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Anti-vascular endothelial growth factor for diabetic macular oedema (Review)

Virgili G, Parravano M, Menchini F, Evans JR

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[Intervention Review]

Anti-vascular endothelial growth factor for diabetic macular oedema

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ABSTRACT

Background

Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Although grid or focal laser photocoagulation has been shown to reduce the risk of visual loss in DMO, or clinically significant macular oedema (CSMO), vision is rarely improved. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) modalities is used to try to improve vision in people with DMO.

Objectives

To investigate the effects in preserving and improving vision and acceptability, including the safety, compliance with therapy and quality of life, of antiangiogenic therapy with anti-VEGF modalities for the treatment of DMO.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to April 2014), EMBASE (January 1980 to April 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to April 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 April 2014.

Selection criteria

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

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. The risk ratios (RR) for visual loss and visual gain of three or more lines of logMAR visual acuity were estimated at one year of follow-up (plus or minus six months) after treatment initiation.

Main results

Eighteen studies provided data on four comparisons of interest in this review. Participants in the trials had central DMO and moderate vision loss.

Compared with grid laser photocoagulation, people treated with antiangiogenic therapy were more likely to gain 3 or more lines of vision at one year (RR 3.6, 95% confidence interval (CI) 2.7 to 4.8, 10 studies, 1333 cases, high quality evidence) and less likely to lose 3 or more lines of vision (RR 0.11, 95% CI 0.05 to 0.24, 7 studies, 1086 cases, high quality evidence). In meta-analyses, no significant subgroup difference was demonstrated between bevacizumab, ranibizumab and aflibercept for the two primary outcomes, but there was little power to detect a difference. The quality of the evidence was judged to be high, because the effect was large, precisely measured and did not vary across studies, although some studies were at high or unclear risk of bias for one or more domains. Regarding absolute benefit, we estimated that 8 out of 100 participants with DMO may gain 3 or more lines of visual acuity using photocoagulation whereas 28 would do so with antiangiogenic therapy, meaning that 100 participants need to be treated with antiangiogenic therapy to allow 20 more people (95% CI 13 to 29) to markedly improve their vision after one year. People treated with anti-VEGF on average had 1.6 lines better vision (95% CI 1.4 to 1.8) after one year compared to laser photocoagulation (9 studies, 1292 cases, high quality evidence). To achieve this result, seven to nine injections were delivered in the first year and three or four in the second, in larger studies adopting either as needed regimens with monthly monitoring or fixed regimens.

In other analyses antiangiogenic therapy was more effective than sham (3 studies on 497 analysed participants, high quality evidence) and ranibizumab associated with laser was more effective than laser alone (4 studies on 919 participants, high quality evidence).

Ocular severe adverse events, such as endophthalmitis, were rare in the included studies. Meta-analyses conducted for all antiangiogenic drugs compared with either sham or photocoagulation did not show a significant difference regarding serious systemic adverse events (15 studies, 441 events in 2985 participants, RR 0.98, 95% CI 0.83 to 1.17), arterial thromboembolic events (14 studies, 129 events in 3034 participants, RR 0.89, 95% CI 0.63 to 1.25) and overall mortality (63 events in 3562 participants, RR 0.88, 95% CI 0.52 to 1.47). We judged the quality of the evidence on adverse effects as moderate due to partial reporting of safety data and the exclusion of participants with previous cardiovascular events in some studies.

Authors' conclusions

There is high quality evidence that antiangiogenic drugs provide a benefit compared to current therapeutic options for DMO, that is grid laser photocoagulation, in clinical trial populations at one or two years. Future research should investigate differences between drugs, effectiveness under real-world monitoring and treatment conditions, and safety in high-risk populations, particularly regarding cardiovascular risk.

PLAIN LANGUAGE SUMMARY

Anti-vascular endothelial growth factor for diabetic macular oedema

Background

Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. The retina at the macula thickens and this can cause gradual loss of central vision. Grid or focal laser photocoagulation is effective in treating DMO and has been used for several years, but vision is rarely improved.

Review question

We have reviewed the evidence on antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) modalities to try to improve vision in people with DMO. Anti-VEGF drugs are delivered by an injection in the vitreous cavity of the eye and need to be repeated for maintenance. We primarily measured the proportion of people improving or losing vision by three or more lines.

Search date

This evidence is current to 28 April 2014.

Study characteristics

We included 18 studies in this review. These studies compared antiangiogenic therapy with macular laser photocoagulation (10 studies, 1333 participants) or compared antiangiogenic therapy with sham treatment (three studies, 497 participants). Four studies (919 participants) assessed the effect of antiangionetic therapy combined with photocoagulation compared to photocoagulation alone.

Study funding sources

Ten out of 18 studies were funded by the manufacturer.

Key results

About one in five more people gained a good amount of vision, that is 3 lines, using antiangiogenic therapy compared with laser, using seven to nine intraocular injections in the first year, and three or four injections in the second year. Benefits were also detected when the drug was compared to no treatment and when it was added to photocoagulation and compared to photocoagulation alone.

Antiangiogenic treatment was well tolerated in these studies, with few reported injection-related adverse events and no increase in the number of reported overall and cardiovascular adverse events.

Quality of the evidence

Although aspects of some studies were judged to be at potential risk of bias, overall the evidence in this review was of high quality regarding efficacy compared to laser photocoagulation, the standard treatment, because the effects were large and consistent between studies. The evidence was also of moderate quality regarding safety, since safety had to be confirmed in patients with higher morbidity, particularly regarding cardiovascular risk.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Anti-VEGF versus laser for diabetic macular oedema

Patient or population: people with diabetic macular oedema
Settings: Ophthalmology clinics
Intervention: anti-VEGF
Comparison: laser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Anti-VEGF versus laser				
Gain 3+ lines of visual acuity at 1 year	77 per 1000	**276 per 1000** (207 to 368)	**RR 3.6** (2.7 to 4.8)	1333 (10 studies)	⊕⊕⊕⊕ **high**[1]	Overall heterogeneity: I^2 = 0% Test for subgroup drug differences: P value 0.80
Loss 3+ lines of visual acuity at 1 year	115 per 1000	**13 per 1000** (6 to 28)	**RR 0.11** (0.05 to 0.24)	1086 (7 studies)	⊕⊕⊕⊕ **high**[1]	Overall heterogeneity: I^2 = 0% Test for subgroup drug differences: P value 0.56
Visual acuity at 1 year	**no change (0 logMAR, median value)**	The mean visual acuity at 1 year in the intervention groups was **-0.16 logMAR better** (-0.14 to -0.18 better)		1292 (9)	⊕⊕⊕⊕ **high**[1]	Overall heterogeneity: I^2 = 59% Test for subgroup drug differences: P value < 0.001
Central macular thickness at 1 year	**67 μm lower (median value)**	The mean central macular thickness at 1 year in the intervention groups was		1215 (8)	⊕⊕⊕⊕ **high**[1]	Overall heterogeneity: I^2 = 68% Test for subgroup drug differences: P value < 0.

	78.8 μm lower (94.6 to 63.1 μm lower)		001

Adverse events: see Summary of findings 2

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

1 Although some studies had some domains that were judged to be at risk of bias we did not downgrade because the effect size was large, precise and consistent between studies. Although I^2 was relatively high for mean visual acuity and central macular thickness all results were in the same direction and in most studies statistically significantly in favour of anti-VEGF treatment.

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 and an increase in vascular permeability (Antcliff 1999). The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (Williams 2004) reported that within five years of diagnosis 0% of type I patients showed evidence of DMO compared with 29% after 20 years (Klein 1984). Similarly, within five years of diagnosis only 3% of type II patients presented with DMO compared with 28% after 20 years. In this Wisconsin population the four-year incidence of clinically significant macular oedema (CSMO) was 4.3%, 5.1%, and 1.3% in type I, insulin-treated type II, and non-insulin treated type II patients respectively. The 10-year incidence was 20.1%, 25.4%, and 13.9% respectively in these groups (Klein 1984). The presence of DMO has been associated with longer duration of diabetes, higher systolic blood pressure, insulin use, diuretic use, male gender, higher glycosylated haemoglobin and presence of proteinuria (abnormal presence of proteins in urine) (Klein 1984).

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).

CSMO, as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), presents with the following characteristics: 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). Chronic DMO can be associated with cystic degeneration of the macular retina, called cystoid macular oedema (CMO). Fluorescein angiography (FA) can be useful to assess the integrity of the blood retinal barrier as the amount of fluorescein leakage is related to the dysfunction of the retinal vascular endothelium. Apart from being a significant diagnostic modality, FA improves the accuracy of laser treatment of DMO (Kylstra 1999). With FA, DMO could be divided into two subtypes: focal and diffuse. Focal DMO is caused primarily by focal leakage from individual microaneurysms or small clusters of microaneurysms and dilated retinal capillaries (Cunha-Vaz 1998), often demarcated by hard exudates. Diffuse DMO is characterised by generalised leakage from extensive areas of the posterior retinal capillary bed, a generalised breakdown of the inner blood-retinal barrier (Aroca 2004). Retinal ischaemia is often a major complicating feature of diabetic maculopathy and it can easily be visualised on FA. Different degrees of capillary nonperfusion can be observed in the oedematous diabetic macula; and when the ischaemia is extensive the visual prognosis is generally poor (Bresnick 1976; Bresnick 1984; Ticho 1973). From the point of view of aetiology and pathogenesis, DMO can be classified according to the presence of a tractional component or taut attached posterior hyaloid component. In those cases OCT is useful in documenting the presence of a thick, taut, premacular posterior hyaloid or vitreous strands that contribute to DMO and may benefit from vitrectomy (Harbour 1996; Lewis 1992). Recently, 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).

Description of the intervention

The ETDRS demonstrated that immediate focal photocoagulation reduced moderate visual loss by 50% (from 24% to 12%, three years after initiation of treatment), even if 12% of treated eyes still lost $\geq$ 15 ETDRS letters at the three-year follow-up interval. Approximately 40% of treated eyes that had retinal thickening involving the centre of the macula at baseline still had thickening involving the centre at 12 months, as did 25% of treated eyes at 36 months. Furthermore, only 3% of laser-treated eyes experienced a gain of $\geq$ 3 lines of vision (ETDRS 1985). This suggests the existence of a distinct subgroup of eyes with DMO resistant to conventional laser photocoagulation, in particular eyes with diffuse DMO (Bresnick 1983; ETDRS 1985; Ferris 1984; Ladas 1993; Lee 1991).

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).

Vitrectomy is considered in patients with progression of visual loss despite laser photocoagulation treatment and in patients with

DMO associated with a thickened, taut, posterior hyaloid or other tractions (epiretinal membrane).

Anti-vascular endothelial growth factor (VEGF) treatments were originally hypothesised as an alternative adjunctive treatment for DMO (Cunningham 2005), following recent evidence that VEGF-A plays a key role in the occurrence of increased vascular permeability in ocular diseases such as DMO (Aiello 2005). At present, different types of VEGF antagonists are available and they have increasingly replaced laser photocoagulation for DMO (Jampol 2014). All these drugs inhibit VEGF angiogenic activity, binding to VEGF protein and thus preventing its receptor activation or interaction. Pegaptanib (Macugen, Eyetech Pharmaceuticals, Inc., New York, NY) is an example of an anti-VEGF drug. It is a pegylated aptamer, a chemically synthesised short strand of a ribonucleic acid (RNA) molecule that targets only the VEGF 165 isoform, and it is currently approved for the treatment of neovascular age-related macular degeneration (AMD) (Gragoudas 2004; Solomon 2014). Phase II and III trial results in DMO have been reported recently (Cunningham 2005; Macugen 2011). Another example of an anti-VEGF antagonist is ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA), a humanised monoclonal antibody fragment that binds all active forms of VEGF-A (Presta 1997). It is currently approved for the treatment of neovascular AMD, diabetic macular oedema, macular oedema in retinal vein occlusion (RVO) and choroidal neovascularisation due to pathologic myopia (Campochiaro 2010; Brown 2011; Brown 2010; Campochiaro 2011; Ferrara 2006; RESOLVE 2010; RESTORE 2011; Rosenfeld 2006). Bevacizumab (Avastin, Genetech Inc., San Francisco, CA) is a full-length humanised antibody that binds to all types of VEGF and is used successfully in tumour therapy as a systemic drug (Ferrara 2004). Recent studies have suggested the potential usefulness of off-label intravitreal injections of bevacizumab in the reduction of macular oedema secondary to central retinal vein occlusion, DMO and the decrease of vascular permeability and fibrovascular proliferation in retinal neovascularisation secondary to proliferative DR and choroidal neovascularisation secondary to AMD (Arevalo 2007; Avery 2006; Iturralde 2006; Spaide 2006). Recently aflibercept (Eylea, Regeneron-Bayer HealthCare), a new, fully human recombinant fusion protein designed to bind all isoforms of VEGF-A as well as placental growth factor (PGF), thereby inhibiting the binding and activation of VEGF receptors, has been evaluated in phase II and III trials on people with AMD (Heier 2011) and RVO (Ogura 2014); it has been approved for such indications. The phase II and III trials to evaluate the efficacy and safety of aflibercept on DMO have recently been published (DA VINCI 2011, Korobelnik 2014).

How the intervention might work

VEGF-A 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 in a selective or nonselective manner, or both.

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 aim of this review was to investigate the effects in preserving and improving vision and acceptability, including the safety, compliance with therapy and quality of life, of antiangiogenic therapy with anti-VEGF modalities for the treatment of DMO.

Since antiangiogenic therapy is widely approved for treatment of DMO, in the 2014 updated version of this review we have no longer reviewed cost-effectiveness.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled clinical trials (RCTs) to investigate efficacy and safety.

Types of participants

We included people with DR and CSMO causing significant sight loss. We defined CSMO as: thickening of the retina located $\leq$ 500 μm from the centre of the macula; hard exudates with thickening of the adjacent retina located $\leq$ 500 μm from the centre of the macula; a zone of retinal thickening of one disc diameter or larger in size located < one disc diameter from the centre of the macula. We considered that recent studies on anti-VEGF drugs could use definitions that incorporated or were centred on OCT.

Types of interventions

Any antiangiogenic drug with anti-VEGF modalities compared with another treatment, sham treatment or no treatment. We also included comparisons between different anti-VEGF drugs in this review. However, we did not consider intravitreal steroids as a

comparator because another Cochrane review has been published on this subject (Grover 2008).

Regarding dose and regimens, we extracted data for schemes that were more similar to EU and USA approved labels, as follows.

For ranibizumab, the EU label prescribes a 0.5 mg dosage, and "treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended. Thereafter patients should be monitored monthly for visual acuity", accessed on EMA on 28 August 2014. In the USA, ranibizumab "0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)", accessed on FDA on 28 August 2014.

Aflibercept has been approved in the USA, as accessed on REGENERON on 28 August 2014, 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). In the second year, a "treat-and-extend" regimen can be adopted where treatment interval may be extended based on visual and anatomic outcomes".

Bevacizumab is used off-label and we extracted the available data.

Types of outcome measures

Primary outcomes

Best-corrected visual acuity (BCVA) measured after one year (plus or minus six months). The proportion of patients with at least 15 ETDRS letters, that is 3 ETDRS lines or 0.3 logMAR, of worsening and improvement were analysed.

Secondary outcomes

Other functional measures: contrast sensitivity; quality of life evaluated with specific questionnaires.

Anatomic measures: presence of macular oedema with stereoscopic fundus photography or biomicroscopy; assessment of retinal macular thickness with optical coherence tomography (OCT); presence of leakage on fluorescein angiography (FA).

Safety: frequency and severity of ocular and systemic adverse events.

Measurements at varying lengths of follow-up were pooled at annual intervals, plus or minus six months, the primary analysis being that at one year. The time point closer to one year, or the latest time point in the window frame in the case of symmetry, was chosen where multiple time points were available.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to April 2014), EMBASE (January 1980 to April 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to April 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 April 2014.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (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 (http://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 (a) definitely include and (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 (3) excluded were excluded and documented in the review. Studies identified as (1) 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 (RevMan 2014.) The entered data were checked by a second author.

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 as specified in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions*. As reported in the Handbook, other sources of bias were: risk of bias related to the specific study design used; or trial stopped early due to some data-dependent process (including a formal stopping rule); or an extreme baseline imbalance; or the study claimed to have been fraudulent. 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 planned that if they did not respond within six months we would classify the trial based on the available information. However, in the latest update of this review we awaited unpublished information for no longer than one month.

Regarding the overall quality of evidence for each outcome included in the summary of findings table, we followed guidance in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schunemann 2011). To assess precision, we considered both the width of the 95% confidence interval (CI) and the Optimal Information Size according to Guyatt 2011, that is a sufficient number of participants is included in the meta-analysis to have 80% power to detect 1/3 control risk reduction, or 1/4 increase, using conventional sample size calculations for RCTs.

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). The primary outcome was the proportion of patients with at least 15 letters improvement or, separately, at least 15 letters worsening in visual acuity at one year (separate analyses). For dichotomous outcomes we calculated a summary risk ratio (RR). We also reported the risk difference (RD) and number needed to treat (NNT). We calculated the mean difference (MD) for continuous outcomes. We planned to calculate a standardised mean difference (SMD) if different scales had been used to measure any continuous outcomes. Continous measures were pooled provided that they were not very skewed, such as when the distance between the mean value and its maximum or minimum physical limit was larger than the standard deviation.

Dichotomous outcome measures were the primary outcome measures, as previously defined, the presence of macular oedema and presence of leakage on FA.

Since other secondary outcome measures were variably reported, we considered both dichotomous (as defined by the investigator) and continuous measures (as the mean or mean change from baseline) for contrast sensitivity, quality of life and retinal macular thickness with OCT.

Unit of analysis issues

The unit of randomisation was the eye of individual participants. If studies using a paired design are found for future updates of this review, that is studies assigning one eye to treatment and the fellow eye to control, the generic inverse variance method will be used to combine the results of such studies with those of studies randomising only one eye of each participant. However, these studies have special problems. First, comparisons between treatment and control regarding systemic adverse events cannot be made. Second, they need to be properly analysed by taking into account within-patient correlation statistically, which would otherwise result in incorrect variance estimation at least. Third, methods for random assignment of either eye to treatment must be made explicit.

We decided to include studies with eyes, not individuals, as the unit of analysis in the main meta-analysis and then conduct a sensitivity analysis excluding studies with paired design from the primary outcome. Such studies were also excluded from analyses of systemic adverse events.

Dealing with missing data

Where data were missing due to dropping out of participants, we conducted a primary analysis based on patients with complete data (available case analysis). Although in the protocol we planned to conduct a sensitivity analysis with missing imputation based on the worst-case and best-case scenarios, given the further guidance available in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), we considered that missing outcome data are not a problem if both loss to follow-up is balanced in the study arms and causes of loss to follow-up are documented and judged to be unrelated to outcome in both study arms. When causes of missingness were not available for the majority of studies, we planned to use the Stata 10.2 software (StataCorp, College Station, Tx) user written function *metamiss* to take into account missing data and conduct sensitivity meta-analyses if sufficient studies were found. The underlying theory and a link to download *metamiss* are provided in White 2008. In the update

of this review we felt such an approach was not needed and relied on risk of bias assessment.

Assessment of heterogeneity

We looked for clinical heterogeneity by examination of the study details then tested for statistical heterogeneity between trial results using the Chi^2 test and the I^2 statistic (Deeks 2011) if a meta-analysis of three or more studies was possible. We considered I^2 values of more than 50% to be substantial heterogeneity, but we were aware that I^2 estimates are very uncertain when few studies are included in a meta-analysis. We considered sources of heterogeneity related to study design, such as paired studies (that is randomising one eye of the participant to one treatment and then assigning the fellow eye to the alternative treatment) versus studies including only one eye of each participant. Clinical sources of heterogeneity to be considered in future updates are type of diabetes (type I versus type II), lower versus higher baseline visual acuity, longer versus shorter duration of diabetes, and baseline central retinal thickness more than 400 µm versus less, if subgroup data are reported.

Assessment of reporting biases

In future updates of this review, we plan to prepare a funnel plot to examine other sources of heterogeneity if 10 or more studies can be combined in a meta-analysis.

We investigated selective outcome reporting by preparing an 'outcome matrix' and classifying missing outcomes according to the following classification adapted from a list provided by Williamson 2010.

A: states outcome analysed but only reported the P value > 0.05 i.e. not significant.

B: states outcome analysed but only reported that P < 0.05.

C: clear that outcome was analysed but insufficient data presented to be included in the meta-analysis or full tabulation.

D: clear that outcome was analysed but no results reported.

E: clear that outcome was measured (e.g. includes structurally-related outcomes) but not necessarily analysed.

F: states that outcome was not measured.

G: not mentioned but clinical judgement says likely to have been measured.

H: not mentioned but clinical judgement says unlikely to have been measured.

I: other (give details).

Data synthesis

We used the following criteria to synthesise the data. 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 (that is I^2 value more than 50%) or clinical heterogeneity we did not combine study results but presented a narrative or tabulated summary of each study, with similar rules applied to subgroups represented by drug type. However, if substantial statistical heterogeneity was detected (that is a high I^2 value), we pooled the results of the studies if examination of the forest plot indicated that 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).

Regarding drug type, we chose to present all drugs in the same forest plot, using subgroups to be able to test for subgroup differences. We were aware of the fact that there was little power to test for subgroup difference given the small number of studies included in this review. Moreover, when only one study per drug is available, any differences can be due to known or unknown study characteristics rather than to drug effect. Thus, readers are invited to examine individual drug groups, as well as pooled estimates, considering the significance of the test for subgroup differences and overall heterogeneity. Additionally, we used random-effects logistic regression models with studies as random-effects (*melogit* command in Stata 13.1 software, StataCorp, College Station, TX) to explore differences among antiangiogenic drugs and obtain a relative odds ratio (OR), both regarding the gain of 3 or more lines. These analyses should be considered exploratory.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were carried out to investigate heterogeneity, especially regarding drug type. If more data are available in future updates, other subgroups will be based on: baseline visual acuity; baseline macular oedema severity defined by OCT thickness; and adequacy of glycaemic control. See above for our decisions regarding drug type subgroups.

Sensitivity analysis

If more studies are available for each drug in future updates of this review, we will conduct sensitivity analyses to determine the impact of exclusion of studies with lower methodological quality, exclusion of unpublished studies, and exclusion of industry-funded studies.

RESULTS

Description of studies

See 'Characteristics of included studies'; 'Characteristics of excluded studies'; 'Characteristics of ongoing studies'.

Results of the search

Previous searches

2009

The search strategy was designed to be broad and inclusive, including terms for diabetic retinopathy and macular oedema. The electronic searches retrieved a total of 1733 citations. The Trials Search Co-ordinator scanned these search results and removed references which were not relevant to the scope of the review. A total of 56 citations were forwarded to the authors for assessment for inclusion in the review. Six full-text papers were obtained, of which four studies were eligible for inclusion (Ahmadieh 2008; Macugen 2005; Paccola 2008; Soheilian 2007), but two of the potentially relevant studies were excluded because of the follow-up of less than six months (DRCRnet 2007; Faghihi 2008) (see 'Characteristics of excluded studies' table).

2012

An update search was undertaken in June 2012 which yielded 681 citations. The Trials Search Co-ordinator scanned these search results and removed 593 references which were not relevant to the scope of the review. We screened the remaining 183 records and obtained full-text records of 27 references. We assessed nine full-text reports and included the following studies: BOLT 2010; DA VINCI 2011; DRCRnet 2010; Macugen 2011; READ2 2009; RESOLVE 2010; RESTORE 2011; RISE-RIDE; Soheilian 2007. A report of the DA VINCI 2011 study published in 2012 was not retrieved by the search at that time, however the authors were aware of this publication and included it in the review.

