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Title:

Current treatments in Diabetic Macular Oedema: systematic review and meta-analysis

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

No additional data available.

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Abstract (300 words max)

Objectives: The aim of this systematic review is to appraise the evidence for the use of anti-VEGF drugs and steroids in diabetic macular oedema (DMO) as assessed by change in best corrected visual acuity (BCVA), central macular thickness and adverse events

Data source: MEDLINE, Embase, Web of Science with Conference Proceedings and the Cochrane Library (inception to July 2012). Certain conference abstracts and drug regulatory websites were also searched.

Study eligibility criteria, participants and interventions: Randomised controlled trials were used to assess clinical effectiveness and observational trials were used for safety. Trials which assessed triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO were included.

Study appraisal and synthesis methods: Risk of bias was assessed using the cochrane risk of bias tool. Study results are narratively described and, where apprpriate, data was pooled using random effects meta-analysis.

Results: Anti-VEGF drugs are effective compared to both laser and placebo and seem to be more effective than steroids in improving BCVA. They have been shown to be safe in the short-term but require frequent injections. Studies assessing steroids (triamcinolone, dexamethasone, fluocinolone) have reported mixed results when compared with laser or placebo. Steroids have been associated with increased incidence of cataracts and intra-ocular pressure rise but require fewer injections, especially when steroid implants are used.

Limitations: The quality of included studies varied considerably. Five out of fourteen meta-analyses had moderate or high statistical heterogeneity.

Conclusions and implications of key findings: The anti-VEGFs, ranibizumab and bevacizumab, have consistently shown good clinical effectiveness without major unwanted side effects. Steroids results have been mixed and are usually associated with cataract formation and IOP increase.

Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision ($\geq$20/40) and, thus, the search for new therapies needs to continue.

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Article focus

- To review the evidence for triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib and aflibercept in the treatment of diabetic macular oedema

Key messages

- The anti-VEGFs ranibizumab and bevacizumab, have consistently shown good clinical effectiveness in the short-term without major unwanted side effects
- Steroids results have been mixed and are usually associated with cataract formation and IOP increase

Strengthens and limitations

- A robust, detailed review of the literature has been undertaken and, when appropriate, data has been combined in meta-analysis
- The quality of studies included varied considerably.

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I - Introduction

Diabetic macular oedema (DMO) is a complication of diabetic retinopathy and a leading cause of blindness. The prevalence of DMO is likely to increase with more people suffering from diabetes.[1] Increasing DMO has significant implications for patients, healthcare providers and wider society. Laser has been the mainstay of treatment, but recently anti-vascular endothelial growth factor (anti-VEGF) drugs and steroids have been introduced as potential alternatives to laser photocoagulation.

a. Burden of disease

Diabetic retinopathy is present at the time of diagnosis of diabetes mellitus in 0-30% of individuals.[2] The incidence is estimated to be 2.3/100 person-years for the overall diabetic population and 4.5 for patients on insulin therapy.[3] There is good evidence that progression to DMO is associated with duration of disease[4-7], poor glycaemic control [8], and in type 2 diabetes, the need for insulin[9], though the need for insulin therapy is more a marker for duration, and poor control.

The number of people with DMO is likely to increase as diabetes becomes more common. Some reports have suggested a decrease in progression to severe visual loss between 1975-1985 and 1986-2008 in a combined population of type 1 and 2.[10] Regular screening for retinopathy and better glycaemic control are thought to have reduced the progression to severe visual loss. Diabetic retinopathy is associated with a reduced quality of life. Compared with all diabetic complications, blindness was perceived to be the third worst health state after a major stroke and amputation.[11]

In the US, the presence of DMO at diagnosis is associated with 29% additional costs within the first three years compared with individuals without retinopathy at diagnosis.[12] In 2010 the estimated healthcare costs for DMO in England were £92 million, with £65.6 million being spent on hospital treatment and related costs.[13]

Visual impairment results in increased welfare costs, early retirement, and costs of home help and carers.[14] In England in 2010 (total population 52.23 million) the estimated population with diabetes was 2.34 million; the above social costs were estimated to be £11.6 million for DMO.[13]

b. Overview of pathophysiology

DMO is caused mainly by disruption of the blood-retinal barrier. The complex pathway that leads to this disruption has been previously described in this journal.[15] Sustained hyperglycaemia causes a multi-factorial cascade of physiological processes, involving increased permeability, cytokine activation, altered blood flow, hypoxia and inflammation. Vascular endothelial growth factor-A (VEGF-A) is a major contributor to the inflammatory process and, in particular, to angiogenesis and permeability.[16] Hypoxia caused by microvascular disease stimulates release of VEGF-A to aid perfusion. There are six major isoforms of VEGF-A: 121, 145, 165, 183, 189 and 206. In addition to causing widespread microvascular injury, there is now evidence that hyperglycaemia results in preceding neuronal dysfunction, which may contribute to visual loss.[17]

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c. Overview of current treatments

Laser photocoagulation has been the mainstay of treatment for DMO. The landmark Diabetic Retinopathy Study[18] and the Early Treatment Diabetic Retinopathy Study (ETDRS)[19,20] demonstrated its clinical effectiveness. However, although laser photocoagulation was clearly effective in preserving vision, it was less successful in restoring it, once lost. Furthermore, patients with perifoveal ischaemia are not amenable to this form of therapy. In EDTRS, although laser was shown to reduce the risk of moderate visual loss (a loss of 3 ETDRS lines) by 50%, visual acuity improved in only 3% of patients.[20] However in some recent trials, laser has improved the proportion of patients with more than or equal to 10 letters by 7-31%.[21-24] In addition, laser is not without side effects. Foveal burns, visual field defects, retinal fibrosis and laser scars have been reported.[25] Over the following decade it became apparent that certain patients suffered severe visual loss despite aggressive treatment.[26]

Steroids and anti-VEGF drugs are newer treatments in DMO. Intravitreal corticosteroids have potent anti-inflammatory effects. Triamcinolone (Kenalog) is not licensed for eye use but has been used to treat DMO for over ten years. Triamcinolone (Trivaris), more recently, was licensed for eye use. The development of intravitreal implants has allowed sustained release formulations. Fluocinolone acetonide (Iluvien, Alimera Sciences) and dexamethasone (Ozudex, Allergan) are implants that have been introduced recently.

Anti-VEGF agents have shown efficacy compared with laser. Bevacizumab (Avastin, Genenetch /Roche) is a monoclonal antibody that targets all VEGF isoforms. Although being developed for colorectal cancer, it is widely used off-label, as an intravitreal treatment for macular oedema of different aetiologies. Ranibizumab (Lucentis, Genentech/Roche) is a fragment of the bevacizumab antibody (molecular weight of ranibizumab 48.4 KDa compared with 149 KDa for bevacizumab). It was designed specifically for use in the eye. Ranibizumab is considerably more expensive than bevacizumab (the estimated cost of ranibizumab is $2,000 per dose compared with $50 for bevacizumab).[27] Pegaptanib (Macugen, Eyetech Pharmaceuticals/Pfizer) is a PEGylated aptamer, with a high affinity to the VEGF isoform 165 and was approved for the treatment of exudative AMD in 2004. Aflibercept (Regeneron/Bayer HealthCare) is a recent addition to the anti-VEGF class that targets all forms of VEGF-A and placental growth factor.

d. Aim of the review

The aim of this review is to provide clinicians with an up-to-date overview of current treatments for DMO. It is hoped that the information contained herein will assist clinicians to present their patients with the best evidence supporting each treatment, including possible complications. In addition, this review may be helpful to policy makers. The review focuses on the current evidence for the use of anti-VEGF drugs and steroids to treat DMO, as assessed by change in best corrected visual acuity (BCVA) (mean and proportion with more than two lines improvement), central macular thickness (CMT), as determined by optical coherence tomography (OCT), and their adverse events.

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II - Evidence acquisition

A systematic literature search was performed. The databases searched included MEDLINE, Embase, Web of Science with Conference Proceedings and the Cochrane Library. The dates searched were from the inception of each database until July 2012

The search terms combined the following key words:

ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*

AND

diabetic macular oedema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy

AND

(masked or sham or placebo OR control group or random*) OR (systematic review or meta-analysis) OR (risk or safety or adverse or harm or pharmacovigilance or side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic)

The meeting abstracts of the Association for Research in Vision and Ophthalmology, the American Diabetes Association (2002-2012) and the European Association for the Study of Diabetes were searched from 2002-2012.

In addition the web sites of the European Medicines Agency and the US Food and Drug Association were searched for data on registration status and safety. Clinicaltrials.gov and the EU Clinical Trials Register were searched in July 2012 for data on ongoing research.

Full details of the searches are shown in appendix 1.

Randomised controlled trials (RCT) were used to evaluate clinical effectiveness. Safety was assessed through both RCTs and observational studies.

RCTs were included provided that they 1) addressed the use of triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO, 2) had a minimum follow-up of six months, and 3) had a minimum of 25 eyes per study arm. Studies were excluded if they 1) evaluated laser only, 2) assessed the effect of the above mentioned treatments in macular oedema due to other retinal diseases (instead of DMO), 3) used only a single dose , 4) were combined with a surgical intervention or 5) published studies in languages other than English. There were no exclusions based on drug dose.

