular pressure > 22 mmHg) • an ocular condition (other than diabetes) that, in the opinion of the investigator, might affect macular oedema or alter VA during the course of the study (e.g. retinal vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc) • systemic corticosteroid therapy • any condition that, in the opinion of the investigator, might preclude follow-up throughout the study period
Interventions	Intervention: • bevacizumab (1.5 mg) n = 32 eyes Comparator: • ranibizumab (0.5 mg) n = 28 eyes *"Retreatment with the originally assigned treatment was performed monthly if central subfield thickness was greater than 275 mm."* *"If, after 3 consecutive injections, there was not a reduction in central subfield thickness of at least 10% or an increase in BCVA of at least 5 letters compared with baseline, the patient could, at the discretion of the treating ophthalmologist, receive focal/grid laser photocoagulation or continue to receive the same intravitreal medication for an additional 3 consecutive visits."* Page 503

Outcomes	Outcomes reported in publication (primary outcome not specified): • BCVA (standardised ETDRS refraction protocol) • retinal thickness (using OCT) On ClinicalTrials.gov following outcomes listed: • Primary outcome measures: CSFT change (time frame: monthly from baseline to week 48; not designated as a safety issue); CSFT measured with SD-OCT • Secondary outcome measures: BCVA change (time frame: monthly from baseline to week 48; not designated as a safety issue); BCVA using ETDRS charts
Notes	Dates participants enrolled: July 2010 to August 2011 Funding: *"Fundacao de Amparo a' Pesquisa do Estado de Sao Paulo (FAPESP), grant number 2010/013368; and Fundacao Apoioao Ensino, Pesquisa e Assistencia (FAEPA) do Hospital das Cl nicas da Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paulo."* Conflict of interest: Rodrigo Jorge received travel support from Novartis to attend the 2012 American Society of Retina Specialists (ASRS) meeting Trial registration: NCT01487629

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"…. received the randomised treatment according to a computer-generated sequence"* Page 503
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"Examiners (E. T., F.P.P.A., R.P.) were masked regarding which treatment drug was used for each patient. Throughout the study, a single masked, certified examiner performed BCVA measurements prior to any other study procedure. Patients, OCT technicians, and fundus photographers were also masked to treatment group"*. Page 504
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Examiners (E. T., F.P.P.A., R.P.) were masked regarding which treatment drug was used for each patient. Throughout the study, a single masked, certified examiner performed BCVA measurements prior to any other study procedure. Patients, OCT technicians, and fundus photographers were also masked to treatment group"*. Page 504
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"The 3 patients excluded from the outcomes analyses consisted of 1 patient in the IV ranibizumab group who developed Staphylo-*

		coccus aureus endophthalmitis after the first injection (this patient chose to exit the study and he did not complete any further study visits); 1 patient in the IV bevacizumab group who developed advanced posterior subcapsular cataract, which precluded adequate SDOCT images, after the ninth follow-up visit; and 1 patient from the IV bevacizumab group who missed 3 consecutive follow-up visits." Page 504
Selective reporting (reporting bias)	Low risk	Both outcomes listed on trial registration reported
Other bias	Unclear risk	Fifteen out of 48 participants with both eyes in analyses
Overall risk of bias	Low risk	Low risk of bias for most items

READ2 2009

Methods	Parallel group RCT One eye per person; if both eyes were eligible, the eye with the greater centre subfield thickness was entered
Participants	Country: USA Number of people randomised: 126 (126 eyes) Average age: 62 years Sex: 59% women Inclusion criteria: • 18 years and older • diabetes • DMO • reduction in VA between 20/40-20/320 • centre subfield thickness measured by OCT ≥ 250 µm • HbA1c ≥ 6% within 12 months before randomisation • no potential contributing causes to reduced VA other than DMO • reasonable expectation that scatter laser photocoagulation would not be required for the next 6 months Exclusion criteria: • received focal/grid laser treatment within 3 months • intraocular injection of steroid within 3 months • intraocular injection of a VEGF antagonist within 2 months
Interventions	Intervention: • ranibizumab 0.5 mg n = 42 (42 eyes) • ranibizumab 0.5 mg plus laser photocoagulation n = 42 (42 eyes) Comparator: • laser photocoagulation n = 42 (42 eyes)

	Participants were randomised 1:1:1 to receive 0.5 mg ranibizumab at baseline and months 1, 3, and 5 (group 1), focal or grid laser photocoagulation at baseline and month 3 if needed (group 2), or a combination of 0.5 mg ranibizumab and focal or grid laser at baseline and month 3 (group 3). Starting at month 6, if retreatment criteria were met, all participants could be treated with ranibizumab Duration: primary outcome at 6 months, extension to 24 and 36 months
Outcomes	As reported in publications: Primary outcome: • change in BCVA between baseline and follow-up Secondary outcomes: • change in BCVA between baseline and month 24 • 3 or more lines or 2 or more lines improvement at month 24 • change in foveal thickness between baseline and month 24 • elimination of 90% or 50% excess foveal thickness On ClinicalTrials.gov *"Primary Outcome Measures: Improvement in vision of 15 or more letters, or achieve a final vision of 50 letters (20/25) or better if baseline VA was 40 letters (20/40) [Time Frame: 6 mos, 12 mos and 24 mos. Study Extended to 36 mos.] [Designated as safety issue: Yes]* *Secondary Outcome Measures: Several outcomes related to OCT measurements and fluorescein angiography. [Time Frame: 6 mos, 12 mos and 24 mos, study extended to 36 mos.] [Designated as safety issue: Yes]"* Follow-up: 6 months and 24 months.
Notes	Dates participants enrolled: not reported Funding: *"Sponsored by the Juvenile Diabetes Research Foundation and Genentech, Inc."* Conflict of interest: *"QDN and PAC have served as members of Expert Panels for Genentech, Inc. without receiving an honorarium during the time of this study, but JHU has recently negotiated a contract through which JHU receives compensation. QDN is a consultant for Bausch and Lomb and has research support from Genentech, Inc., and Regeneron, Inc. PAC serves on the data and safety monitoring committee for a phase III trial sponsored by Regeneron, Inc., and has research support from Genentech, Alimera, and CoMentis for diabetic macular edema trials. Diana Do receives research support from Genentech. These activities are being managed by the Conflict of Interest Committee of the Johns Hopkins University School of Medicine. JSH is a consultant for Genentech, Alcon, Allergan, Bausch and Lomb, Eyemaginations, Fovea, Genzyme, Heidelburg, IScience, ISTA, Jerini, LPath, NeoVista, Nodal Vision, Novagali, Novartis, Optherion, Oxigene, Paloma, Pfizer, Regeneron, Resolvyx, Schering Plough, Scyfix, and VisionCare and has received honoraria from Genentech, Heidelberg, Jerini, NeoVista, Optimedica, and Regeneron. JL has received honoraria from Genentech. DB is a consultant and has received honoraria from Genentech, Novartis, Alcon, Allergan, and Pfizer. PA is a consultant for Genentech"* Page 2181 Trial registration: NCT00407381

Risk of bias

Bias	Authors' judgement	Support for judgement

READ2 2009 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Unclear method of sequence generation and information could not be obtained from the authors
Allocation concealment (selection bias)	Unclear risk	Unclear method of allocation concealment and information could not be obtained from the authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear if masked and who was masked and information could not be obtained from the authors
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unclear if masked and who was masked and information could not be obtained from the authors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants randomised to each group: 33 ranibizumab, 34 ranibizumab + laser, 34 laser Completed participants at 1 year: 29, 29, 30 (85% to 88%) Completed participants at 2 years: 24, 26, 24 (71% to 76%) Causes of missing data were balanced across groups
Selective reporting (reporting bias)	High risk	The primary outcome differed in the protocol and the final report
Other bias	Low risk	No other source of bias identified
Overall risk of bias	High risk	High risk of bias for nearly half the items and unclear risk for the others

RELATION 2012

Methods	Parallel group RCT One eye per person, eye with worse VA selected
Participants	Country: Germany Number of people randomised: 128 (128 eyes) Average age: 64 years (range 31 to 79) Sex: 37% women Inclusion criteria: • 18 years or older • diabetes • visual impairment (BCVA between 78-39 letters, testing distance 4 m) due to focal or diffuse DMO in at least one eye eligible for laser treatment in the opinion of

RELATION 2012 (*Continued*)

	the investigator Exclusion criteria: • other eye diseases and conditions that might affect VA • other eye and systemic treatments • pregnancy or possibility of being pregnant • Inability to comply with follow-up
Interventions	Intervention: • ranibizumab (0.5 mg) plus laser n = 85 (85 eyes) • laser plus sham injection n = 43 (43 eyes) Ranibizumab was applied at baseline, 30, 60, 90 days and reapplied at intervals no shorter than 28 days and laser was applied at baseline and re-applied if needed at intervals no shorter than 3 months
Outcomes	Primary outcome: • mean change in BCVA from baseline to month 12 (ETDRS chart, 4 m) Secondary outcomes: • adverse events
Notes	Dates participants enrolled: July 2010 to May 2011, terminated early Funding: Novartis Conflict of interest: Novartis Trial registration: NCT01131585

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as double-masked, but no details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as double-masked, but no details given
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: combined laser and ranibizumab: 7/85 (7%); laser 11/43 (26%)
Selective reporting (reporting bias)	High risk	Only mean change of VA and harms reported

RELATION 2012 (*Continued*)

Other bias	Low risk	Study terminated early due to European Medicine Agency approval of ranibizumab for DMO but this is independent of effect estimates
Overall risk of bias	Unclear risk	Unclear risk of bias for most items

RESOLVE 2010

Methods	Parallel group RCT One eye per person, eye with worse VA selected
Participants	Country: unclear exactly where conducted. Investigators from Australia, Denmark, Austria, France, Germany, Italy, Korea, Portugal, Spain, Switzerland, UK Number of people randomised: 151 (151 eyes) Average age: 64 years (range 32 to 85) Sex: 46% women Inclusion criteria: • 18 years or older • diabetes mellitus • stable HbA1c levels (≤ 12%) • DMO with centre involvement in at least one eye (study eye) • CRT ≥ 300 μm (Stratus Zeiss Meditec) • BCVA score between 73-39 letters inclusively, using ETDRS charts at a testing distance of 4 m (approximate Snellen equivalent of 20/40-20/160) • decreased vision attributed to foveal thickening from DMO, that was not explained by any other causes in the opinion of the investigator • laser photocoagulation, additional or first treatment, could be withheld for at least 3 months after randomisation Exclusion criteria: • PRP (focal peripheral laser photocoagulation) performed within 6 months prior to study entry. Grid/central laser photocoagulation was excluded except for participants with only mild laser burns at least 1000 µm from the centre of the fovea performed more than 6 months before the trial commenced • PDR in the study eye, with the exception of tufts of neovascularization < 1 disc area with no vitreous haemorrhage. As well as those with area of retinal ischaemia ≥ 500 µm and located ≤ 500 µm from the centre of the macula of the study eye as assessed by fluorescein angiography at visit 1 and confirmed by a central reading centre • participants with unstable medical conditions such as poor glycaemic or BP control • participants with hypertension for whom a change in antihypertensive treatment was initiated within 2 months preceding start of trial were not enrolled unless BP was maintained below 160/100 mmHg for at least 1 month prior to the first day of the trial by antihypertensive treatment • history of treatment with systemic corticosteroids within 4 months prior to randomisation or topical, rectal or inhaled corticosteroids in current use more than 2 times per week