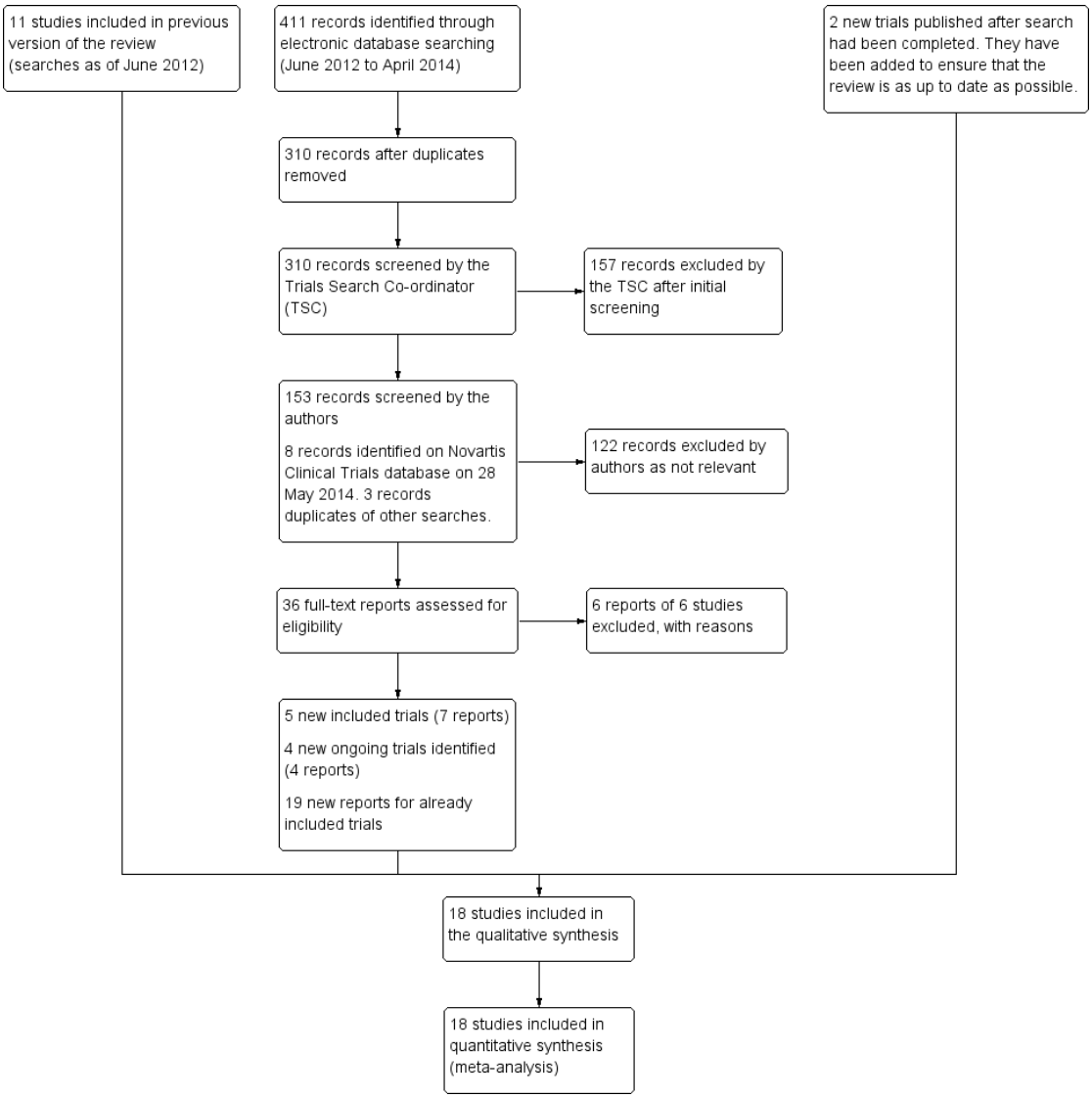
We identified 18 ongoing studies; two of these 18 studies, which were ongoing in 2012, are now included in the current update (LUCIDATE 2014; NCT01131585 (RELATION)) and one study is awaiting assessment (NCT01171976 (RETAIN)).

We excluded three studies (DRCRnet 2011; DRCRnet 2012; Solaiman 2010). A new potentially interesting study (Solaiman 2010) was excluded because a single bevacizumab injection was delivered by design. For the same reason, as well as because intravitreal triamcinolone was the comparator, we excluded Paccola 2008 which was included in the original version of this review (see the 'Characteristics of excluded studies' table).

Searches for current update

An update search run in April 2014 identified a further 411 references (Figure 1). The Trials Search Co-ordinator removed 101 duplicates and screened the remaining 310 references, of which 157 were not relevant to the scope of the review. We searched the Novartis clinical trials database and after de-duplication found five additional records. We reviewed 158 references and discarded 122 reports as not relevant. We obtained 36 full-text reports for potential inclusion in the review and included seven reports of five new studies (Azad 2012; Ekinci 2014; Nepomuceno 2013; NCT01131585 (RELATION); RESPOND 2013). We also found 19 new reports for studies which are already included in the review. We excluded six studies (Ahmadieh 2013; CRFB002DFR08 (LUDIC); CRFB002DNO02 (PTIMAL); CRFB002DGB14 (RELIGHT); Zehetner 2013; Zhang 2013). We identified three new ongoing trials (ChiCTR-TRC-12002417; NCT01635790 (BRDME); NCT01845844 (ROTATE)). Finally, we included Korobelnik 2014 and LUCIDATE 2014, which were found using other sources as they became available after our electronic searches were conducted.

Figure 1. #Results from searching for studies for inclusion in the review.



Included studies

We included a total of 18 studies in this updated review. BOLT 2010; DA VINCI 2011; DRCRnet 2010; Korobelnik 2014; Macugen 2005; Macugen 2011; READ2 2009; NCT01131585 (RELATION); RESOLVE 2010; RESPOND 2013; RESTORE 2011; RISE-RIDE were industry-sponsored, multicentre RCTs conducted in the USA or Europe. Ahmadieh 2008; Azad 2012; Ekinci 2014; LUCIDATE 2014; Nepomuceno 2013; Soheilian 2007 were independent studies conducted in Iran, India, UK, Turkey, Brasil and Iran, respectively; five of which included bevacizumab. See the 'Characteristics of included studies' table for further information.

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, since this comparison is the subject of another Cochrane Review (Grover 2008). Moreover, in the 2014 update we did not update economic evidence since antiangiogenic therapy is now widely approved for the treatment of DMO.

Types of participants

Studies included participants with DMO diagnosed clinically, and often used OCT for confirmation of macular centre involvement. Baseline visual acuity was generallybetween 20/200 and 20/40. The number of participants and other characteristics are given for each comparison in the following sections.

There was variability regarding the inclusion of participants with previous macular laser photocoagulation since Ahmadieh 2008, BOLT 2010 and Ekinci 2014 included participants who had received laser and were unresponsive, while Soheilian 2007 excluded participants with previous laser treatment. Most of the other studies required a three to six-month interval from previous central or peripheral laser, as well as that no previous antiangiogenic treatment had been received.

Types of interventions

Eight studies assessed ranibizumab (DRCRnet 2010; LUCIDATE 2014; READ2 2009; NCT01131585 (RELATION); RESOLVE 2010; RESPOND 2013; RESTORE 2011; RISE-RIDE), 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 USA and Europe using the same protocol, which we will refer to as a single study, Korobelnik 2014). The drug dose was identical in all 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 RISE-RIDE where 0.3 mg ranibizumab was also delivered.

Anti-VEGF treatment regimens were monthly for ranibizumab in RISE-RIDE. 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 data extraction because this is current practice with other anti-VEGF drugs. 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) (treatment regimen 'treat-and-extend' in year two, but results are not available yet). We selected 2q8 for extraction because the total number of injections in the first year was lower and this is more similar to PRN regimens of most other studies, and because it is the regimen approved in the USA. Ahmadieh 2008 was a short-term study which delivered only the first three injections. All other studies adopted three initial injections followed by various maintenance regimens.

PRN retreatment criteria were based on: visual acuity only in Nepomuceno 2013; OCT only in BOLT 2010, Macugen 2011 and READ2 2009; OCT and visual acuity in Azad 2012, DRCRnet 2010, 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 NCT01131585 (RELATION) and RESPOND 2013.

The average numbers of injections in each study are summarised in Table 1.

Types of outcomes

Completeness of reporting of our primary outcomes can be seen in Table 2. Out of 18 studies with six to 12 months of follow-up, 15 reported visual gain of 3 or more lines and 11 reported visual loss. At 24 months, four out of five studies reported such measures.

Among secondary outcomes, mean BCVA was reported by 16 out of 18 studies at six to 12 months. Azad 2012 reported only values rounded up to the nearest Snellen equivalent. Ekinci 2014 reported baseline and final decimal visual acuity, which were converted to logMAR to extract the change in logMAR visual acuity, but SDs had to be imputed from Nepomuceno 2013 since conversion was inappropriate.

Mean change of OCT retinal thickness was reported by 15 studies at six to 12 months. Two large studies with two-year follow-up did not give one-year data (Macugen 2011; RISE-RIDE) and Azad 2012 did not provide data. Mean change was derived as a difference in LUCIDATE 2014 and SDs of the mean final values were used conservatively.

Excluded studies

See 'Characteristics of excluded studies' table.

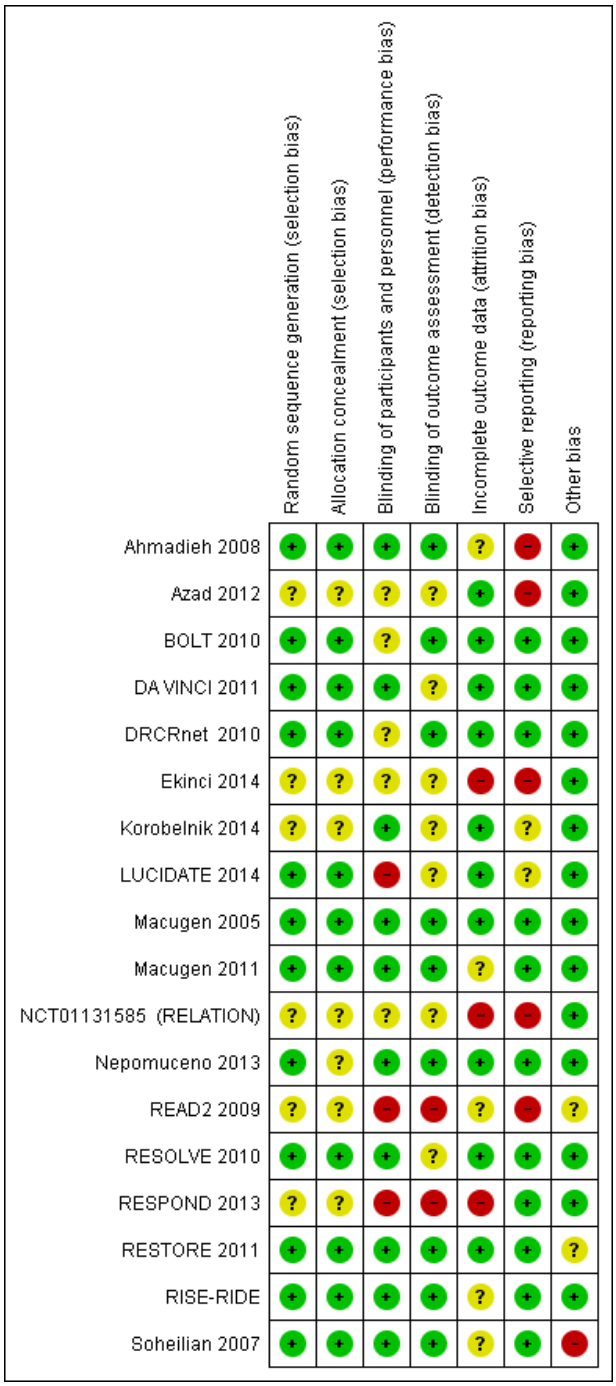
DRCRnet 2007 and Faghihi 2008 were excluded because the follow-up was too short. Solaiman 2010 and Paccola 2008 were excluded since a single antiangiogenic drug injection was delivered, which is an insufficient regimen. In addition, Paccola 2008 and Lim 2012 compared bevacizumab with triamcinolone, a comparison which we did not consider in this updated review. DRCRnet 2011 assessed the short-term effect of ranibizumab (two injections) or triamcinolone (one injection) compared with sham in patients with centre-involved DMO and proliferative diabetic retinopathy (DR) undergoing both grid and panretinal laser photocoagulation, finding an advantage of about 1 Snellen line with pharmacological treatment. Finally, DRCRnet 2012 compared the effect of prompt versus deferred laser in patients with DMO who were also treated with ranibizumab, so the timing of laser was in fact investigated.

In the 2014 update we excluded six studies (Ahmadieh 2013; CRFB002DFR08 (LUDIC); CRFB002DNO02 (PTIMAL); CRFB002DGB14 (RELIGHT); Zehetner 2013; Zhang 2013). See Characteristics of excluded studies for the reasons for exclusion.

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 low risk of bias in 12 studies and was unclear in six (Azad 2012; Ekinci 2014; Korobelnik 2014; READ2 2009; NCT01131585 (RELATION); RESPOND 2013). Methods for allocation concealment were also unclear in these studies, as they were in Nepomuceno 2013.

Blinding

Masking of participants and outcome assessors was obtained in 10 and eight studies respectively, and was unclear in five and seven respectively. LUCIDATE 2014, READ2 2009 and RESPOND 2013 were unmasked.

Incomplete outcome data

Ten studies were judged to be at low risk of attrition bias (Azad 2012; BOLT 2010; DA VINCI 2011; DRCRnet 2010; Korobelnik 2014; LUCIDATE 2014; Macugen 2005; Nepomuceno 2013; RESOLVE 2010; RESTORE 2011) and unclear in five studies in which participants were missing but causes of missingness were not fully reported (Ahmadieh 2008; Macugen 2011; READ2 2009; RISE-RIDE; Soheilian 2007). Three studies were judged to be at high risk of attrition bias: Ekinci 2014 excluded 15 participants after randomisation due to ocular and systemic complications; NCT01131585 (RELATION)and RESPOND 2013 lost many more participants in the laser arm than in the ranibizumab arms.

Selective reporting

As reported above, most studies including larger studies reported our primary outcomes at 12 months, plus or minus six months (Table 2); we primarily considered such availability for GRADE assessment of this bias, even if there were discrepancies between the protocol and published study. Reporting was complete regarding visual gain for the comparison of anti-VEGF versus laser treatment, our main analysis; which was not available in only one small study (Ahmadieh 2008). Because effects consistently favoured antiangiogenic therapy we did not downgrade the quality of other key outcomes, mean visual acuity and central macular thickness, even if they were not completely reported in this and other comparisons.

Only five studies reached two years of follow-up (BOLT 2010; DRCRnet 2010; Macugen 2011; READ2 2009; RISE-RIDE), four of which reported our primary outcomes (BOLT 2010; DRCRnet 2010; Macugen 2011; RISE-RIDE), which we believe is at low risk of bias.

Other potential sources of bias

Soheilian 2007 suffered from an imbalance of visual acuity across groups at baseline since the bevacizumab and bevacizumab-triamcinolone arms were around 20/100 and eyes assigned to laser were around 20/70, suggesting that milder CSMO was included in the laser group. The trial investigators adjusted for baseline values in analyses on mean change of visual acuity, 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.

Ahmadieh 2008 included 14 participants (14%) and Nepomuceno 2013 included 15 participants (33%) with both eyes in the analyses.

NCT01131585 (RELATION) was terminated early when ranibizumab was approved for DMO in Germany, but this was assumed not to be related to treatment effect.

No other source of bias was found in other studies.

Effects of interventions

See: **Summary of findings for the main comparison** Anti-VEGF versus laser for diabetic macular oedema; **Summary of findings 2** Adverse events: Anti-VEGF compared with control for diabetic macular oedema

Anti-VEGF versus laser

Eleven studies compared anti-VEGF versus laser photocoagulation.

Three (249 participants) of these 11 studies used bevacizumab (Azad 2012; BOLT 2010; Soheilian 2007), five studies (1529 participants) used ranibizumab (DRCRnet 2010; READ2 2009; NCT01131585 (RELATION); RESPOND 2013; RESTORE 2011), and three studies (1120 participants) used aflibercept (DA VINCI 2011, Korobelnik 2014; LUCIDATE 2014).

Soheilian 2007 delivered an unusually low number of bevacizumab injections (3.1 ± 1.6 in two years), but the results were comparable to other studies.

Korobelnik 2014 provided data on one-year outcomes for two aflibercept regimens compared to laser: 2 mg monthly (2q4), and five initial injections followed by bimonthly injections (2q8). We used the latter for our main meta-analysis since the total number of injections was lower and more similar to other included studies. Furthermore, this is the registered regimen in the USA.

Data on the primary outcomes were available for 10 of these studies for visual gain and seven of these studies for visual loss. The results are summarised in Summary of findings for the main comparison.

Primary outcomes at one year

Compared to people treated with laser photocoagulation, people receiving antiangiogenic therapy were more likely to gain 3 or more lines of visual acuity over one year (RR 3.60, 95% CI 2.70 to 4.80, 1333 participants, 10 studies; I^2 = 0%) (Figure 3) and less likely to lose 3 or more lines of visual acuity (RR 0.11, 95% CI 0.05 to 0.24, 1086 participants, 7 studies; I^2 = 0%) (Figure 4).

Figure 3. Forest plot of comparison: 1 Anti-VEGF versus laser, outcome: 1.1 Gain 3+ lines of visual acuity at 1 year.

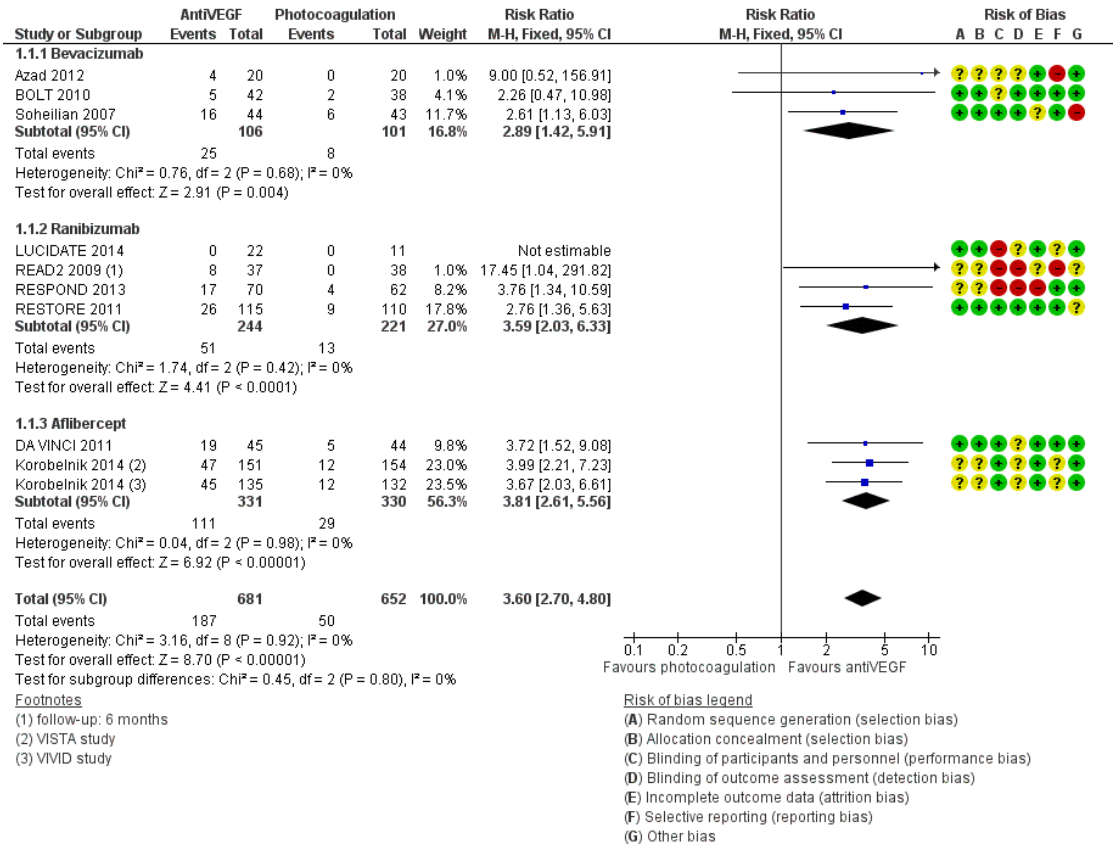
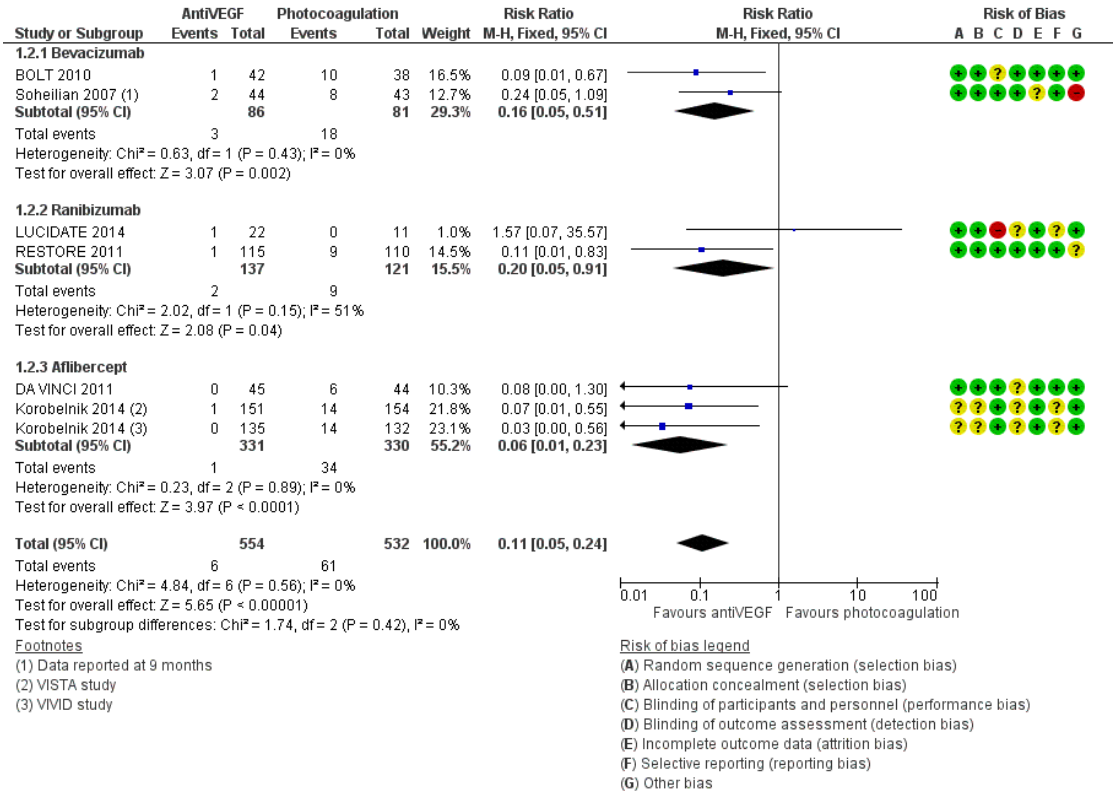


Figure 4. Forest plot of comparison: 1 Anti-VEGF versus laser, outcome: 1.2 Loss 3+ lines of visual acuity at 1 year.



There were no statistically significant differences between type of anti-VEGF, but the power to detect such a difference may have been limited in the meta-analysis.

In terms of absolute effects, 5 people (95% CI 3 to 8) had to be treated with antiangiogenic therapy, compared to laser, to allow one person to markedly improve their vision.

Secondary outcomes at one year

Secondary outcomes also favoured antiangiogenic therapy (Analysis 1.3; Analysis 1.4; Analysis 1.5). A significant subgroup difference (P < 0.001) was found between bevacizumab, ranibizumab and aflibercept regarding mean visual change versus photocoagulation, which was around 1 ETDRS line for ranibizumab in LUCIDATE 2014, READ2 2009, RESPOND 2013 and RESTORE 2011 versus 2 lines for bevacizumab in BOLT 2010 and Soheilian 2007 and aflibercept in DA VINCI 2011 and Korobelnik 2014 (Analysis 1.3). The reduction of retinal thickening with OCT also favoured anti-VEGF treatment over laser photocoagulation (Analysis 1.4) with significant drug differences (P < 0.001), the largest reduction achieved by aflibercept.

RESTORE 2011 reported quality of life findings at one year using the National Eye Institute Visual Function Questionnaire (NEI-VFQ score) and showed a benefit of about 4.4 units (95% CI 1.33 to 7.47) favouring ranibizumab (Analysis 1.5).

Outcome at two years

Regarding anti-VEGF versus laser, only one study of bevaciuzmab (BOLT 2010) reported complete two-year data. This study confirmed the increased chance of improving vision with bevacizumab (RR 9.08, 95% CI 1.25 to 65.77, 65 participants) (Analysis 1.6). People receiving anti-VEGF were less likely to lose vision but the number of events was small and the effect uncertain (RR 0.08, 95% CI 0.00 to 1.51, 65 participants) (Analysis 1.7).

BOLT 2010 and Soheilian 2007 provided data at this time point for mean change of visual acuity, which showed a benefit of about 1.5 lines of vision favouring bevacizumab over laser (MD -0.14 logMAR, 95% CI -0.24 to -0.05, 142 participants; I^2=29%) (Analysis 1.8). Central macular thickness at two years was slightly lower in the anti-VEGF group but the CI around the MD included

0 and therefore the effect of anti-VEGF treatment on macular thickness at two years was uncertain (MD -18.35 μm, 95% CI -62.23 to 25.52, 142 participants, 2 studies; I^2 = 0%) (Analysis 1.9).

Two-year data from RESTORE 2011 were published but participants in the laser arm could receive rescue ranibizumab after one year, which made it impossible to include long-term data on the effect of ranibizumab versus laser photocoagulation for the PRN regimen.

Quality of the evidence

Differently from the previous version of this review, in this update we assessed the quality of evidence separately for the main question, that is overall effectiveness of any anti-VEGF treatment, and for the question on differences between antiangiogenic drugs. A similar efficacy of different drugs has been demonstrated for some agents in AMD (CATT 2011; CATT 2012; Schmidt-Erfurth 2014). In the update of this review, we acknowledge that the ability to investigate heterogeneity due to drug differences in efficacy and safety is a further question, preferentially dealt with in network meta-analysis exploiting both direct and indirect comparisons. The response to such a question will be largely supported by the Diabetic Retinopathy Clinical Research Network (DRCRnet) ongoing multicentre study (NCT01627249) entitled 'A Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab and Ranibizumab for Diabetic Macular Edema'. See a following paragraph presenting the results of subgroup analyses.

The overall quality of the evidence for the effects of anti-VEGF treatment was high (Summary of findings for the main comparison). Although some individual studies were judged at high or unclear risk of bias for some domains, RRs of visual gain were all large (> 2) and RRs of visual loss were all small (< 0.5), and they were consistent between studies. Moreover, although the meta-analysis did not meet 'Optimal Information Size criteria' according to Guyatt 2011, the overall effect was large (RR > 2 or < 0.5) and precisely estimated. Thus, no quality downgrade was applied.

Anti-VEGF versus sham treatment

Five studies compared anti-VEGF with sham treatment at one year. Two studies (460 participants) used pegaptanib (Macugen 2005; Macugen 2011), two studies (910 participants) used ranibizumab (RESOLVE 2010; RISE-RIDE) and one study (101 participants) bevacizumab (Ahmadieh 2008).