Search results were screened by two independent authors (JF and PR/DS). Data were extracted by one author (CC) and checked by a second (JF). Data extracted included inclusion/exclusion criteria, baseline demographics, BCVA expressed as a change in logMAR/ETDRS letters or proportion of participants with more than 2 or 3 lines BCVA improvement, CMT and adverse events. Risk of bias was assessed using the cochrane risk of bias tool.

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Studies were assessed for similarity in study population, interventions (dose and frequency), outcomes and time to follow up, with a view to including similar studies in a meta-analysis. Only full text articles were included in the meta-analysis. A difference of six months was allowed between study follow-ups. If salient data were not reported, such as standard deviations, data were sought by personal communication with authors. Data were analysed using Review Manager software. If data from multiple time points were available, the primary end point data was used. Data were entered by one author (JF) and double-checked by a second (DS). Mean difference and odds ratios, with 95% confidence intervals were calculated. Statistical heterogeneity was measured through I^2 scores. A score of less than 30% was considered low heterogeneity, a score of more than 70% was considered high heterogeneity and scores between 30% and 70% were considered moderate. A random effects model was used throughout.

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III - Results

The literature search identified 430 unique articles for possible inclusion, as shown in figure 1. 328 articles were excluded on the basis of title and abstract, leaving 102 full papers to be read. Fifty-one of these articles were excluded; the reasons for their exclusion are summarised in table 1. Fifty-one articles from 29 studies met the inclusion criteria and were included in the review; these are described in tables 2 to 15. Seven studies were suitable for meta-analysis.

a. Study quality

The quality of the included studies was, in general, good as is shown in table 16. (Note that the meeting abstracts were not quality assessed, due to lack of details reported on the methods). Most studies adequately described sequence generation, except in three studies where it was unclear.[28-30] However allocation concealment was poorly described throughout, with only eight reports addressing this issue appropriately. [31-38] Reporting of masking also varied. A number of studies masked patients using sham injection or sham laser.[21,24,29,31,33,36,39,40] [38]. Various studies reported that masking of patients was impossible. Assessors, where reported, were masked. In two studies incomplete outcomes were not addressed.[31,41] Baseline characteristics were consistent within study treatment arms. Administration of laser followed the ETDRS protocol, or a modified version, in all studies that described laser administration.[21-24,28,30,33,34,42,43] Two studies, both available only as meeting abstracts, did not report the laser administration details. [44,45]

b. Intravitreal anti-VEGFs

The characteristics of all published studies including design, inclusion/exclusion criteria, intervention, outcomes and their timing are shown in tables 2 to 7. Safety data for each drug is shown in tables 8 to 15.

1. Ranibizumab

Nine RCTs have evaluated ranibizumab as a potential new treatment for patients with DMO (table 2 and 7); seven were sponsored by industry, and two were an independent investigators-led.) [21,46](table 7). READ-2 was the first large RCT (n=126).[28,47] It compared ranibizumab (0.5 mg) alone, ranibizumab in combination with laser and laser alone. At six months BCVA had improved significantly in the ranibizumab alone group compared with laser alone or ranibizumab plus laser. Addition of laser to ranibizumab did not provide additional BCVA gain. REVEAL (n=396) compared ranibizumab (0.5mg) with ranibizumab plus laser and laser alone.[48] At 12 months both ranibizumab arms resulted in a statistically significantly better improvement in BCVA compared to laser alone. The addition of laser did not confer further benefit.

Within the past two years the results of RESOLVE[36], RESTORE[24], and RISE and RIDE[38] have been published in peer-reviewed journals. RESTORE (n=345) randomised similar groups as the READ-2 study (ranibizumab (0.5 mg) alone, laser alone and ranibizumab plus laser); outcomes were evaluated at 12 months. Ranibizumab improved mean BCVA, with laser providing no additional

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benefit. Two year extended follow-up suggested that these results continued.[49] RESOLVE (n=151) compared two doses of ranibizumab (0.3 mg and 0.5 mg) with sham injection. The greatest improvement in BCVA at 12 months was in the 0.3 mg group (11.8 letter gain) compared to the 0.5 mg group (8.8 letters gain) or sham injection (1.4 letter loss). In this study, rescue laser was allowed after three months of treatment, if BCVA had decreased by 10 letters or more, or if the investigator considered the macula not to be flat as assessed by OCT. Only 4.9% of the ranibizumab group required rescue laser, compared with 34.7% in the sham injection group.

READ-2 and RESTORE were suitable for pooling through meta-analysis and, when doing so, it was found that ranibizumab statistically significantly improved mean BCVA compared with laser (figure 2). In regards to the proportion of patients gaining more than or equal to 15 letters, individual trials showed a statistically significant difference between laser and ranibizumab but when these two trials were pooled using a random effects model the result was no longer statistically significant. When a fixed effects model was used the result was statistically significant (figure not shown). The random effects model assumes variability between studies and therefore models uncertainty into the meta-analysis. Fixed assumes no variability. Generally speaking the random effects model results in wider confidence intervals. Adding laser to ranibizumab did not add any significant benefit (figure 3). In fact the mean change in BCVA and the proportion of patients with more than 15-letter gain favoured, although not statistically significantly so, ranibizumab alone compared with ranibizumab plus laser. This was probably a chance effect.

RISE (n=377) and RIDE (n=382) were identical in design. The study arms are similar to those in the RESOLVE study; 0.3 mg or 0.5 mg ranibizumab compared with sham. In the RISE study the proportion of patients with 15 or more letter gain was greatest in the 0.3 mg group at 24 months, whereas in the RIDE study this was greatest in the 0.5 mg group. In the DRCRN trial (n = 854), Elman and colleagues compared ranibizumab (0.5 mg) plus prompt (within 3-10 days post ranibizumab) or deferred ($\geq$ 24 weeks) laser with sham injection plus prompt laser, or triamcinolone (4m g, Trivaris) plus prompt laser (table 7). At one year both ranibizumab groups reported greater gains in mean BCVA change than triamcinolone or laser alone. Interestingly at 2 years (n= 628), the proportion of patients with 10 or more letter gain was not statistically significantly different between ranibizumab plus prompt laser and laser alone groups, but was statistically significant in the ranibizumab plus deferred laser compared with laser alone comparison. The reason for this is not clear.

READ-3 (n=152) has been published in abstract form and compared monthly injections of intravitreal ranibizumab high dose (2.0 mg) and low dose (0.5 mg).[50] At six months there was not a statistically significant difference in BCVA between groups.

One study (n=63), published in abstract form, was identified which directly compared monthly injections of ranibizumab (0.5 mg) with bevacizumab (1.5 mg).[51] At 48 weeks the authors found no statistically significant difference between bevacizumab and ranibizumab.

RESTORE, READ-2 and DRCRN (12 month data used) were suitable for pooling through meta-analysis to compare ranibizumab plus laser and laser alone (figure 4). Ranibizumab plus laser resulted in a statistically significantly greater change in mean BCVA, proportion of patients with more than 15 letter gain and CMT reduction versus laser alone.

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Adverse events are shown in tables 8 and 15. Conjunctival hemorrhages were higher in the ranibizumab arms compared with laser (RESTORE) or no treatment (RESOLVE). In the RESOLVE, RISE and RIDE studies a considerably higher incidence of intra-ocular pressure (IOP) increase was reported in the ranibizumab arm compared to control. This increase in IOP was not demonstrated in the RESTOREstudy. There were no consistent differences in systemic adverse events between ranibizumab and laser or placebo.

2. Bevacizumab

Eight RCTs investigating the use of bevacizumab in DMO were identified (table 3 and 7). One RCT, the BOLT study (n=80), randomised patients to laser therapy or 1.25 mg intravitreal bevacizumab.[23,52] At 24 months, the mean change in BCVA and the proportion of patients who gained 10 ETDRS letters or more was statistically significantly higher in the bevacizumab arm than in the laser arm. Faghihi and colleagues (n=80), compared 1.25 mg bevacizumab (average 2.23 injections per patient) with 1.25 mg bevacizumab plus a single laser treatment (average 2.49 injections per patient).[53] After six months, the authors found both treatments to be effective at improving BCVA but neither treatment was found to result in a greater benefit.

Lam and colleagues (n=52) compared two doses of bevacizumab (1.25 mg and 2.5 mg) in patients with diffuse DMO.[35] Patients with focal DMO associated with localised retinal thickening were excluded. At 6 months, following 3 initial monthly injections (no treatment in the remaining 3 months), both groups showed a statistically significant increased mean BCVA compared with baseline vision, but there was no difference between doses.

Four trials have investigated the combination of bevacizumab and triamcinolone. Ahmadieh and colleagues (n=115), compared combined bevacizumab (three 1.25 mg injections at six week intervals) plus triamcinolone (2 mg baseline injection only, Triamhexal) with bevacizumab alone (three 1.25 mg at six week intervals) and sham injection in patients who had DMO unresponsive (definition not reported) to previous laser (last session more than three months prior).[31] The combination arm and bevacizumab alone arm improved mean BCVA more than sham injection. For BCVA the combination of bevacizumab plus triamcinolone was non-statistically significantly better than bevacizumab alone.

Soheilian and colleagues (n=150) compared combined bevacizumab (1.25 mg) plus triamcinolone (2 mg) with bevacizumab alone and laser alone in patients who were laser naïve.[37,41] At 36 weeks, bevacizumab alone improved BCVA more than either combination therapy or laser, although the difference was not statistically significant. Extended follow up at 24 months showed that there was no statistically significant difference between groups for BCVA, however the direction of effect favour the bevacizumab and combination arms more than the laser[54]

Lim and colleagues (n=111) also evaluated the combination of bevacizumab plus triamcinolone when compared with bevacizumab alone or triamacinolone alone.[55] At 12 months the authors found no statistically significant difference between groups for BCVA or CMT.