	• previous participation in a study on antiangiogenic drugs • ocular disorders and history of any condition that might confound the interpretation of study results or might render participant at high risk for treatment complications • ocular inflammation in either eye or history of cataract surgery in the study eye within 6 months before study initiation • pre-menopausal women not using adequate contraception and pregnant or nursing women
Interventions	Intervention: • ranibizumab (0.3 mg or 0.5 mg) n = 102 (102 eyes) Comparator: • sham injection n = 49 (49 eyes)
Outcomes	Primary outcome: • mean change in BCVA from baseline at 1 month and 12 months Secondary outcomes: • mean change in BCVA and CRT from baseline at 12 months • categorised BCVA outcome • safety
Notes	Dates participants enrolled: not reported Funding: Novartis Conflict of interest: authors served on advisory boards for Novartis and received honoraria and travel and accommodation payments; Novartis employees assisted with the analysis, interpretation and writing Trial registration:NCT00284050

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"Eligible patients were randomised 1:1:1 to either ranibizumab (0.3 mg or 0.5 mg) or sham treatment according to a computer-generated randomised allocation schedule"* Online appendix page 1
Allocation concealment (selection bias)	Low risk	"*...allocation schedule (kept at a secure site and accessible only to the injecting physician"* Online appendix page 1 *"Based on the patient strata the injecting physician would take the treatment allocation card and tear-off the cover and follow instructions to choose vial from the box as indicated (3 boxes, randomisation block size 3). The randomisation data were kept strictly confidential until database*

RESOLVE 2010 (*Continued*)

		lock; not accessible to anyone involved in the study with the exception of injecting physician (s) and drug accountability monitor." Online appendix page 1
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham injection for masking participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	*"Masking was maintained through appointment of a minimum of 2 investigators at each study site; unmasked injecting physician and a masked evaluating physician (roles could not be switched)."* Online appendix page 1
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants who completed the trial at 1 year: 92/102 ranibizumab and 40/49 sham. Causes of missingness were balanced ITT analysis with LOCF was used
Selective reporting (reporting bias)	Low risk	We could not find a protocol, but primary outcomes were stated in the methods and were those routinely used in the field
Other bias	Low risk	No other source of bias identified
Overall risk of bias	Low risk	Low risk of bias for most items

RESPOND 2013

Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: Canada Number of people randomised: 239 (239 eyes) Average age: 62 years (range 26 to 87) Sex: 40% women Inclusion criteria: • 18 years or older • stable type 1 or type 2 diabetes with HbA1c $\leq$ 10% • visual impairment due to focal or diffuse DMO in at least one eye eligible for laser treatment in the opinion of the investigator Exclusion criteria: • active conditions in study eye that could prevent improvement in VA • active eye infection or inflammation • history of stroke, renal failure or active hypertension

RESPOND 2013 (*Continued*)

Interventions	Intervention: • ranibizumab (0.5 mg) n = 80 (80 eyes) • ranibizumab (0.5 mg) plus laser n = 78 (78 eyes) Comparator: • laser n = 81 (81 eyes) For combination and monotherapy, ranibizumab was administered as 3 monthly injections, then 10 months PRN injections given/withheld based on DME stability criteria. Laser was administered according to ETDRS guidelines at intervals of > 3 months
Outcomes	On ClinicalTrials.gov *Primary Outcome Measures: Measure: mean change from baseline in Best Correct Visual Acuity (BCVA) [Time Frame: 12 months] [Designated as safety issue: No]* *Secondary Outcome Measures: Measure: number of patients with visual acuity above 73 letters [Time Frame: 3, 6, 9 and 12 months]* *Measure: number of patients with improvement in BCVA [Time Frame: 3, 6, 9 and 12 months]* *Measure: time course of BCVA changes [Time Frame: 3, 6, 9 and 12 months]* *Measure: change in central retinal thickness and other anatomical changes [Time Frame: 3, 6, 9 and 12 months]* *Measure: 15-letter (3-line) gain in BCVA [Time Frame: 3, 6, 9 and 12 months]*
Notes	Dates participants enrolled: July 2010 to March 2013 Funding: Novartis Conflict of interest: authors not reported since the study was obtained as a Novartis public report Trial registration: NCT01135914

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Randomization was stratified by centre and followed a permutated block size of 6.*"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked study (described as open-label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked study (described as open-label)
Incomplete outcome data (attrition bias) All outcomes	High risk	More missing data in the laser arm (27%) , mainly due to lack of efficacy, compared to the 2 ranibizumab arms (5% to 6%)

RESPOND 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	VA, OCT data and harms adequately reported (only loss of vision not reported)
Other bias	Low risk	No other bias identified
Overall risk of bias	High risk	High risk of bias for most items

RESTORE 2011

Methods	Parallel group RCT One eye per person, eye with worse VA selected unless other eye more suitable for treatment
Participants	Country: 10 European countries, Australia, Canada, Turkey Number of people randomised: 345 (345 eyes) Average age: 63 years Sex: 42% women Inclusion criteria: • 18 years or older • diabetes mellitus (according to the American Diabetes Association or World Health Organization guidelines) • HbA1c ≤ 10% • visual impairment due to DMO • stable medication for the management of diabetes within 3 months before randomisation and expected to remain stable during the study • visual impairment due to focal or diffuse DMO in at least 1 eye that was eligible for laser treatment in the opinion of the investigator • BCVA letter score between 78-39, both inclusive, based on ETDRS-like VA testing charts administered at a starting distance of 4 m (approximate Snellen equivalent 20/32-20/160) • decreased vision due to DMO and not other causes, in the investigator's opinion (at visit 1) Exclusion criteria: • concomitant conditions in the study eye that could prevent the improvement in VA on the study treatment in the investigator's opinion • active intraocular inflammation or infection in either eye • uncontrolled glaucoma in either eye (e.g. IOP > 24 mmHg on medication, or from the investigator's judgement) • laser PRP (within 6 months) or focal/grid laser photocoagulation (within 3 months) before study entry • treatment with antiangiogenic drugs in the study eye within 3 months before randomisation • history of stroke • systolic BP > 160 mmHg or diastolic BP > 100 mmHg • untreated hypertension • change in antihypertensive treatment within 3 months preceding baseline

Interventions	Intervention: • ranibizumab (0.5 mg) plus sham laser n = 116 (116 eyes) • ranibizumab (0.5 mg) plus laser n = 118 (118 eyes) Comparator • laser treatment plus sham injections n = 111 (111 eyes)
Outcomes	Primary outcome: • mean average change in BCVA from baseline over 12 months Secondary outcomes: • VA improvement • BCVA letter score 73 (20/40 Snellen equivalent) at month 12 • mean change in BCVA letter score • mean change in central retinal (subfield) thickness • patient-reported outcomes • safety Follow-up: 12 months
Notes	Dates participants enrolled: not reported Funding: Novartis Conflict of interest: authors reported financial support of Novartis or were Novartis employees Trial registration: NCT00906464

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"A randomization list was produced by, or under the responsibility of, Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio."* Appendix 1
Allocation concealment (selection bias)	Low risk	Central randomisation using an electronic Case Report Form after each participant was included by study investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"The masked BCVA assessor evaluated the visual acuity of the patient and provided the results to the evaluating investigator who also was masked to the treatment assignment. The evaluating investigator was responsible for all other aspects of the study, excluding the injection procedures. Based on all the performed clinical assessments and the visual acuity (VA) results received from the BCVA assessor, the evaluating investigator had to decide on the*

		treatment requirements for the patient each month and communicated this decision to the treating investigator. The treating investigator was unmasked to the treatment assignment and performed all injections or laser treatment as well as the corresponding sham treatments. He/she was required not be involved in any other aspect of the study and not to divulge the patient's treatment assignment to anyone. Once the designated roles were determined, the roles could not be switched at any time during the conduct of the study. Every effort was made to limit the number of unmasked study personnel to ensure the integrity of this masked study. An independent review and standardized grading of fundus photography, fluorescein angiography, and optical coherence tomography (OCT) images for the patients screened and enrolled in the study was performed at a central reading center that did not have access to any other data of the patients." Appendix 1
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants randomised in each group were: 116 ranibizumab, 118 ranibizumab + laser, 111 laser At 1 year complete participants were 87.9%, 87.3% and 88.3% respectively There were 2 deaths in each of the 3 treatment arms Used ITT analysis with LOCF
Selective reporting (reporting bias)	Low risk	We could not find a protocol, but primary outcomes were stated in the methods and were those routinely used in the field
Other bias	Low risk	No other source of bias identified
Overall risk of bias	Low risk	Low risk of bias for most items

REVEAL 2015

Methods	Parallel group RCT One eye per person, eye with worse VA selected unless other eye more suitable for treatment
Participants	Country: Asian population from 52 centres across 6 countries, or regions: China, Hong Kong, Japan, South Korea, Singapore, and Taiwan Number of people randomised: 396 (396 eyes) Average age: 61 years Sex: 44% women Inclusion criteria: • 18 years or older • diabetes mellitus (according to the American Diabetes Association or World Health Organization guidelines) • HbA1c ≤ 10% • visual impairment due to DMO • stable medication for the management of diabetes within 3 months before randomisation and expected to remain stable during the study • visual impairment due to focal or diffuse DMO in at least 1 eye that was eligible for laser treatment in the opinion of the investigator • BCVA letter score between 78-39, both inclusive, based on ETDRS-like VA testing charts administered at a starting distance of 4 m (approximate Snellen equivalent 20/32-20/160) • decreased vision due to DMO and not other causes, in the investigator's opinion (at visit 1) Exclusion criteria: • concomitant conditions in the study eye that could prevent the improvement in VA on the study treatment in the investigator's opinion • active intraocular inflammation or infection in either eye • uncontrolled glaucoma in either eye (e.g. IOP > 24 mmHg on medication, or from the investigator's judgement) • laser PRP (within 6 months) or focal/grid laser photocoagulation (within 3 months) before study entry • treatment with antiangiogenic drugs in the study eye within 3 months before randomisation • history of stroke • systolic BP > 160 mmHg or diastolic BP > 100 mmHg • untreated hypertension • change in antihypertensive treatment within 3 months preceding baseline
Interventions	"*Patients were randomised in a 1:1:1 ratio to 1 of 3 treatment arms: intravitreal ranibizumab 0.5 mg injection + sham laser, intravitreal ranibizumab 0.5 mg injection + active laser, or active laser + sham injections for 12 months*" Page 1404 Number in each group: ranibizumab + sham laser (n = 133), ranibizumab + active laser (n =132), or sham injection + active laser (n = 131)
Outcomes	Primary outcome: • mean average change in BCVA from baseline over 12 months Secondary outcomes: • several BCVA expressions • mean change in central retinal (subfield) thickness

	• safety Follow-up: 12 months
Notes	Dates participants enrolled: not reported Funding: Novartis Conflict of interest: authors reported financial support of Novartis or were Novartis employees Trial registration: NCT00989989

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"At Visit 2, all patients who fulfilled all the inclusion/exclusion criteria were given the lowest available number on the randomization list. This number assigned them to one of the treatment arms. The investigator entered the randomization number on the electronic case report form. A randomization list was produced by, or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio"*
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*To ensure successful masking in this double-masked study, at the start of the study and at each study site, the following site personnel were required to demonstrate their role: BCVA assessor and evaluating investigator (masked to the treatment assignment) and treating investigator (unmasked to the treatment assignment*" Page 1404
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	High risk	Higher proportion of loss to follow-up in the laser group; this can decrease the benefit with anti-VEGF (see below) *"Overall, 345 (87.1%) patients completed the study. The proportion of patients who discontinued the study was 7.5% in the ranibizumab arm, 13.6% in the ranibizumab active laser treatment arm, and*