Macugen 2005 did not report on loss of 3 or more lines visual acuity but reported on loss of 2 or more lines. Ahmadieh 2008 reported mean visual acuity data at six months.

The studies presented above used less intensive or discontinuous regimens, while RISE-RIDE provided data on the comparison between monthly continuous ranibizumab and sham treatment at 24 months, but not at one year, also comparing 0.3 mg versus 0.5 mg doses.

It must also be considered that rescue grid laser was allowed in RESOLVE 2010 (35% sham, 5% ranibizumab) and RISE-RIDE (74% sham, 35% to 39% ranibizumab).

Primary outcomes at one year

People treated with anti-VEGF (pegaptanib or ranibizumab) were more likely to gain 3 or more lines of visual acuity (RR 2.19, 95% CI 1.36 to 3.53, 497 participants, 3 studies; I^2 = 0%) (Analysis 2.1) and less likely to lose 3 or more lines of visual acuity (RR 0.28, 95% CI 0.13 to 0.59, 411 participants, 2 studies; I^2 = 44%) (Analysis 2.2) compared to sham treatment. Effects were larger for ranibizumab than for pegaptanib, but no significant subgroup (treatment) effect was detected, although there was little power to do so with only three studies in the meta-analysis of which one study was small.

About nine people (95% CI 4 to 29) had to be treated with antiangiogenic therapy to allow one person to markedly improve vision compared to sham. Although this figure seemed less beneficial than the effect of antiangiogenic therapy versus laser, this may have been due to differences in study populations as well as to the fact that rescue laser was allowed in RESOLVE 2010, as previously explained.

Secondary outcomes at one year

A significant subgroup difference was found between bevacizumab, pegaptanib and ranibizumab for mean visual change, which was less than 1 ETDRS line for pegaptanib in Macugen 2005 and Macugen 2011 versus slightly more than 2 lines for ranibizumab in RESOLVE 2010 (Analysis 2.3). One small study comparing bevacizumab with sham treatment at six months (Ahmadieh 2008) found a mean benefit point estimate of 1.5 visual acuity lines, but this estimate was imprecise (Analysis 2.3). A similar trend, although not significant, was also found for the reduction of retinal thickening with OCT (Analysis 2.4).

Outcome at two years

RISE-RIDE compared monthly ranibizumab injections with sham treatment and found effects grossly similar to one-year data and superior to Macugen 2011 (Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.9).

Quality of life data (NEI-VFQ score) were available in Macugen 2011 and showed a benefit of about 4.5 units at two years, which was imprecisely estimated (Analysis 2.9; Analysis 2.10).

Quality of life data (NEI-VFQ 25 near and distance activity scales) were available only as mean values in Korobelnik 2014, except for one significant analysis, and could not be used.

Quality of the evidence

Overall quality of this evidence was high. Risk of bias was low for most items in the three studies which guided our conclusions for the primary outcome at about one year (Figure 2). Ahmadieh 2008 provided only mean visual acuity at six months, thus being subject to selective outcome reporting, and RISE-RIDE reported only two-year data in detail, although one-year data were also available. However, as previously stated for the comparison with grid laser, effects were large and consistent. Although there were few studies and the 'Optimal Information Size' was not met, results were consistent with those versus active control and we did not downgrade the overall quality.

Anti-VEGF plus laser versus laser

Five studies (919 participants) assessed the effect of ranibizumab additionally to prompt photocoagulation (DRCRnet 2010 (one study arm); READ2 2009; NCT01131585 (RELATION); RESPOND 2013; RESTORE 2011) or deferred photocoagulation (one study arm with 188 participants of DRCRnet 2010) compared with immediate photocoagulation alone. Because the two arms of DRCRnet 2010 used the same control arm, these subgroups were not pooled.

Primary outcomes at one year

The amount of relative benefit in combining ranibizumab with photocoagulation was about the same as that of ranibizumab alone compared with photocoagulation alone. Regarding gain of vision, no significant difference (P = 0.33) could be demonstrated between ranibizumab plus prompt photocoagulation (RR 2.37, 95% CI 1.76 to 3.21, 919 participants, 4 studies) versus plus deferred photocoagulation (RR 1.88, 95% CI 1.31 to 2.70, 481 participants, 1 study) (Analysis 3.1).

Secondary outcomes at one year

About 1 ETDRS line was gained using ranibizumab plus photocoagulation compared with photocoagulation alone, which was a consistent estimate (Analysis 3.3). The reduction of retinal thickness also favoured ranibizumab (Analysis 3.4).

Outcome at two years

Only the DRCRnet 2010 study provided dichotomous and continous data at this time point and found a significant benefit with ranibizumab combined therapy (Analysis 3.6; Analysis 3.7). Long-term OCT data were available from DRCRnet 2010 and showed no difference in retinal thickness (Analysis 3.9).

Quality of the evidence

The overall quality was high. Studies were also included in previous analyses and we used identical criteria for overall judgement.

Adverse events: antiangiogenic therapy versus control

Only Macugen 2011, RESOLVE 2010 and RISE-RIDE reported that the Medical Dictionary for Regulatory Activities (MedDRA) classification was used to code adverse events and that active safety data collection was used, whereas this was unclear for the other studies. We suggest that at least the industry-sponsored studies must have adopted such methods, to comply with regulatory standards.

Endophthalmitis and ocular adverse events (per patient data)

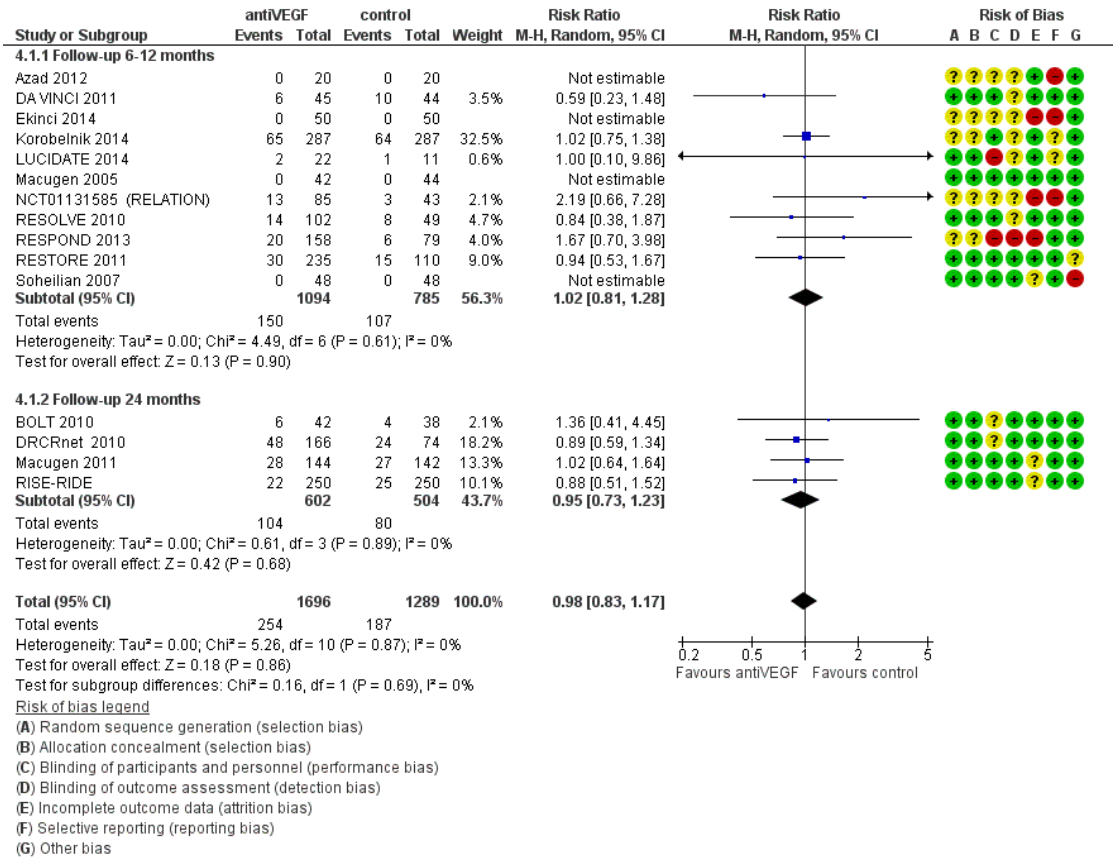
Endophthalmitis can occur within a few days after the intravitreal injection procedure. The number of intravitreal injections in the first year was generally 7 to 10 and the total number of injections in the first two years was 10 to 13 (Table 1). Because the planned number of injections was 24 in two years, the largest number of injections was found in RISE-RIDE, which adopted a monthly schedule (20 to 22 injections across groups). The RESTORE 2011 open-label study extension showed that a mean of 14.2 injections (median 12 injections) were delivered in the first three years of treatment in the prior ranibizumab monotherapy study arm. Rates of endophthalmitis due to intraocular injection were imprecisely estimated in these relatively small or medium sized RCTs since this is a rare adverse event (Table 3). There were only zero to three cases in each interventional study arm. The risk of this type of adverse event may be preferably studied by means of large non-comparative studies since it is procedure rather than drug-related, but the number of cases was very low in the studies included in this review. Other serious ocular adverse events such as retinal detachment were also extremely rare and were no longer reported in this update of the review.

Serious systemic adverse events

In the update of this review, we extracted and meta-analysed all serious systemic adverse events (SSAEs), as defined by the investigators, arterial thromboembolic events (including nonfatal myocardial infarction, nonfatal stroke, and death from a vascular or unknown cause, on the basis of the classification system of the Antiplatelet Trialists' Collaboration (ATC 1994)), and also overall mortality. Although SSAEs may be differentially defined across studies, the International Conference on Harmonisation Good Clinical Practice (ICH GCP) Guideline identifies SSAEs as medical occurrences that: result in death; are life threatening; require hospital admission or prolongation of hospital stay; cause persistent or significant disability and incapacity, a congenital anomaly or birth defect.

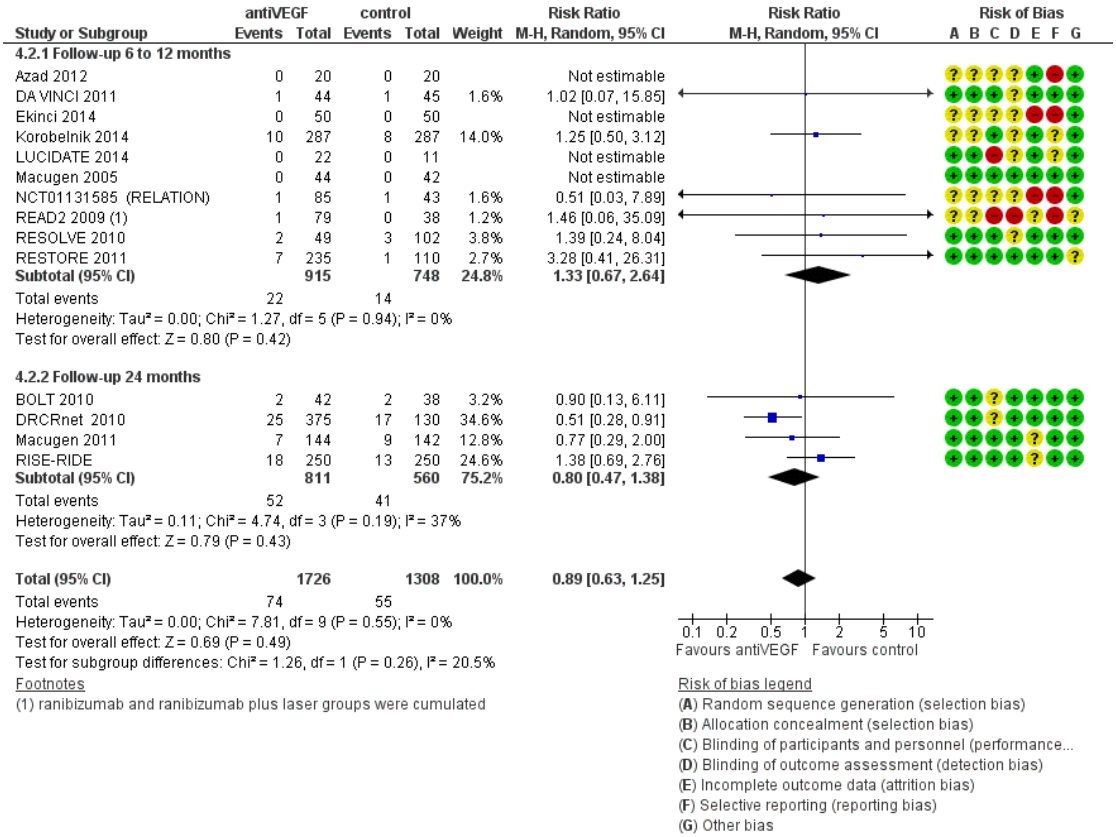
Overall, SSAEs were recorded in up to 20% of participants in the treatment and control arms, including all controls not using anti-VEGF drug. Data were extracted for the participants, rather than eyes, as the unit of analysis and were included in the meta-analysis. The estimate, based on 441 SSAEs in 2895 participants, excluded a moderate to large increased risk with anti-VEGF treatments compared to control (RR 0.98, 95% CI 0.83 to 1.17) (Figure 5; Analysis 4.1). Absolute differences presented in Summary of findings 2 excluded an increase by more than 3%, according to the 95% CI upper limit, which is below the 5% threshold suggested to be acceptable in another recently published systematic review of the safety of antiangiogenic therapy in AMD (Moja 2014).

Figure 5. Forest plot of comparison: 4 Adverse events: Anti-VEGF versus control, outcome: 4.1 Systemic serious adverse events.



The diabetic population included in these studies appeared to be at low risk of arterial thromboembolic events (less than 5% per year in each study arm). In 14 studies (3034 participants) there was no difference between anti-VEGF and controls for arterial thromboembolic events (129 events, RR 0.89, 95% CI 0.63 to 1.25) (Figure 6; Analysis 4.2; Summary of findings 2).

Figure 6. Forest plot of comparison: 4 Adverse events: anti-VEGF versus control, outcome: 4.2 Total ATC thromboembolic events at 6 to 24 months.



Similarly, no difference was apparent for overall mortality (63 events, RR 0.88, 95% CI 0.52 to 1.47) (Analysis 4.3); and clinically significant differences by more than 1% (Moja 2014) were excluded by the upper limit of the 95% CI estimate in Summary of findings 2.

The quality of evidence on adverse events was moderate since some studies excluded participants with previous cardiovascular adverse events and there were consistency problems, resolved by agreement, with extracting data from some studies. As discussed above, the precision of the estimates was considered adequate when both RR and absolute differences were jointly considered, thus no overall quality downgrade was applied despite the relatively small number of adverse events.

Other comparisons

Monthly ranibizumab dose 0.3 mg and 0.5 mg versus sham:

efficacy and safety

Monthly 0.3 mg ranibizumab injections are approved in the USA as a treatment regimen and this was a treatment arm, together with the 0.5 mg monthly dose, in RISE-RIDE, although the study was not powered to prove dose equivalence. The effects of the two doses were very similar in Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8, as acknowledged in RISE-RIDE. Since the safety of the higher dose (0.5 mg) was a potential problem, particularly for mortality, which led the Food and Drug Administration (FDA) to choose the lower ranibizumab dose (0.3 mg), we used logistic regression to compare the ORs for death with the two doses using data presented in Table 4. The respective ORs for 0.3 and 0.5 mg ranibizumab versus sham were 2.37 (95% CI 0.61 to 9.27) and 3.79 (95% CI 1.04 to 13.75) for death, 0.96 (95% CI 0.66 to 1.40) and 1.15 (95% CI 0.80 to 1.66) for SSAEs, and 1.08 (95% CI 0.50 to 2.35) and 1.41 (95% CI 0.68 to 2.95) for ATC arterial thromboembolic events. Although the OR for death versus sham for the 0.5 mg dose was of borderline significance (P = 0.04), no comparison between doses approached statistical significance.

Direct comparisons of differences in efficacy between anti-VEGF drugs: bevacizumab versus ranibizumab

Nepomuceno 2013 and Ekinci 2014 compared bevacizumab with ranibizumab at one year in 45 participants (60 eyes) and 100 participants, respectively. Only Nepomuceno 2013 reported our primary outcomes and did not show a difference regarding gain and loss of 3 or more lines, but their was little power to do so given the imprecision (Analysis 5.1; Analysis 5.2). Nepomuceno 2013 reported the difference in mean change of visual acuity but Ekinci 2014 only gave initial and final decimal values, which we converted to logMAR in order to extract the difference (SDs were imputed as the mean SD from Nepomuceno 2013). Analysis 5.3 did not suggest a difference between bevacizumab and ranibizumab but the calculation approximations regarding Ekinci 2014, the discordant direction of effects and the low quality of both studies made estimates unreliable (0.0 logMAR, 95% CI -0.05 to 0.05). The change in central retinal thickness favoured ranibizumab in Nepomuceno 2013 but when pooled with Ekinci 2014 no difference could be shown (MD 27 µm, 95% CI -6 to 60). Although not an outcome of this review, Nepomuceno 2013 reported the need for about one more injection with bevacizumab compared to ranibizumab (9.8 versus 7.7 injections on average, P = 0.005 as reported by the authors using Wilcoxon rank-sum test).

Exploratory indirect comparisons of differences in efficacy among anti-VEGF drugs

We used all extracted data for a gain of 3 or more lines (491 events, 2566 participants) at one year in random-effects logistic regression models to explore differences among antiangiogenic drugs, considering ranibizumab as the reference as it is widely approved. The dataset used in this analysis is shown in Table 5.
Ranibizumab approached statistically significant superiority with respect to pegaptanib (relative OR 1.98, 95% CI 0.99 to 3.95). We did not find evidence of superiority or equivalence of ranibizumab versus bevacizumab (relative OR 1.15, 95% CI 0.67 to 2.08) or aflibercept (relative OR 1.35, 95% CI 0.92 to 2.00) since estimates were imprecise, regarding a gain of 3 or more lines of vision.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Adverse events: Anti-VEGF compared with control for diabetic macular oedema

Patient or population: people with diabetic macular oedema
Settings:
Intervention: adverse events: anti-VEGF
Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Adverse events: anti-VEGF				
Serious systemic adverse events Follow-up: 6 to 24 months	**145 per 1000**	**142 per 1000** (120 to 170)	**RR 0.98** (0.83 to 1.17)	2985 (15 studies)	⊕⊕⊕◯ moderate[1,2]	heterogeneity: I^2 = 0%
Total ATC thromboembolic events Follow-up: 6 to 24 months	**42 per 1000**	**37 per 1000** (26 to 53)	**RR 0.89** (0.63 to 1.25)	3034 (14 studies)	⊕⊕⊕◯ moderate[1,2,3]	heterogeneity: I^2 = 0%
Death Follow-up: 6 to 24 months	**16 per 1000**	**14 per 1000** (8 to 24)	**RR 0.88** (0.52 to 1.47]	3562 (15 studies)	⊕⊕⊕◯ moderate[1,2]	heterogeneity: I^2 = 0%

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[1] Some studies excluded patients with previous cardiovascular adverse events and there were consistency problems, resolved by agreement, with extracting data from some studies (-1 for indirectness).
[2] 95% confidence intervals of relative risks are relatively large for death, but absolute differences are small (see text) (no downgrade).
[3] Incomplete reporting of Antiplatelet Trialists' Collaboration (ATC) events in Macugen 2011 and RISE-RIDE , but these should be balanced across treatment arms (no downgrade).
ATC: Antiplatelet Trialists Collaboration

DISCUSSION

Summary of main results

We found high quality evidence that antiangiogenic therapy provides benefit, both as an alternative and as an adjunct, over laser treatment. Consistently, we also found evidence that intravitreal injections of antiangiogenic drugs confer a significant benefit over sham treatment. At one year, about five people need to be treated to achieve a 3 plus line gain of vision in one person and the mean gain of vision is about one and a half Snellen lines. We were unable to estimate subgroup differences in effects, particularly according to DMO severity of retinal thickness at baseline.

Direct comparisons between different drugs were available only in two small head-to-head trials comparing bevacizumab and ranibizumab, which did not show a difference in visual acuity but did not have the power to show clinically relevant differences, that is at least 5 ETDRS letters or one Snellen line. The quality of these studies was low.

When subgroup analyses were used for indirect comparisons among drugs in meta-analyses, these were based on few trials for each drug type, and trials were of small size for bevacizumab. For the visual gain primary outcome, no subgroup differences were shown between bevacizumab, ranibizumab and aflibercept compared to grid laser. This was confirmed using random-effects model logistic regression to fit indirect comparisons (Simmonds 2014) for the gain of 3 plus lines of vision, but differences were not precisely estimated. However, in meta-analyses there were significant subgroup differences regarding mean change of visual acuity and mean change of central macular thickness, with aflibercept having the largest effects.

Reported safety was good in the included RCTs since clinically significant increases in SSAEs, arterial thromboembolic events and death (Moja 2014) were excluded for patients at low average risk such as in these studies. However, since some studies excluded patients with uncontrolled hypertension or previous cardiovascular events, this could limit generalisability to the real-world diabetic population, for which we downgraded this evidence to moderate.

Overall completeness and applicability of evidence

Two-year data were available and reported in only four RCTs in this review. Studies such as RESTORE 2011 were open-label after one year. Thus, long-term effects will have to be inferred from observational trials.

We suggest there are still insufficient data on drug differences. The possibility of making indirect comparisons between different anti-VEGF drugs was limited by the small numbers of trials, as mentioned above. Two small studies directly comparing bevacizumab with ranibizumab provided only very low quality evidence. A large number of RCTs are ongoing in this area of biomedical research (Characteristics of ongoing studies) and can be found on ClinicalTrial.Gov. The results of these studies will clearly be important in informing this review, especially regarding differences among drugs that are being investigated in an ongoing DRCRnet multicentre study (NCT01627249) entitled 'A Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab and Ranibizumab for Diabetic Macular Edema'.

We found no useful data from RCTs, for example from subgroup analyses, regarding issues that can be of specific interest to clinicians, such as patients that are difficult to treat with laser. We acknowledge that many specialists would not treat people with CSMO with laser if a thickened and adherent vitreous hyaloid is found, which is best seen with OCT; or perhaps based on other clinical and fluorescein angiographic findings, such as macular ischaemia, diffuse rather than focal leakage with no exudates, or OCT findings such as large foveal cysts and loss of photoreceptor layers. This premise underlines the belief by retina specialists that laser is not always applicable, and it may be that anti-VEGF may have wider indications than laser, being less selective.

Regarding the combination of laser and antiangiogenic therapy, Elman 2012 published a three-year follow-up study of DRCRnet 2010, suggesting that the mean change in visual acuity from baseline through to the three-year visit was 2.9 letters more (9.7 versus 6.8 letters, MD 2.9 letters, 95% CI 0.4 to 5.4; P = 0.02), about -0.06 logMAR, in the deferral group compared with the prompt laser treatment group. However, this evidence regards the additional use of laser rather than anti-VEGF therapy and we did not use such data.

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 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). DRCRnet 2010 possibly meets this goal in this review, whereas other registration trials usually adopt strict monitoring regimens that are not easily implemented in busy clinical practices. We recognise that this may be more of a problem for age-related macular degeneration (AMD) than for DMO, which is a more stable condition.

Quality of the evidence

As remarked above, the overall quality of the evidence in this review was high for the main question regarding drug class efficacy, because large effects were precisely measured and did not vary according to trial quality. The evidence on drug differences is still limited and of low quality in direct comparisons, and the quality of our indirect comparisons is difficult to assess formally but should be low too.

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, we retrieved several other reviews which are described below.

Arevalo 2009, O'Doherty 2008 and Salam 2010 could not include studies that were published later and are included in our review. Thus, their conclusions are hard to compare with our review.

Boscia 2010 was a broad purpose review on DMO from its epidemiology and pathophysiology to the efficacy of several treatments, finding that preliminary efficacy of anti-VEGF data was confirmed. The author also provided information on the investigation of other agents targeting VEGF, as well as drugs directed against TNFa and PKC-b2 which are under study.

Nicholson 2010 included four trials (Ahmadieh 2008; Macugen 2005; READ2 2009; Soheilian 2007) that we included, as well as RCTs with shorter follow-up and case series. Their conclusions were in favour of antiangiogenic drugs to treat DMO, and they stated that "we eagerly await the results of appropriate safety studies in diabetic populations".

Goyal 2011 assessed studies on bevacizumab and included Ahmadieh 2008, DRCRnet 2007 and Soheilian 2007. They pooled results of comparisons of bevacizumab with sham or laser, which makes the meta-analysis hard to compare with our data. They concluded that intravitreal bevacizumab is an effective short-term treatment for DMO, and that its efficacy wanes after six weeks.

Manousaridis 2012 assessed RCTs and case series to study the effect of anti-VEGF drugs on macular ischaemia. They concluded that "anti-VEGF therapy rarely seems to further compromise the retinal circulation; however, worsening of macular ischaemia in the long term cannot be denitely excluded, particularly in eyes with significant ischaemia at baseline and after repeated intraocular anti-VEGF injections".

Zechmeister-Koss 2012 systematically reviewed RCTs as well as non-randomised studies to investigate safety and reported on individual study results without pooling them. They included all studies found by us except for RISE-RIDE and included studies with shorter follow-up. Using GRADE they found that quality was mostly moderate, mainly because of unclear randomisation methods, and that the quality was lower for pegaptanib and bevacizumab compared to ranibizumab. They concluded that "in a proportion of patients (on average 25%), VEGF inhibitors result in better visual acuity (≥ 15 ETDRS letters or equivalent) than in patients treated with laser photocoagulation or sham injection. The number of injections required for long-term improvement as well as the general long-term efcacy is unknown. The evidence is not sufficient to conrm safety of the products in patients with DMO and does not suggest superiority of a single product". These conclusions are similar to ours.