The Efficacy Study of Triamcinolone and Bevacizumab Intravitreal for Treatment of Diabetic Macular Oedema (ATEMD) study, currently only published in abstract form, compared combined therapy with bevacizumab (1.25 mg) and triamcinolone (4 mg) with each of these alone.[56] At six months

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they found no statistically significant difference between groups. One study comparing bevacizumab with ranibizumab is discussed above.[51] No bevacizumab trials were suitable for meta-analysis because treatment arms were not comparable among included studies.

Adverse events are shown in tables 9 and 15.There was a low frequency of adverse events reported in the included trials. A higher incidence of mild anterior chamber reaction was reported in bevacizumab groups compared with controls. The incidence of IOP increase was comparable between bevacizumab and laser. Soheilian and colleagues, were the only authors to report the incidence of lens opacity.[37,41] No patients in the bevacizumab alone group were found to have lens opacities but in four patients (8%) in the bevacizumab plus triamcinolone group this finding was observed over the 36 week follow-up period.

3. Pegaptanib

Two studies have evaluated pegaptanib in DMO and both compared it with sham injection (table 4). Cunningham and colleagues compare three doses of pegaptanib (0.3 mg, 1 mg and 3 mg) and sham injection in laser naive patients (n=172).[39,57] At six months patients in the 0.3 mg and 1 mg groups performed statistically significantly better than those in either 3mg or sham groups. Six injections (median) were administered in the 0.3 mg and 1 mg group, whereas only five (median) injections were administered in the 3 mg group.

The second trial (n=260), reported by Sultan and colleagues in 2011, compared pegaptanib (0.3 mg) and sham injection. At two years, the pegaptanib group showed a statistically significantly greater improvement in mean BCVA compared with sham.[40] However there was no statistically significant difference in the proportion of patients with an improvement of 10 letters or more. Patients were allowed rescue laser at the assessors' discretion (25.2% of patients in the pegaptanib group and 45% of patients in the sham group received rescue treatment). In regards to meta-analysis, data were only available to combine these trials for proportion of patients with more than 15 letter gain. Although individually neither trial demonstrated a statistically significant difference favouring pegaptanib over sham (figure 5), when pooled together in meta-analysis a statistically significant difference in favour of pegaptanib was found (OR 1.94, 95%CI 1.01 to 3.71).

Adverse events for pegaptanib are shown in table 10. There was a higher incidence of eye pain compared to control (31% versus 17%). [39,57] Cataract formation was similar between pegaptanib and control groups. There was a higher incidence of IOP increase in the pegaptanib arm compared to control (17.4% versus 6.3%).[40]

4. Other anti-VEGF

Aflibercept has been evaluated in the Da Vinci study (n=219)[30,58] (table 4). Four regimens of aflibercept (0.5 mg 4 weekly, 2 mg 4 weekly, 2 mg monthly for three months then every 8 weeks, and 2 mg monthly for three months followed by treatment as required) were compared with laser. At six months, all aflibercept arms had a statistically better BCVA and CMT change than the laser arm. The regimen that resulted in greatest BCVA gain and CMT reduction was 2 mg every 4 weeks, however statistical significance between aflibercept arms was not reported. One year extended follow-up showed that all aflibercept arms were found to have a statistically significantly better BCVA compared to laser.[58]

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Adverse events are shown in table 11. There was a higher incidence of IOP increase and eye pain in the aflibercept group compared with laser. Other adverse events were too infrequent to draw meaningful conclusions. The incidence of cataracts was not reported.

c. Steroids

1. Dexamethasone

Two included trials assessed the use of dexamethasone to treat DMO (table 5); Haller 2010 (full text available)[59] and Callanan (available to date only in an abstract form).[44] Haller 2010 (n=171) compared two doses of dexamethasone, administered as an intravitreal implant (350 µm and 700 µm) through a 20-gauge transscleral incision, with no treatment. At 90 days only the 700 µm group showed a statistically significant higher proportion of patients with 10 or more letter gain compared to no treatment (33% compared with 12%, p = 0.007). The 350 µm group showed a non-statistically significant improvement compared with laser alone (21% compared with 12%). At 180 days there was no statistically significant difference between either the dexamethasone group and no treatment group. The treatment effect appeared to peak at three months.

The second trial, by Callanan and colleagues (n=253), compared dexamethasone (dose not reported) plus laser with laser alone. Although a greater improvement in mean BCVA was seen at 1-9 months in the dexamethasone plus laser group compared with laser alone, there was no statistically significant difference at 12 months. A mean of 1.6 implants were used over the 12 month period.

These trials were not suitable for meta-analysis since one study is only available in abstract form.

Adverse events are shown in table 12. In the 350 µm and 700 µm groups compared with no treatment, there was a higher incidence of anterior chamber cells (29.1/26.4% compared with 1.8%), anterior chamber flare (27.3/20.8% compared with 8.8%), vitreous hemorrhage (20/22.6% compared with 5.3%) and increased IOP (14.5/9.4% compared with 0%). However there was no statistically significant difference in the cataract formation between the groups at 12 months. [59] Callanan and colleagues reported an increase in IOP in the dexamethasone plus laser group compared with laser alone (20% compared with 1.6%).[44]

2. Fluocinolone

Two trials assessed fluocinolone implant for DMO (table 5). The FAME study (n=956) compared two doses of fluocinolone (0.2 µg/day and 0.5 µg/day) with sham injection in patients with at least one prior laser treatment.[29] Approximately 25% of patients in each group had more than one prior laser treatment. At 24 months both doses of fluocinolone showed a statistically significant improvement in mean BCVA compared to sham. There was a modest difference between fluocinolone groups. Rescue laser was given after the first six weeks for persistent oedema and was allowed every three months. 35-37% of patients in the fluocinolone group and 59% in the sham injection group required rescue laser. Extended follow-up at 36 months showed that the both fluocinolone arms continued to result in a statistically significant benefit compared with sham.[60]

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Pearson and colleagues (n=196) compared fluocinolone (0.59 mg) with standard of care, either laser or no treatment.[43] At three years there was no statistically significant difference in the proportion of patients with 15 letters gain or more (31% fluocinolone compared with 20% standard of care) between groups and proportion of patients losing 15 letters or more in the fluocinolone group (17% compared with 14%). Increased incidence of cataracts may have contributed to this difference.

These trials were not suitable for meta-analysis.

Adverse events are shown in table 13. Pearson and colleagues reported a higher incidence of cataracts at three years in the fluocinolone group compared with standard of care (55.9% compared with 21.7%).In the extended report of the FAME study there was a considerably higher incidence of cataract surgery in phakic eyes in the 0.2 µg/day and 0.5µg/day fluocinolone groups (80.0% and 87.2% compared with 27.3%) and increased IOP at any point (37% and 46% compared with 12%).

Following the demonstration in the FAME trial that a lower dose was about as good as higher ones, the higher doses are unlikely to be used.

3. Triamcinolone

Ten trials evaluating triamcinolone were identified (table 6 and 7). All trials evaluated intravitreal administration of triamcinolone, there were no trials evaluating posterior or anterior sub-tenon injections. Two trials used Trivaris[21,61], two trials used Kenacort [32,33], one trial used Kenalog[62], one trial used Trimahexal [31] and four trials did not report the type of triamcinolone used.[34,37].[45,56] Three doses were assessed in the included studies (1 mg, 4 mg and 8 mg) and triamcinolone has been combined with laser or bevacizumab.

Ip and colleagues (n=840) were the only authors to evaluate triamcinolone 1mg (Trivaris).[22,61,63,64] They found a statistically significant improvement in mean BCVA at two years in the laser group compared with the triamcinolone group and no significant difference between 1 mg compared with 4 mg.

Several trials compared 4 mg intravitreal triamcinolone. Ip and colleagues (n=840) found that laser therapy resulted in a greater improvement in mean BCVA at two years compared to 4 mg triamcinolone (Trivaris). [22,61,63,64] Lam and colleagues (n=111), found no statistically significant difference between laser and triamcinolone at six months (triamcinolone type not reported).[34] When these two trials were pooled through meta-analysis, the treatment effect favoured laser but differences were not statistically significant (figure 6). Ockrim and colleagues (n=88) compared 4 mg intravitreal triamcinolone (Kenalog) with laser alone.[62] At 12 months they found no statistically significant BCVA improvement between the triamcinolone and laser groups. Gillies and colleagues (n=69) compared 4 mg of triamcinolone (Kenacort) with sham injection.[32] Mean BCVA improved statistically significantly with triamcinolone at 24 months compared with sham injection (3.1 letters gain compared with 2.9 letters loss, p = 0.01).

Lam and colleagues (n=111) compared triamcinolone 4 mg alone with 4 mg of triamcinolone plus laser or laser alone.[34] At six months the authors found no difference in BCVA between any of the groups. Elman and colleagues (n=854) compared 4 mg of triamcinolone (Trivaris) plus laser with ranibizumab plus prompt (within 3-10 days) or deferred (more than 24 week) laser and laser alone.[21] At two years they found a statistically significant difference in mean BCVA between

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ranibizumab plus prompt/deferred laser compared with laser alone (7 letters gain/9 letters gain compared with 3 letters gain), but no difference with triamcinolone plus laser compared with laser alone (2 letters gain compared with 3 letters gain). Oliveira-Neto and colleagues (n=120) compared 4 mg triamcinolone alone (triamcinolone type not reported) with 4 mg plus 1.25 mg bevacizumab.[56] At six months they found no statistically significant difference between groups.