REVEAL 2015 (*Continued*)

		17.6% in the laser treatment arm (Fig 2, available at www.aaojournal.org). Adverse events (range, 3.0%-6.8%) were the most common reason for discontinuation across all treatment arms (Fig 2, available at www.aaojournal.org). Unsatisfactory therapeutic effect (n= 7 [5.3%]) was reported only in the laser arm." Page 1405
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other bias identified
Overall risk of bias	Low risk	Low risk for most items

RISE-RIDE

Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: USA and South America Number of people randomised: 759 (759 eyes) Average age: 62 years Sex: 43% women Inclusion criteria: • 18 years or older • diabetes mellitus • decreased vision from DMO (study eye BCVA, 20/40-20/320 Snellen equivalent using ETDRS testing) • macular oedema (TD-OCT) central subfield thickness ≥ 275 µm Exclusion criteria: • prior vitreoretinal surgery • recent history (within 3 months of screening) of panretinal or macular laser in the study eye • intraocular corticosteroids antiangiogenic drugs • uncontrolled hypertension • uncontrolled diabetes (HbA1c > 12%) • recent (within 3 months) cerebrovascular accident, or myocardial infarction
Interventions	Intervention: • ranibizumab (0.3 mg or 0.5 mg) n = 244 (244 eyes) Comparator: • sham injection n = 122 (122 eyes) *"The median number of ranibizumab injections was 24. The mean number of macular laser treatments over 24 months was 1.8 and 1.6 in the sham groups and 0.3 to 0.8 in the ranibizumab groups. Substantially more sham-treated patients received macular laser under the protocol-specied criteria or underwent panretinal photocoagulation for proliferative diabetic retinopathy."* Page 5

RISE-RIDE (*Continued*)

Outcomes	Primary outcome: • gain of 15 or more ETDRS letters in BCVA score from baseline at 24 months (corresponding to 3 lines on the eye chart) Secondary outcomes: (at 24 months) • mean change from baseline BCVA score over time • proportion of participants with BCVA Snellen equivalent of 20/40 • mean change from baseline BCVA score over time in participants with focal oedema as assessed on fluorescein angiography • proportion of participants losing 15 letters in BCVA score from baseline • mean change from baseline in OCT CFT over time • proportion of participants with a 3-step progression from baseline in ETDRS retinopathy severity on fundus photography • proportion of participants with resolution of leakage on FA • mean number of macular laser treatments Follow-up: 24 months
Notes	Dates participants enrolled: June 2007 to January 2009 Funding: "*This study was supported by Genentech Inc. Support for third-party writing assistance by Ivo Stoilov, MD, CMPP, of Envision Scientific Solutions was provided by Genentech Inc.*" "*The sponsor participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript.*" Page 1121 Conflict of interest: "*Dr Ip is a consultant/advisor for Eye Technology Ltd, Genentech Inc, NicOx, Notal Vision, QLT Phototherapeutics Inc, Regeneron, and Sirion and has received grant support from Allergan Inc. Drs Hopkins and Ehrlich and Ms Wong are employees of Genentech Inc, a member of the Roche Group. Drs Hopkins and Ehrlich hold equity and/or options in Roche.*" Page 1121 Trial registration: RIDE NCT00473382 RISE NCT00473330

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Randomization was stratified by study eye BCVA (55 vs 55 ETDRS letters), baseline HbA1c (<=8% vs >8%), prior DME therapy in the study eye (yes vs no), and study site. Dynamic randomization was used to obtain approximately a 1:1:1 ratio among groups (Fig 1). Randomization was done via interactive phone system. The sponsor developed the specifications for the randomization, and a third party programmed and held the randomization algorithm.*" Page 3, Nguyen et al
Allocation concealment (selection bias)	Low risk	"*Randomization was stratified by study eye BCVA (55 vs 55 ETDRS letters), baseline HbA1c (<=8% vs >8%), prior DME therapy*

RISE-RIDE (*Continued*)

		in the study eye (yes vs no), and study site. Dynamic randomization was used to obtain approximately a 1:1:1 ratio among groups (Fig 1). Randomization was done via interactive phone system. The sponsor developed the specifications for the randomization, and a third party programmed and held the randomization algorithm." Page 3, Nguyen et al
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Ocular assessments, including the need for macular laser, were made by evaluating ophthalmologists masked to patients' treatment assignments. Study treatments were administered by treating ophthalmologists unmasked to treatment assignments but masked to ranibizumab dose. To improve patient masking, all patients received subconjunctival anesthesia before sham or active injections (performed as previously described).22 Study site personnel (except treating physicians and assistants), central reading center personnel, and the sponsor and its agents (except drug accountability monitors) were masked to treatment assignment. Treating physicians were masked to the assigned dose of ranibizumab.* " Page 3, Nguyen et al
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The 2-year study period was completed by 83.3% of participants in RISE and by 84.6% in RIDE; causes of missingness not reported
Selective reporting (reporting bias)	Low risk	All VA cut-offs and secondary outcomes available at 2 years, although not at 1 year, as pre-planned
Other bias	Low risk	No other bias identified
Overall risk of bias	Low risk	Low risk of bias for most items

Soheilian 2007

Methods	Parallel group RCT One or two eyes per person, in bilateral cases unclear how the second eye allocated
Participants	Country: Iran Number of people randomised: 129 (150 eyes) Average age: 61 years Sex: 49% women Inclusion criteria: • clinically significant DMO based on ETDRS criteria Exclusion criteria: • previous PRP or focal laser photocoagulation • prior intraocular surgery or injection • history of glaucoma or ocular hypertension • VA of 20/40 or better, or worse than 20/300 • presence of iris neovascularisation • high-risk PDR • significant media opacity • monocularity • pregnancy • serum creatinine ≥ 3 mg/dL • uncontrolled diabetes mellitus
Interventions	Intervention: • bevacizumab (1.25 mg) n = 50 eyes Comparator: • laser photocoagulation n = 50 eyes Re-treatment was performed at 12-week intervals whenever indicated There was another intervention arm which combined bevacizumab with triamcinolone, but this is not included in this review (n = 50 eyes)
Outcomes	Primary outcome: • change in BCVA (logMAR) at week 24 (data available at 36 weeks) Secondary outcomes: • VA change • CRT change assessed by OCT • injection-related complications
Notes	Dates participants enrolled: September 2005 to May 2007 Funding: "*Supported by the Ophthalmic Research Center of Shahid Beheshti University (MC) Tehran, Iran.*" Page 1150 Conflict of interest: "*The author(s) have no proprietary or commercial interest in any materials discussed in this article*" Page 1150 Trial registration: NCT00370669

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	*"Randomization was performed using random block permutation method according to a computer-generated randomization list. The block length varied randomly (6, 12). Random allocation sequence was performed by a biostatistician. The detail of series was unknown by the study investigators."* Page 2 Soheilian 2009
Allocation concealment (selection bias)	Low risk	*"Randomization was performed using random block permutation method according to a computer-generated randomization list. The block length varied randomly (6, 12). Random allocation sequence was performed by a biostatistician. The detail of series was unknown by the study investigators."* Page 2 Soheilian 2009
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"A sham laser procedure (20 seconds) was performed by aiming the laser beam on the macula for the eyes in the IVB and IVB/IVT groups. In the MPC group, a sham injection was done by a needleless syringe pressed against the conjunctiva. To keep the masking process, patients were prevented from seeing the syringes. All procedures were run by staff members other than the study investigators to preserve investigator masking. Best-corrected VA measurement and OCT were performed by certified examiners masked both to the randomization and to the findings of previous measurements."* Page 2-3 Soheilian 2009
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 6 missing eyes out of 50 at 36 weeks in the IVB group and 12 out of 50 in the photocoagulation group and causes were not clearly unrelated to VA outcome, except for 2 deaths. In a subsequent publication in 2012 the authors reported 39 (78%) and 38 (76%) eyes in the two arms; 8 participants (12 eyes) missing were dead for causes unrelated to treatment, but other causes of death were not reported

Soheilian 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	The primary outcomes are continuous measures and no arbitrary cut-points were used
Other bias	High risk	There was an imbalance of baseline VA in the IVB and photocoagulation groups: 0.71 logMAR versus 0.55 logMAR. Although there was a potential unit of analysis issue (150 eyes of 129 patients, 16% of participants had both eyes included), comparisons were made in a marginal regression model (based on generalised estimating equation methods) adjusted for the baseline values and to eliminate any possible correlation effects between the 2 eyes of participants in bilateral enrolled cases. However, we could not take correlation into account when analysing dichotomous VA definitions
Overall risk of bias	Unclear risk	High or unclear risk of bias for two items to a degree which we believe may influence effect estimates

Turkoglu 2015

Methods	Prospective study, treatment in the better-seeing eye
Participants	Country: Turkey Number of people randomised: 70 participants (35 ranibizumab, 35 grid laser) Average age: 64.6 ± 8.2 years ranibizumab; 63.8 ± 7.4 years laser Sex: 21% male ranibizumab, 18% male laser Inclusion criteria: • evidence of CSME by means of FFA • at least 6 months of follow-up • no other systemic or ocular disease that might affect vision Exclusion criteria: • participants with a history of intravitreal injection and laser photocoagulation for proliferative diabetic retinopathy or CSME • participants with vitreous haemorrhage present at the time of recruitment or vitreous haemorrhage which developed after enrolment
Interventions	Focal or grid laser photocoagulation treatment was performed in 35 participants and laser settings, including power, spot size, duration and number of burns, were recorded 35 participants received initial injection of ranibizumab 0.5 mg/0.05 mL. All participants of both groups received treatment in their better-seeing eye. After the induction phase, the intravitreal injections were administered if any of the following changes were observed: presence of visual acuity loss; persistent or recurrent subretinal or intraretinal fluid

Turkoglu 2015 (*Continued*)

Outcomes	Group comparisons of absolute scores and mean changes from baseline scores at 6-month visit were performed using analysis of the Turkish version of VFQ-25; it has modifications to adjust for Turkish culture and lifestyle
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No data available
Allocation concealment (selection bias)	Unclear risk	No data available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No data available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data available
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported
Selective reporting (reporting bias)	Unclear risk	No specific statement nor protocol available
Other bias	Low risk	No other bias identified
Overall risk of bias	Unclear risk	Most items not reported