Ford 2012 used Bayesian indirect comparisons to compare the efficacy of bevacizumab and ranibizumab in people with DMO. They included five studies, also included by us, and found the OR of a gain of 2 or more lines was 0.95 (95% credible interval (CrI) 0.23 to 4.32) for bevacizumab compared to ranibizumab, whereas the MD in change of vision was −0.08 logMAR units (95% CI −0.19 to 0.04). They concluded that "results suggest no difference in effectiveness between bevacizumab and ranibizumab, but the wide credible intervals cannot exclude the possibility that either drug might be superior" and that "sufficiently powered, direct head to head trials are needed".

Wang 2012 conducted a systematic review and meta-analysis including four trials also included in our review. They concluded that ranibizumab and ranibizumab combined with focal or grid laser is more advantageous than non-drug treatment or focal or grid laser in improving visual acuity (plus 1.5 lines and plus 1.2 lines at 12 months respectively compared with laser) and reducing retinal thickness in DMO, and can be well tolerated based on the safety assessment. They also found that intravitreal ranibizumab may be equivalent to ranibizumab combined with focal or grid laser.

Through searching the references of an editorial and review (O' Malley 2012) we also found MEDCAC 2012, a health technology assessment (HTA) conducted by the Institute for Clinical and Economic Review (ICER) (www.icer-review.org), which prepared this review for the Medicare Evidence Development & Coverage Advisory Committee. This review included all studies included by us plus others assessing comparisons between interventions not included in our review, such as subthreshold photocoagulation and intravitreal triamcinolone (total of 15 studies). This HTA conducted a multiple treatment meta-analysis of all studies, also linking these treatments that were not considered in our review. They could not show differences among the antiangiogenic drugs (ranibizumab, pegaptanib, bevacizumab, aflibercept). Although 95% CIs were narrower, possibly thanks to the larger evidence network and a visual change cut-off closer to the mean (gain of 10 or more letters), the main comparison between ranibizumab and bevacizumab found an RR of 0.94 (95% CI 0.47 to 1.85), which cannot exclude a relevant difference between the two such as almost twice the risk. This result is not comparable to our exploratory indirect comparisons since the conduct of a full multiple treatment meta-analysis was beyond the objective of this review.

The American Academy of Ophthalmology (AAO) has published an ophthalmic technology assessment which reviewed the literature available (Ho 2012). All included studies were also included in our review and no meta-analysis was conducted. They con-

cluded that "anti-VEGF pharmacotherapy, delivered by intravitreal injection, is reasonably safe and effective for the treatment of DME". They also assessed economic evidence and included only Smiddy 2011, finding that "the cost of these treatments, however, is relatively high, and further study is required to evaluate the long-term cost-effectiveness of these treatments".

Regnier 2014 used Bayesian network meta-analysis methods to compare ranibizumab and aflibercept indirectly, using the gain of 10 or more ETDRS letters (2 lines) as an outcome measure. They found the direction of the effect favoured ranibizumab but differences were not statistically significant (OR 1.59, 95% credible interval 0.61 to 5.37).

Several reviews have been published on the safety of antiangiogenic therapy in people with AMD, reviewing which is beyond the purpose of our systematic review. Among recent reviews, Schmucker 2012 conducted a systematic review of safety in AMD patients using direct and indirect comparisons. Using direct comparisons of bevacizumab and ranibizumab, they found that bevacizumab increased ocular adverse events (RR 2.8, 95% CI 1.2 to 6.5) as well as serious infections and gastrointestinal disorders (RR 1.3, 95% CI 1.0 to 1.7), but no difference could be shown for arterial thromboembolic events. Using indirect comparisons, the authors found that ranibizumab increased the risk of serious ocular adverse events (RR 3.1, 95% CI 1.1 to 8.9) as well as non-ocular haemorrhage (RR 1.7, 95% CI 1.1 to 2.7) compared with sham treatment. Another review and meta-analysis of RCTs of ranibizumab in AMD (Bressler 2012) could not find an increase in the risk of cerebrovascular events, but suggested that these can be increased in high-risk patients.

Finally, Abouammoh 2013 and Yanagida 2014 conducted safety meta-analyses of ranibizumab trials in DMO and concluded there was no safety concern.

AUTHORS' CONCLUSIONS

Implications for practice

There is high quality evidence that anti-VEGF drugs are superior to laser photocoagulation in treating DMO after one year. Less two-year data confirmed longer-term efficacy. Clinicians and policy makers should be aware that clinical practice should adhere to treatment and follow-up standards used in RCTs since undertreatment could limit benefits. This was shown for age-related macular degeneration in a European observational study of ranibizumab by Pagliarini 2014.

Differences among drugs were investigated directly only in two small, low quality trials comparing bevacizumab to ranibizumab and even indirect comparisons are limited by the number and types of studies currently available for this purpose.

In the included RCTs the safety of anti-VEGF intravitreal injection was good, suggesting that a generic indicator such as SSAEs, mostly including death and hospitalisation, as well as adverse outcomes such as death and systemic arterial thromboembolic events, appear unlikely to be increased in the short to medium term in a sensitive population such as people with diabetic microangiopathy. We cannot exclude that adverse events can be increased in high-risk populations that differ from those included in our studies, and questions have been raised about dose dependence of adverse events.

Implications for research

Treatment of DMO with antiangiogenic therapy is now established. Future research should compare different drugs and treatment regimens, as well as investigate effects in the real world. This review will not be updated in its present form. We recommend that some of these goals could better be accomplished by a network meta-analysis comparing the efficacy of antiangiogenic drugs, intravitreal steroids, laser and control.

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Meagan Huggins provided clarification regarding the randomisation process in DRCRnet 2010.

Dr Oliver Comyn provided data on LUCIDATE 2014.

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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 randomised controlled trial 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 CMT *"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)

Ahmadieh 2008 (*Continued*)

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

Risk of bias ***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 patients 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

Other bias	Low risk	28 eyes of 14 patients (14%) with bilateral CSMO were included in the analysis

Azad 2012

Methods	Parallel group randomised controlled trial 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 • CMT > 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) • CMT assessed using OCT • 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 ***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

BOLT 2010

Methods	Parallel group randomised controlled trial 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 40-86) Sex: 31% women Inclusion criteria: • 18 years or older • diabetes mellitus • BCVA in the study eye between 35-69 ETDRS letters at 4 m (Snellen equivalent 6/60 or 6/12) • centre-involving CSMO with CMT 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 enrollment 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 enrollment • 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 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 CMT was less than 270 m at 18 weeks, then treatment was continued only if macular thickness was not "stable." If CMT 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 CMT within 20 m of the patient's thinnest recorded CMT. 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 CMT and mean change in CMT • 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 ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"Patients were randomized 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*

BOLT 2010 (*Continued*)

		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

DA VINCI 2011

Methods	Parallel group randomised controlled trial 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 40-86) Sex: 31% women Inclusion criteria: • 18 years or older • diabetes mellitus • DMO involving the central macula defined as CRT $\geq$ 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 diopters 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 • 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-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 ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
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.*"
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"Two randomized 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

DA VINCI 2011 (*Continued*)

Other bias	Low risk	No other bias identified

DRCRnet 2010

Methods	Parallel group and within-person randomised controlled trial 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 Test11) 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 (patient) • 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 3-10 days of the injection and deferred laser photocoagulation (188 eyes) which happened after 24 weeks. All eyes in comparator group were treated within 3-10 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)

DRCRnet 2010 (*Continued*)

Outcomes	Primary outcome: • BCVA and safety at 12 months Secondary outcomes: 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-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 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 ***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 website (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*

DRCRnet 2010 (*Continued*)

		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	Patients randomised in each group were: 293 laser, 187 ranibizumab + prompt laser, 188 ranibizumab + deferred laser and 186 IVTA + laser. At 1 year complete patients were 274, 171, 178, 176 respectively (91%-95%) At 2 years complete patients were 211, 136, 139, 142 respectively (72%-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

Ekinci 2014

Methods	Parallel group randomised controlled trial 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 50-89) Sex: 68% women Inclusion criteria: • clinically significant DMO (CMT >300 mm), as found through FFA and OCT evaluations and dilate fundus examination, after 1-year follow-up period Exclusion criteria: • patients 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

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 ther 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 • CMT 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: 2011-2014 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 ***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 patients 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

Korobelnik 2014

Methods	Parallel group randomised controlled trial Eyes: 862 eyes from 862 patients. One eye per patient. *"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 randomized 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-June 2013 Funding: "T*he 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		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Korobelnik 2014 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No details available
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

LUCIDATE 2014

Methods	Parallel group randomised controlled trial 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 randomized 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 patients 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 enrollment 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 randomized 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-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 ***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	Treatments were different
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

Macugen 2005

Methods	Parallel group randomised controlled trial One eye per person, chosen by patient 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 27-89) 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 (patients) • 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 diopters, 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 enrollment. known serious allergies to fluorescein dye • glycosylated haemoglobin (GHb) levels of ≥ 13% • 3 episodes of severe hypoglycemia 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
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 ***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

Macugen 2005 (*Continued*)

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 patients by request at weeks 12 and 16 and 1 by other reason at week 1), 6 in sham group (5 patients 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

Macugen 2011

Methods	Parallel group randomised controlled trial 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 (20-83) 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 $\geq$ 250 µm (centre point thickness measured on OCT) • BCVA with a letter score of 65-35 (20/50-20/200 Snellen equivalents) • IOP $\leq$ 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 (panretinal) photocoagulation 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) Patients 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, patients 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-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 ***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."*

Macugen 2011 (*Continued*)

		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
Selective reporting (reporting bias)	Low risk	All primary outcomes reported
Other bias	Low risk	No other biases identified

NCT01131585 (RELATION)

Methods	Parallel group randomised controlled trial One eye per person, eye with worse VA selected
Participants	Country: Germany Number of people randomised: 128 (128 eyes) Average age: 64 years (range 31-79) 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 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

NCT01131585 (RELATION) (*Continued*)

	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-May 2011, terminated early Funding: Novartis Conflict of interest: Novartis Trial registration: NCT01131585

Risk of bias ***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-blind, but no details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as double-blind, 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
Other bias	Low risk	Study terminated early due to European Medicine Agency approval of ranibizumab for DMO but this is independent of effect estimates

Nepomuceno 2013

Methods	Parallel group randomised controlled trial 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 (eg 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 clinical trials.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-August 2011 Funding: *"Fundac¸a˜o de Amparo a' Pesquisa do Estado de Sa˜o Paulo (FAPESP), grant number 2010/013368; and Fundac¸a˜o Apoio ao Ensino, Pesquisa e Assistencia (FAEPA) do Hospital das Cl ´ nicas da Faculdade de Medicina de Ribeira˜o Preto da Universidade de Sa˜o 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 ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*".... received the randomized 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 Staphylococcus 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*

Nepomuceno 2013 (*Continued*)

		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	Low risk	No other bias identified

READ2 2009

Methods	Parallel group randomised controlled trial 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 $\geq$ 250 µm • HbA1c $\geq$ 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) Patients 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 clinical trials.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 activites 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 honoriaria from Genentech, Heidelberg, Jerini, NeoVista, Optimedica, and Regeneron. JL has received honoriaria 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 ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
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

READ2 2009 (*Continued*)

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 particpants at 1 year: 29, 29, 30 (85%-88%) Completed particpants at 2 years: 24, 26, 24 (71%-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	Unclear risk	No other source of bias identified

RESOLVE 2010

Methods	Parallel group randomised controlled trial 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 32-85) Sex: 46% women Inclusion criteria: • 18 years or older • diabetes mellitus, • stable HbA1c levels ($\leq$ 12%) • DMO with centre involvement in at least one eye (study eye) • CRT $\geq$ 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 patients with only mild laser burns at least 1000 µm from the center of the fovea performed more than 6 months before the trial commenced • proliferative diabetic retinopathy 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 center of the macula of the study eye as assessed by fluorescein angiography at visit 1 and confirmed by a central reading centre • patients with unstable medical conditions such as poor glycaemic or BPcontrol • patients 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 patient 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 CMT 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 ***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

RESOLVE 2010 (*Continued*)

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* *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 patients
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

RESPOND 2013

Methods	Parallel group randomised controlled trial One eye per person, unclear how eye selected
Participants	Country: Canada Number of people randomised: 239 (239 eyes) Average age: 62 years (range 26-87) 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
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 clinical trials.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-March 2013 Funding: Novartis Conflict of interest: Trial registration: NCT01135914

Risk of bias ***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	High risk	Unmasked study (described as open-label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked study (described as open-label)

RESPOND 2013 (*Continued*)

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%-6%)
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

RESTORE 2011

Methods	Parallel group randomised controlled trial 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 ***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 patient 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	Patients randomised in each group were: 116 ranibizumab, 118 ranibizumab + laser, 111 laser At 1 year complete patients 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	Unclear risk	No other source of bias identified

RISE-RIDE

Methods	Parallel group randomised controlled trial 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)*
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

RISE-RIDE (*Continued*)

Notes	Dates participants enrolled: June 2007-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 ***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 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*

RISE-RIDE (*Continued*)

		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

Soheilian 2007

Methods	Parallel group randomised controlled trial 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 $\geq$ 3 mg/dL • uncontrolled diabetes mellitus

Soheilian 2007 (*Continued*)

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 • CMT change assessed by OCT • injection-related complications
Notes	Dates participants enrolled: September 2005-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 ***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
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

Abbreviations
BCVA: best-corrected visual acuity

BP: blood pressure
CMT: central macular thickness
CRT: central retinal thickness
CSFT: central subfield macular thickness
CSMO: clinically significant macular oedema
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
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
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
DRCRnet 2011	Follow-up at 14 weeks only. RCT comparing ranibizumab (2 injections), triamcinolone (1 injection) to sham in patients with DMO undergoing grid and panretinal laser photocoagulation

(*Continued*)

DRCRnet 2012	Follow-up of DRCRnet 2010 comparing prompt to deferred laser in patients treated for ranibizumab for DMO: does not report on comparison of ranibizumab with laser
Faghihi 2008	Follow-up at 16 weeks only
Lim 2012	Bevacizumab compared to intravitreal triamcinolone
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
Zhang 2013	Bevacizumab was combined with triamcinolone

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

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

NCT01171976 (RETAIN)

Methods	Allocation: randomised Intervention model: parallel assignment Masking: single masked (investigator)
Participants	374 at 52 centres in Europe
Interventions	Experimental: 0.5 mg ranibizumab TE + laser Experimental: 0.5 mg ranibizumab TE alone Active comparator: 0.5 mg ranibizumab alone given PRN
Outcomes	Primary outcome: Mean average change from baseline in BCVA over a 12-month treatment period Secondary outcomes: Evaluate whether the mean average change from baseline in BCVA obtained with either a 0.5 mg ranibizumab TE with adjunctive laser, or with 0.5 mg ranibizumab TE is non-inferior to 0.5 mg ranibizumab PRN Investigate, within the TE dosing concepts, the impact of laser treatment on the number of re-treatments Investigate the efficacy of 0.5 mg ranibizumab TE with adjunctive laser, 0.5 mg ranibizumab TE and 0.5 mg ranibizumab PRN measured by the overall score assessed by VFQ-25 and EQ-5D Time course of mean BCVA change from baseline to month 12, and up to month 24 obtained with either a 0.5 mg

NCT01171976 (RETAIN) (*Continued*)

	ranibizumab TE with adjunctive laser, or with 0.5 mg ranibizumab TE and with 0.5 mg ranibizumab PRN To compare the changes in development of CSFT of 0.5 mg ranibizumab TE with adjunctive laser, 0.5 mg ranibizumab TE and 0.5 mg ranibizumab PRN over time
Notes	Sponsor: Novartis Pharmaceuticals Trial ID: NCT01171976

Abbreviations
BCVA: best-corrected visual acuity
CFST: central subfield macular thickness
EQ-5D: EuroQol 5D
PRN: Pro Re Nata
TE: treat and extend
VFQ-25: Visual Function Questionnaire 25-item

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

ChiCTR-TRC-12002417

Trial name or title	A randomized 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 diabetic macular oedema
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	joycekung@cuhk.edu.hk
Notes	

NCT00387582

Trial name or title	Lucentis in the treatment of macular edema - a phase II, single center, randomized study to evaluate the efficacy of ranibizumab versus focal laser treatment in subjects with diabetic macular edema
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	49, country: USA
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 visual acuity Secondary outcome: Reduction in retinal thickening based on OCT
Starting date	Study start date: July 2006 Study completion date: February 2009
Contact information	Roy A Goodart, MD, Principal Investigator, Rocky Mountain Retina Consultants
Notes	Investigator contacted

NCT00901186

Trial name or title	A randomized, open label, multicenter, laser-controlled phase II study assessing the efficacy and safety of ranibizumab (intravitreal injections) vs laser treatment in patients with visual impairment due to diabetic macular edema
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	84, country: Spain
Interventions	Drug: ranibizumab Procedure: laser

NCT00901186 (*Continued*)

Outcomes	Primary outcome: Change BCVA with ranibizumab 0.5 mg versus laser 12-month Secondary outcomes: Improvement in BCVA with ranibizumab (0.5 mg) versus laser 12-month measure Mean BCVA change with ranibizumab (0.5 mg) versus laser % of participants with VA > 73 letters with ranibizumab (0.5 mg) versus laser Time and mean change in central retinal thickness 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
Starting date	Study first received: 11 May 2009 Last updated: 16 November 2011 Study completion date: August 2012
Contact information	Novartis (Novartis Pharmaceuticals)
Notes	Sponsor: Novartis (Novartis Pharmaceuticals)

NCT00989989 (REVEAL)

Trial name or title	Efficacy and safety of ranibizumab (intravitreal injections) in patients with visual impairment due to diabetic macular edema (REVEAL)
Methods	Allocation: randomised Intervention model: parallel assignment Masking: double masked (patient, investigator) Primary purpose: treatment
Participants	395, country: China, Hong Kong, Korea, Japan, Singapore, Taiwan
Interventions	Experimental Group 1 (adjunctive group): drug, ranibizumab; procedure, laser photocoagulation Experimental Group 2 (monotherapy group): drug, ranibizumab Active comparator Group 3 (laser control group): procedure, laser photocoagulation
Outcomes	Primary Outcome Measures: · Average Change From Baseline of Best-Corrected Visual Acuity (BCVA) Over 12 Months Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (EDTRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. A positive average change from baseline of BCVA indicates improvement Secondary Outcome Measures: · Change From Baseline on Central Retinal Subfield Thickness (CRST) at Month 12 Central Retinal Subfield Thickness (CRST) was measured using Optical Coherence Tomography (OCT) in micrometers. A negative change from baseline of CRST indicates improvement · Percent of Participants With Anatomical Changes in Intra-retinal Cysts at End of Study Compared to Baseline

	Presence or absence of intra-retinal cysts in any of the 6 sections of the study eye was measured using Optical Coherence Tomography (OCT). A complete resolution or decrease from baseline of intra-retinal cysts indicates improvement · Percent of Participants With Anatomical Changes in Sub-retinal Fluid at End of Study Compared to Baseline Presence or absence of sub-retinal fluid in any of the 6 sections of the study eye was measured using Optical Coherence Tomography (OCT). A complete resolution or decrease from baseline of sub-retinal fluid indicates improvement · Percent of Participants With Visual Acuity Above 73 Letters at Month 12 Best Corrected Visual Acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart at baseline and month 12 while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. BCVA above 73 letters at month 12 indicates a positive outcome · Percent of Participants Who Gained >= 10 Letters at Month 12 Compared to Baseline Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (EDTRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. A gain of 10 or more BCVA letters from baseline indicates improvement. A BCVA of 84 letters or more at Month 12 indicates improvement · Percent of Participants Who Lost >= 10 Letters at Month 12 Compared to Baseline Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (EDTRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. A loss of 10 or more BCVA letters from baseline indicates worsening · Percent of Participants Who Gained >= 15 Letters at Month 12 Compared to Baseline Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (EDTRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. A gain of 15 or more BCVA letters from baseline indicates improvement. A BCVA of 84 letters or more at Month 12 indicates improvement · Percent of Participants Who Lost >= 15 Letters at Month 12 Compared to Baseline Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (EDTRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. A loss of 15 or more BCVA letters from baseline indicates worsening · Best-Corrected Visual Acuity (BCVA) Mean Change From Baseline at Month Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (EDTRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. A positive change from baseline of BCVA indicates improvement · Patient Outcome Measure Euro Quality of Life Questionnaire (EQ-5D) The Euro Quality of Life Questionnaire (EQ-5D) standardized instrument was utilized to measure health outcomes related to mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Participants self-rate their health on a visual, vertical analogue scale from 0 to 100 where the endpoints are labeled "Best imaginable health state" (100) and "worst imaginable health state" (0)
Starting date	Study start date: September 2009 Study completion date: August 2011
Contact information	Novartis
Notes	Results posted on clinical trials.gov

NCT00997191 (IBeTA)

Trial name or title	Intravitreal bevacizumab and intravitreal triamcinolone associated to laser photocoagulation for diabetic macular edema (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 CMT
Starting date	Study start date: October 2009 Estimated study completion date: October 2011
Contact information	Bianka Yukari Nakase Yamasato Katayama, Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo
Notes	

NCT01100307

Trial name or title	A phase 3 study to compare the efficacy and safety of 0.3 mg pegaptanib sodium to sham injections in subjects with diabetic macular edema
Methods	Allocation: randomised endpoint classification; safety/efficacy study intervention model; parallel assignment Masking: double masked
Participants	243, country: Japan
Interventions	Drug: pegaptanib sodium Other: sham injection
Outcomes	Number of participants who experience a $\geq$ 10 letter improvement of VA in ETDRS chart from baseline to week 24: Double masked phase (time frame: baseline and week 24; designated as safety issue: no) • Change from baseline in VA: double masked phase (time frame: baseline, weeks 6, 12, 18, and 24) (designated as safety issue: no) changes in VA were monitored through refraction and BCVA measurements using retro-illuminated, modified Ferris-Bailey ETDRS charts

NCT01100307 (*Continued*)

	• Number of participants underwent focal/grid laser, or vitrectomy: double masked phase (time frame: up to 24 weeks; designated as safety issue: no) 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; designated as safety issue: no) 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; designated as safety issue: no) 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: ppen phase (time frame: weeks 24 to 54; designated as safety issue: no) Included focal laser photocoagulation, grid laser photocoagulation, and vitrectomy
Starting date	Study start date: May 2010 Estimated study completion date: August 2012
Contact information	See http://clinicaltrials.gov/ct2/show/NCT01100307
Notes	Sponsor: Pfizer

NCT01100401 (READ3)

Trial name or title	Ranibizumab for edema of the macula in diabetes: Protocol 3 with high dose - the READ 3 study
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: double masked
Participants	92, country: USA
Interventions	Drug: pegaptanib sodium Other: sham injection
Outcomes	Adverse events (time frame: 3, 6, 9 and 12 months; designated as safety issue: yes). The primary outcomes for safety and tolerability include: incidence and severity of systemic and ocular adverse events associated with repeated intravitreal injections of 2 doses of ranibizumab in subjects with DMO such as cardiovascular events, intraocular reactions (inflammation), vitreous haemorrhage, retinal detachment, endophthalmitis (intraocular infection), increased IOP, and cataract formation, among others Secondary outcomes: VA (time frame: 3, 6, 9 and 12 months; designated as safety issue: no) mean change in BCVA (ETDRS) at 4 m in the study eye over time through month 12 Anatomic retinal changes (time frame: 3, 6, 9 and 12 months; designated as safety issue: yes) anatomic retinal changes in the study eye as assessed by colour fundus photography, fluorescein angiography, and OCT, from baseline to months 6 and 12, including: extent of fluorescein leakage from CSMO progression to proliferative diabetic retinopathy by ETDRS grade. Change in CRT, as assessed by OCT. Change in central retinal volume, as assessed by OCT

NCT01100401 (READ3) (*Continued*)

Starting date	Starting date: February 2010 Study completion date: March 2013
Contact information	Jennifer Denton jdenton2@jhmi.edu
Notes	

NCT01112085 (MINIMA-2)

Trial name or title	MIcrodoses of raNIbizumab in Diabetic MAcular Edema (MINIMA-2)
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: single masked (patient)
Participants	Estimated enrolment: 72, country: Mexico
Interventions	Experimental: ranibizumab 0.05 mg (low dose). Intravitreal injections of 0.05 mg ranibizumab over 6 months then additional treatment with ranibizumab 0.05 mg as needed (according to re-treatment criteria) Experimental: ranibizumab 0.5 mg (high dose). Intravitreal injections of 0.5 mg ranibizumab over 6 months then additional treatment with ranibizumab 0.5 mg as needed (according to re-treatment criteria)
Outcomes	Primary outcome (time frame: 6 months and 12 months): BCVA: Improvement in vision of BCVA of 15 or more letters, or a final vision of 20/25 (50 letters) or better if BCVA was 20/40 (40 letters) Secondary outcomes (time frame: 6 months and 12 months): Mean change in CRT and volume by OCT Changes in CRT and volume assessed by OCT
Starting date	Study start date: April 2010 Estimated study completion date: December 2011 Estimated primary completion date: September 2011 (final data collection date for primary outcome measure)
Contact information	Fundación Mexicana de Retina
Notes	Sponsor: Especialistas en Retina Medica y Quirurgica Grupo de Investigacion Investigators contacted

NCT01445899 (MATISSE)