The Elman and Lam studies were suitable for meta-analysis, which showed non-statistically significant improvements in mean BCVA and the proportions of patients with more or equal than 15 letter gain in the triamcinolone plus laser group compared with laser alone (figure 7).

Adverse events are shown in table 14 and 15. Triamcinolone was associated with consistently higher incidences of IOP increase and cataracts. Gilles and colleagues reported a cataract rate of over 50% by three years in patients treated with triamcinolone.

d. Other pertinent studies

Only one study in abstract form directly compared bevacizumab with ranibizumab.[51] Bevacizumab and ranibizumab have been compared through indirect comparison of five trials.[65] There was no evidence of a difference between the drugs, however wide credible intervals meant that superiority of either drug could not be excluded.

Two-year results of the CATT (Comparison of AMD Treatment Trials) and one year results of the IVAN (Inhibit VEGF in Age-related choroidal Neovascularisation), recently published, have demonstrated a good safety profile of anti-VEGF therapies when used to treat patients with age-related macular degeneration.[66,67] The CATT study randomised 1208 patients with AMD to monthly or as required injection of either ranibizumab or bevacizumab. At 1 year the mean BCVA was similar in both groups (8.0 letter gain in bevacizumab and 8.5 in ranibizumab). Over two years, the rates of deaths, myocardial infarction and stroke did not differ between ranibizumab and bevacizumab treatment groups. However, there was a higher rate of serious adverse events in the bevacizumab compared with the ranibizumab group. This increased event rate was driven mainly by hospitalisations, (RR 1.29, 95%CI 1.01 to 1.66). However the hospitalisations were not caused by known adverse events of bevacizumab. Arterio-thrombotic events and heart failure occurred in less than 2% of participants in the IVAN, and there were more often observed in the ranibizumab group than in the bevacizumab group (p = 0.03). Further data from other ongoing clinical trials may provide more insight on the safety or anti-VEGF treatment and possible differences on this respect among available drugs.

Campbell and colleagues conducted a population based nested case-control study of 91,378 older adults with a history of physician diagnosed retinal disease.[68] The authors found that neither ranibizumab nor bevacizumab were associated with significant risks of ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism."

A recent systematic review specifically assessing adverse events in anti-VEGF drugs found a low incidence of serious (below 1 in 100) and non-serious ocular events (below 1 in 500) from ranibizumab, bevacizumab and pegaptanib.[69]

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Fung and colleagues used an internet-based survey of clinicians to assess the safety of bevacizumab.[70] The survey covered over 5000 patients and found that bevacizumab was associated with an infrequent incidence of adverse events (all less than 0.21%).

One study which assessed diclofenac did not meet the inclusion criteria (follow-up for only 12 weeks).[71] The authors randomised 32 patients to either intravitreal diclofenac or triamcinolone and found that both diclofenac and triamcinolone reduced CMT, but a statistically significant visual improvement was observed only in the triamcinolone group.

Sfikakis and colleagues undertook a 30-week randomised crossover trial comparing infliximab and placebo.[72] The study failed to meet our inclusion criteria (only 11 patients included). The authors found that infliximab resulted in a 28.6% improvement in vision compared with 4.3% with placebo. The improvement seen with placebo could be due to a "carry over effect", seen in cross over trials.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was primarily a study to see if the lipid-lowering agent fenofibrate, could reduce macrovascular and microvascular events in type 2 diabetes.[73] However a substudy within FIELD recruited 1012 patients to a retinopathy study. The primary outcome in the main study was need for laser therapy (3.4% on fenofibrate versus 4.9% on placebo) but the substudy used retinal photography to assess progression of retinopathy or development of macular oedema. The hazard ratio at six years for DMO was 0.69 (95%CI 0.54 to 0.87) in the fenofibrate group compared to placebo.

Ruboxistaurin is another oral agent which has been assessed for the treatment of DMO. Aiello and colleagues randomised 686 patients to receive placebo or one of three doses of ruboxistaurin. [74,75] There was no statistically significant difference in delay to sight-threatening DMO in any ruboxistaurin group compared to placebo. The authors suggest that differences in laser treatment between groups may have contributed to the non-significant finding.

e. Assessment of heterogeneity within meta-analysis

Heterogeneity was assessed methodologically and statistically. Methodological heterogeneity was assessed by comparing study population, interventions, outcome measures and follow-up. Studies that were not methodologically comparable were excluded from the meta-analysis. For example bevacizumab trials were not pooled because Soheilian and colleagues included patients who were laser naïve[37] and Ahmadieh and colleagues included patients who were unresponsive to laser.[31] Some analyses were also excluded because sufficient details were not reported in the studies. For example several studies failed to report standard deviations.[35,39]

Statistical heterogeneity was assessed through I^2 scores. High statistical heterogeneity was found in two analyses (2.3, 4.3). Therefore these results should be interpreted with due caution. Moderate heterogeneity was found in three analyses (2.2, 3.1, 3.2). Low heterogeneity was found in the remaining eight analyses.

f. Ongoing trials

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There are numerous on-going studies listed in appendix 2. The most salient studies include a study to compare ranibizumab and bevacizumab (Schmidt-Erfurth), a study investigating rescue ranibizumab treatment for patients who have failed on bevacizumab (Chaudhry), a study evaluating two algorithms for ranibizumab, 'treat and extend' and 'as required' (RETAIN), further studies of Trap-eye (VIVID and VISTA) and trials which are examining the use of NSAIDs, such as diclofenac and nepafenac (NEVANAC and Soheilian).

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IV – Discussion

It appears that anti-VEGF treatment is effective in DMO, especially ranibizumab and bevacizumab. Meta-analysis of available short-term data (up to 2 years) suggests that ranibizumab is superior to laser and that adding laser to ranibizumab treatment does not confer additional benefit. Steroid treatment has demonstrated mixed success and, almost uniformly, increased incidence of cataracts and increased IOP. The licence for fluocinolone takes note of this and it is positioned as a treatment when others have failed.

a. Strengths and limitations of the review

There are a number of strengths of this review. A robust systematic review methodology was used. Reliability was improved by excluding trials with small sample sizes or short follow up. Since a number of trials included similar intervention arms, consistent treatment effects further improve reliability. Validity was improved by assessing the quality of trials using the Cochrane risk of bias tables. Including abstracts from ARVO provided up to date results. Pooling results through meta-analysis provided further evidence. The random effects model was used throughout to allow for heterogeneity among studies.

This review, however, has limitations. Although the inclusion of abstracts provides a more up to date results, the studies contained in these abstracts could not be assessed for risk of bias and should therefore be interpreted with caution. In addition, reporting of quality assessment criteria was variable. Allocation concealment was especially poorly reported. There was only one study which compared different anti-VEGFs[51] and none that compared steroids (fluocinolone vs dexamethasone vs. triamcinolone). Therefore it is difficult to assess the effectiveness within drug classes. As with any meta-analysis questions of heterogeneity arise. Follow-up periods varied among studies. A difference of six months was allowed for studies to be pooled for meta-analysis but this could have still resulted in heterogeneity. High statistical heterogeneity was found in a quarter of analyses. Furthermore because of the low number of trials included, publication bias could not be assessed by funnel plot analysis. The manufacturers funded most of the trials for ranibizumab, pegaptanib, dexamethasone and fluocinolone, whereas trials for bevacizumab and triamcinolone were generally funded by non-pharmaceutical organisations. Generally, the non-commercial studies had smaller numbers, perhaps because of funding restraints.

It is important to note that there may be differences in laser treatment protocol between studies. This applies to trials which combine drug treatments with laser or include laser as a comparator. All studies referred to the ETDRS protocol [19,20] or a modified version of it. In the ETDRS, once the diagnosis of clinically significant macular oedema was made, an angiogram was obtained to identified "treatable lesions". "Treatable lesions" included discrete points of retinal hyperfluorescence or leakage (most of these are often microaneurisms), areas of diffuse leakage within the retina related to microaneurisms, intraretinal microvascular abnormalities, diffusely leaking retinal capillary bed and retinal avascular zones. In the ETDRS protocol, treatment of lesions closer than 500 microns from the centre of the macula was not required initially; however if vision was less than 20/40 and the oedema and leakage persisted, treatment up to 300 microns from the

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centre of the macula was recommended unless there was capillary dropout; in the latter case treatment was not recommended as it may lead to further loss of perifoveal capillaries

However in routine clinical practice clinicians generally use lighter and less intense treatment than specified in the ETDRS protocol.[76] In addition, some centres do not use fluorescein angiography (unlike the ETDRS study[19]) to guide treatment. The exact adherence to the ETDRS protocol within studies is unclear. For example, in the BOLT study a modified ETDRS protocol was used. One of the aims of the protocol was "not darkening/whitening of microaneuysms", which is not consistent with the ETDRS protocol.

b. Interpretation of the results

The anti-VEGF drugs appear to be clinically effective in treating DMO in short-term studies (up to 2 years). Ranibizumab has the most robust evidence base and has shown superiority compared to laser and sham injection in all trials and meta-analyses, except for the proportion of patients with 10 or more letter gain in the DRCR.net study published by Elman and colleagues at two years follow up.[46] Adding laser to ranibizumab conferred no benefit. Bevacizumab has also been shown to be superior to laser. Three doses have been used (1.25 mg, 1.5 mg and 2.5 mg). The higher dose does not appear to add further benefit, and most studies in the literature use 1.25 mg. Addition of triamcinolone to bevacizumab did not provide further benefits. Pegaptanib has only been compared to sham injection. Mean change in BCVA favoured pegaptanib, but only through meta-analysis did the proportion of patients with more than 15 letter gain favour pegaptanib. Further published data are required before drawing conclusions on aflibercept. However although the anti-VEGF drugs are a significant advance, they fail to improve BCVA by 10 or more letters in half or more patients, and so they do not provide a complete answer to DMO.