Wiley 2016

Methods	Randomised, double-masked, 3-period, 2-treatment crossover design with 4 treatment sequence patterns Each of 3 12-week periods consisted of 3 intravitreous injections of ranibizumab (0.3 mg) or bevacizumab (1.25 mg), given every 4 weeks, with evaluation of the treatment period 4 weeks after the third dose (i.e. weeks 12, 24, and 36)
Participants	Country: USA and UK Number of people randomised: 56 participants (62 eyes, 6 pz both eyes) Average age: 62 years Sex: 38.7% women Inclusion criteria: Eligible participants had type 1 or type 2 diabetes mellitus, were at least 18 years of age, and could enter one or both eligible eyes in the study. Principal eligibility criteria for a

	study eye included: (1) presence of DME involving the centre of the macula, (2) ETDRS BCVA letter score of 78 to 24 (Snellen equivalent, 20/32-20/400), and (3) CSMT of 330 mm or more on Cirrus (Carl Zeiss Meditec, Inc, Dublin, CA) OCT Exclusion criteria: Eye included presence of factors or other conditions judged to impact the course of oedema or to preclude possible improvement in vision with treatment; PRP, focal or grid laser photocoagulation, or depot corticosteroid injection within the previous 3 months; ocular injection with an anti-VEGF agent within the previous 2 months; more than 4 injections with an anti-VEGF agent within the previous year; or prior vitrectomy. Potential participants were excluded for history of renal failure (requiring haemodialysis or renal transplantation) and for a measured systolic BP of more than 180 mmHg or a diastolic BP of more than 110 mmHg
Interventions	Each of 3 12-week periods consisted of 3 intravitreous injections of ranibizumab (0.3 mg) or bevacizumab (1.25 mg), given every 4 weeks, with evaluation of the treatment period 4 weeks after the third dose (i.e. weeks 12, 24, and 36) Each study eye received 9 monthly injections over the course of the trial, according to a pattern of treatments determined by 1 of 4 randomly assigned sequences: R-R-B (n = 17), R-B-B (n = 15), B-B-R (n = 16), or B-R-R (n = 14), where R indicates a series of 3 consecutive ranibizumab injections, and B represents a series of 3 consecutive bevacizumab injections. Study eyes meeting predefined criteria for significant worsening of DME at week 12 or later could receive focal or grid laser photocoagulation. Fellow eyes in participants only enrolling 1 eye could receive any necessary ocular treatment
Outcomes	The primary outcome: mean change in BCVA from baseline, estimated for a 3-month dosing period in a linear mixed-effects model The main prespecified secondary outcome was the change in CRT, measured as OCT CSMT, estimated for a 3-month dosing period using the linear mixed-effects model
Notes	June 2012 and January 2014

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Participants were assigned to 1 of the 4 treatment sequences using a randomization list generated by the Data and Statistical Coordinating Center before study initiation, with balance after every 12 enrollments. The list was provided to unmasked pharmacists at each site, who confirmed a valid participant identification code before dispensing study treatment. Both clinical sites used the same randomised list, but selected treatment assignments from opposite ends. For participants entering both eyes in the trial, the right eye was assigned randomly as above to 1 of the*

		4 treatment sequences, and the left eye was assigned automatically to the sequence*with the inverse schedule (for example, B-R-R in the right eye and R-B-B in the left eye).* Page 2
Allocation concealment (selection bias)	Low risk	*Participants were assigned to 1 of the 4 treatment sequences using a randomization list generated by the Data and Statistical Coordinating Center before study initiation, with balance after every 12 enrollments. The list was provided to unmasked pharmacists at each site, who confirmed a valid participant identification code before dispensing study treatment. Both clinical sites used the same randomised list, but selected treatment assignments from opposite ends. For participants entering both eyes in the trial, the right eye was assigned randomly as above to 1 of the 4 treatment sequences, and the left eye was assigned automatically* to the sequence*with the inverse schedule (for example, B-R-R in the right eye and R-B-B in the left eye).* Page 2
Blinding of participants and personnel (performance bias) All outcomes	Low risk	*"Participants and investigators were masked to treatment. Site staff collecting study data, including research coordinators, technicians, and photographers, were also masked."*
Blinding of outcome assessment (detection bias) All outcomes	Low risk	*"Site staff collecting study data, including research coordinators, technicians, and photographers, were also masked."*
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"*One participant with a single eye assigned to the R-B-B group* *withdrew after the week 4 visit after a hemorrhagic stroke. All* *remaining participants completed the study, including the week 12, 24, and 36 visits, and were included in this analysis*"
Selective reporting (reporting bias)	Low risk	VA (no SD), OCT (no SD) data and harms adequately reported
Other bias	Low risk	Six out of 56 participants had both eyes included in analyses
Overall risk of bias	Low risk	Low risk of bias for most items

Abbreviations
BCVA: best-corrected visual acuity
BP: blood pressure
CRT: central retinal thickness
CSFT: central subfield thickness
CSMO: clinically significant macular oedema
CSMT: central subfield mean thickness
DMO: diabetic macular oedema (DME: US spelling edema)
ECG: electrocardiogram
EQ-5D: EuroQol 5D
ETDRS: Early Treatment Diabetic Retinopathy Study
FAZ: foveal avascular zone
FFA: fundus fluorescein angiography
GLD: greatest linear dimension
HbA1c: glycated haemoglobin
IOP: intraocular pressure
ITT: intention-to-treat
iv: intravenous
IV: intravitreal injection
IVB: intravitreal bevacizumab
IVT: intravitreal triamcinolone
LOCF: last observation carried forward
logMAR: log of the Minimum Angle of Resolution
NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25
OCT: optical coherence tomography
PDR: proliferative diabetic retinopathy
PFCL: perifoveal capillary loss
PRP: panretinal photocoagulation
RCT: randomised controlled trial
SD: standard deviation
SD-OCT: spectral-domain optical coherence tomography
TD-OCT: time-domain optical coherence tomography
VA: visual acuity
VEGF: vascular endothelial growth factor

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

Study	Reason for exclusion
Ahmadieh 2013	Not an RCT
CRFB002DFR08 (LUDIC)	Single-arm study
CRFB002DGB14 (RELIGHT)	Single-arm study
CRFB002DNO02 (PTIMAL)	Single-arm study
DRCRnet 2007	Follow-up at 12 weeks only

(*Continued*)

DRCRnet 2011	Follow-up at 14 weeks only. RCT comparing ranibizumab (2 injections), triamcinolone (1 injection) to sham in participants with DMO undergoing grid and panretinal laser photocoagulation
DRCRnet 2012	Follow-up of DRCRnet 2010 comparing prompt to deferred laser in participants treated for ranibizumab for DMO: does not report on comparison of ranibizumab with laser
Faghihi 2008	Follow-up at 16 weeks only
NCT02985619 (BEVATAAC)	Triamcinolone as comparator, unpublished study
Paccola 2008	Single injection of intravitreal triamcinolone acetonide (4 mg/0.1 mL) compared to single injection of intravitreal bevacizumab (1.5 mg/0.06 mL). Duration: 24 weeks
Solaiman 2010	Single intravitreal injection of bevacizumab (inadequate dose); follow-up 6 months
Zehetner 2013	Physiological study of anti-VEGF levels only

Abbreviations
DMO: diabetic macular oedema
RCT: randomised controlled trial
VEGF: vascular endothelial growth factor

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chen 2016

Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: unclear Primary purpose: treatment
Participants	42 (72 eyes); country: China Male 55%, average age 60 years
Interventions	Experimental: ranibizumab 0.5 mg; one week after ranibizumab, the participants received grid photocoagulation intervention: macular area C-shaped manner, spot size 100 μm to 200 μm, 1 spot width apart, level I to II power and exposure time 0.1 second Active comparator: laser only
Outcomes	Primary outcome (time frame: 3 and 6 months): • Improvement of VA (2 or more lines on a letter chart, but not ETDRS) • Ranibizumab plus laser: 28/36 (78%) • Laser only: 18/36 (50%) Secondary outcome:

Chen 2016 (*Continued*)

	• Reduction in retinal thickening based on OCT • Baseline: ranibizumab plus laser: 487 (SD: 85) micron; laser 480 (SD: 83) micron • 6 months: ranibizumab plus laser: 246 (SD: 26) micron; laser: 370 (SD: 36) micron
Notes	Articles in Chinese Authors contacted to obtain additional data

Fouda 2017

Methods	Allocation: randomised study but no other information reported Endpoint classification: efficacy study Intervention model: parallel assignment Masking: unclear Primary purpose: treatment
Participants	70 eyes randomised (42 participants); country: Egypt Male % not reported, average age 55 years
Interventions	Experimental: ranibizumab 0.5 mg; aflibercept 2 mg
Outcomes	Primary outcome (time frame: 12 months): VA and CRT (cut-off and instrument not specified) Decimal VA used: no significant difference between ranibizumab and aflibercept Reduction in retinal thickening based on OCT: no significant difference between ranibizumab and aflibercept Number of re-injections after the loading dose: 2.62 (SD 0.68) aflibercept, 3.03 (SD 0.95) ranibizumab (P = 0.02)
Notes	Authors contacted to obtain additional data

Huang 2016

Methods	Allocation: quasi-randomised, participants with even visit numbers were allocated to intervention group, whereas participants with odd visit numbers were allocated to control group Endpoint classification: efficacy study Intervention model: parallel assignment Masking: unclear Primary purpose: treatment
Participants	78; country: China Male 55%, average age 51 to 54 years
Interventions	Experimental: ranibizumab 0.5 mg Active comparator: argon laser 532μm, green, 50 μm to 100 μm spots, intensity 100 mW to 200 mW and exposure time 0.1 second
Outcomes	Primary outcome (time frame: 3 and 6 months): • Improvement of VA (cut-off and instrument not specified) • Ranibizumab plus laser: 24/41 (59%) • Laser only: 11/27 (30%) Secondary outcome:

Huang 2016 (*Continued*)

	• Reduction in retinal thickening based on OCT • Baseline: ranibizumab: 401 (SD: 39) micron; laser: 387 (SD: 31) micron • 6 months: ranibizumab: 289 (SD: 34) micron; laser: 320 (SD: 37) micron
Notes	Article in Chinese Authors contacted to obtain additional data

Jovanovic 2015

Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: unclear Primary purpose: treatment
Participants	72 (120 eyes); country: Poland Average age: 60 years Inclusion criteria: severe DMO that affects the fovea, reduction in VA and/or metamorphopsia, diffuse oedema with or without cystic oedema (confirmed by fluorescein angiography and by OCT), CRT $\geq$ 300 μm, the absence of hard lipid exudates in the form of plaque in the subfoveal region, no prior laser treatment, no prior VEGF inhibitor treatment, and no previous intravitreal or subtenonian corticosteroid administration. The exclusion criteria were: high risk and advanced proliferative DR (PDR), the presence of other eye diseases that could affect VA, prior eye surgeries
Interventions	Experimental: bevacizumab 1.25 mg, one or more injections, with or without laser photocoagulation after 4 to 6 weeks depending on clinical response Active comparator: laser only
Outcomes	Primary outcome: not specified Outcommes reported: VA (logMAR), CRT based on OCT Quantitative results are available, but not at specified follow-up times and by number of injection and combination rather than by assigned subgroup
Notes	Sponsor: none reported Authors contacted to obtain additional information

NCT00387582

Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	49, country: USA

NCT00387582 (*Continued*)

Interventions	Experimental: I • Lucentis injections for the first 3 months of the study and then according to the protocol for the duration of the trial Active comparator: II • Argon laser treatment at enrolment and then according to the protocol for the duration of the study
Outcomes	Primary outcome (time frame: 6 and 12 months): • Prevention of vision loss at 1 year as evidenced by ETDRS VA Secondary outcome: • Reduction in retinal thickening based on OCT
Notes	Completion Date: February 2009 (No Results) Author contact not found Sponsor: Rocky Mountain Retina Consultants Collaborator: Genentech, Inc.