Trial name or title	An open-label dose escalation study of PF-04523655 (Stratum I) combined with a prospective, randomized, double-masked, multi-center, controlled study (Stratum II) evaluating the efficacy and safety of PF-04523655 alone and in combination with ranibizumab versus ranibizumab alone in diabetic macular edema (MATISSE STUDY)
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: double masked (subject, 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 patients with DMO Efficacy (Stratum II): to evaluate the ability of PF-04523655 alone and in combination with ranibizumab to improve visual acuity compared to ranibizumab alone in people with DMO
Starting date	Study start date: February 2012 Estimated study completion date: July 2014
Contact information	Quark Pharmaceuticals
Notes	Sponsor: Quark Pharmaceuticals Consider putting in excluded studies

NCT01476449

Trial name or title	Monthly ranibizumab versus treat and extend ranibizumab for diabetic macular edema
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open-label
Participants	20, country: USA

NCT01476449 (*Continued*)

Interventions	Active comparator: monthly intravitreal injections of ranibizumab for the duration of the study Experimental (TE ranibizumab): intravitreal injections of ranibizumab administered until participants' maculae are anatomically 'dry', at which point the evaluation and injection interval will be extended
Outcomes	Not available
Starting date	Study start date: November 2011 Estimated study completion date: June 2013
Contact information	Retina Vitreous Associates of Florida
Notes	

NCT01487629 (IBERA-DME)

Trial name or title	Bevacizumab versus ranibizumab for the treatment of diabetic macular edema (IBERA-DME)
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label
Participants	53, country: Brazil
Interventions	Drug: bevacizumab 1.5 mg, intravitreal, throughout the study Drug: ranibizumab 0.5 mg, intravitreal, throughout the study
Outcomes	Primary outcomes: CSFT change CSFT measured with spectral-domain OCT Secondary outcomes: BCVA change BCVA using ETDRS charts
Starting date	Study start date: April 2010 Estimated study completion date: September 2012
Contact information	Rodrigo Jorge, Principal Investigator, University of Sao Paulo
Notes	Sponsor: University of Sao Paulo

NCT01552408 (DAVE)

Trial name or title	A phase I/II, randomized, study for diabetic macular edema using 0.5 mg ranibizumab combined with targeted PRP monthly for 4 months,then PRN vs 0.5 mg ranibizumab 4 months monotherapy, then as needed (DME-AntiVEgf) DAVE
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: single group assignment Masking: Open Label
Participants	40, country: USA
Interventions	Active Comparator: 0.50mg ranibizumab 4 mandatory monthly injections of 0.50mg ranibizumab, retreatment will be as needed Experimental: Targeted PRP with 0.50mg ranibizumab 4 mandatory monthly injections of 0.50mg ranibizumab, and at V3 (day7) will receive Targeted PRP, then treatment with ranibizumab will be PRN
Outcomes	NA
Starting date	Study Start date: March 2012 Estimated Study completion date: March 2014
Contact information	David M Brown, MD, Director Greater Houston Retina Research, Greater Houston Retina Research
Notes	Sponsor: David M Brown, MD Collaborator: Genentech

NCT01565148 (IDEAL)

Trial name or title	A Randomized, Multi-center, Phase II Study of the Safety, Tolerability and Bioactivity of Repeated Intravitreal Injections of iCo-007 as Monotherapy or in Combination With Ranibizumab or Laser Photocoagulation in the Treatment of Diabetic Macular Edema (the iDEAL Study)
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

NCT01565148 (IDEAL) (*Continued*)

	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
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 patients 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
Starting date	Study start date: February 2012 Estimated study completion date: December 2013
Contact information	Quan Dong Nguyen, MD, Johns Hopkins University
Notes	Sponsors and Collaborators Quan Dong Nguyen Juvenile Diabetes Research Foundation iCo Therapeutics Inc Consider moving to excluded studies

NCT01572350 (ALBA)

Trial name or title	Safety and efficacy of triamcinolone acetonide combined with laser, bevacizumab combined with laser versus laser alone for the treatment of diffuse non-tractional diabetic macular edema (ALBA)
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: factorial assignment Masking: open-label
Participants	105, country: Spain
Interventions	Grid laser Triamcinolone acetonide Bevacizumab

NCT01572350 (ALBA) (*Continued*)

Outcomes	Primary outcome: BCVA (time frame: 12 months; designated as safety issue: yes) Type of adverse events, severity and number of participants with adverse events at baseline, 3, 6 and 12 months in order to assess safety and tolerability of intravitreal Triesence (r) (designated as safety issue: yes) Secondary outcomes: To assess the safety of intravitreal Triesence (time frame: baseline, 3, 6 and 12 months; designated as safety issue: yes) Type of adverse events, severity and number of participants with adverse events as a measure of safety and tolerability Average change in mean CMT in each group (time frame: baseline and 3, 6 and 12 months after initiation of treatment; designated as safety issue: no), measured in µm by OCT at each follow-up visit, compared to the baseline visit in each of the 3 groups To assess the safety of intravitreal Avastin (time frame: baseline, 3, 6 and 12 months; designated as safety issue: yes) Type of adverse events, severity and number of participants with adverse events as a measure of safety and tolerability To assess the safety of intravitreal grid photocoagulation (time frame: baseline, 3, 6 and 12 months; designated as safety issue: yes) Type of adverse events, severity and number of participants with adverse events as a measure of safety and tolerability
Starting date	Starting date: October 2010 Study completion date: October 2012
Contact information	Alicia Pareja, MD, Hospital Universitario de Canarias
Notes	

NCT01610557 (CADME)

Trial name or title	A phase II randomized study to compare anti-VEGF agents in the treatment of diabetic macular edema (CADME)
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: cross-over assignment Masking: double-masked
Participants	60, country: USA
Interventions	Drug: ranibizumab and bevacizumab Eyes are randomly assigned to receive a set sequence of monthly eye injections; all eyes receive ranibizumab at some time points and bevacizumab at others during the cross-over study
Outcomes	Primary outcome: Mean change in BCVA Secondary outcome: Retinal thickness on OCT

NCT01610557 (CADME) (*Continued*)

Starting date	Study start date: May 2012 Estimated study completion date: August 2014
Contact information	Henry E Wiley IV, National Eye Institute, National Institutes of Health
Notes	Sponsor: National Eye Institute (NEI)

NCT01627249

Trial name or title	Comparative effectiveness study of intravitreal aflibercept, bevacizumab, and ranibizumab for DME (protocol T)
Methods	Allocation: randomised Intervention model: parallel assignment Masking: single-masked (patient)
Participants	660
Interventions	Drug: 0.5 mg intravitreal injection of ranibizumab (Lucentis™) at baseline and up to every 4 weeks using defined retreatment criteria Experimental: 2.0 mg intravitreal injection of aflibercept at baseline and up to every 4 weeks using defined re-treatment criteria Experimental: 1.25 mg intravitreal injection of bevacizumab at baseline and up to every 4 weeks using defined re-treatment criteria
Outcomes	Endpoint classification: Safety/efficacy study
Starting date	Study start date: August 2012 Estimated study completion date: September 2015
Contact information	Diabetic Retinopathy Clinical Research Network
Notes	Sponsor: Diabetic Retinopathy Clinical Research Network

NCT01635790 (BRDME)

Trial name or title	Comparing the effectiveness and costs of bevacizumab to ranibizumab in patients with diabetic macular edema (BRDME)
Methods	Parallel group RCT
Participants	246 people with DMO
Interventions	Ranibizumab compared to bevacizumab

NCT01635790 (BRDME) (*Continued*)

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 patients 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 occured 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) {roportion of patients with a BCVA of 20/40 or more at 6 months compared to baseline BCVA (designated as safety issue: no)
Starting date	June 2012
Contact information	r.schlingemann@amc.uva.nl
Notes	http://clinicaltrials.gov/show/NCT01635790

NCT01845844 (ROTATE)

Trial name or title	Ranibizumab for persistent diabetic macular edema after bevacizumab (ROTATE)
Methods	Parallel group RCT
Participants	30 people with persistent DMO after treatment with bevacizumab
Interventions	Ranibizumab versus control
Outcomes	From clinical trials record: Primary outcomes: Incidence of ocular and systemic adverse events will be compared between experimental and active comparator groups (time frame: 1 year; designated as safety issue: yes). Examples include worsened acuity of > 30 letters, retinal detachment, endophthalmitis, cataract progression, vitreous haemorrhage, new PDR or neovascularisation of the iris or angle, incidence and severity of other adverse events, as identified by physical examination, subject reporting, and changes in vital signs and will include thromboembolic events, deaths and systemic serious adverse events Severity of ocular and systemic adverse events will be compared between experimental and active comparator groups (time frame: 1 year; designated as safety issue: yes). Examples include worsened acuity of > 30 letters, retinal detachment, endophthalmitis, cataract progression, vitreous haemorrhage, new PDR or neovascularisation of the iris or angle, incidence and severity of other adverse events, as identified by physical examination, subject reporting, and changes in vital signs and will include thromboembolic events, deaths and systemic

NCT01845844 (ROTATE) (*Continued*)

	serious adverse events Secondary outcome: Proportion of eyes with absence of fluorescein angiographic macular leakage at 12 months; proportion of eyes with unchanged, worsened, or improved fluorescein angiographic macular leakage from baseline at 1, 6 and 12 months; proportion of eyes with unchanged, worsened, or improved fundus photographic DMO appearance from baseline at 1, 6 and 12 months; proportion of eyes with new vitreous hemorrhage or traction retinal detachment secondary to PDR; proportion of eyes with progression from baseline non-PDR to PDR Other outcomes: Mean BCVA letter changes from baseline at 1, 3, 6, 9 and 12 months (designated as safety issue: yes) OCT CSF thickness and macular volume mean changes from baseline at 1, 3, 6, 9 and 12 months (designated as safety issue: yes)
Starting date	April 2013
Contact information	dmarcus@southeastretina.com
Notes	http://clinicaltrials.gov/ct2/show/NCT01845844?term=NCT01845844&rank=1

Abbreviations
BCVA: best-corrected visual acuity
CMT: central macular thickness
CRT: central retinal thickness
CSMO: clinically significant macular oedema
DMO: diabetic macular oedema (DME: US spelling edema)
ETDRS: Early Treatment Diabetic Retinopathy Study
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
VA: visual acuity

DATA AND ANALYSES

Comparison 1. Anti-VEGF versus laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gain 3+ lines of visual acuity at 1 year	9	1333	Risk Ratio (M-H, Fixed, 95% CI)	3.60 [2.70, 4.80]
1.1 Bevacizumab	3	207	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [1.42, 5.91]
1.2 Ranibizumab	4	465	Risk Ratio (M-H, Fixed, 95% CI)	3.59 [2.03, 6.33]
1.3 Aflibercept	2	661	Risk Ratio (M-H, Fixed, 95% CI)	3.81 [2.61, 5.56]
2 Loss 3+ lines of visual acuity at 1 year	6	1086	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.05, 0.24]
2.1 Bevacizumab	2	167	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.05, 0.51]
2.2 Ranibizumab	2	258	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.05, 0.91]
2.3 Aflibercept	2	661	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.23]
3 Visual acuity at 1 year	8	1292	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.18, -0.14]
3.1 Bevacizumab	2	165	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.12]
3.2 Ranibizumab	4	466	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.15, -0.08]
3.3 Aflibercept	2	661	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.24, -0.17]
4 Central macular thickness at 1 year	7	1215	Mean Difference (IV, Fixed, 95% CI)	-78.83 [-94.55, -63.12]
4.1 Bevacizumab	2	165	Mean Difference (IV, Fixed, 95% CI)	-43.61 [-82.11, -5.11]
4.2 Ranibizumab	3	390	Mean Difference (IV, Fixed, 95% CI)	-47.94 [-73.15, -22.73]
4.3 Aflibercept	2	660	Mean Difference (IV, Fixed, 95% CI)	-119.02 [-142.58, -95.45]
5 Quality of life at 1 year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Ranibizumab	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Gain 3+ lines of visual acuity at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Bevacizumab	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Loss 3+ lines of visual acuity at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Bevacizumab	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Visual acuity at 2 years	2	142	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.24, -0.05]
8.1 Bevacizumab	2	142	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.24, -0.05]
9 Central macular thickness at 2 years	2	142	Mean Difference (IV, Fixed, 95% CI)	-18.35 [-62.23, 25.52]
9.1 Bevacizumab	2	142	Mean Difference (IV, Fixed, 95% CI)	-18.35 [-62.23, 25.52]
10 Quality of life (near activities) at 1 year	1	195	Mean Difference (IV, Fixed, 95% CI)	4.4 [1.33, 7.47]
10.1 Ranibizumab	1	195	Mean Difference (IV, Fixed, 95% CI)	4.4 [1.33, 7.47]
11 Quality of life (far activities) at 1 year	1	195	Mean Difference (IV, Fixed, 95% CI)	4.4 [1.33, 7.47]
11.1 Ranibizumab	1	195	Mean Difference (IV, Fixed, 95% CI)	4.4 [1.33, 7.47]

Comparison 2. Anti-VEGF versus sham

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gain 3+ lines of visual acuity at 1 year	3	497	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.36, 3.53]
1.1 Pegaptanib	2	346	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.01, 3.16]
1.2 Ranibizumab	1	151	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [1.32, 7.62]
2 Loss 3+ lines of visual acuity at 1 year	2	411	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.13, 0.59]
2.1 Pegaptanib	1	260	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.16, 1.21]
2.2 Ranibizumab	1	151	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.04, 0.50]
3 Visual acuity at 1 year	4	575	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.17, -0.08]
3.1 Bevacizumab	1	78	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.26, -0.04]
3.2 Pegaptanib	2	346	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.13, -0.03]
3.3 Ranibizumab	1	151	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.32, -0.15]
4 Central macular thickness at 1 year	3	315	Mean Difference (IV, Fixed, 95% CI)	-126.38 [-160.27, -92.49]
4.1 Bevacizumab	1	78	Mean Difference (IV, Fixed, 95% CI)	-130.6 [-187.27, -73.93]
4.2 Pegaptanib	1	86	Mean Difference (IV, Fixed, 95% CI)	-71.7 [-149.71, 6.31]
4.3 Ranibizumab	1	151	Mean Difference (IV, Fixed, 95% CI)	-145.80 [-196.12, -95.48]
5 Gain 3+ lines of visual acuity at 2 years	2	1223	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [2.02, 3.09]
5.1 Pegaptanib	1	207	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.87, 2.78]
5.2 Ranibizumab 0.5 mg monthly.	1	509	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [2.03, 3.86]
5.3 Ranibizumab 0.3 mg monthly	1	507	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.86, 3.58]
6 Loss 3+ lines of visual acuity at 2 years	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Pegaptanib	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Ranibizumab 0.5 mg monthly	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Ranibizumab 0.3 mg monthly	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Visual acuity at 2 years	2	1223	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.20, -0.15]
7.1 Pegaptanib	1	207	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.17, -0.02]
7.2 Ranibizumab 0.5 mg monthly	1	509	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.23, -0.14]
7.3 Ranibizumab 0.3 mg monthly	1	507	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.24, -0.15]
8 Central macular thickness at 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Ranibizumab 0.5 mg monthly	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Ranibizumab 0.3 mg monthly	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

9 Quality of life at 1 year	1	Mean Difference (Fixed, 95% CI)	Totals not selected
10 Quality of life at 2 years	1	Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 3. Anti-VEGF plus laser versus laser alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gain 3+ lines of visual acuity at 1 year	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Prompt photocoagulation	4	919	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [1.76, 3.21]
1.2 Deferred photocoagulation	1	481	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.31, 2.70]
2 Loss 3+ lines of visual acuity at 1 year	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Prompt photocoagulation	2	708	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.13, 0.67]
2.2 Deferred photocoagulation	1	481	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.10, 0.77]
3 Visual acuity at 1 year	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Prompt photocoagulation	5	1045	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.13, -0.08]
3.2 Deferred photocoagulation	1	481	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.17, -0.07]
4 Central macular thickness at 1 year	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Prompt photocoagulation	3	801	Mean Difference (IV, Fixed, 95% CI)	-50.66 [-66.71, -34.61]
4.2 Deferred photocoagulation	1	446	Mean Difference (IV, Fixed, 95% CI)	-35.0 [-62.00, -6.00]
5 Quality of life at 1 year	1	200	Mean Difference (IV, Fixed, 95% CI)	4.80 [1.85, 7.75]
5.1 Prompt photocoagulation	1	200	Mean Difference (IV, Fixed, 95% CI)	4.80 [1.85, 7.75]
6 Gain 3+ lines of visual acuity at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Prompt photocoagulation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Deferred photocoagulation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Loss 3+ lines of visual acuity at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Prompt photocoagulation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Deferred photocoagulation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Visual acuity at 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Prompt photocoagulation	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Deferred photocoagulation	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Central macular thickness at 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Prompt photocoagulation	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

9.2 Deferred photocoagulation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Adverse events: anti-VEGF versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systemic serious adverse events	15	2985	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.83, 1.17]
1.1 Follow-up 6-12 months	11	1879	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.28]
1.2 Follow-up 24 months	4	1106	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.23]
2 Total ATC thromboembolic events at 6 to 24 months	14	3034	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.63, 1.25]
2.1 Follow-up 6 to 12 months	10	1663	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.67, 2.64]
2.2 Follow-up 24 months	4	1371	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.38]
3 Death	15	3562	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.52, 1.47]
3.1 Follow-up 6 to 12 months	12	2271	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.29, 1.81]
3.2 Follow-up 24 months	3	1291	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.36, 3.45]

Comparison 5. Bevacizumab versus ranibizumab

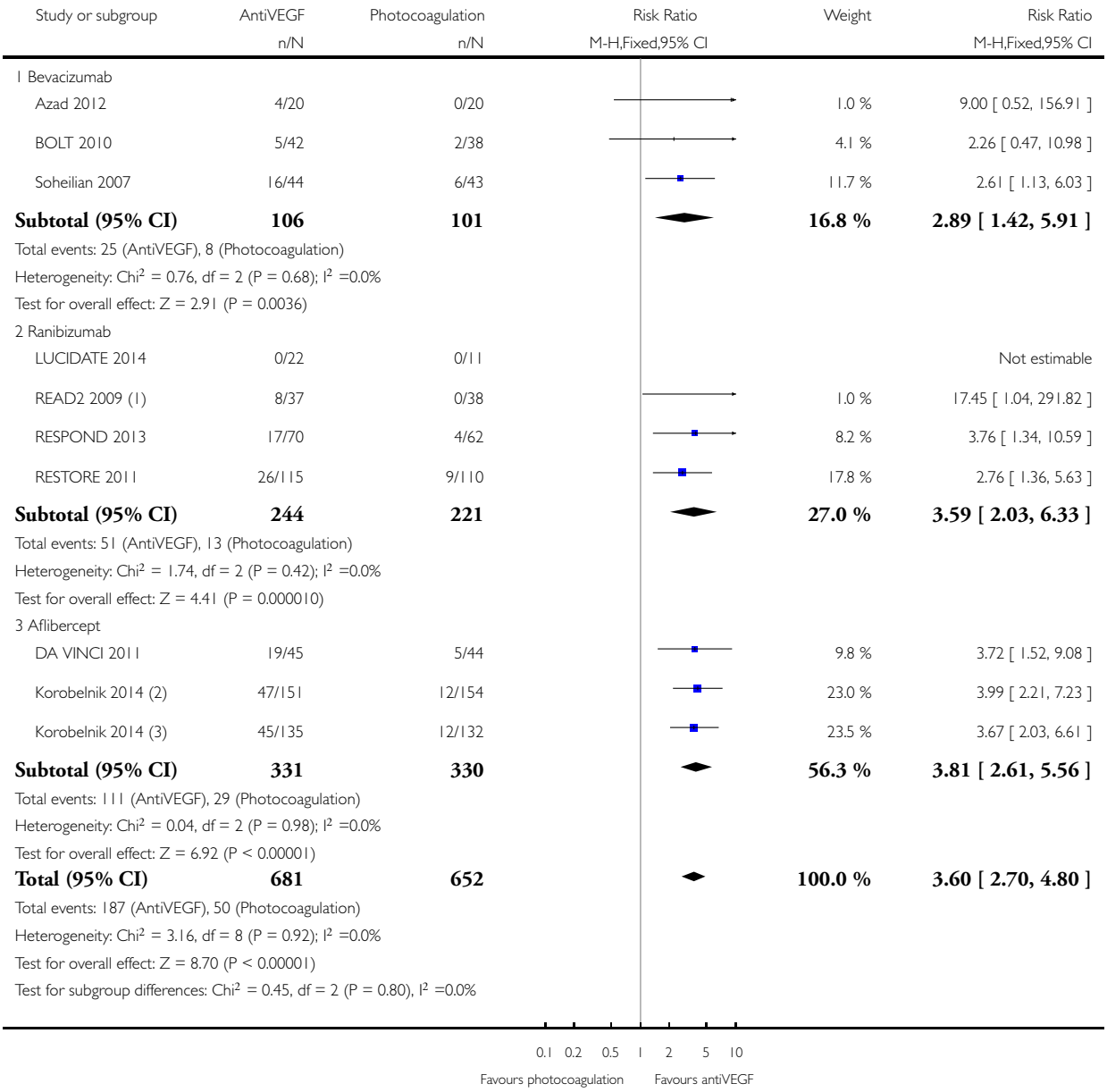
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gain 3+ lines of visual acuity at 1 year	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.44, 1.47]
2 Loss 3+ lines of visual acuity at 1 year	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [0.11, 62.23]
3 Visual acuity at 1 year	2	160	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.05, 0.05]
4 Central macular thickness at 1 year	2	160	Mean Difference (IV, Fixed, 95% CI)	27.02 [-5.70, 59.73]

Analysis 1.1. Comparison 1 Anti-VEGF versus laser, Outcome 1 Gain 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 1 Gain 3+ lines of visual acuity at 1 year



(1) follow-up: 6 months

(2) VISTA study

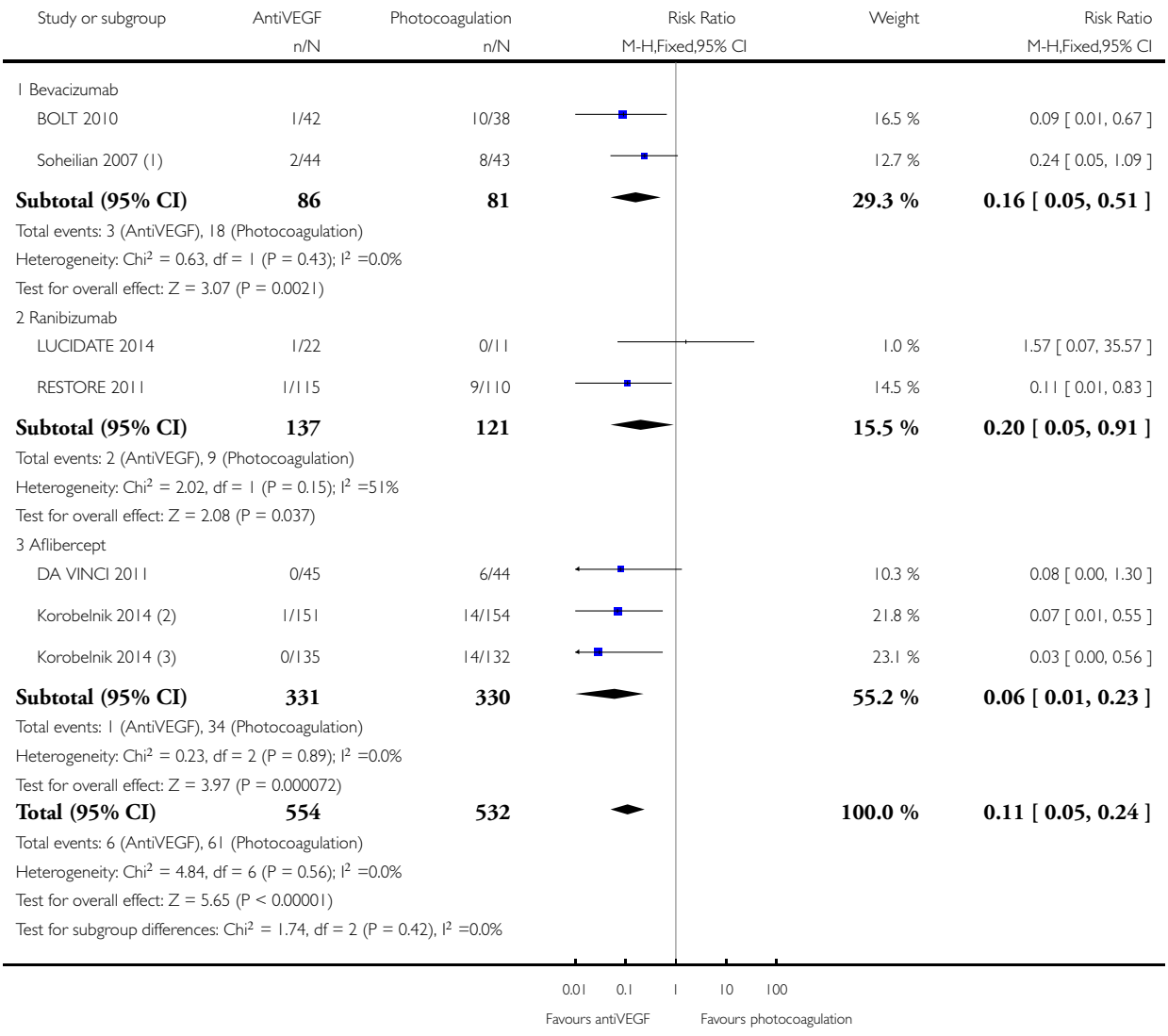
(3) VIVID study

Analysis 1.2. Comparison 1 Anti-VEGF versus laser, Outcome 2 Loss 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 2 Loss 3+ lines of visual acuity at 1 year