Steroid treatments have inconsistent results and are undoubtedly associated with increased IOP and cataract. The effects of dexamethasone appear to peak at three months. At six months there was no significant difference compared with laser. This might imply that earlier re-treatment is needed if the beneficial effect is to be maintained, but increasing the number of treatments would likely increase the associated complications, especially with the relatively large needle size. The addition of laser did not appear to add further benefit. There was no significant difference in cataract formation at six months with dexamethasone compared to observation but it is likely that a higher incidence of cataracts would be seen with longer follow-up. Significantly more patients suffered increased IOP in the dexamethasone group compared with observation. Fluocinolone has been shown to be effective compared with sham injection (FAME)[29,60], however when compared to standard of care (laser or observation at clinician's discretion) there was no significant difference in the proportion of patients with a 15 letter or more gain. Both studies reported higher incidence of cataract formation in the fluocinolone group, over 80% at three years at the higher dose. Results for triamcinolone are inconsistent. Ip and colleagues found that laser was more effective[61], others have found no statistically significant difference. Triamcinolone combined with laser, however, seemed to have similar efficacy as ranibizumab combined with laser in pseudophakic eyes.[21,46] Triamcinolone is more effective than sham injection. Triamcinolone has consistently been associated with increased incidence of cataract and raised IOP.

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Steroids and laser therapy may affect CMT in a different manner from anti-VEGF drugs. For example, when ranibizumab alone is compared with ranibizumab plus laser, ranibizumab alone appears to be more effective in terms of mean change in BCVA and proportion of patients with more than 15 letters gain. However ranibizumab plus laser is more effective at reducing CMT. Furthermore when triamcinolone plus laser is compared with ranibizumab plus laser, ranibizumab plus laser appears to be more effective in terms of change in BCVA and proportion of patients with more than 15 letters gain, but triamcinolone plus laser is more effective at reducing CMT. The reasons for this are unclear. There is a weak correlation between CMT and BCVA. However the long term benefits of reducing CMT are currently unknown.

No large observational studies were identified that compared anti-VEGF drugs. Fung and colleagues, using an internet based survey, found the incidence of adverse events in bevacizumab to be low.[70] One small outbreak of sterile endophthalmitis was reported with a single batch of bevacizumab in Canada, emphasising the need for sterility when preparing aliquots.[77] Curtis and colleagues carried out a very large retrospective cohort study in 146,942 patients aged 65 and over with age-related macular degeneration (AMD).[78] Their aim was to examine the cardiovascular outcomes in patients treated with the four options: photodynamic therapy (PDT), pegaptanib, bevacizumab and ranibizumab. The authors reported that one of their comparisons showed an increase in overall mortality and stroke risk with bevacizumab compared to ranibizumab, with hazard ratios 0.86 (95%CI 0.75 to 0.98) and 0.78 (0.64 to 0.96) respectively. However because of the very large cost differences between bevacizumab and ranibizumab, the authors noted that selection bias might be operating, with poorer people (with poorer health) more likely to be treated with bevacizumab. They therefore carried out another analysis using only ophthalmological clinics which used only one drug, to avoid selection bias. This analysis showed no significant difference: overall mortality hazard ratio for ranibizumab 1.10 (95%CI 0.85 to 1.141); MI 0.87 (0.53 to 1.14); stroke 0.87 (0.61 to 1.24).

Gower and colleagues analysed 77,886 anti-VEGF injections from Medicare data (46% ranibizumab and 54% bevacizumab).[79] Results have only been published in abstract form. The authors found an increased risk of overall mortality and cerebrovascular events in the bevacizumab group (HR 1.11 99%CI 1.01 to 1.23 and 1.57, 1.04 to 2.37 respectively). There was no statistically significant increased risk in the ranibizumab group. The authors acknowledge that a limitation of the study is a failure to adjust for important confounding factors (such as smoking, hypertension and hyperlipidaemia). Considering the cost difference, it is likely that patients treated with bevacizumab would have been in a lower socio-economic class and therefore would be at high risk of mortality and vascular disease.

c. Implications for clinicians

The anti-VEGF drugs appear to be a significant advance in the treatment of DMO and are regarded now as the treatment of choice for patients affected by this condition. Studies assessing the effectiveness of steroids have reported mixed results. The high rates of cataract and increased IOP are a drawback. Triamcinolone combined with laser may be a good option for pseudophakic patients and may be more cost-effective than treatment with ranibizumab. However the need for fewer administrations, potentially one every three years with fluocinolone, is advantageous. From an administration perspective, some patients might prefer infrequent steroid injections with a sizeable

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risk of cataract, and a small, but existent, risk of glaucoma, to frequent anti-VEGF injections, even if the potential gain may not be fully comparable. Steroids may be also considered for patients that do not adequately respond to anti-VEGFs. Currently, the role of laser in the treatment of DMO is debatable. Short term data from available trials have demonstrated the superiority of anti-VEGF with regards to laser treatment and have failed to demonstrate a benefit of combining both treatment approaches. It is possible that some ophthalmologists may still opt to offer laser treatment to patients with very focal areas of leakage.

Currently there is more evidence for the effectiveness of ranibizumab and bevacizumab than for pegaptanib and VEGF-trap eye. The results of direct head to head trials of ranibizumab and bevacizumab are awaited. Bevacizumab is not licensed for intraocular use but costs considerably less than other forms of therapy. Ranibizumab is licensed and more expensive, but its use is supported by large manufacturer funded trials demonstrating its clinical effectiveness. In the UK, the General Medical Council recommends that unlicensed medications should only be prescribed if "an alternative, licensed medicine would not meet the patient's needs" and there is "a sufficient evidence base and/or experience of using the medication to demonstrate its safety and efficacy".[80] The FDA says that when using a drug "off-label" clinicians "have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sounded medical evidence, and to maintain records of the product's use and effects".[81] Patients should be fully aware of the use of any unlicensed medication and consent to any safety or efficacy uncertainties.

The place of intravitreal steroids needs consideration now that we have the anti-VEGFs drugs, as does the role of laser. The anti-VEGFs drugs may now be the first-line treatment in place of laser, with laser being used selectively for focal lesions, and in sequence after anti-VEGF therapy once the retinal thickness has been reduced. However it should be noted that about half of patients do not get good results with anti-VEGFs. In RESTORE, only 50% of patients had gains in VA of 10 or more letters. So the anti-VEGFs are "game-changers" but their impact should not be over-estimated.

In those who do not respond to anti-VEGFs or laser, there remains a place for steroids, despite their high adverse effect rates. The European licence for fluocinolone recognises this, by stating that it should be used when other therapies have not had sufficient effect.[82] The commonest adverse effect is cataract, but that is very common in people with diabetes, and many are already pseudophakic when treatment of DMO is required.

d. Implications for policy makers

In the UK, the National Institute of Health and Clinical Excellence (NICE) has recently made the decision not to recommend ranibizumab for the treatment of DMO.[83] NICE concluded that ranibizumab, although clinically effective, was not cost-effective compared to laser therapy. Bevacizumab is less than a tenth of the cost of ranibizumab. Bevacizumab is unlikely to be licensed. This beckons the question as to whether policy makers should recommend cheaper unlicensed medications over a more expensive licensed alternative when efficacy and side effects appear similar.

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e. Unanswered questions

Several unanswered questions remain. Studies evaluating the effectiveness of ranibizumab compared with bevacizumab are needed. Although the anti-VEGFs are clinically effective and a major step forward in the management of DMO, it has to be noted that they have little effect in a large number of patients. Generally speaking, the proportion of patients who have demonstrated 10 or more letter gain using anti-VEGFs is between 30-50% in the trials that demonstrate greatest effectiveness. Most of these patients would not achieve the 20/40 visual acuity required for driving. More effective treatments, or combinations of treatments, are required.

There is a lack of specific evidence for the use of anti-VEGF drugs or steroids in patients with macular ischemia secondary to DMO. A number of trials excluded patients with macular ischemia.[23,34,35,40,53,62] The RESTORE trial included patients with macular ischemia and undertook a subgroup analysis.[24] The authors compared patients with (n=34) and without (n=35) macular ischemia at baseline. They found that those without macular ischemia responded better to ranibizumab (mean average change in BCVA at 12 months 7.2 letters gain compared with 6.3 letters). Larger trials are needed to assess the use of anti-VEGF drugs and steroids in patients with macular ischemia.

The duration of treatment is as yet uncertain. Most of the included studies use a retreatment protocol based on clinical need or OCT results. For example, in the BOLT study patients received a median of 9 injections of bevacizumab over 24 months.[23,84] However, it is not yet known how frequent long-term maintenance injections will be needed for and whether laser treatment in sequence could potentially reduce the number of anti-VEGF injections required. Other treatment strategies to apply laser, such as using laser power at sub-threshold levels, may prove more effective.[85] Future trials should use active comparators which are used in routine clinical practice and avoid placebo controlled trials.