NCT00997191 (IBeTA)

Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	12; country: Brazil
Interventions	Procedure: laser photocoagulation Drug: intravitreal triamcinolone Drug: intravitreal bevacizumab
Outcomes	Primary outcome (time frame: 1 year): • BCVA Secondary outcomes: • macular mapping test • multifocal electroretinogram • CRT
Notes	Completion date: November 2011 (no results) Author could not be contacted Sponsor: University of Sao Paulo Collaborator: Fundacao de Amparo a Pesquisa do Estado de Sao Paolo

NCT01445899 (MATISSE)

Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: double-masked (participant, caregiver, investigator)
Participants	264; countries: USA, Israel
Interventions	Drug: PF-04523655 (Stratum I) Drug: PF-04523655 and ranibizumab Drug: ranibizumab Drug: PF-04523655 (Stratum II)
Outcomes	Primary outcomes: Safety and dose-limiting toxicities (Stratum I): to determine the safety and dose-limiting toxicities of a single intravitreal (IVT) injection of PF-04523655 in people with low vision Pharmacokinetics (Stratum I): to determine the pharmacokinetics (PK) of a single IVT injection of PF-04523655 in people with low vision Safety and tolerability (Stratum II): to evaluate the safety and tolerability of PF-04523655 alone and in combination with ranibizumab in participants with DMO Efficacy (Stratum II): to evaluate the ability of PF-04523655 alone and in combination with ranibizumab to improve VA compared to ranibizumab alone in people with DMO
Notes	Completion date: November 2013 (no results) Author contact not found Sponsor: Quark Pharmaceuticals Consider putting in excluded studies

NCT01565148 (IDEAL)

Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: factorial assignment Masking: open-label
Participants	208; country: USA
Interventions	Experimental Group 1: drug: iCo-007 350 µg as an intravitreal injection at baseline followed by another iCo-007 dose (350 μg) at month 4 Experimental Group 2: drug: iCo-007 700 µg as an intravitreal injection at baseline followed by another iCo-007 dose (700 μg) at month 4 Experimental Group 3: drug: iCo-007 350 µg as an intravitreal injection at baseline followed 7 days later by laser photocoagulation. At month 4, intravitreal injection of iCo-007 (350 μg) will be given as mandatory treatment. If the eye also meets retreatment criteria, it will also receive the second laser photocoagulation Experimental Group 4: drug: ranibizumab 0.5 mg intravitreal injection at baseline followed by iCo-007 350 μg intravitreal injection 2 weeks later; re-treatment with ranibizumab 0.5 mg mandatory at month 4 followed by iCo-007 350 μg 2 weeks later

NCT01565148 (IDEAL) (*Continued*)

Outcomes	Primary outcome: • Change in VA from baseline to month 8 Secondary outcomes: • Number of participants in a given study arm experiencing the same drug-related serious adverse event as a measure of safety and tolerability • Safety of repeated iCo-007 intravitreal injections in treatment of people with DMO as monotherapy and in combination with ranibizumab or laser photocoagulation. Serious consideration will be given if 2 or more participants in a particular treatment arm experience the same drug-related serious adverse event • Change in VA from baseline to month 12 • Change in retinal thickness measured by OCT from baseline to month 8 • Change in retinal thickness measured by OCT from baseline to month 12 • Duration of iCo-007 treatment effect during the 12-month follow-up period as measured by VA and OCT thickness • Peak plasma concentration (Cmax) of iCo-007 after multiple injections
Notes	Study has passed its completion date and status has not been verified in more than 2 years on ClinicalTrials.gov Author contacted Sponsor: Quan Dong Nguyen Collaborators: Juvenile Diabetes Research Foundation, iCo Therapeutics Inc

Abbreviations
BCVA: best-corrected visual acuity
CFST: central subfield macular thickness
CRT: central retinal thickness
DMO: diabetic macular oedema
EQ-5D: EuroQol 5D
ETDRS: Early Treatment Diabetic Retinopathy Study
OCT: optical coherence tomography
PRN: pro re nata
SD: standard deviation
TE: treat and extend
VA: visual acuity
VEGF: vascular endothelial growth factor
VFQ-25: Visual Function Questionnaire 25-item

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

ChiCTR-TRC-12002417

Trial name or title	A randomised controlled trial to compare the efficacy and safety of 1) macular laser vs 2) repeated intravitreal bevacizumab vs 3) combined repeated intravitreal bevacizumab with macular laser for diabetic macular edema
Methods	Parallel group RCT
Participants	People with type 2 diabetes and DMO

ChiCTR-TRC-12002417 (*Continued*)

Interventions	Group 1 (Control): macular laser photocoagulation performed every 4 months unless the deferral criteria are met. Group 2: intravitreal bevacizumab injections (1.25 mg each) given at 0, 1, 2 months and repeated en bloc every 4 months unless the deferral criteria are met Group 3: Intravitreal bevacizumab injections (1.25 mg each) given at 0, 1, 2 months, followed by macular laser photocoagulation at month 3; and repeated en bloc every 4 months unless the deferral criteria are met
Outcomes	BCVA at 2 years
Starting date	Unknown; trial registered 13 August 2013
Contact information	Joyce Kung (joycekung@cuhk.edu.hk); Carmen Chan (kmcc2001@hotmail.com)
Notes	Status checked on Chictr.Org.Cn on 1 December 2016. Author contacted

NCT01635790 (BRDME)

Trial name or title	Comparing the effectiveness and costs of bevacizumab to ranibizumab in participants with diabetic macular edema (BRDME)
Methods	Parallel group RCT
Participants	246 people with DMO
Interventions	Ranibizumab compared to bevacizumab
Outcomes	From clinical trials record: Primary outcome: • change in BCVA in the study eye from baseline to month 6 (designated as safety issue: no) Secondary outcome measures: • proportion of participants with a gain or loss of 15 letters or more at 6 months compared to baseline BCVA (designated as safety issue: no) • change in leakage on fluorescein angiography, baseline compared to 6 month exit visit (designated as safety issue: no) • change in foveal thickness (central retinal area) by OCT, 6 month exit visit compared to baseline (designated as safety issue: no) • total number of adverse events that occurred during the 6 month study, with secondary a classification of the types of adverse events (designated as safety issue: yes) • costs per quality adjusted life-year of the 2 treatments (time frame: 6 months; designated as safety issue: no), results will be based on the use of standardised health questionnaires (EQ-5D or Health Utility Index Mark 3) • proportion of participants with a BCVA of 20/40 or more at 6 months compared to baseline BCVA (designated as safety issue: no) http://clinicaltrials.gov/show/NCT01635790
Starting date	Study start date: June 2012 Estimated primary completion date: June 2016 (Final data collection date for primary outcome measure)

NCT01635790 (BRDME) (*Continued*)

Contact information	Reinier O Schlingemann (r.schlingemann@amc.uva.nl); Monique Wezel (m.wazel@amc.uva.nl)
Notes	Recruiting (status checked on ClinicalTrials.gov on 1 December 2016)

NCT02194634

Trial name or title	Safety and Efficacy Study of Conbercept in Diabetic Macular Edema (DME) (Sailing)
Methods	Parallel group RCT
Participants	type 1 or type 2 diabetes mellitus with DMO
Interventions	Experimental: Conbercept treatment group Conbercept injection and sham laser treatment at day 0 for 1st time, the investigators will decide whether the participants need to get repeated treatment according to monthly assessment Active Comparator: Laser treatment group Laser treatment and sham injection at day 0 for 1st time, the investigators will decide whether the repeated laser treatment is needed according to monthly results during the visit after 3 months
Outcomes	Primary outcome measures: • Mean change from baseline in BCVA at month 12 (time frame: baseline and month 12) (designated as safety issue: no) • To compare mean change from baseline BCVA between treatment group and controlled group at month 12 Secondary outcome measures: • Mean change from baseline in CRT between two groups (time frame: baseline and month 12 (designated as safety issue: no) • To compare mean change from baseline CRT between two groups at month 12 • Safety (e.g. incidence of adverse events) of Conbercept ophthalmic injection (time frame: 12 months) (designated as safety issue: yes) • To assess safety parameters during the study, such as incidence of adverse events, incidence of adverse drug reactions etc
Starting date	July 2014 Estimated Study Completion Date: September 2017 Estimated Primary Completion Date: December 2016 (Final data collection date for primary outcome measure)
Contact information	Chengdu Kanghong Biotech Co.,Ltd.
Notes	This study is recruiting participants. (Status checked on ClinicalTrials.Gov on 5 December 2016)

NCT02259088

Trial name or title	A 12-month, Randomized, Efficacy and Safety Study of 0.5 mg Ranibizumab vs Laser in Chinese DME Patients
Methods	Parallel group RCT
Participants	Participants with DMO with BCVA score between 78 and 39
Interventions	Ranibizumab PRN versus laser
Outcomes	Primary outcome measures: • Mean average BCVA change (time frame: 12 months) • Mean average BCVA change from Month 1 through Month 12 compared to baseline. Secondary Outcome Measures: • Mean BCVA change by visit (time frame: 12 months) • Mean BCVA change from baseline at each visit • Mean change in CSFT (time frame: 12 months) • Mean change in CSFT from baseline at each visit • BCVA improvement of ≥ 10 and ≥ 15 letters (time frame: 12 months) • Proportion of participants achieving BCVA improvement of ≥ 10 and ≥ 15 letters from baseline to Month 12 • BCVA loss of < 10 and < 15 letters (time frame: 12 months) • Proportion of participants with BCVA loss of < 10 and < 15 letters from baseline to Month 12 • VA ≥ 73 letters (time frame: 12 months) • Proportion of participants with VA ≥ 73 letters (approximate 20/40 Snellen chart equivalent) at Month 12 • Mean average BCVA change after month 3 (time frame: 12 months) • Mean average BCVA change from Month 4 to Month 12 compared to Month 3 • Mean change in patient-reported visual functioning scale (time frame: 6 and 12 months)Mean change in the patient-reported visual functioning through VFQ-25 composite and subscale scores at Month 6 and Month 12 compared to baseline. • Adverse events (time frame: 12 months) • To evaluate the safety of 0.5 mg ranibizumab intravitreal injections relative to laser photocoagulation, as assessed by the type, frequency and severity of ocular and non-ocular adverse events over 12 months. • Evaluation of treatment patterns (time frame: 12 months) • To evaluate the number of re-treatments and retreatment patterns (assessed by time of stabilization/ time to re-initiation of treatment) in participants treated with 0.5 mg ranibizumab
Starting date	November 2014 Estimated study completion date: January 2017 Estimated primary completion date: January 2017 (final data collection date for primary outcome measure)
Contact information	Novartis (Novartis Pharmaceuticals)
Notes	This study is ongoing, but not recruiting participants. (Status checked on ClinicalTrials.gov on 5 December 2016)