(1) Data reported at 9 months

(2) VISTA study

(3) VIVID study

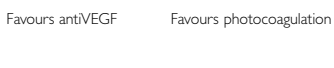
Analysis 1.3. Comparison 1 Anti-VEGF versus laser, Outcome 3 Visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 3 Visual acuity at 1 year

Study or subgroup	AntiVEGF N	AntiVEGF Mean(SD)[Δ logMAR]	Photocoagulation N	Photocoagulation Mean(SD)[Δ logMAR]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bevacizumab							
BOLT 2010	-0.1128571 (0.1528794)	42	38	0.09 (0.2631054)		5.2 %	-0.20 [-0.30, -0.11]
Soheilian 2007	43	-0.21 (0.27)	42	-0.02 (0.34)		2.8 %	-0.19 [-0.32, -0.06]
Subtotal (95% CI)	**85**		**80**			**8.0 %**	**-0.20 [-0.28, -0.12]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² =0.0%							
Test for overall effect: Z = 5.07 (P < 0.00001)							
2 Ranibizumab							
LUCIDATE 2014	22	-0.12 (0.17)	11	0.02 (0.212)		2.3 %	-0.14 [-0.28, 0.01]
READ2 2009 (1)	37	-0.1322 (0.182)	38	-0.05 (0.185)		6.9 %	-0.08 [-0.17, 0.00]
RESPOND 2013	71	-0.178 (0.15906)	62	-0.01 (0.25712)		8.7 %	-0.17 [-0.25, -0.10]
RESTORE 2011	115	-0.122 (0.1286)	110	-0.02 (0.1712)		30.0 %	-0.11 [-0.15, -0.07]
Subtotal (95% CI)	**245**		**221**			**47.8 %**	**-0.12 [-0.15, -0.08]**
Heterogeneity: Chi² = 3.09, df = 3 (P = 0.38); I² =3%							
Test for overall effect: Z = 7.25 (P < 0.00001)							
3 Aflibercept							
DA VINCI 2011	45	-0.24 (0.2218)	44	0.03 (0.4144)		2.5 %	-0.27 [-0.40, -0.13]
Korobelnik 2014 (2)	151	-0.214 (0.164)	154	0 (0.25)		21.1 %	-0.21 [-0.26, -0.16]
Korobelnik 2014 (3)	135	-0.214 (0.186)	132	-0.02 (0.212)		20.6 %	-0.19 [-0.24, -0.14]
Subtotal (95% CI)	**331**		**330**			**44.2 %**	**-0.20 [-0.24, -0.17]**
Heterogeneity: Chi² = 1.16, df = 2 (P = 0.56); I² =0.0%							
Test for overall effect: Z = 12.21 (P < 0.00001)							



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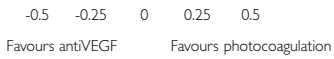
Study or subgroup	AntiVEGF N	AntiVEGF Mean(SD)[Δ logMAR]	Photocoagulation N	Photocoagulation Mean(SD)[Δ logMAR]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Total (95% CI)	**661**		**631**		♦	**100.0 %**	**-0.16 [-0.18, -0.14]**
Heterogeneity: Chi² = 19.53, df = 8 (P = 0.01); I² =59%							
Test for overall effect: Z = 14.56 (P < 0.00001)							
Test for subgroup differences: Chi² = 15.25, df = 2 (P = 0.00), I² =87%							



(1) Follow-up: 6 months; standard deviations derived from a figure

(2) VISTA study

(3) VIVID study

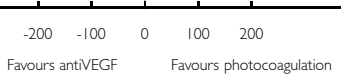
Analysis 1.4. Comparison 1 Anti-VEGF versus laser, Outcome 4 Central macular thickness at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 4 Central macular thickness at 1 year

Study or subgroup	AntiVEGF N	AntiVEGF Mean(SD)[Δ μ m]	Photocoagulation N	Photocoagulation Mean(SD)[Δ μ m]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bevacizumab							
BOLT 2010	42	-130 (122)	38	-68 (171)		5.7 %	-62.00 [-127.71, 3.71]
Soheilian 2007	43	-40 (133)	42	-6 (86)		10.9 %	-34.00 [-81.51, 13.51]
Subtotal (95% CI)	**85**		**80**		◆	**16.7 %**	**-43.61 [-82.11, -5.11]**
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² =0.0%							
Test for overall effect: Z = 2.22 (P = 0.026)							
2 Ranibizumab							
LUCIDATE 2014	22	-131.5 (98)	11	-102.9 (88.4)		5.6 %	-28.60 [-94.98, 37.78]
RESPOND 2013	71	-143.5 (146.38)	61	-107.1 (146.84)		9.8 %	-36.40 [-86.57, 13.77]
RESTORE 2011	115	-118.7 (115.07)	110	-61.3 (132.29)		23.4 %	-57.40 [-89.86, -24.94]



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Study or subgroup	AntiVEGF N	Mean(SD)[Δ μ m]	Photocoagulation N	Mean(SD)[Δ μ m]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**208**		**182**			**38.9 %**	**-47.94 [-73.15, -22.73]**
Heterogeneity: Chi^2 = 0.86, df = 2 (P = 0.65); I^2 =0.0%							
Test for overall effect: Z = 3.73 (P = 0.00019)							
3 Aflibercept							
DA VINCI 2011	44	-180.3 (124.43)	43	-58.4 (177.6)		5.9 %	-121.90 [-186.47, -57.33]
Korobelnik 2014 (1)	136	-192.4 (149.9)	132	-66.2 (139)		20.6 %	-126.20 [-160.80, -91.60]
Korobelnik 2014 (2)	151	-183.1 (153.5)	154	-73.3 (176.7)		17.9 %	-109.80 [-146.93, -72.67]
Subtotal (95% CI)	**331**		**329**			**44.5 %**	**-119.02 [-142.58, -95.45]**
Heterogeneity: Chi^2 = 0.41, df = 2 (P = 0.81); I^2 =0.0%							
Test for overall effect: Z = 9.90 (P < 0.00001)							
Total (95% CI)	**624**		**591**			**100.0 %**	**-78.83 [-94.55, -63.12]**
Heterogeneity: Chi^2 = 21.88, df = 7 (P = 0.003); I^2 =68%							
Test for overall effect: Z = 9.83 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 20.15, df = 2 (P = 0.00), I^2 =90%							

(1) VIVID study

(2) VISTA study

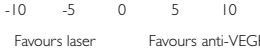
Analysis 1.5. Comparison 1 Anti-VEGF versus laser, Outcome 5 Quality of life at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 5 Quality of life at 1 year

Study or subgroup	AntiVEGF N	Mean(SD)[Δ score]	Photocoagulation N	Mean(SD)[Δ score]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Ranibizumab						
RESTORE 2011	99	5 (11.0102)	96	0.6 (10.84209)		4.40 [1.33, 7.47]

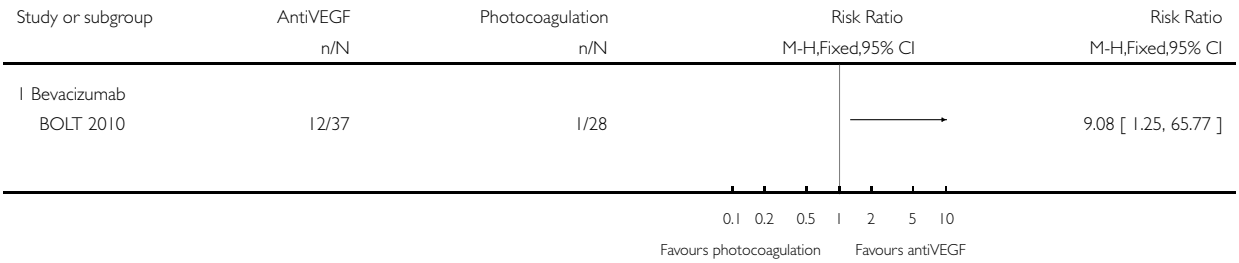


Analysis 1.6. Comparison 1 Anti-VEGF versus laser, Outcome 6 Gain 3+ lines of visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 6 Gain 3+ lines of visual acuity at 2 years

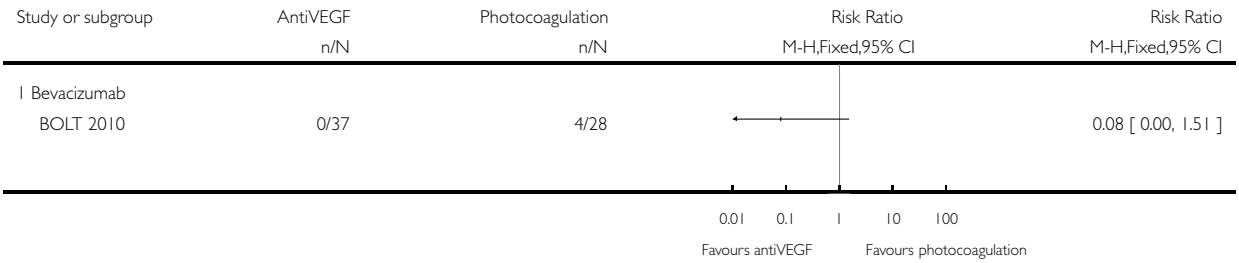


Analysis 1.7. Comparison 1 Anti-VEGF versus laser, Outcome 7 Loss 3+ lines of visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 7 Loss 3+ lines of visual acuity at 2 years



Analysis 1.8. Comparison 1 Anti-VEGF versus laser, Outcome 8 Visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

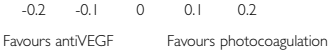
Outcome: 8 Visual acuity at 2 years

Study or subgroup	AntiVEGF N	AntiVEGF Mean(SD)[logMAR]	Photocoagulation N	Photocoagulation Mean(SD)[logMAR]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bevacizumab							
BOLT 2010	37	0.412 (0.266)	28	0.6 (0.252)		60.4 %	-0.19 [-0.32, -0.07]
Soheilian 2007 (1)	39	-0.1 (0.37)	38	-0.03 (0.33)		39.6 %	-0.07 [-0.23, 0.09]
Total (95% CI)	**76**		**66**			**100.0 %**	**-0.14 [-0.24, -0.05]**

Heterogeneity: $Chi^2 = 1.41$, df = 1 (P = 0.24); $I^2 = 29\%$

Test for overall effect: Z = 2.86 (P = 0.0042)

Test for subgroup differences: Not applicable



(1) Change in visual acuity from baseline

Analysis 1.9. Comparison 1 Anti-VEGF versus laser, Outcome 9 Central macular thickness at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

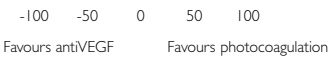
Outcome: 9 Central macular thickness at 2 years

Study or subgroup	AntiVEGF N	Mean(SD)[μ m]	Photocoagulation N	Mean(SD)[μ m]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bevacizumab							
BOLT 2010	37	355 (174)	28	360 (125)		36.4 %	-5.00 [-77.71, 67.71]
Soheilian 2007 (1)	39	-24 (137)	38	2 (108)		63.6 %	-26.00 [-81.03, 29.03]
Total (95% CI)	**76**		**66**			**100.0 %**	**-18.35 [-62.23, 25.52]**

Heterogeneity: $Chi^2 = 0.20$, df = 1 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable



(1) Change in central macular thickness from baseline

Analysis 1.10. Comparison 1 Anti-VEGF versus laser, Outcome 10 Quality of life (near activities) at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

Outcome: 10 Quality of life (near activities) at 1 year

Study or subgroup	AntiVEGF N	Mean(SD)[Δ score]	Photocoagulation N	Mean(SD)[Δ score]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Ranibizumab							
RESTORE 2011	99	5 (11.0102)	96	0.6 (10.84209)		100.0 %	4.40 [1.33, 7.47]
Total (95% CI)	**99**		**96**			**100.0 %**	**4.40 [1.33, 7.47]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.81 (P = 0.0049)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Anti-VEGF versus laser, Outcome 11 Quality of life (far activities) at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 1 Anti-VEGF versus laser

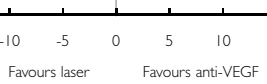
Outcome: 11 Quality of life (far activities) at 1 year

Study or subgroup	AntiVEGF N	Mean(SD)[Δ score]	Photocoagulation N	Mean(SD)[Δ score]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Ranibizumab							
RESTORE 2011	99	5 (11.0102)	96	0.6 (10.84209)		100.0 %	4.40 [1.33, 7.47]
Total (95% CI)	**99**		**96**			**100.0 %**	**4.40 [1.33, 7.47]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.81 (P = 0.0049)

Test for subgroup differences: Not applicable

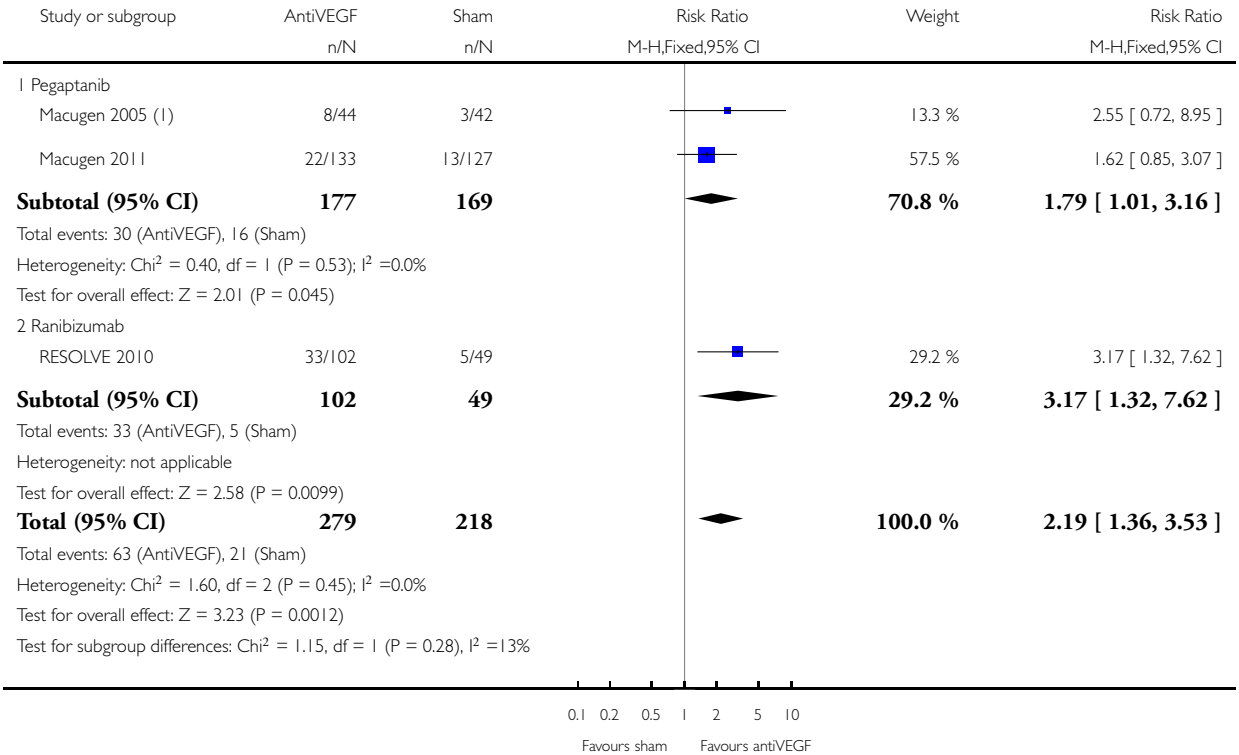


Analysis 2.1. Comparison 2 Anti-VEGF versus sham, Outcome 1 Gain 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 1 Gain 3+ lines of visual acuity at 1 year



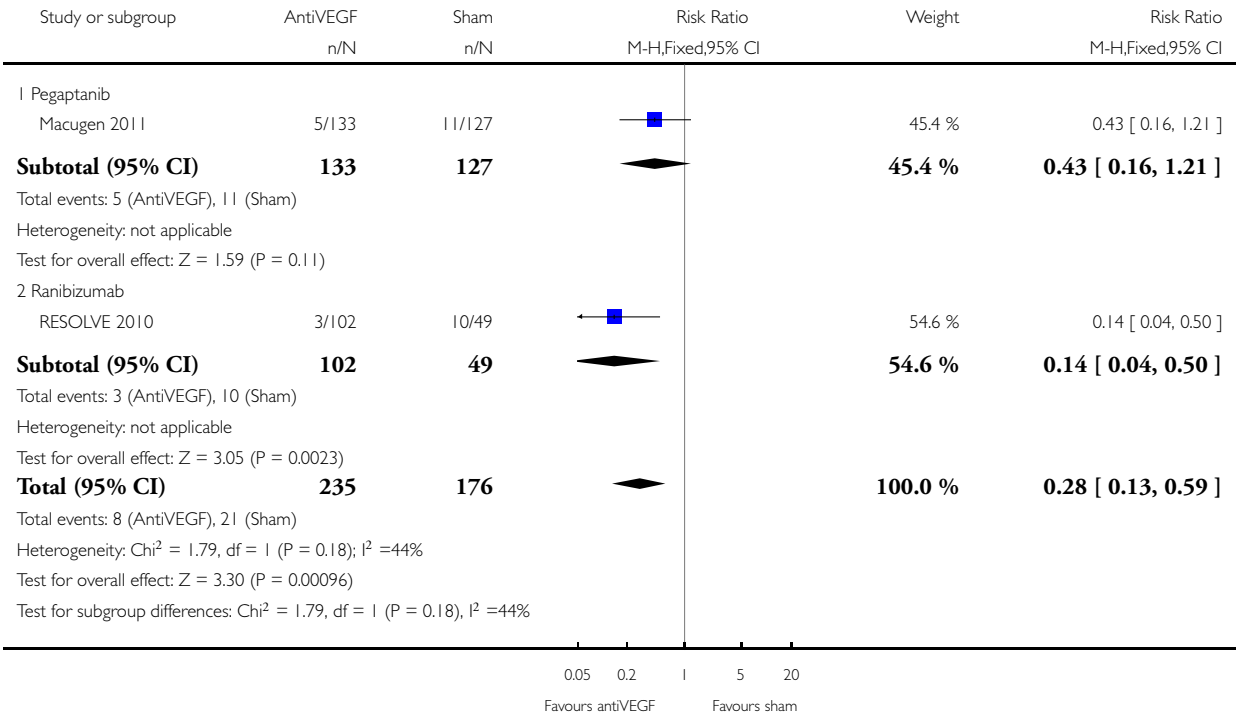
(1) Follow-up: 36 weeks

Analysis 2.2. Comparison 2 Anti-VEGF versus sham, Outcome 2 Loss 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 2 Loss 3+ lines of visual acuity at 1 year



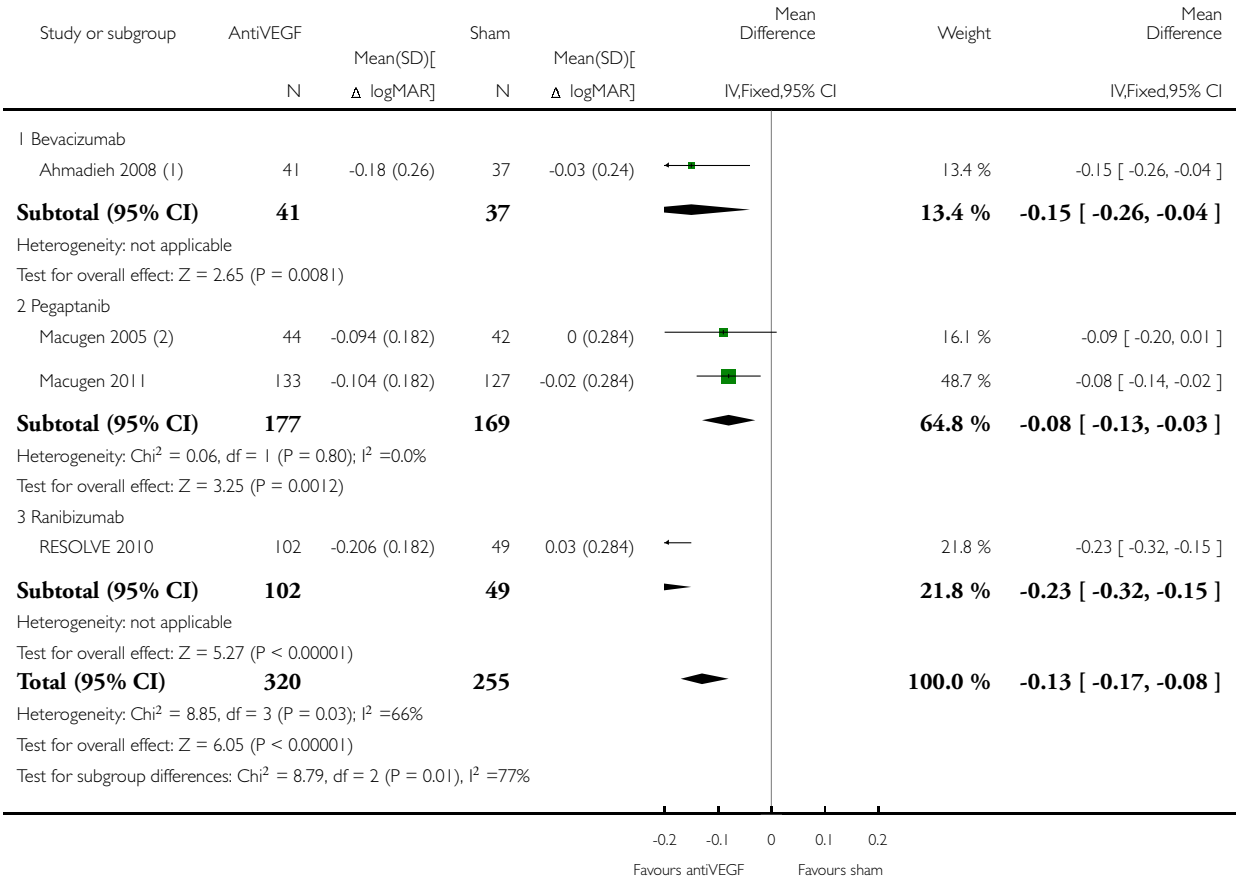
Analysis 2.3. Comparison 2 Anti-VEGF versus sham, Outcome 3 Visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 3 Visual acuity at 1 year

Study or subgroup	AntiVEGF N	Mean(SD)[Δ logMAR]	Sham N	Mean(SD)[Δ logMAR]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bevacizumab							
Ahmadieh 2008 (1)	41	-0.18 (0.26)	37	-0.03 (0.24)		13.4 %	-0.15 [-0.26, -0.04]
Subtotal (95% CI)	**41**		**37**			**13.4 %**	**-0.15 [-0.26, -0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.65 (P = 0.0081)							
2 Pegaptanib							
Macugen 2005 (2)	44	-0.094 (0.182)	42	0 (0.284)		16.1 %	-0.09 [-0.20, 0.01]
Macugen 2011	133	-0.104 (0.182)	127	-0.02 (0.284)		48.7 %	-0.08 [-0.14, -0.02]
Subtotal (95% CI)	**177**		**169**			**64.8 %**	**-0.08 [-0.13, -0.03]**
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 3.25 (P = 0.0012)							
3 Ranibizumab							
RESOLVE 2010	102	-0.206 (0.182)	49	0.03 (0.284)		21.8 %	-0.23 [-0.32, -0.15]
Subtotal (95% CI)	**102**		**49**			**21.8 %**	**-0.23 [-0.32, -0.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.27 (P < 0.00001)							
Total (95% CI)	**320**		**255**			**100.0 %**	**-0.13 [-0.17, -0.08]**
Heterogeneity: Chi^2 = 8.85, df = 3 (P = 0.03); I^2 =66%							
Test for overall effect: Z = 6.05 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 8.79, df = 2 (P = 0.01), I^2 =77%							