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V - Conclusion

This review evaluated current treatments for DMO. Undoubtedly, the use of anti-VEGFs heralds a new era for patients who suffer from DMO. Currently, the anti-VEGFs ranibizumab and bevacizumab, have consistently shown good clinical effectiveness without major unwanted side effects. Steroids results have been mixed and are usually associated with cataract formation and IOP increase. Based on the short term data available, adding laser therapy to anti-VEGFs does not appear to confer additional benefit.

Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision (≥20/40) and, thus, the search for new therapies to prevent and manage DMO needs to continue.

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Contribution of authors

JF screened titles, checked data extraction, performed the meta-analysis and drafted manuscript. NL conceived the idea, interpreted the results and provided clinical expertise throughout. PR performed the literature search, updated the searches, screened titles and managed the references. CC extracted data from the studies. DS screened titles and checked the meta-analysis. NW designed the review and supervised the running of the study. All authors contributed to the final draft.

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Reference List

1. Holman N, Forouhi NG, Goyder E, et al. The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: estimates of total diabetes prevalence for England, 2010-2030. *Diabet Med* 2011;28:575-82.

2. Williams R, Airey M, Baxter H, et al. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond)* 2004;18:963-83.

3. Henricsson M, Sellman A, Tyrberg M, et al. Progression to proliferative retinopathy and macular oedema requiring treatment. Assessment of the alternative classification of the Wisconsin Study. *Acta Ophthalmol Scand* 1999;77:218-23.

4. Chen E, Looman M, Laouri M, et al. Burden of illness of diabetic macular edema: literature review. *Curr Med Res Opin* 2010;26:1587-97.

5. Hirai FE, Knudtson MD, Klein BE, et al. Clinically significant macular edema and survival in type 1 and type 2 diabetes. *Am J Ophthalmol* 2008;145:700-6.

6. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;105:1801-15.

7. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology* 2009;116:497-503.

8. Knudsen LL, Lervang HH, Lundbye-Christensen S, et al. The North Jutland County Diabetic Retinopathy Study (NCDRS) 2. Non-ophthalmic parameters and clinically significant macular oedema. *Br J Ophthalmol* 2007;91:1593-5.

9. Thomas RL, Dunstan F, Luzio SD, et al. Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. *BMJ* 2012;344:e874.

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10. Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. *Diabetes Care* 2009;32:2307-13.

11. Huang ES, Brown SE, Ewigman BG, et al. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care* 2007;30:2478-83.

12. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. *Arch Ophthalmol* 2008;126:1748-54.

13. Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. *Br J Ophthalmol* 2012;96:345-9.

14. Happich M, Reitberger U, Breitscheidel L, et al. The economic burden of diabetic retinopathy in Germany in 2002. *Graefes Arch Clin Exp Ophthalmol* 2008;246:151-9.

15. Bhagat N, Grigorian RA, Tutela A, et al. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol* 2009;54:1-32.

16. Murata T, Ishibashi T, Khalil A, et al. Vascular endothelial growth factor plays a role in hyperpermeability of diabetic retinal vessels. *Ophthalmic Res* 1995;27:48-52.

17. Barile GR, Pachydaki SI, Tari SR, et al. The RAGE axis in early diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2005;46:2916-24.

18. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383-96.

19. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796-806.

20. Early Treatment Diabetic Retinopathy Study research group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology* 1987;94:761-74.

21. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064-77.

22. Ip MS, Bressler SB, Antoszyk AN, et al. A randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema: baseline features. *Retina* 2008;28:919-30.

23. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology* 2010;117:1078-86.

24. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615-25.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

25. Lovestam-Adrian M, Agardh E. Photocoagulation of diabetic macular oedema--complications and visual outcome. *Acta Ophthalmol Scand* 2000;78:667-71.

26. Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema. Long-term visual results. *Ophthalmology* 1991;98:1594-602.

27. Nwanze CC, Akinwale A, Adelman RA. Bevacizumab vs. Ranibizumab in Preserving or Improving Vision in Patients with Wet, Age-Related Macular Degeneration: A Cost-effectiveness Review. *Clinical Medicine Insights: Therapeutics* 2012;4:29-38.

28. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2010;117:2146-51.

29. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology* 2011;118:626-35.

30. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology* 2011;118:1819-26.

31. Ahmadieh H, Ramezani A, Shoeibi N, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol* 2008;246:483-9.

32. Gillies MC, Sutter FK, Simpson JM, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. *Ophthalmology* 2006;113:1533-8.

33. Gillies MC, McAllister IL, Zhu M, et al. Intravitreal triamcinolone prior to laser treatment of diabetic macular edema: 24-month results of a randomized controlled trial. *Ophthalmology* 2011;118:866-72.

34. Lam DS, Chan CK, Mohamed S, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: six-month outcomes. *Ophthalmology* 2007;114:2162-7.

35. Lam DS, Lai TY, Lee VY, et al. Efficacy of 1.25 MG versus 2.5 MG intravitreal bevacizumab for diabetic macular edema: six-month results of a randomized controlled trial. *Retina* 2009;29:292-9.

36. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care* 2010;33:2399-405.

37. Soheilian M, Ramezani A, Bijanzadeh B, et al. Intravitreal bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. *Retina* 2007;27:1187-95.

38. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119:789-801.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

39. Cunningham ET, Jr., Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 2005;112:1747-57.

40. Sultan MB, Zhou D, Loftus J, et al. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology* 2011;118:1107-18.

41. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;116:1142-50.

42. Sivaprasad S, Ockrim Z, Massaoutis P, et al. Posterior hyaloid changes following intravitreal triamcinolone and macular laser for diffuse diabetic macular edema. *Retina* 2008;28:1435-42.

43. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology* 2011;118:1580-7.

44. Callanan D, Gupta S, Ciulla TA, et al. Efficacy and safety of combination therapy with dexamethasone intravitreal implant (DEX Implant) plus laser photocoagulation versus monotherapy with laser for treatment of diffuse diabetic macular edema (DDME) [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 3968.

45. Kim Y, Kang S, Yi CH. Three-year follow-up of intravitreal triamcinolone acetonide injection and macular laser photocoagulation for diffuse diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 11-4-2010;51:E-Abstract 4260.

46. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609-14.

47. Nguyen QD, Shah SM, Heier JS, et al. Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2009;116:2175-81.

48. Ohji M, Ishibashi T, Sr., REVEAL study group. Efficacy and safety of ranibizumab 0.5 Mg as monotherapy or adjunctive to laser versus laser monotherapy in Asian patients with visual impairment due to diabetic macular edema: 12-month results of the REVEAL Study [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 4664.

49. Mitchell P, RESTORE extension study group. 2-year safety and efficacy outcome of ranibizumab 0.5 mg in patients with visual impairment due to diabetic macular edema (DME): an interim analysis of the RESTORE extension study [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 4667.

50. Do DV, Campochiaro PA, Boyer DS, et al. 6 month results of the READ 3 Study: Ranibizumab for Edema of the mAcula in Diabetes [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 5282.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

51. Jorge R, Nepomuceno AB, Takaki E, et al. A prospective randomized trial of intravitreal bevacizumab versus ranibizumab for the management of refractory diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 347.

52. Michaelides M, Fraser-Bell S, Hamilton R, et al. Macular perfusion determined by fundus fluorescein angiography at the 4-month time point in a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (Bolt Study): Report 1. *Retina* 2010;30:781-6.

53. Faghihi H, Esfahani MR, Harandi ZA, et al. Intravitreal bevacizumab vs. combination of intravitreal bevacizumab plus macular photocoagulation in clinically significant diabetic macular edema: 6 months results of a randomized clinical trial. *Iranian J of Ophthalmol* 2010;22:21-6.

54. Soheilian M, Garfami KH, Ramezani A, et al. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. *Retina* 2012;32:314-21.

55. 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;227:100-6.

56. Oliveira Neto HL, Andrade RE, Casella M, et al. A randomized clinical trial to compare the efficacy and safety of isolated or combined intravitreal injection of triamcinolone acetonide and bevacizumab for diabetic macular edema ATEMD protocol - A Brazilian clinical trial [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 5331.

57. Adamis AP, Altaweel M, Bressler NM, et al. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology* 2006;113:23-8.

58. Do DV, Nguyen QD, Boyer D, et al. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 24-4-2012.

59. Haller JA, Kuppermann BD, Blumenkranz MS, et al. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol* 2010;128:289-96.

60. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 Years in patients with diabetic macular edema. *Ophthalmology* 21-6-2012.

61. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* 2009;127:245-51.

62. Ockrim ZK, Sivaprasad S, Falk S, et al. Intravitreal triamcinolone versus laser photocoagulation for persistent diabetic macular oedema. *Br J Ophthalmol* 2008;92:795-9.

63. Bressler NM, Edwards AR, Beck RW, et al. Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. *Arch Ophthalmol* 2009;127:1566-71.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

64. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447-9.

65. Ford J, Elders A, Shyangdan D, et al. The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison. *BMJ* 2012;in press.

66. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;119:1399-411.

67. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388-98.

68. Campbell RJ, Gill SS, Bronskill SE, et al. Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study. *BMJ* 2012;345:e4203.

69. Van der Reis MI, La Heij EC, De Jong-Hesse Y, et al. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. *Retina-the Journal of Retinal and Vitreous Diseases* 2011;31:1449-69.

70. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006;90:1344-9.

71. Elbendary AM, Shahin MM. Intravitreal diclofenac versus intravitreal triamcinolone acetonide in the treatment of diabetic macular edema. *Retina* 2011;31:2058-64.

72. Sfikakis PP, Grigoropoulos V, Emfietzoglou I, et al. Infliximab for diabetic macular edema refractory to laser photocoagulation: a randomized, double-blind, placebo-controlled, crossover, 32-week study. *Diabetes Care* 2010;33:1523-8.

73. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 17-11-2007;370:1687-97.

74. PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty-month results of the randomized PKC-DMES clinical trial. *Arch Ophthalmol* 2007;125:318-24.

75. PKC-DMES Study Group. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy. *Ophthalmology* 2006;113:2221-30.

76. Fong DS, Strauber SF, Aiello LP, et al. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Arch Ophthalmol* 2007;125:469-80.

77. Health Canada. Reports of eye inflammation, endophthalmitis, and Toxic Anterior Segment Syndrome (TASS) following off-label intravitreal use of Avastin (bevacizumab). 2008 [cited 2012 Oct 24];Available from: URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_4_hpc-cps-eng.php

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

78. Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol* 2010;128:1273-9.

79. Gower EW, Cassard S, Chu L, et al. Adverse event rates following intravitreal injection of Avastin or Lucentis for treating age-related macular degeneration [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 6644.

80. General Medical Council. Prescribing medicines for use outside the terms of their licence (off-label). 2012 [cited 2012 Oct 24];Available from: URL: http://www.gmc-uk.org/guidance/ethical_guidance/prescriptions_faqs.asp#10

81. U.S.Food and Drug Administration. Off-Label" and investigational use of marketed drugs, biologics, and medical devices - Information Sheet. 2011 [cited 2012 Oct 24];Available from: URL: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm

82. Alimera Sciences. Alimera Sciences' ILUVIEN® Receives Marketing Authorization in France for the Treatment of Chronic Diabetic Macular Edema. 2012 [cited 2012 Oct 24];Available from: URL: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=692876

83. National Institute for Health and Clinical Excellence. Ranibizumab for the treatment of diabetic macular oedema:TA237. 2011 [cited 2012 Oct 24];Available from: URL: http://publications.nice.org.uk/ranibizumab-for-the-treatment-of-diabetic-macular-oedema-ta237

84. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema: 24-Month Data: Report 3. *Arch Ophthalmol* 9-4-2012.

85. Sivaprasad S, Dorin G. Subthreshold diode laser micropulse photocoagulation for the treatment of diabetic macular edema. *Expert Review of Medical Devices* 2012;9:189-97.

86. Cho WB, Moon JW, Kim HC. Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy. *Br J Ophthalmol* 2010;94:858-63.

87. Googe J, Brucker AJ, Bressler NM, et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011;31:1009-27.

88. Faghihi H, Roohipoor R, Mohammadi SF, et al. Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema. *Eur J Ophthalmol* 2008;18:941-8.

89. Figueroa MS, Contreras I, Noval S. Surgical and anatomical outcomes of pars plana vitrectomy for diffuse nontractional diabetic macular edema. *Retina* 2008;28:420-6.

90. Isaac DL, Abud MB, Frantz KA, et al. Comparing intravitreal triamcinolone acetonide and bevacizumab injections for the treatment of diabetic macular oedema: a randomized double-blind study. *Acta Ophthalmol* 2012;90:56-60.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

91. Paccola L, Costa RA, Folgosa MS, et al. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). *Br J Ophthalmol* 2008;92:76-80.

92. Prager SG, Kriechbaum K, Mylonas G, et al. Comparison of intravitreally applied bevacizumab and triamcinolone on diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 11-4-2010;51:E-Abstract 4262.

93. Ozturk BT, Kerimoglu H, Bozkurt B, et al. Comparison of intravitreal bevacizumab and ranibizumab treatment for diabetic macular edema. *J Ocul Pharmacol Ther* 2011;27:373-7.

94. Marey HM, Ellakwa AF. Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. *Clin Ophthalmol* 2011;5:1011-6.

95. Shahin MM, El-Lakkany RS. A prospective, randomized comparison of intravitreal triamcinolone acetonide versus intravitreal bevacizumab (avastin) in diffuse diabetic macular edema. *Middle East Afr J Ophthalmol* 2010;17:250-3.

96. Loftus JV, Sultan MB, Pleil AM, et al. Changes in vision- and health-related quality of life in patients with diabetic macular edema treated with pegaptanib sodium or sham. *Investigative Ophthalmology & Visual Science* 2011;52:7498-505.

97. Ferrone PJ, Jonisch J. Ranibizumab dose comparison for the treatment of diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 2011;52:E-Abstract 5333.

98. Solaiman KA, Diab MM, Abo-Elenin M. Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. *Retina* 2010;30:1638-45.

99. Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards AR, et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;114:1860-7.

100. Lee SJ, Kim ET, Moon YS. Intravitreal bevacizumab alone versus combined with macular photocoagulation in diabetic macular edema. *Korean J Ophthalmol* 2011;25:299-304.

101. Audren F, Lecleire-Collet A, Erginay A, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular edema: phase 2 trial comparing 4 mg vs 2 mg. *Am J Ophthalmol* 2006;142:794-9.

102. Audren F, Erginay A, Haouchine B, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. *Acta Ophthalmol Scand* 2006;84:624-30.

103. Avitabile T, Longo A, Reibaldi A. Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema. *Am J Ophthalmol* 2005;140:695-702.

104. Bandello F, Pognuz DR, Pirracchio A, et al. Intravitreal triamcinolone acetonide for florid proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2004;242:1024-7.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

105. Bonini MA, Jorge R, Barbosa JC, et al. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: A randomized clinical trial. *Invest Ophthalmol Vis Sci* 2005;46:3845-9.

106. Cellini M, Pazzaglia A, Zamparini E, et al. Intravitreal vs. subtenon triamcinolone acetonide for the treatment of diabetic cystoid macular edema. *BMC Ophthalmol* 2008;8:5TN.

107. Cardillo JA, Melo LA, Jr., Costa RA, et al. Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. *Ophthalmology* 2005;112:1557-63.

108. Chung EJ, Freeman WR, Azen SP, et al. Comparison of combination posterior sub-tenon triamcinolone and modified grid laser treatment with intravitreal triamcinolone treatment in patients with diffuse diabetic macular edema. *Yonsei Medi J* 31-12-2008;49:955-64.

109. Dehghan MH, Ahmadieh H, Ramezani A, et al. A randomized, placebo-controlled clinical trial of intravitreal triamcinolone for refractory diabetic macular edema. *Int Ophthalmol* 2008;28:7-17.

110. Diabetic Retinopathy Clinical Research Network, Chew E, Strauber S, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. *Ophthalmology* 2007;114:1190-6.

111. Gil AL, Azevedo MJ, Tomasetto GG, et al. Treatment of diffuse diabetic maculopathy with intravitreal triamcinolone and laser photocoagulation: randomized clinical trial with morphological and functional evaluation. *Arquivos Brasileiros de Oftalmologia* 2011;74:343-7.

112. Entezari M, Ahmadieh H, Dehghan MH, et al. Posterior sub-tenon triamcinolone for refractory diabetic macular edema: a randomized clinical trial. *Eur J Ophthalmol* 2005;15:746-50.

113. Hauser D, Bukelman A, Pokroy R, et al. Intravitreal triamcinolone for diabetic macular edema: comparison of 1, 2, and 4 mg. *Retina* 2008;28:825-30.

114. Jonas JB, Kamppeter BA, Harder B, et al. Intravitreal triamcinolone acetonide for diabetic macular edema: A prospective, randomized study. *J Ocul Pharmacol Ther* 2006;22:200-7.

115. Joussen AM, Weiss C, Bauer D, et al. Triamcinolone versus inner-limiting membrane peeling in persistent diabetic macular edema (TIME study): design issues and implications. *Graefes Arch Clin Exp Ophthalmol* 2007;245:1781-7.

116. Kaderli B, Avci R. Comparison of topical and subconjunctival anesthesia in intravitreal injection administrations. *Eur J Ophthalmol* 2006;16:718-21.

117. Kang SW, Sa HS, Cho HY, et al. Macular grid photocoagulation after intravitreal triamcinolone acetonide for diffuse diabetic macular edema. *Arch Ophthalmol* 2006;124:653-8.

118. Kim JE, Pollack JS, Miller DG, et al. ISIS-DME: a prospective, randomized, dose-escalation intravitreal steroid injection study for refractory diabetic macular edema. *Retina* 2008;28:735-40.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

119. Lam DS, Chan CK, Mohamed S, et al. A prospective randomised trial of different doses of intravitreal triamcinolone for diabetic macular oedema. *Br J Ophthalmol* 2007;91:199-203.

120. Lee HY, Lee SY, Park JS. Comparison of photocoagulation with combined intravitreal triamcinolone for diabetic macular edema. *Korean J Ophthalmol* 2009;23:153-8.

121. Maia OO, Jr., Takahashi BS, Costa RA, et al. Combined laser and intravitreal triamcinolone for proliferative diabetic retinopathy and macular edema: one-year results of a randomized clinical trial. *Am J Ophthalmol* 2009;147:291-7.

122. Massin P, Audren F, Haouchine B, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. *Ophthalmology* 2004;111:218-24.