NCT02348918

Trial name or title	A Phase 2 Randomized, Controlled, Double-Masked, Multicenter Clinical Trial Designed to Evaluate the Safety and Exploratory Efficacy of Luminate® (ALG-1001) as Compared to Avastin® and Focal Laser Photocoagulation in the Treatment of Diabetic Macular Edema
Methods	Parallel group RCT
Participants	DMO participants
Interventions	Experimental: Luminate 1.0 mg group • Luminate 1.0 mg intravitreal injection administered at baseline (Day 0), 4 weeks and 8 weeks with PRN Luminate injection at week 20 for a total of at least 3 and no more than 4 Luminate injections. Sham injections will be performed at weeks 12 and 16 and may also be performed at week 20 if PRN Luminate is not required; sham laser treatment will be administered at baseline and at 16 weeks Experimental: Luminate 2.0 mg group • Luminate 2.0 mg intravitreal injection administered at baseline (Day 0), 4 weeks and 8 weeks with PRN Luminate injection at week 20 for a total of at least 3 and no more than 4 Luminate injections. Sham injections will be performed at weeks 12 and 16 and may also be performed at week 20 if PRN Luminate is not required; sham laser treatment will be administered at baseline and at 16 weeks Experimental: Luminate 3.0 mg group • Luminate 3.0 mg intravitreal injection administered at baseline (Day 0), 4 weeks and 8 weeks with PRN Luminate injection at week 20 for a total of at least 3 and no more than 4 Luminate injections. Sham injections will be performed at weeks 12 and 16 and may also be performed at week 20 if PRN Luminate is not required; sham laser treatment will be administered at baseline and at 16 weeks Active Comparator: Avastin® group • Avastin 1.25 mg intravitreal injection administered at baseline (Day 0), 4 weeks and 8 weeks with PRN Avastin injection at weeks 12, 16, or 20 for a total of at least 3 and up to 6 Avastin injections. Sham injections may be performed at weeks 12, 16, and 20 if PRN Avastin is not required; sham laser treatment will be administered at baseline and at 16 weeks Active Comparator: focal laser photocoagulation group • Focal laser photocoagulation performed at baseline (Day 0) with possible PRN laser retreatment at week 16. Sham intravitreal injections will be performed at baseline (Day 0), 4 weeks, 8 weeks, 12 weeks, 16 weeks and 20 weeks
Outcomes	Primary outcome measures: • Change in OCT CSFT at Week 24 (time frame: 24 weeks) • The primary efficacy outcome is OCT CSFT at Week 24 as compared to baseline Secondary outcome measures: • Change in BCVA at Week 24 (time frame: 24 weeks) • Secondary efficacy outcome is BCVA changes at Week 24 as compared to baseline
Starting date	October 2014 Estimated study completion date: March 2016 Estimated primary completion date: December 2015 (final data collection date for primary outcome measure)
Contact information	Allegro Ophthalmics, LLC
Notes	This study is recruiting participants; (status checked on ClinicalTrials.gov on 5 Dec. 2016)

NCT02645734

Trial name or title	The Effect of Bevacizumab and Ziv-aflibercept in Diabetic Macular Edema
Methods	Parallel group RCT
Participants	DMO participants
Interventions	Active comparator: injection intravitreous bevacizumab Active comparator: injection ziv-aflibercept at dose of 1.25 mg Active comparator: injection ziv-aflibercept at dose of 2.5 mg
Outcomes	Primary outcome measures: • VA (time frame: until 6 months) Secondary outcome measures: • CSFT (time frame: until 6 months)
Starting date	Study first received: 2 January 2016 Last updated: 4 January 2016 Estimated primary completion date: February 2016 (final data collection date for primary outcome measure)
Contact information	Zahra Rabbani Khah, Shahid Beheshti Medical University
Notes	This study is recruiting participants; (status checked on ClinicalTrials.gov on 5 December 2016)

NCT02699450

Trial name or title	A Phase 2 Study of RO6867461 in Participants With Center-Involving Diabetic Macular Edema (CI-DME) (BOULEVARD)
Methods	Parallel group RCT
Participants	DMO
Interventions	Experimental: RO6867461 1.5 mg • Participants will receive 1.5 milligrams (mg) RO6867461 intravitreal (IVT) every 4 weeks up to Week 20, followed by 1 sham administration at Week 24. Experimental: RO6867461 6 mg • Participants will receive 6 mg RO6867461 IVT every 4 weeks up to Week 20, followed by 1 sham administration at Week 24. Active Comparator: Ranibizumab 0.3 mg • Participants will receive 0.3 mg ranibizumab IVT every 4 weeks up to Week 24
Outcomes	Primary outcome measures: • Mean change from baseline in BCVA at week 24 using ETDRS modified charts (time frame: baseline, Week 24) • Apparent plasma clearance of RO6867461 (time frame: pre-dose on Days 1, 28, 84, 140, and 168; post-dose on Days 7, 182, and 196 or early termination) • Apparent plasma volume of RO6867461 (time frame: pre-dose on Days 1, 28, 84, 140, and 168; post-dose on Days 7, 182, and 196 or early termination)

	Secondary Outcome Measures: Percentage of participants gaining ≥ 15 letters from baseline BCVA at Week 24 (time frame: baseline, and Week 24) Percentage of participants with BCVA ≥ 69 letters (20/40 or better) at Week 24 (time frame: Week 24) Percentage of participants with BCVA ≥ 84 letters (20/20 or better) at Week 24 (time frame: Week 24) Mean change from baseline in BCVA at Week 28 (time frame: baseline, and Week 28) Mean change from baseline in foveal centre point thickness at Week 24 and 28, as measures by spectral domain OCT (SD-OCT) (time frame: baseline, Weeks 24 and 28) Mean change from baseline in mean CSFT at Week 24 and 28, as measures by SD-OCT (time frame: baseline, Weeks 24 and 28) Percentage of participants with resolution of subretinal and intraretinal fluid at Week 24 and 28, as measures by SD-OCT (time frame: Weeks 24 and 28) Percentage of participants with resolution of leakage at the macula at Week 24, as measures by FFA (time frame: Week 24) Change from baseline in the size of the foveal avascular zone at Week 24, as measures by FFA (time frame: baseline and Week 24) Change from baseline in plasma levels of vascular endothelial growth factor (VEGF) (time frame: baseline, Weeks 1, 4, 12, 24, 26, and 28 or early termination) Change from baseline in plasma levels of angiopoietin-2 (Ang-2) (time frame: baseline, Weeks 1, 4, 12, 24, 26, and 28 or early termination) (designated as safety issue: no) Maximum observed plasma concentration (Cmax) of RO6867461 (time frame: pre-dose on Days 1, 28, 84, 140, and 168; post-dose on Days 7, 182, and 196 or early termination) Area under the plasma concentration-time curve from time zero to extrapolated infinite time [AUC (0-inf)] of RO6867461 (time frame: pre-dose on Days 1, 28, 84, 140, and 168; post-dose on Days 7, 182, and 196 or early termination) Area under the plasma concentration-time curve from time zero to end of dosing interval [AUC (0-tau)] of RO6867461 (time frame: pre-dose on Days 1, 28, 84, 140, and 168; post-dose on Days 7, 182, and 196 or early termination) Time to reach maximum observed plasma concentration (Tmax) of RO6867461 (time frame: pre-dose on Days 1, 28, 84, 140, and 168; post-dose on Days 7, 182, and 196 or early termination) Plasma decay half-life (t1/2) of RO6867461 (time frame: pre-dose on Days 1, 28, 84, 140, and 168; post-dose on Days 7, 182, and 196 or early termination) Number of participants with adverse events (time frame: baseline up to Week 28 or early termination) Number of participants with anti-RO6867461 antibodies (time frame: baseline, Weeks 1, 4, 12, 20, 24, 26, and 28 or early termination)
Starting date	March 2016 Estimated Study Completion Date: October 2017 Estimated Primary Completion Date: October 2017 (final data collection date for primary outcome measure)
Contact information	Hoffmann-La Roche
Notes	This study is recruiting participants; (status checked on ClinicalTrials.gov on 5 December 2016)

NCT02712008

Trial name or title	Anti-vasculaR Endothelial Growth Factor plUs Anti-angiopoietin 2 in Fixed comBination therapY: Evaluation for the Treatment of Diabetic Macular Edema (RUBY)
Methods	Parallel group RCT
Participants	participants with DMO
Interventions	Experimental: Group 1 Participants in Group 1 will receive REGN910-3 dosing regimen 1 Experimental: Group 2 Participants in Group 2 will receive REGN910-3 dosing regimen 2 Active Comparator: Group 3 Participants in Group 3 will receive IAI
Outcomes	Primary outcome measures: • Change from baseline in BCVA measured by the ETDRS letter score at week 12 (time frame: baseline to week 12) Secondary outcome measures: • Change from baseline in CSFT at week 12 (time frame: baseline to week 12) • Change from baseline in CSFT at week 36 (time frame: baseline to week 36) • Proportion of participants with a ≥2-step improvement in Diabetic Retinopathy Severity Scale from baseline at week 12 (time frame: baseline to week 12) • Proportion of participants with a ≥2-step improvement in Diabetic Retinopathy Severity Scale from baseline at week 36 (time frame: baseline to week 36) • Change from baseline in BCVA measured by the ETDRS letter score at week 36 (time frame: baseline to week 36) • Proportion of participants with no retinal and/or subretinal fluid at week 12 (time frame: baseline to week 12) • Proportion of participants with no retinal and/or subretinal fluid at week 36 (time frame: baseline to week 36) • Time to no retinal and/or subretinal fluid at week 12 (time frame: baseline to week 12) • Time to no retinal and/or subretinal fluid at week 36 (time frame: baseline to week 36)
Starting date	March 2016 Estimated study completion date: October 2017 Estimated primary completion date: April 2017 (final data collection date for primary outcome measure)
Contact information	Regeneron Pharmaceuticals
Notes	This study is on ongoing, but not recruiting participants; (status checked on ClinicalTrials.gov on 5 December 2016)

Abbreviations

BCVA: best-corrected visual acuity
CSFT: central subfield thickness
CRT: central retinal thickness
CSMO: clinically significant macular oedema
DMO: diabetic macular oedema (DME: US spelling edema)

ETDRS: Early Treatment Diabetic Retinopathy Study
FFA: fundus fluorescein angiography
IOP: intraocular pressure
NA: not available
OCT: optical coherence tomography
PDR: proliferative diabetic retinopathy
PRN: pro re nata (as required in the circumstances)
PRP: panretinal photocoagulation
RCT: randomised controlled trial
VA: visual acuity

DATA AND ANALYSES

Comparison 1. Ranibizumab versus laser photocoagulation at 6 to 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life: NEI-VFQ composite score at 6 to 12 months	3	412	Mean Difference (Fixed, 95% CI)	5.14 [2.96, 7.32]

ADDITIONAL TABLES

Table 1. Reporting of all outcomes across studies

Study	Gain 3+ VA lines		Mean VA change		Mean CMT change		QOL		SSAE		ATC		Death	
Follow-up year	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Ahmadieh 2008			78		78									
Azad 2012	40								40		40		40	
BOLT 2010	80	65	80	65	80	65				80		80	80	
DA VINCI 2011	89		89		87				89		89		89	
DR-CR-net 2010	668	486	668	486	617	483				240		505		505
DR-CR-net 2015	620	577	620	577	620	577				660		660		660

Table 1. Reporting of all outcomes across studies (*Continued*)

Ekinci 2014			100		100				100		100		100	
Ishibash 2014	233		233				233		233		233	
Koro-belnik 2014	573		573		573					865		865		865
LU-CI-DATE 2014	33		33		33				33		33		33	
Macu-gen 2005	86		86						86		86		86	
Macu-gen 2011	260	207	260				236			286		286		286
Nepo-mu-ceno 2013	60		60		60				60					
READ2 2009	115		115								117		117	
RE-LA-TION 2012			128						128		128		128	
RE-SOLVE 2010	151		151		151				151		151		151	
RE-SPONI 2013	203		203		202				237				237	
RE-STORE 2011	343		343		343		299		345		345		345	

Table 1. Reporting of all outcomes across studies (*Continued*)

RE-VEAL 2015	390		390		268								
RISE-RIDE		509						504		500			500
So-heil-ian 2007	87		85		85				96				
Turkogl 2015			70		70		70						
Wiley 2016			124		124								
Total studies	**17**	**5**	**21**	**3**	**16**	**3**	**4**	**1**	**12**	**6**	**10**	**5**	**12**	**5**
Total participants	**4031**	**1844**	**4489**	**1128**	**3491**	**1125**	**838**	**504**	**1598**	**2631**	**1322**	**2396**	**1639**	**2816**

Numbers in the table are the total number of eyes for each study,as available by follow-up year (1 or 2) and outcome measure.