(1) Follow-up: 24 weeks

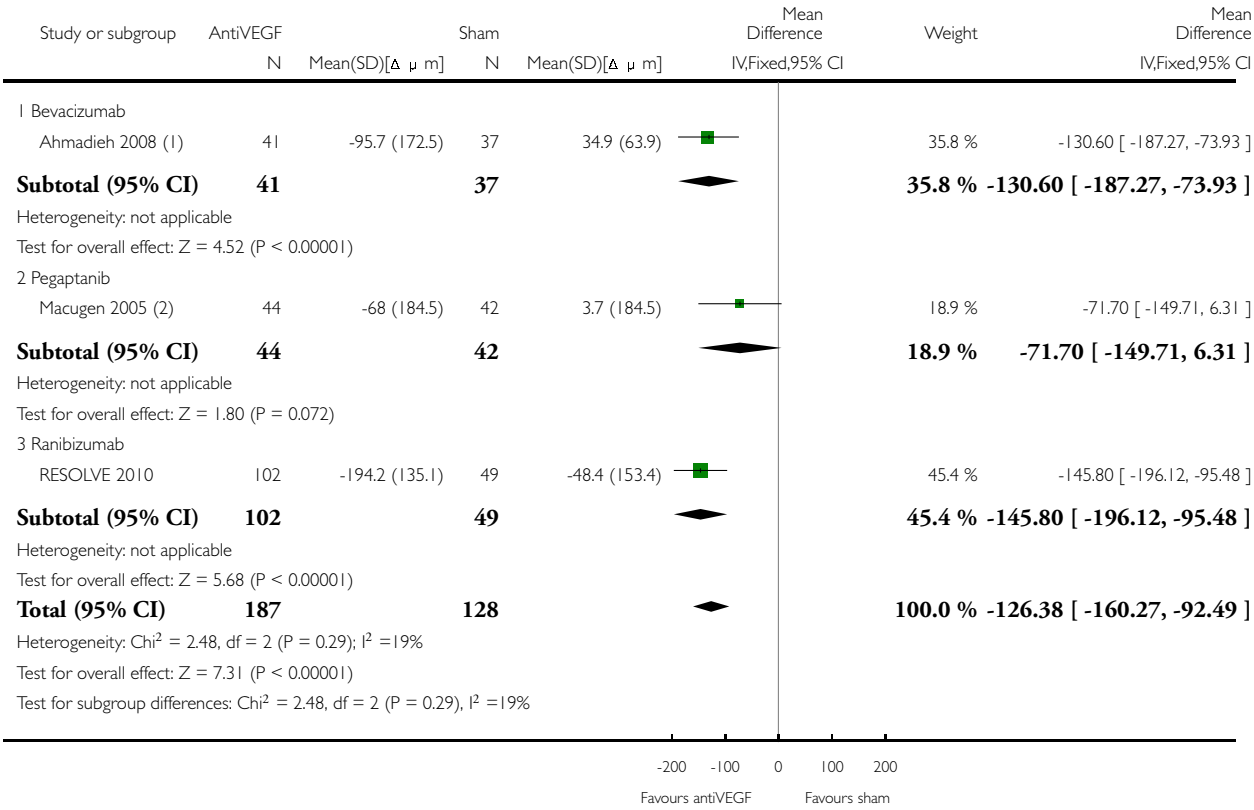
(2) Follow-up: 36 weeks

Analysis 2.4. Comparison 2 Anti-VEGF versus sham, Outcome 4 Central macular thickness at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 4 Central macular thickness at 1 year



(1) Follow-up: 24 weeks

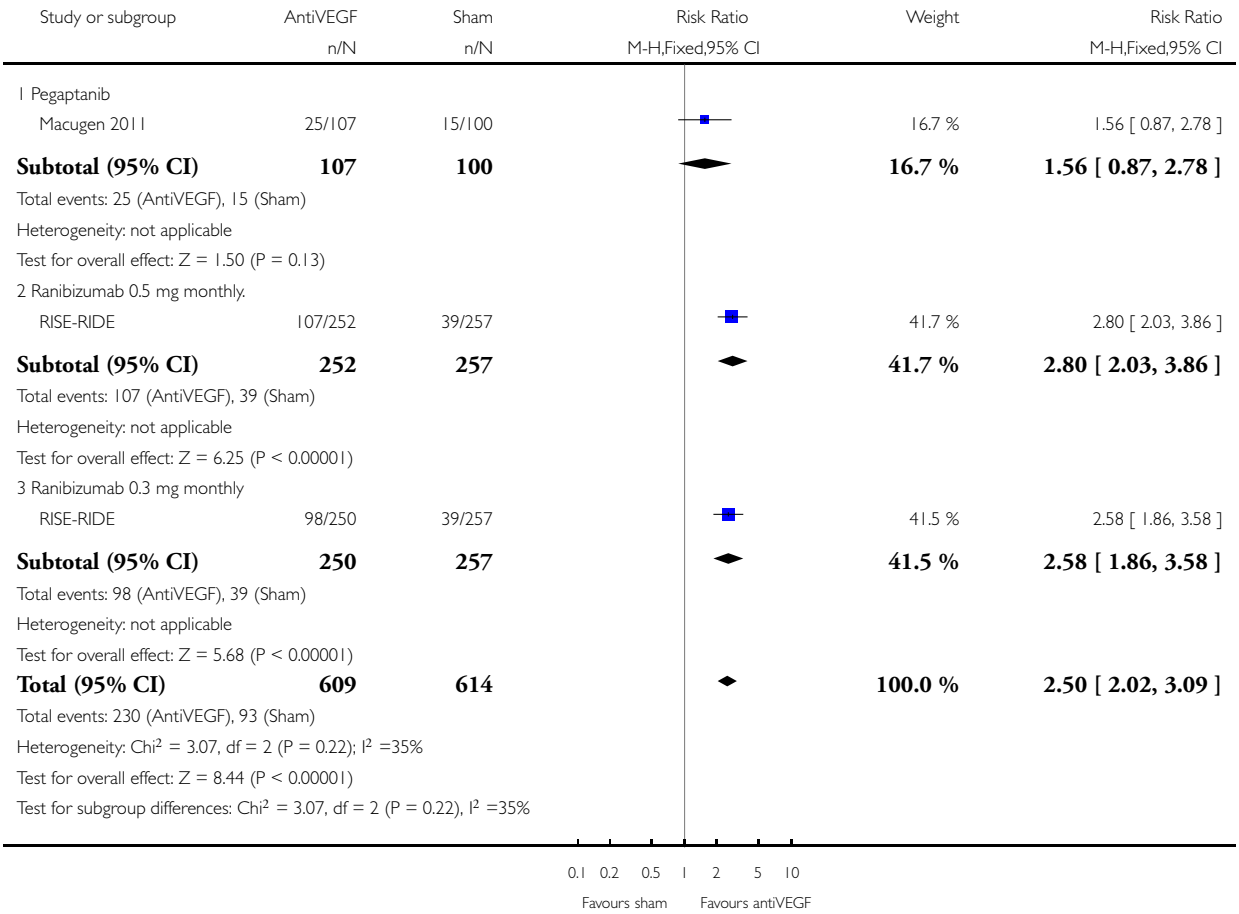
(2) Follow-up: 36 weeks.

Analysis 2.5. Comparison 2 Anti-VEGF versus sham, Outcome 5 Gain 3+ lines of visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 5 Gain 3+ lines of visual acuity at 2 years



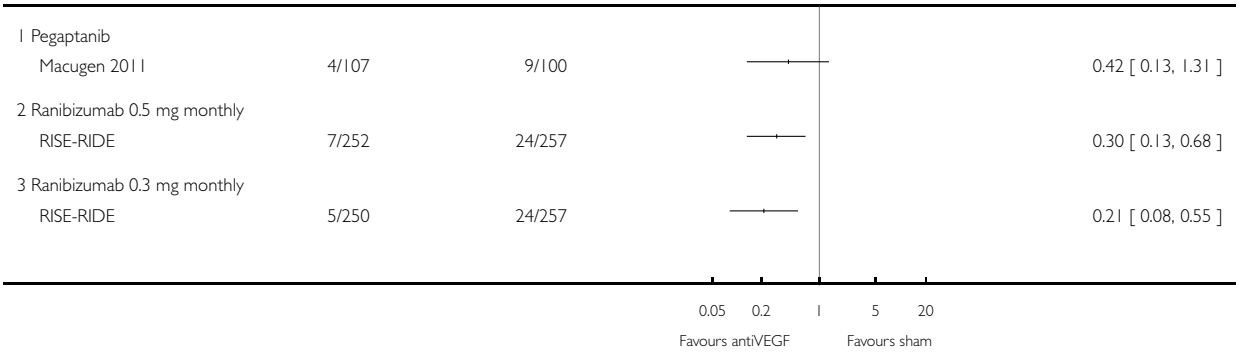
Analysis 2.6. Comparison 2 Anti-VEGF versus sham, Outcome 6 Loss 3+ lines of visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 6 Loss 3+ lines of visual acuity at 2 years

Study or subgroup	AntiVEGF n/N	Sham n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Pegaptanib				
Macugen 2011	4/107	9/100		0.42 [0.13, 1.31]
2 Ranibizumab 0.5 mg monthly				
RISE-RIDE	7/252	24/257		0.30 [0.13, 0.68]
3 Ranibizumab 0.3 mg monthly				
RISE-RIDE	5/250	24/257		0.21 [0.08, 0.55]



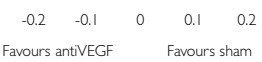
Analysis 2.7. Comparison 2 Anti-VEGF versus sham, Outcome 7 Visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 7 Visual acuity at 2 years

Study or subgroup	AntiVEGF N	Mean(SD)[Δ logMAR]	Sham N	Mean(SD)[Δ logMAR]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Pegaptanib							
Macugen 2011	107	-0.122 (0.242)	100	-0.03 (0.278)		17.0 %	-0.10 [-0.17, -0.02]
Subtotal (95% CI)	**107**		**100**			**17.0 %**	**-0.10 [-0.17, -0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.64 (P = 0.0082)							
2 Ranibizumab 0.5 mg monthly							
RISE-RIDE	252	-0.238 (0.242)	257	-0.05 (0.278)		42.0 %	-0.19 [-0.23, -0.14]
Subtotal (95% CI)	**252**		**257**			**42.0 %**	**-0.19 [-0.23, -0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.06 (P < 0.00001)							
3 Ranibizumab 0.3 mg monthly							
RISE-RIDE	250	-0.25 (0.2478)	257	-0.05 (0.278)		41.0 %	-0.20 [-0.24, -0.15]
Subtotal (95% CI)	**250**		**257**			**41.0 %**	**-0.20 [-0.24, -0.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.47 (P < 0.00001)							
Total (95% CI)	**609**		**614**			**100.0 %**	**-0.18 [-0.20, -0.15]**
Heterogeneity: Chi^2 = 5.92, df = 2 (P = 0.05); I^2 =66%							
Test for overall effect: Z = 11.74 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 5.92, df = 2 (P = 0.05), I^2 =66%							



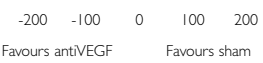
Analysis 2.8. Comparison 2 Anti-VEGF versus sham, Outcome 8 Central macular thickness at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 8 Central macular thickness at 2 years

Study or subgroup	antiVEGF N	Mean(SD)[Δ μ m]	sham N	Mean(SD)[Δ μ m]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Ranibizumab 0.5 mg monthly						
RISE-RIDE	250	-261.08 (192.93)	257	-129.4 (203.7)		-131.68 [-166.21, -97.15]
2 Ranibizumab 0.3 mg monthly						
RISE-RIDE	250	-256.22 (191.95)	257	-129.4 (203.7)		-126.82 [-161.26, -92.38]



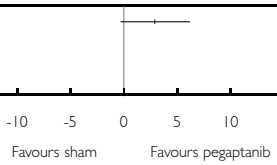
Analysis 2.9. Comparison 2 Anti-VEGF versus sham, Outcome 9 Quality of life at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 9 Quality of life at 1 year

Study or subgroup	sham N	pegaptanib N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Macugen 2011 (1)	133	127	2.92 (1.653)		2.92 [-0.32, 6.16]



(1) Change in NEI-VFQ 25 composite score

Analysis 2.10. Comparison 2 Anti-VEGF versus sham, Outcome 10 Quality of life at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 2 Anti-VEGF versus sham

Outcome: 10 Quality of life at 2 years

Study or subgroup	sham N	pegaptanib N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Macugen 2011 (1)	107	100	4.47 (2.148)		4.47 [0.26, 8.68]

(1) Change in NEI-VFQ 25 composite score

Analysis 3.1. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 1 Gain 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 1 Gain 3+ lines of visual acuity at 1 year

Study or subgroup	ranibizumab + photocoag. n/N	laser photocoag-ulation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Prompt photocoagulation					
DRCRnet 2010	57/187	43/293		70.4 %	2.08 [1.46, 2.95]
READ2 2009 (1)	3/40	0/38		1.1 %	6.66 [0.36, 124.77]
RESPOND 2013	15/71	4/62		9.0 %	3.27 [1.15, 9.35]
RESTORE 2011	27/118	9/110		19.6 %	2.80 [1.38, 5.68]
Subtotal (95% CI)	**416**	**503**		**100.0 %**	**2.37 [1.76, 3.21]**
Total events: 102 (ranibizumab + photocoag.), 56 (laser photocoagulation)					
Heterogeneity: Chi^2 = 1.60, df = 3 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 5.62 (P < 0.00001)					
2 Deferred photocoagulation					

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Study or subgroup	ranibizumab + photocoag. n/N	laser photocoag-ulation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
DRCRnet 2010	52/188	43/293		100.0 %	1.88 [1.31, 2.70]
Subtotal (95% CI)	**188**	**293**		**100.0 %**	**1.88 [1.31, 2.70]**
Total events: 52 (ranibizumab + photocoag.), 43 (laser photocoagulation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.45 (P = 0.00056)					
Test for subgroup differences: Chi^2 = 0.93, df = 1 (P = 0.33), I^2 =0.0%					

(1) follow-up: 6 months

Analysis 3.2. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 2 Loss 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 2 Loss 3+ lines of visual acuity at 1 year

Study or subgroup	ranibizumab + photocoag. n/N	laser photocoag-ulation n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Prompt photocoagulation					
DRCRnet 2010	3/187	23/293		48.3 %	0.20 [0.06, 0.67]
RESTORE 2011	4/118	9/110		51.7 %	0.41 [0.13, 1.31]
Subtotal (95% CI)	**305**	**403**		**100.0 %**	**0.29 [0.13, 0.67]**
Total events: 7 (ranibizumab + photocoag.), 32 (laser photocoagulation)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.73, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 2.90 (P = 0.0037)					
2 Deferred photocoagulation					
DRCRnet 2010	4/188	23/293		100.0 %	0.27 [0.10, 0.77]
Subtotal (95% CI)	**188**	**293**		**100.0 %**	**0.27 [0.10, 0.77]**

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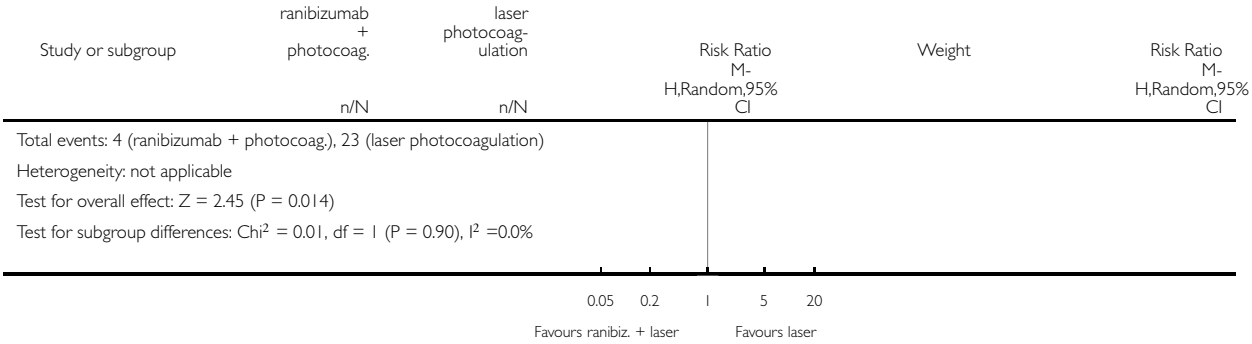
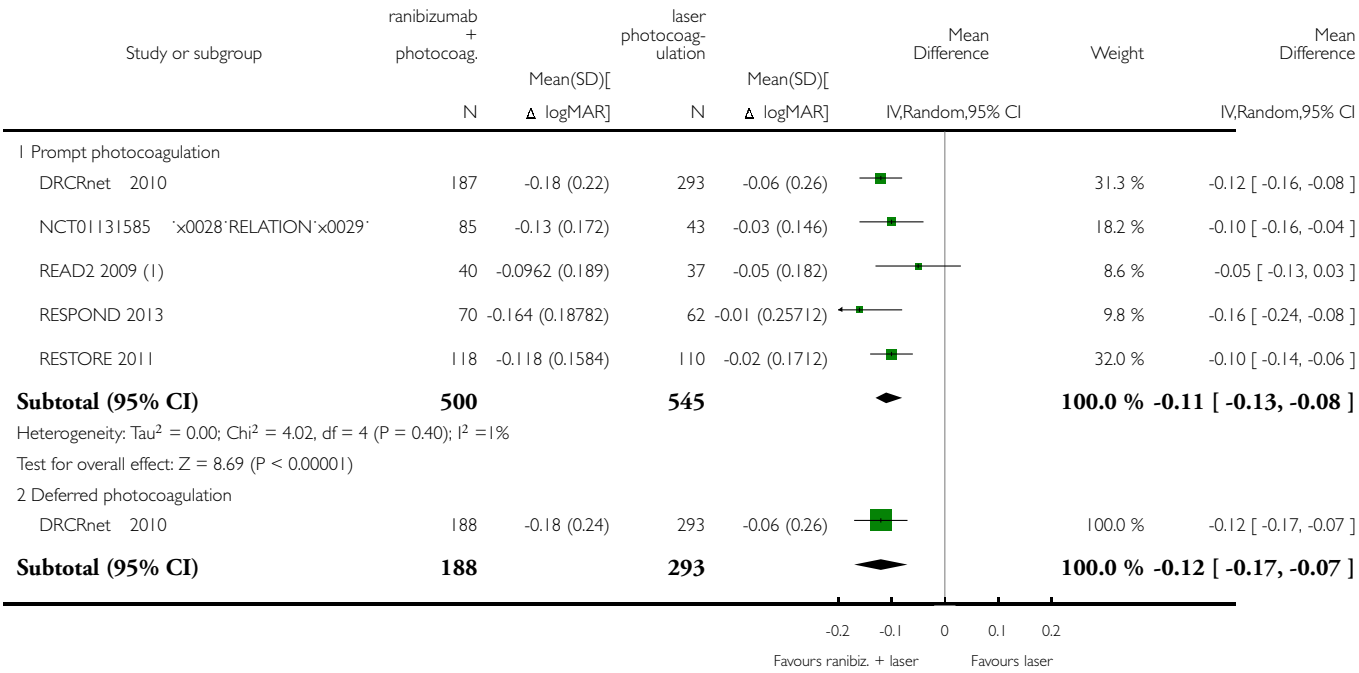


Analysis 3.3. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 3 Visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 3 Visual acuity at 1 year



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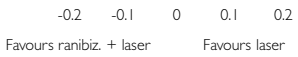
Study or subgroup	ranibizumab + photocoag. N	Mean(SD)[Δ logMAR]	laser photocoag-ulation N	Mean(SD)[Δ logMAR]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: not applicable							
Test for overall effect: Z = 5.18 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² =0.0%							



(1) Follow-up: 6 months; standard deviations derived from a figure

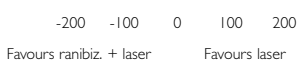
Analysis 3.4. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 4 Central macular thickness at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 4 Central macular thickness at 1 year

Study or subgroup	ranibizumab + photocoag. N	Mean(SD)[Δ μ m]	laser photocoag-ulation N	Mean(SD)[Δ μ m]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Prompt photocoagulation							
DRCRnet 2010	171	-131 (129)	271	-102 (151)		37.0 %	-29.00 [-55.40, -2.60]
RESPOND 2013	70	-152.2 (141.93)	61	-107.1 (146.84)		10.5 %	-45.10 [-94.73, 4.53]
RESTORE 2011	118	-128.3 (114.34)	110	-61.3 (43)		52.6 %	-67.00 [-89.14, -44.86]
Subtotal (95% CI)	**359**		**442**			**100.0 %**	**-50.66 [-66.71, -34.61]**
Heterogeneity: Chi² = 4.73, df = 2 (P = 0.09); I² =58%							
Test for overall effect: Z = 6.19 (P < 0.00001)							
2 Deferred photocoagulation							
DRCRnet 2010	175	-137 (136)	271	-102 (151)		100.0 %	-35.00 [-62.00, -8.00]
Subtotal (95% CI)	**175**		**271**			**100.0 %**	**-35.00 [-62.00, -8.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.54 (P = 0.011)							
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² =0.0%							



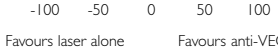
Analysis 3.5. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 5 Quality of life at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 5 Quality of life at 1 year

Study or subgroup	AntiVEGF plus laser		Laser alone		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[Δ score]	N	Mean(SD)[Δ score]	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Prompt photocoagulation							
RESTORE 2011	104	5.4 (10.42955)	96	0.6 (10.84209)		100.0 %	4.80 [1.85, 7.75]
Total (95% CI)	**104**		**96**			**100.0 %**	**4.80 [1.85, 7.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.19 (P = 0.0014)							
Test for subgroup differences: Not applicable							



Analysis 3.6. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 6 Gain 3+ lines of visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 6 Gain 3+ lines of visual acuity at 2 years

Study or subgroup	ranibizumab + photocoag. n/N	laser photocoag-ulation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Prompt photocoagulation				
DRCRnet 2010	39/136	37/211		1.64 [1.10, 2.43]
2 Deferred photocoagulation				
DRCRnet 2010	39/139	37/211		1.60 [1.08, 2.38]

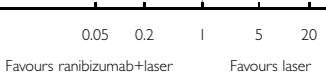
Analysis 3.7. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 7 Loss 3+ lines of visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 7 Loss 3+ lines of visual acuity at 2 years

Study or subgroup	ranibizumab + photocoag. n/N	laser photocoag-ulation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Prompt photocoagulation				
DRCRnet 2010	6/136	21/211		0.44 [0.18, 1.07]
2 Deferred photocoagulation				
DRCRnet 2010	3/139	21/211		0.22 [0.07, 0.71]



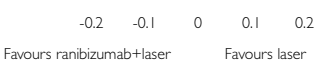
Analysis 3.8. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 8 Visual acuity at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 8 Visual acuity at 2 years

Study or subgroup	ranibizumab + photocoag. N	Mean(SD)[Δ logMAR]	laser photocoag-ulation N	Mean(SD)[Δ logMAR]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Prompt photocoagulation						
DRCRnet 2010	136	-0.14 (0.26)	211	-0.06 (0.3)		-0.08 [-0.14, -0.02]
2 Deferred photocoagulation						
DRCRnet 2010	139	-0.18 (0.28)	211	-0.06 (0.3)		-0.12 [-0.18, -0.06]



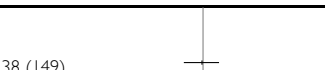
Analysis 3.9. Comparison 3 Anti-VEGF plus laser versus laser alone, Outcome 9 Central macular thickness at 2 years.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 3 Anti-VEGF plus laser versus laser alone

Outcome: 9 Central macular thickness at 2 years

Study or subgroup	ranibizumab + photocoag. N	Mean(SD)[Δ μ m]	laser photocoag-ulation N	Mean(SD)[Δ μ m]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Prompt photocoagulation						
DRCRnet 2010	136	-141 (155)	211	-138 (149)		-3.00 [-35.91, 29.91]
2 Deferred photocoagulation						
DRCRnet 2010	136	-150 (143)	211	-138 (149)		-12.00 [-43.33, 19.33]

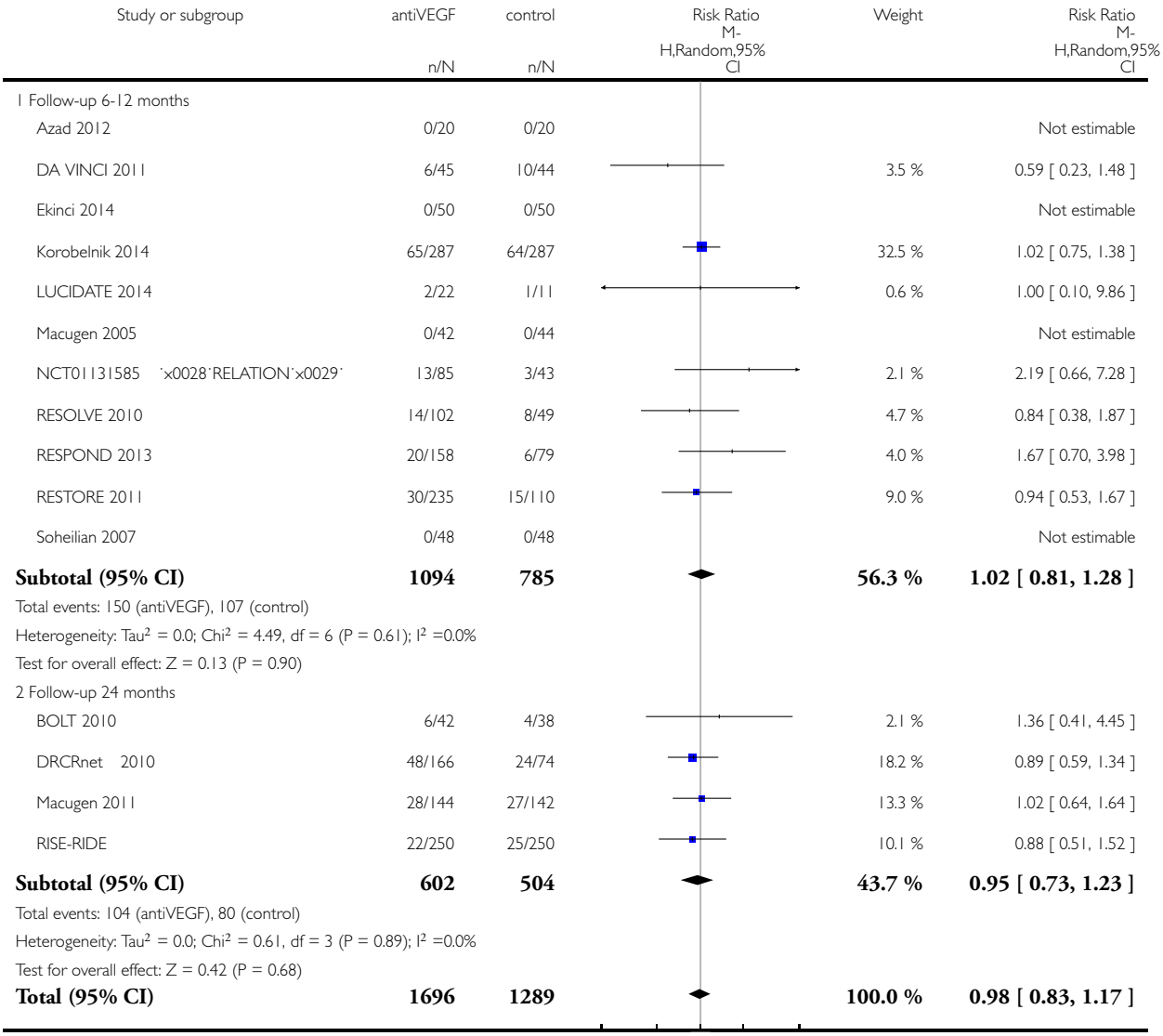


Analysis 4.1. Comparison 4 Adverse events: anti-VEGF versus control, Outcome 1 Systemic serious adverse events.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 4 Adverse events: anti-VEGF versus control