Table 2. Network structure: efficacy at 12 months

	Laser	Aflibercept	Beva-cizumab	Pegap-tanib	Ranibizumal	Ranibizumal deferred-laser	Ranibizumal prompt laser	Sham	Overall
Gain 3+ lines	12	4	5	3	8	1	5	3	17
	1074	539	344	410	713	188	545	218	4031
Mean VA change	13	4	7	3	11	1	6	4	21
	1131	539	476	410	861	188	629	255	4489

Table 2. Network structure: efficacy at 12 months (*Continued*)

Mean CRT change	11	4	7		10	1	4	2	16
	986	538	476		779	175	451	86	3491
QOL				4					4
				838					838

For each efficacy outcome, numbers in the table are the total number of studies (upper line for each outcome) and the total number of eyes (lower line for each outcome), as available by treatment and measured at one year.

Table 3. Gain of 3 or more lines of visual acuity at 12 months: direct (upper-right triangle) and mixed (lower-left triangle) estimates

LASER	**3.82 (2.61 to 5.58)**	**2.74 (1.34 to 5.61)**		**2.82 (1.82 to 4.38)**	**1.88 (1.31 to 2.70)**	**2.30 (1.74 to 3.03)**	
3.66 (2.79 to 4.79)	**AFLI**	**0.68 (0.52 to 0.90)**		**0.77 (0.59 to 0.99)**			
2.47 (1.81 to 3.37)	**0.68 (0.53 to 0.86)**	**BEVA**		1.14 (0.88 to 1.48)			
1.70 (0.58 to 4.94)	0.46 (0.16 to 1.34)	0.69 (0.24 to 1.89)	**PEGA**				**0.51 (0.30 to 0.89)**
2.76 (2.12 to 3.59)	**0.75 (0.60 to 0.94)**	1.11 (0.87 to 1.43)	1.62 (0.58 to 4.57)	**RANI**		0.90 (0.67 to 1.21)	**0.31 (0.13 to 0.76)**
2.02 (1.46 to 2.81)	**0.55 (0.37 to 0.82)**	0.82 (0.54 to 1.24)	1.19 (0.40 to 3.58)	0.73 (0.51 to 1.06)	**RANI-DL**	1.10 (0.80 to 1.51)	
2.33 (1.81 to 3.00)	**0.64 (0.47 to 0.86)**	0.94 (0.68 to 1.31)	1.37 (0.47 to 3.99)	0.85 (0.65 to 1.09)	1.15 (0.85 to 1.56)	**RANI-PL**	
0.87 (0.35 to 2.17)	**0.24 (0.10 to 0.59)**	**0.35 (0.14 to 0.87)**	**0.51 (0.30 to 0.89)**	**0.32 (0.13 to 0.76)**	0.43 (0.17 to 1.11)	**0.37 (0.15 to 0.93)**	**SHAM**

P value for overall inconsistency = 0.883 in the network meta-analysis.

Values in the table are risk ratios and 95% confidence intervals. Values in **bold** are ones where the 95% confidence intervals does not include 1 (null effect).

Table 4. Mean visual acuity change at 12 months: direct (upper-right triangle) and mixed (lower-left triangle) estimates

LASER	**−0.20 (−0.24 to −0.17)**	**−0.20 (−0.28 to −0.12)** [a]		**−0.11 (−0.13 to −0.08)**	**−0.12 (−0.16 to −0.075)**	**−0.10 (−0.13 to −0.08)**	
−0.20 (−0.22 to −0.17)	**AFLI**	**0.07 (0.03 to 0.11)**		**0.04 (0.00 to 0.08)**			
−0.12 (−0.15 to −0.09) [a]	**0.08 (0.05 to 0.11)**	**BEVA**		−0.02 (−0.05 to 0.01)			
0.01 (−0.09 to 0.07)	**0.19 (0.11 to 0.27)**	**0.11 (0.04 to 0.19)**	**PEGA**				**0.08 (0.03 to 0.13)**
−0.12 (−0.14 to −0.10)	**0.08 (0.05 to 0.11)**	0.00 (−0.02 to 0.03)	**−0.11 (−0.19 to −0.04)**	**RANI**		0.01 (−0.02 to 0.03)	**0.23 (0.15 to 0.32)**
−0.11 (−0.13 to −0.09)	**0.08 (0.04 to 0.13)**	0.01 (−0.04 to 0.06)	**−0.11 (−0.19 to −0.02)**	0.00 (−0.04 to 0.05)	**RANI-DL**	0.00 (−0.05 to 0.05)	
−0.11 (−0.14 to −0.08)	**0.09 (0.06 to 0.12)**	0.01 (−0.02 to 0.05)	**−0.10 (−0.18 to −0.02)**	0.01 (−0.01 to 0.03)	0.01 (−0.04 to 0.05)	**RANI-PL**	
0.08 (0.01 to 0.15)	**0.28 (0.21 to 0.35)**	**0.20 (0.13 to 0.27)**	**0.09 (0.06 to 0.12)**	**0.20 (0.13 to 0.27)**	**0.20 (0.11 to 0.28)**	**0.19 (0.12 to 0.26)**	**SHAM**

[a] P value for differences between direct and indirect estimates = 0.031 in the network meta-analysis.
P value for overall inconsistency = 0.665.

Table 5. Mean central retinal thickness change at 12 months: direct (upper-right triangle) and mixed (lower-left triangle) estimates

LASER	**−119 (−143 to −95)**	**−44 (−82 to −5)**	**−71 (−120 to −22)**[^]	**−35 (−62 to −8)**	**−64 (−103 to −25)**[b*]	
−114 (−147 to −81)	**AFLI**	**68 (43 to 94)**	22 (−4 to 48)			
−46 (−78 to −14)	**68 (29 to 108)**	**BEVA**	**−38 (−56 to −20)**			**132 (72 to 187)**
−75 (−100 to −50)	**39 (2 to 76)**	**−29 (−58 to −1)**	**RANI**		−19 (−39 to 2) [a]	**1470 (95 to 196)**
−57 (−111 to −2)	57 (−6 to 120)	−11 (−73 to 51)	18 (−40 to 76)	**RANI-DL**	6 (−22 to 34)	

Table 5. Mean central retinal thickness change at 12 months: direct (upper-right triangle) and mixed (lower-left triangle) estimates (*Continued*)

−72.90 (−103 to −42)[b]	41 (−2 to 84)	−27 (−68 to 13)	2 (−31 to 35)[a]	−16 (−71 to 38)	**RANI-PL**	
77 (18 to 137)	**191 (127 to 256)**	**123 (67 to 179)**	**153 (97 to 208)**	**134 (55 to 213)**	**150 (87 to 214)**	**SHAM**

[a] P value for differences between direct and indirect estimates = 0.003.
[b] P value for differences between direct and indirect estimates = 0.044.
* P value for heterogeneity = 0.002; I^2 = 80% in the direct meta-analysis.
^ P value for heterogeneity = 0.000; I^2 = 91% in the direct meta-analysis.
P value for overall inconsistency = 0.209 in the network meta-analysis.

Table 6. Network structure: safety at the longest available follow-up

	Laser	Aflibercept	Bevacizumab	Pegaptanib	Ranibizumab	Sham	Overall
SSAE	9	3	6	2	10	5	18
	1013	556	410	186	1303	528	4229
ATC*	10	3	4	2	8	2	15
	824	846	330	188	1113	184	3718
Death	11	3	4	2	10	3	17
	903	846	333	188	1521	434	4455

For each safety outcome, numbers in the table are the total number of studies (upper line for each outcome) and the total number of eyes (lower line for each outcome), as available by treatment and measured at the longest available follow-up.
(*) combined incidence of (1) cardiovascular, hemorrhagic, and unknown death; (2) nonfatal MI; and (3) nonfatal stroke.

Table 7. All serious systemic adverse events (longest available follow-up)

CONTROL	0.95 (0.75 to 1.20)	1.29 (0.43 to 3.84)	1.02 (0.67 to 1.53)	0.98 (0.76 to 1.25)
0.98 (0.83 to 1.16)	**AFLI**	0.95 (0.75 to 1.20)		1.04 (0.83 to 1.32)
0.93 (0.73 to 1.19)	0.95 (0.76 to 1.18)	**BEVA**		0.96 (0.77 to 1.20)
1.02 (0.64 to 1.64)	1.04 (0.63 to 1.72)	1.09 (0.64 to 1.86)	**PEGA**	
0.97 (0.80 to 1.17)	0.98 (0.82 to 1.19)	1.04 (0.84 to 1.28)	0.95 (0.57 to 1.58)	**RANI**

P value for overall inconsistency = 0.859.

Table 8. Antiplatelet Trialists Collaboration arterial thromboembolic events at the longest available follow-up

CONTROL	1.50 (0.81 to 2.79)	0.92 (0.17 to 5.12)	0.78 (0.31 to 1.97)	0.64 (0.38 to 1.07)
0.88 (0.37 to 2.13)	**AFLI**	1.46 (0.71 to 2.98)		2.26 (1.15 to 4.23)[a]
0.94 (0.33 to 2.66)	1.06 (0.36 to 3.11)	**BEVA**		1.51 (0.85 to 2.69)
0.79 (0.20 to 3.02)	0.89 (0.18 to 4.43)	0.83 (0.15 to 4.61)	**PEGA**	
1.09 (0.52 to 2.29)	1.24 (0.48 to 3.19)[a]	1.17 (0.43 to 3.13)	1.17 (0.43 to 3.16)	**RANI**

[a] P value for differences between direct and indirect estimates = 0.002.
P value for overall inconsistency = 0.274 in the network meta-analysis.

Table 9. All-cause mortality at the longest available follow-up

CONTROL	1.69 (0.30 to 9.42)[a]	0.95 (0.06 to 14.85)	0.82 (0.25 to 2.65)	0.64 (0.32 to 1.25)[d]
1.01 (0.34 to 3.03)[a]	**AFLI**	2.67 (0.97 to 7.37)[b]		2.26 (0.80 to 6.40)[c]
1.61 (0.45 to 5.69)	1.59 (0.43 to 5.94)[b]	**BEVA**		0.85 (0.40 to 1.83)
0.81 (0.16 to 4.03)	0.81 (0.12 to 5.62)	0.51(0.07 to 3.90)	**PEGA**	
0.90 (0.40 to 2.01)	1.16 (0.38 to 3.58)[c]	0.73 (0.22 to 2.37)	1.44 (0.24 to 8.48)	**RANI**

[a] P value for differences between direct and indirect estimates = 0.011.
[b] P value for differences between direct and indirect estimates = 0.030.
[c] P value for differences between direct and indirect estimates = 0.015.
[d] P value for differences between direct and indirect estimates = 0.022.
P value for overall inconsistency = 0.087 in the network meta-analysis.