Outcome: 1 Systemic serious adverse events



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	antiVEGF n/N	control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 254 (antiVEGF), 187 (control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.26$, df = 10 (P = 0.87); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.18 (P = 0.86)					
Test for subgroup differences: $Chi^2 = 0.16$, df = 1 (P = 0.69), $I^2 = 0.0\%$					

Analysis 4.2. Comparison 4 Adverse events: anti-VEGF versus control, Outcome 2 Total ATC thromboembolic events at 6 to 24 months.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 4 Adverse events: anti-VEGF versus control

Outcome: 2 Total ATC thromboembolic events at 6 to 24 months

Study or subgroup	antiVEGF n/N	control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Follow-up 6 to 12 months					
Azad 2012	0/20	0/20			Not estimable
DA VINCI 2011	1/44	1/45		1.6 %	1.02 [0.07, 15.85]
Ekinci 2014	0/50	0/50			Not estimable
Korobelnik 2014	10/287	8/287		14.0 %	1.25 [0.50, 3.12]
LUCIDATE 2014	0/22	0/11			Not estimable
Macugen 2005	0/44	0/42			Not estimable
NCT01131585 ˙x0028˙RELATION˙x0029˙	1/85	1/43		1.6 %	0.51 [0.03, 7.89]
READ2 2009 (1)	1/79	0/38		1.2 %	1.46 [0.06, 35.09]
RESOLVE 2010	2/49	3/102		3.8 %	1.39 [0.24, 8.04]
RESTORE 2011	7/235	1/110		2.7 %	3.28 [0.41, 26.31]
Subtotal (95% CI)	**915**	**748**		**24.8 %**	**1.33 [0.67, 2.64]**

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	antiVEGF n/N	control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 22 (antiVEGF), 14 (control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.27, df = 5 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 Follow-up 24 months					
BOLT 2010	2/42	2/38		3.2 %	0.90 [0.13, 6.11]
DRCRnet 2010	25/375	17/130		34.6 %	0.51 [0.28, 0.91]
Macugen 2011	7/144	9/142		12.8 %	0.77 [0.29, 2.00]
RISE-RIDE	18/250	13/250		24.6 %	1.38 [0.69, 2.76]
Subtotal (95% CI)	**811**	**560**		**75.2 %**	**0.80 [0.47, 1.38]**
Total events: 52 (antiVEGF), 41 (control)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 4.74, df = 3 (P = 0.19); I^2 =37%					
Test for overall effect: Z = 0.79 (P = 0.43)					
Total (95% CI)	**1726**	**1308**		**100.0 %**	**0.89 [0.63, 1.25]**
Total events: 74 (antiVEGF), 55 (control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.81, df = 9 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Chi^2 = 1.26, df = 1 (P = 0.26), I^2 =20%					

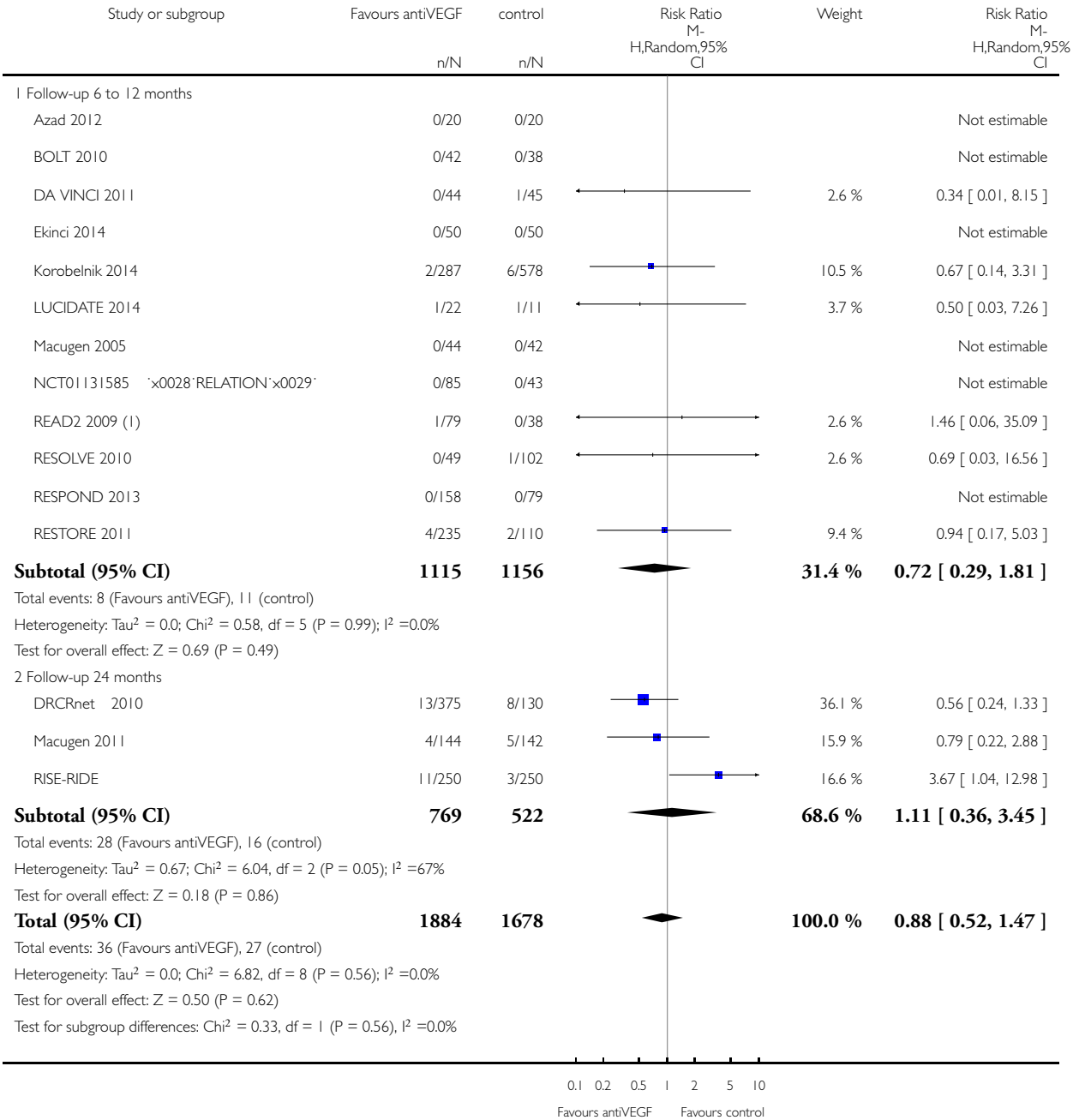
(1) ranibizumab and ranibizumab plus laser groups were cumulated

Analysis 4.3. Comparison 4 Adverse events: anti-VEGF versus control, Outcome 3 Death.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 4 Adverse events: anti-VEGF versus control

Outcome: 3 Death



(1) ranibizumab and ranibizumab plus laser groups were cumulated

Analysis 5.1. Comparison 5 Bevacizumab versus ranibizumab, Outcome 1 Gain 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 5 Bevacizumab versus ranibizumab

Outcome: 1 Gain 3+ lines of visual acuity at 1 year

Study or subgroup	Favours ranibizumab n/N	Ranibizumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nepomuceno 2013 (1)	12/32	13/28		100.0 %	0.81 [0.44, 1.47]
Total (95% CI)	**32**	**28**		**100.0 %**	**0.81 [0.44, 1.47]**

Total events: 12 (Favours ranibizumab), 13 (Ranibizumab)

Heterogeneity: not applicable

Test for overall effect: Z = 0.70 (P = 0.48)

Test for subgroup differences: Not applicable

(1) Follow-up: 48 weeks

Analysis 5.2. Comparison 5 Bevacizumab versus ranibizumab, Outcome 2 Loss 3+ lines of visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 5 Bevacizumab versus ranibizumab

Outcome: 2 Loss 3+ lines of visual acuity at 1 year

Study or subgroup	Bevacizumab n/N	Ranibizumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nepomuceno 2013 (1)	1/32	0/28		100.0 %	2.64 [0.11, 62.23]
Total (95% CI)	**32**	**28**		**100.0 %**	**2.64 [0.11, 62.23]**

Total events: 1 (Bevacizumab), 0 (Ranibizumab)

Heterogeneity: not applicable

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable

(1) Follow-up: 36 weeks

Analysis 5.3. Comparison 5 Bevacizumab versus ranibizumab, Outcome 3 Visual acuity at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 5 Bevacizumab versus ranibizumab

Outcome: 3 Visual acuity at 1 year

Study or subgroup	Bevacizumab N	Mean(SD)[logMAR]	Ranibizumab N	Mean(SD)[logMAR]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ekinci 2014	50	-0.23736 (0.16)	50	-0.21 (0.16)		66.1 %	-0.03 [-0.09, 0.04]
Nepomuceno 2013 (1)	32	-0.23 (0.113137)	28	-0.29 (0.21166)		33.9 %	0.06 [-0.03, 0.15]
Total (95% CI)	**82**		**78**			**100.0 %**	**0.00 [-0.05, 0.05]**

Heterogeneity: Chi^2 = 2.47, df = 1 (P = 0.12); I^2 =60%

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable

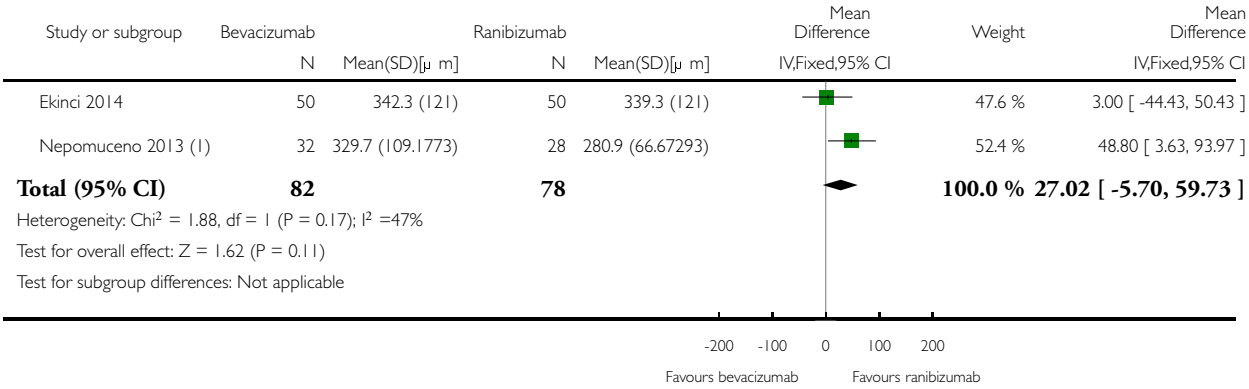
(1) Follow-up: 48 weeks

Analysis 5.4. Comparison 5 Bevacizumab versus ranibizumab, Outcome 4 Central macular thickness at 1 year.

Review: Anti-vascular endothelial growth factor for diabetic macular oedema

Comparison: 5 Bevacizumab versus ranibizumab

Outcome: 4 Central macular thickness at 1 year



(1) Follow-up: 48 weeks

ADDITIONAL TABLES

Table 1. Mean (SD) or median (*) number of intravitreal injections in studies

Study	Follow-up	Sham	Ranibizuma	Beva-cizumab	Pegap-tanib	Sham + laser	An-tiVEGF + laser (prompt)	Ranibizuma + laser (deferred)	Aflibercep
Macugen 2005	36 weeks (re-ported at 30 weeks)	4.5 (1.5)			5 (1.2)				
Soheilian 2007	2 years			3.1 (1.6)		1 (0.1)			
Ahmadieh 2008	24 weeks	3		3					
DRCRnet 2010	1 year						8 (7,11)*	9 (7,11)*	

Table 1. Mean (SD) or median (*) number of intravitreal injections in studies (*Continued*)

DRCRnet 2010	year 2 only						2 (0,4)*	3 (1,7)*	
RE-STORE 2011	1 year		7 (2.81)			7.3 (3.22)	6.8 (2.95)		
RE-SOLVE 2010	1 year	8.9 (3.5)	10.2 (2.5)						
READ2 2009	1.5 years		5.3			4.4	2.9		
BOLT 2010	1 year			9 (8,9)*		3 (2, 4)*			
Macugen 2011	1 year	8.4 (1.4)			8.3 (1.7)				
Macugen 2011	2 years	12.9 (4.4)			12.7 (4.6)				
RISE-RIDE (two studies)	2 years	20 (7.5) 20.8 (7.1)	20.9 (6.3) 21.9 (5.8)						
DA VINCI 2011§	6 months					Not reported			3.8 to 5.6
Azad 2012	6 months			2.7 (0.4)					
Nepomuceno 2013	1 year		7.7 (2.9)	9.8 (3.4)					
Ekinci 2014	1 year		5.1 (0.74)	6.5 (0.85)					
NCT01131 (RELATION)	1 year		Not reported			Not reported			
RE-SPOND 2013	1 year		Not reported			Not reported	Not reported		

Table 1. Mean (SD) or median (*) number of intravitreal injections in studies (*Continued*)

LUCIDATE 2014	48 weeks		9						
Korobelnik 2014 (VISTA and VIVID)#	1 year					Not reported			8.4 (1.3) 8.7 (1.2)

(*): median (interquartile range) number of injection; mean otherwise
(#): only one aflibercept regimen was selected, based on similarity to current clinical practice

Table 2. Outcome reporting grid: visual acuity

	Outcome	Gain 3+ lines	Loss 3+ lines	Gain 3+ lines	Loss 3+ lines
Study	**Antiangiogenic drug**	**6 to 12 months**		**2 years**	
Soheilian 2007	Bevacizumab	Yes	Yes	Yes	Yes
Ahmadieh 2008	Bevacizumab	E	E	E	E
BOLT 2010	Bevacizumab	Yes	Yes	NA	NA
Macugen 2005	Pegaptanib	Yes	E	NA	NA
Macugen 2011	Pegaptanib	Yes	Yes	Yes	Yes
DRCRnet 2010	Ranibizumab	Yes	Yes	Yes	Yes
READ2 2009	Ranibizumab	Yes	E	NA	NA
RESOLVE 2010	Ranibizumab	Yes	Yes	NA	NA
RESTORE 2011	Ranibizumab	Yes	Yes	NA	NA
RISE-RIDE	Ranibizumab	E	E	Yes	Yes
DA VINCI 2011	Aflibercept	Yes	Yes	NA	NA
Nepomuceno 2013	Bevacizumab, ranibizumab	yes	yes	NA	NA
Ekinci 2014	Bevacizumab, ranibizumab	Yes	Yes	NA	NA

Table 2. Outcome reporting grid: visual acuity *(Continued)*

NCT01131585 (RELATION)	Ranibizumab	E	E	NA	NA
RESPOND 2013	Ranibizumab	Yes	E	NA	NA
LUCIDATE 2014	Ranibizumab	E	E	NA	NA
Korobelnik 2014 (VISTA and VIVID)	Aflibercept	Yes	Yes	NA	NA

Yes: outcome analysed and fully reported allowing its inclusion in the meta-analysis.
E: clear that outcome was measured (for example, includes structurally related outcomes) but not necessarily analysed (adapted from list provided by Paula Williamson at Cochrane training workshop on selective outcome reporting bias, Edinburgh March 2009).
NA: not applicable, since follow-up less than 2 years

Table 3. Ocular adverse events: endophthalmitis

Study	Follow-up	Sham	Ranibizumal	Beva-cizumab	Pegap-tanib	Laser	Ranibizumab + laser (prompt)	Ranibizumab + laser (deferred)	Aflibercept
Macugen 2005	36 weeks	0/42			1/44				
Soheilian 2007 *	2 years			0/48		0/48			
Ahmadieh 2008(#)	24 weeks	0		0					
DRCRnet 2010	2 years					1/293	2/187	2/188	
RE-STORE 2011	1 year		0/115			0/110	0/120		
RE-SOLVE 2010	1 year	0/49	2/102						
READ2 2009	2 years								
BOLT 2010	2 years			0/42		0/38			

Table 3. Ocular adverse events: endophthalmitis *(Continued)*

Macugen 2011	2 years	0/127			0/133				
RISE-RIDE	2 years	0/250	3/250*						
DA VINCI 2011§	1 year					0/44			1/45
Azad 2012	6 months			0/20		0/20			
Nepomuceno 2013	1 year			2/28	0/32				
Ekinci 2014	1 year		0/60		0/60				
NCT01131 (RELATION)	1 year			NA			NA		
RESPOND 2013	1 year			NA		NA	NA		
LUCIDATE 2014	48 weeks					0/11			0/22
Korobelnik 2014 (VISTA and VIVID)§	1 year					0/287			0/287

(*): denominator is total number of participants at mean follow-up
(#): no cases mentioned but number of eyes, not patients, given for each group
(§): only one aflibercept regimen was selected, based on similarity to most other trials

Table 4. Safety comparing 0.3 mg with 0.5 mg monthly ranibizumab in RISE-RIDE

Treatment	Frequency	Status	Outcome
Sham	3	Event	Death
Sham	247	Non-event	Death
ranibizumab 0.3 mg	7	Event	Death
ranibizumab 0.3 mg	243	Non-event	Death
ranibizumab 0.5 mg	11	Event	Death
ranibizumab 0.5 mg	239	Non-event	Death
Sham	83	Event	SSAEs
Sham	167	Non-event	SSAEs
ranibizumab 0.3 mg	81	Event	SSAEs
ranibizumab 0.3 mg	169	Non-event	SSAEs
ranibizumab 0.5 mg	91	Event	SSAEs
ranibizumab 0.5 mg	159	non-event	SSAEs
Sham	13	Event	ATC TE
Sham	237	Non-event	ATC TE
ranibizumab 0.3 mg	14	Event	ATC TE
ranibizumab 0.3 mg	236	Non-event	ATC TE
ranibizumab 0.5 mg	18	Event	ATC TE
ranibizumab 0.5 mg	232	Non-event	ATC TE

Abbreviations
SSAE: serious systemic adverse event
ATC TE: arterial thromboembolic events according to Antiplatelet Trialists' Collaboration (ATC 1994)

Table 5. Dataset used in indirect comparisons among antiangiogenic drugs

Study	Treatment	Gain 3+ lines	Total
BOLT 2010	Laser	2	38
BOLT 2010	Bevacizumab	5	42
DRCRnet 2010	Laser	43	293
DRCRnet 2010	Ranibizumab/laser	57	187
Macugen 2005	Sham	3	42
Macugen 2005	Pegaptanib	8	44
Macugen 2011	Sham	13	127
Macugen 2011	Pegaptanib	22	133
READ2 2009	Laser	0	38
READ2 2009	Ranibizumab	8	37
READ2 2009	Ranibizumab/laser	3	40
RESOLVE 2010	Sham	5	49
RESOLVE 2010	Ranibizumab	33	102
RESTORE 2011	Laser	9	110
RESTORE 2011	Ranibizumab	26	115
RESTORE 2011	Ranibizumab/laser	27	118
Soheilian 2007	Laser	6	43
Soheilian 2007	Bevacizumab	16	44
DA VINCI 2011	Laser	5	44
DA VINCI 2011	Aflibercept*	19	45
Nepomuceno 2013	Bevacizumab	12	32
Nepomuceno 2013	Ranibizumab	13	28
RESPOND 2013	Ranibizumab	17	70
RESPOND 2013	Ranibizumab/laser	15	71

Table 5. Dataset used in indirect comparisons among antiangiogenic drugs (*Continued*)

RESPOND 2013	Laser	4	62
Azad 2012	Bevacizumab	4	20
Azad 2012	Laser	0	20
Korobelnik 2014 (VISTA)	Laser	12	152
Korobelnik 2014 (VISTA)	Aflibercept*	47	152
Korobelnik 2014 (VIVID)	Laser	12	133
Korobelnik 2014 (VIVID)	Aflibercept*	45	135

(*): only one aflibercept regimen was selected, based on similarity to current clinical practice

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Macular Edema] explode all trees
#2 macula* near/3 oedema
#3 macula* near/3 edema
#4 maculopath*
#5 CME or CSME or CMO or CSMO
#6 DMO or DME
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Diabetes Mellitus] explode all trees
#9 MeSH descriptor: [Diabetic Retinopathy] this term only
#10 MeSH descriptor: [Diabetes Complications] this term only
#11 diabet*
#12 retinopath*
#13 #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees
#15 MeSH descriptor: [Angiogenesis Inducing Agents] explode all trees
#16 MeSH descriptor: [Endothelial Growth Factors] explode all trees
#17 macugen* or pegaptanib* or lucentis* or rhufab* or ranibizumab* or bevacizumab* or avastin* or or aflibercept*
#18 anti adj2 VEGF*
#19 #14 or #15 or #16 or #17 or #18
#20 #7 and #13 and #19

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp macular edema/
14. (macula$ adj3 oedema).tw.
15. (macula$ adj3 edema).tw.
16. maculopath$.tw.
17. (CME or CSME or CMO or CSMO).tw.
18. (DMO or DME).tw.
19. or/13-18
20. exp diabetes mellitus/
21. diabetic retinopathy/
22. diabetes complications/
23. diabet$.tw.
24. retinopath$.tw.
25. or/20-24
26. exp angiogenesis inhibitors/
27. angiogenesis inducing agents/
28. endothelial growth factors/
29. exp vascular endothelial growth factors/
30. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin$ or aflibercept$).tw.
31. (anti adj2 VEGF$).tw.
32. or/26-31
33. 19 and 25 and 32
34. 12 and 33

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

Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.

14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula edema/
34. (macula$ adj3 oedema).tw.
35. (macula$ adj3 edema).tw.
36. maculopath$.tw.
37. (CME or CSME or CMO or CSMO).tw.
38. (DMO or DME).tw.
39. or/33-38
40. exp diabetes mellitus/
41. diabetic retinopathy/
42. diabet$.tw.
43. retinopath$.tw.
44. or/40-43
45. angiogenesis/
46. exp angiogenesis inhibitors/
47. angiogenic factor/
48. endothelial cell growth factor/
49. exp vasculotropin/
50. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept$).tw.
51. (anti adj2 VEGF$).tw.
52. (endothelial adj2 growth adj2 factor$).tw.
53. or/45-52
54. 39 and 44 and 53
55. 32 and 54

Appendix 4. LILACS search strategy

macula$ edema or macula$ oedema or DMO or DME or CMO or CME or CSMO and angiogenesis or endothelial growth factor or macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept$

Appendix 5. *meta*Register of Controlled Trials search strategy

(diabetic macular edema) AND (macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept)

Appendix 6. ClinicalTrials.gov search strategy

Diabetic Macular Edema AND (Macugen OR Pegaptanib OR Lucentis OR Rhufab OR Ranibizumab OR Bevacizumab OR Avastin OR aflibercept)

Appendix 7. ICTRP search strategy

diabetic macular edema = Condition AND macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept = Intervention

F E E D B A C K

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

Comment from Ruth Ubago Pérez, Pharmacist Technician, Andalusian Agency for Health Technology Assessment, Spain
Reply from Gianni Virgili (lead author of review)

WHAT'S NEW

Last assessed as up-to-date: 28 April 2014.

Date	Event	Description
4 November 2014	Amended	Plain language summary title has been amended

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 4, 2009

Date	Event	Description
17 October 2014	New search has been performed	Issue 10, 2014: Electronic searches updated.
17 October 2014	New citation required but conclusions have not changed	Issue 10, 2014: Five new studies (Azad 2012; Ekinci 2014; Nepomuceno 2013; NCT01131585 (RELATION); RESPOND 2013) have been included in the update.
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: MP, FM, GV

Designing the review: MP, FM, GV

Coordinating the review: MP

Data collection for the review

- Designing electronic search strategies: Cochrane Eyes and Vision Group editorial base

- Undertaking manual searches: MP, FM, JE, GV

- Screening search results: MP, JE, GV

- Organizing retrieval of papers: MP, JE, GV

- Screening retrieved papers against inclusion criteria: MP, FM, JE, GV

- Appraising quality of papers: MP, FM, JE, GV

- Extracting data from papers: MP, FM, JE, GV

- Writing to authors of papers for additional information: MP, FM, GV

- Providing additional data about papers: MP, FM, GV

- Obtaining and screening data on unpublished studies: MP, FM, JE, GV

Data management for the review

- Entering data into RevMan: MP, FM, GV

Analysis of data: MP, FM, JE, GV

Interpretation of data

- Providing a methodological perspective: MP, JE, GV

- Providing a clinical perspective: MP, FM, GV

- Providing a policy perspective: MP, FM, JE, GV

- Writing the review: MP, FM, JE, GV

Providing general advice on the review: JE, GV

Securing funding for the review: MP, FM, JE, GV

DECLARATIONS OF INTEREST

Gianni Virgili - none known

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

Francesca Menchini - none known

Jennifer R Evans - none known

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The views expressed in this publication are those of the authors and not necessarily those of the 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 trimacinolone, 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 5 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.

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