Table 10. Similarity among studies. baseline values and number of injections

Study	Participants	Interventions	Mean n. injections	Visual acuity (logMAR)	Retinal thickness (µm)	Study sponsor
Ahmadieh 2008	78	Bevacizumab Sham				None reported
BOLT 2010	80	Bevacizumab Laser	9* 3*	0.59 0.61	507 482	Public
DA VINCI 2011	89	Aflibercept Laser	3.6 to 5.5 1.7	0.55	441	Industry

Table 10. Similarity among studies. baseline values and number of injections (*Continued*)

DRCRnet 2010	668	Laser Ranibizumab-DL Ranibizumab-PL	3* 9* 8*	0.38 0.39 0.38		Public
DRCRnet 2015	620	Aflibercept Bevacizumab Ranibizumab	9.2 9.4 9.7	0.40	412 414 407	Public
Ekinci 2014	100	Bevacizumab Ranibizumab	5.1 6.5	0.22 0.24	484 490	Public
Ishibashi 2014	233	Pegaptanib Sham	4	0.56		Industry
Korobelnik 2014	268	Aflibercept Laser	8.5 2.4	0.50		Industry
Lopez-Galvez 2014	83	Ranibizumab Laser	5.3 2.1			Industry
LUCIDATE 2014	33	Laser Ranibizumab	2.6 9	0.42 0.30	489 455	No details
Macugen 2005	86	Pegaptanib Sham	5 4.5	0.56 0.58	476 423	Industry
Macugen 2011	260	Pegaptanib Sham	8.3 8.4	0.56 0.58	442 465	Industry
RELATION 2012	128	Laser Ranibizumab-PL				Industry
Nepomuceno 2013	60	Bevacizumab Ranibizumab	9.8 7.7	0.60 0.63	451 421	Public
READ2 2009	115	Laser Ranibizumab Ranibizumab-PL	4.4 5.3 2.9	0.60 0.54 0.60	228 190 263	Industry
RESOLVE 2010	151	Ranibizumab Sham	10.2 8.9	0.50 0.48	455 449	Industry
RESPOND 2013	203	Laser Ranibizumab Ranibizumab-PL	9.2 8.8	0.46 0.44 0.40	458 448 422	Industry
RESTORE 2011	343	Laser Ranibizumab Ranibizumab-PL	7.3 7 6.8	0.46 0.40 0.42	412 427 416	Industry

Table 10. Similarity among studies. baseline values and number of injections (*Continued*)

REVEAL 2015	390	Laser Ranibizumab Ranibizumab-PL	1.9 7.8 7	0.54 0.52 0.52	395 419 430	Industry
Soheilian 2007	85	Bevacizumab Laser		0.71 0.55	352 319	Public
Turkoglu 2015	70	Laser Ranibizumab		0.84 0.80	460 488	None reported
Wiley 2016	124	Bevacizumab Ranibizumab	3 3	0.42	477	Public

DL: plus deferred laser
PL: plus prompt laser
(*): median, not mean, available and reported

FEEDBACK

Feedback, 25 June 2013

Summary

Comments:1. In the electronic searches,did you not find the article: Lim JW, Lee HK, Shin MC. Comparison of intravitreal bevacizumab alone or combined with triamcinolone versus triamcinolone in diabetic macular edema: A randomized clinical trial. Ophthalmologica. 2012;227(2):100-6. The article was published online: October 12, 2011, so it should have been found in the last electronic search, June 2012. I understand this article would have been excluded because of the triamcinolone comparison (it compares bevacizumab 1.25 mg versus bevacizumab 1.25 mg plus triamcinolone 2 mg versus triamcinolone 2 mg) but maybe It should appear in the 'Characteristics of excluded studies' section?

2. About the outcome results for 'Quality of life': Quality of life results should be included from the RESTORE 2011 trial. In the RESTORE 2011 trial (RESTORE 2011) data on quality of life have been reported using EQ-5D and NEI VFQ-25. It reported 12 months results, so it could also have been included. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang G, Massin P, Schlingemann R, et al. The RESTORE 2011 Study ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011;118(4):615-25.

3. In the section Effects of interventions/Anti-VEGF versus sham treatment/ Quality of the evidence: "READ2 2009 provided visual gain, but not visual loss data". This section evaluates anti-VEGF versus sham treatment and the READ trial is about ranibizumab versus laser.

4. For the included study: DRCRnet 2010 {published data only} Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117(6):1064-77. It seems that you have also considered results from this trial, from the 2011 publication for 2 years results (Analysis 3.7-3.11): Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, et al. Expanded 2-year follow-up of ranibizumab plus prompt laser or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011;118(4):609-614. The values of "N", total population evaluated belong to 2011 publication; the numbers are higher than those belonging to the 2010 publication. So this reference should also be cited.

5. For the included study: READ2 2009 {published data only} Nguyen QD, Shah SM, Khwaja AA, Channa R, Hatef E, Do DV, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology 2010;117(11):2146-51. The results that are considered in the review belong to the article by Nguyen 2009 (results and follow up at 6 months). Nguyen QD, Shah SM, Heier JS, Do DV, Lim J, Boyer D, et al. Primary end point (six months) results of the Ranibizumab for Edema of the mAcula in diabetes. Ophthalmology. 2009;116 (11):2175-81. All the analyses have been done with the 6 months follow up. Because after six months all patients could be treated with ranibizumab, data were not collected beyond six months. So this reference should also be cited.

6. In the 'Characteristics of included studies' table for RISE-RIDE, the 'outcomes' section should be completed.
7. In Tables 2, 5, 6, 7, 8 and 9 'bevacacizumab' should be corrected to 'bevacizumab'.

Reply

We thank Ruth Ubago Pérez for her comments submitted through the Feedback system in *The Cochrane Library*.
1. In the 'Characteristics of excluded studies' table, we have added that not only Paccola 2008, but also Lim 2012 were excluded because another Cochrane review focuses on the use of intravitreal steroids in people with diabetic macular oedema.
2. We will include quality of life data in the next review update.
3. We have removed this sentence.
4 and 5. We have added these references.
6. We have completed the 'Outcomes' section.
7. We have corrected these typos.

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 26 April 2017.

Date	Event	Description
2 May 2017	New search has been performed	Issue 6, 2017: Updated protocol: objectives revised as comparing different antiangiogenic drugs using network meta-analysis technique
2 May 2017	New citation required and conclusions have changed	Issue 6, 2017: Searches updated and six new studies added (DRCRnet 2015, Ishibashi 2014, Lopez-Galvez 2014, REVEAL 2015, Turkoglu 2015, Wiley 2016) and conclusions changed

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 4, 2009

Date	Event	Description
4 November 2014	Amended	Plain language summary title has been amended
17 October 2014	New citation required but conclusions have not changed	Issue 10, 2014: Five new studies (Azad 2012; Ekinci 2014; Nepomuceno 2013; RELATION 2012; RESPOND 2013) have been included in the update.
17 October 2014	New search has been performed	Issue 10, 2014: Electronic searches updated.
4 November 2013	Feedback has been incorporated	The authors have made some edits to the review in response to feedback received. See 'Feedback 1' for further details.
14 March 2013	Amended	The abstract has been amended to focus on the comparison with laser and presenting absolute effects
11 November 2012	New search has been performed	Updated searches yielded seven new trials for inclusion. One trial that had previously been included was excluded. An economic section has been added. One new author Massimo Brunetti has been added to the review team
11 November 2012	New citation required and conclusions have changed	Inclusion of seven new studies has changed the conclusions to this review from the previous version

CONTRIBUTIONS OF AUTHORS

Conceiving the review: GV, MP

Designing the review: GV, MP, EL

Co-ordinating the review: GV

Data collection for the review.

- Designing search strategies: IG
- Undertaking searches: IG
- Screening search results: GV, MP
- Organising retrieval of papers: IG
- Screening retrieved papers against inclusion criteria: GV, Cochrane Eyes and Vision
- Appraising quality of papers: GV, MP
- Extracting data from papers: GV, MP, EL

- Writing to authors of papers for additional information: GV, MP
- Obtaining and screening data on unpublished studies: GV, Cochrane Eyes and Vision

Data management for the review.

- Entering data into Review Manager 5: GV, MP, EL

Analysis of data: GV, EL

Interpretation of data.

- Providing a methodological perspective: GV, EL
- Providing a clinical perspective: GV, MP
- Providing a policy perspective: GV, MP, EL
- Providing a consumer perspective: none

Writing the review: GV, MP, EL

DECLARATIONS OF INTEREST

Gianni Virgili: none known

Mariacristina Parravano received payment for participating on the Advisory Board for Allergan, Bayer and Novartis.

Jennifer Evans: none known

Iris Gordon: none known

Ersilia Lucenteforte: none known

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- The Cochrane Review Incentive Scheme provided funding for Jennifer Evans to assist with the 2014 update of this review.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between protocol and review in the first published version of this review

We have added LILACS to the list of databases which have been searched for this review. We have used a sensitivity analysis for the robustness of results in comparisons including only one trial according to a statistical technique derived from a recent publication (Borm 2009).

Changes in update, 2012 compared to the protocol of the previous version

1. We have specified that studies comparing different anti-VEGF drugs will also be included in this review, but intravitreal steroids will be excluded as they are the subject of another Cochrane Review. Moreover, we decided not to consider the comparison of bevacizumab with bevacizumab plus triamcinolone, which included two studies; in fact this comparison investigates the additional effect of triamcinolone rather than the benefit of anti-VEGF drugs.
2. We have computed indirect comparison odds ratios (OR) of a gain of 3+ and 2+ lines for bevacizumab and pegaptanib versus ranibizumab as the reference drug using random-effects model logistic regression.

Changes in update, 2014 compared to the protocol of the previous version

1. We have included five more studies but the conclusions did not change.
2. We no longer consider economic evidence since antiangiogenic therapy is widely approved and reimbursed.
3. We eliminated the table on retinal detachment as an ocular adverse event since it proved to be extremely rare in all studies.
4. Units of analysis issue: in the update of this review we no longer performed a sensitivity analysis regarding the primary outcome to determine the impact of excluding studies with eyes, rather than participants, as the unit of analysis. In fact, a significant amount of evidence from studies with individuals as unit of analysis was achieved for the main comparisons.
5. Single trial issue: in the 2012 and 2014 updates of the review we did not use the sensitivity analysis on the robustness of single trial results recommended by Borm 2009, as was originally planned. Instead, we calculated the 'Optimal Information Size' to rate the quality of evidence regarding imprecision as recommended by the GRADE study group in Guyatt 2011.

Changes in update, 2016 compared to the protocol of the previous version

1. The objective was now to compare different anti-VEGF drugs and a new protocol was developed.
2. We used network meta-analysis technique to augment direct evidence with indirect evidence.
3. We restricted the number of outcomes to three efficacy outcomes, three safety outcomes and quality of life.
4. We have included six more studies and conclusions are changed.
5. The sensitivity analysis restricted to low risk of bias studies was added to the protocol.
6. We included a cross-over study and treated it as a parallel arm study in efficacy analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Angiogenesis Inhibitors [*therapeutic use]; Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized [therapeutic use]; Aptamers, Nucleotide [therapeutic use]; Bevacizumab; Diabetic Retinopathy [*complications]; Laser Coagulation [methods]; Macular Edema [*drug therapy; surgery]; Randomized Controlled Trials as Topic; Ranibizumab; Receptors, Vascular Endothelial Growth Factor [therapeutic use]; Recombinant Fusion Proteins [therapeutic use]; Triamcinolone [therapeutic use]; Vascular Endothelial Growth Factor A [*antagonists & inhibitors]

MeSH check words

Humans