123. Mohamed S, Leung GM, Chan CK, et al. Factors associated with variability in response of diabetic macular oedema after intravitreal triamcinolone. *Clin Experiment Ophthalmol* 2009;37:602-8.

124. Nakamura A, Shimada Y, Horio N, et al. Vitrectomy for diabetic macular edema with posterior subtenon injection of triamcinolone acetonide. [Japanese]. *Folia Ophthalmol Japonica* 2004;55:958-62.

125. Spandau UH, Derse M, Schmitz-Valckenberg P, et al. Dosage dependency of intravitreal triamcinolone acetonide as treatment for diabetic macular oedema. *Br J Ophthalmol* 2005;89:999-1003.

126. Tunc M, Onder HI, Kaya M. Posterior sub-Tenon's capsule triamcinolone injection combined with focal laser photocoagulation for diabetic macular edema. *Ophthalmology* 2005;112:1086-91.

127. Verma LK, Vivek MB, Kumar A, et al. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. *J Ocul Pharmacol Ther* 2004;20:277-84.

128. Wickremasinghe SS, Rogers SL, Gillies MC, et al. Retinal vascular caliber changes after intravitreal triamcinolone treatment for diabetic macular edema. *Invest Ophthalmol Vis Sci* 2008;49:4707-11.

129. Yalcinbayir O, Gelisken O, Kaderli B, et al. Intravitreal versus sub-Tenon posterior triamcinolone injection in bilateral diffuse diabetic macular edema. *Ophthalmologica* 2011;225:222-7.

130. Haller JA, Bandello F, Belfort R, Jr., et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010;117:1134-46.

131. Haller JA, Dugel P, Weinberg DV, et al. Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema. *Retina* 2009;29:46-51.

132. Kuppermann BD, Blumenkranz MS, Haller JA, et al. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol* 2007;125:309-17.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

133. Boyer DS, Faber D, Gupta S, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina* 2011;31:915-23.

134. Campochiaro PA, Hafiz G, Shah SM, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology* 2010;117:1393-9.

135. Brown DM, Nguyen QD, Rubio RG, et al. Ranibizumab for Diabetic Macular Edema (DME): 24-Month Efficacy and Safety Results of RISE - a Phase 3 Randomized Controlled Trial [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 6647.

136. Boyer D, Sy J, Rundle AC, et al. Ranibizumab (Anti-VEGF) for vision loss due to diabetic macular edema - results of two phase III randomized trials [abstract]. *71st Scientific Sessions June 24 - 28, 2011, San Diego Convention Center - San Diego, California* 2011;Abstract No, 133-LBOR.

137. Gillies MC, Islam FM, Zhu M, et al. Efficacy and safety of multiple intravitreal triamcinolone injections for refractory diabetic macular oedema. *Br J Ophthalmol* 2007;91:1323-6.

138. Gillies MC, Simpson JM, Gaston C, et al. Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. *Ophthalmology* 2009;116:2182-7.

139. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology* 2004;111:2044-9.

140. Soheilian M, Ramezani A, Yaseri M, et al. Initial macular thickness and response to treatment in diabetic macular edema. *Retina* 2011;31:1564-73.

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Appendix 1: Methods of the literature search

Searches for clinical trials

Ovid MEDLINE 1948-July week 2, 2012 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012

1. Diabetic Retinopathy/dt [Drug Therapy]
2. Macular Edema/dt [Drug Therapy]
3. (diabet* adj2 macular adj (edema or oedema)).tw.
4. (diabet* adj2 maculopathy).tw.
5. (diabet* adj2 retinopathy).tw.
6. 1 or 2 or 3 or 4 or 5
7. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).tw.
8. exp Vascular Endothelial Growth Factor A/
9. exp Fluocinolone Acetonide/
10. exp Triamcinolone/
11. 7 or 8 or 9 or 10
12. 6 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. (masked or sham or placebo or control group or random*).tw.
16. 13 or 14 or 15
17. 12 and 16
18. (case reports or editorial or letter or review).pt.
19. 17 not 18
20. limit 19 to humans

Embase 1947 to 2012 Week 27

1. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).m_titl.

2. (diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy).m_titl.
3. 1 and 2
4. random*.tw.
5. 3 and 4

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Cochrane Central Register of Controlled Trials, Issue 7 of 12, July 2012

ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor* in Record Title and diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy in Record Title

Web of Science® – with Conference Proceedings (updated 2012-07-12)

Title=(ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*) AND Title=(diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy) AND Title=(random*)

Searches for systematic reviews

Ovid MEDLINE(R) Daily Update July 11, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012

1. Diabetic Retinopathy/dt [Drug Therapy]
2. Macular Edema/dt [Drug Therapy]
3. (diabet* adj2 macular adj (edema or oedema)).tw.
4. (diabet* adj2 maculopathy).tw.
5. (diabet* adj2 retinopathy).tw.
6. 1 or 2 or 3 or 4 or 5
7. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).tw.
8. exp Vascular Endothelial Growth Factor A/
9. exp Fluocinolone Acetonide/
10. exp Triamcinolone/
11. 7 or 8 or 9 or 10
12. 6 and 11
13. (systematic review or meta-analysis or pubmed or medline).tw.
14. meta-analysis.pt.
15. cochrane.af.
16. 13 or 14 or 15
17. 12 and 16

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Cochrane Database of Systematic Reviews and Technology Assessments Database, Cochrane Library July Issue, 2012

"ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor* in Record Title and diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy in Record Title

Searches for safety and adverse events

Ovid MEDLINE(R) Daily Update July 11, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012 ; Embase 1980to 2012 week 27

1. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or aflibercept or vegf trap-eye or macugen or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).m_titl.
2. (diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy).m_titl.
3. 1 and 2
4. (risk or safety or adverse or harm or pharmacovigilance).tw.
5. (side-effect* or precaution* or warning* or contraindication$ or contra-indication* or tolerability or toxic*).tw.
6. 4 or 5
7. 3 and 6

Searches of the annual meeting abstracts (for trials, reviews and safety studies)

- ARVO (Association for Research in Vision and Ophthalmology) (2002 to 2012)
- ADA (American Diabetes Association) (2002-2012)
- EASD (European Association for the Study of Diabetes) (2002-2012)

Other searches

Web sites of the following

- Drugs@FDA: FDA Approved Drug Products
- European Medicines Association
- ClinicalTrials.gov
- EU Clinical Trials Register

National Institute for Health and Clinical Excellence

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Appendix 2: Ongoing Trials in ClinicalTrials.gov

- Schmidt-Erfurth and colleagues are comparing ranibizumab and bevacizumab in DME (NCT00545870)
- TRIASTIN study is comparing ranibizumab, triamcinolone and sham injection (NCT00682539)
- Maturi and colleagues are comparing bevacizumab plus dexamethasone with bevacizumab alone (NCT01309451)
- IBeTA study (Jorge and colleagues) is comparing bevacizumab (1.5mg) plus laser, triamcinolone (4mg) plus laser with laser alone (NCT00997191)
- Chaudhry and colleagues are evaluating ranibizumab in patients who have failed with 3-6 injections of bevacizumab (NCT01253694)
- MIDME study (Pfizer) is comparing pegaptanib 0.3mg with sham injection. NCT01175070
- Figueira and colleagues are comparing pegaptanib plus laser with laser alone (NCT01281098)
- RESPOND (Novartis) is comparing ranibizumab (0.5mg) alone with ranibizumab plus laser or laser alone (NCT01135914)
- RETAIN (Novartis) study is comparing two different ranibizumab algorithms; "treat and extend" versus as needed (NCT01171976)
- RED-ES (Novartis) is comparing ranibizumab with laser in patients with visual impairment due to DME (NCT00901186)
- READ 3 study (Do and colleagues) are comparing two doses of ranibizumab 0.5 mg and 2 mg (NCT01077401)
- VIVID-DME and VISTA DME studies (Bayer) are comparing aflibercept with laser. (NCT01331681 and NCT01363440)
- Gillies and colleagues are comparing bevacizumab with dexamethasone (NCT01298076)
- Soheilian and colleagues are performing a phase I study looking at the use of diclofenac compared with bevacizumab in DME (NCT00999791)
- López-Miranda and colleagues are comparing the use of bevacizumab before and after laser therapy (NCT00804206)
- NEVANAC study is comparing triamcinolone alone with triamcinolone plus nepafenac (NSAID) (NCT00780780)
- Elman and colleagues are comparing laser alone, laser combined with an intravitreal injection of triamcinolone, laser combined with an intravitreal injection of ranibizumab, or intravitreal injection of ranibizumab alone (NCT00444600)
- BRDME (Schlingemann and collagues) study is comparing the use of bevacizumab and ranibizumab in the treatment of patients with DME (OCT central area thickness > 275 µm) (NCT01635790)
- Wiley and colleagues are comparing bevacizumab and ranibizumab in patients with DME in at least one eye(NCT01610557)
- Protocol T study (Wells and colleagues) is comparing effectiveness of a aflibercept, bevacizumab, and ranibizumab for DME (NCT01627249)
- Allergan funded study comparing safety and efficacy of 700 µg dexamethasone implant against 0.5 mg ranibizumab in patients with DME (NCT01492400)
- Pfizer funded study comparing effectiveness of 0.3 mg pegaptanib against sham injection (NCT01100307)

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- Allergan funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 µg and 350 µg) against sham in patients with DME (NCT00168389)
- Allergan funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 µg and 350 µg) against sham in patients with DME (NCT00168337)

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Figure 1 - PRISMA

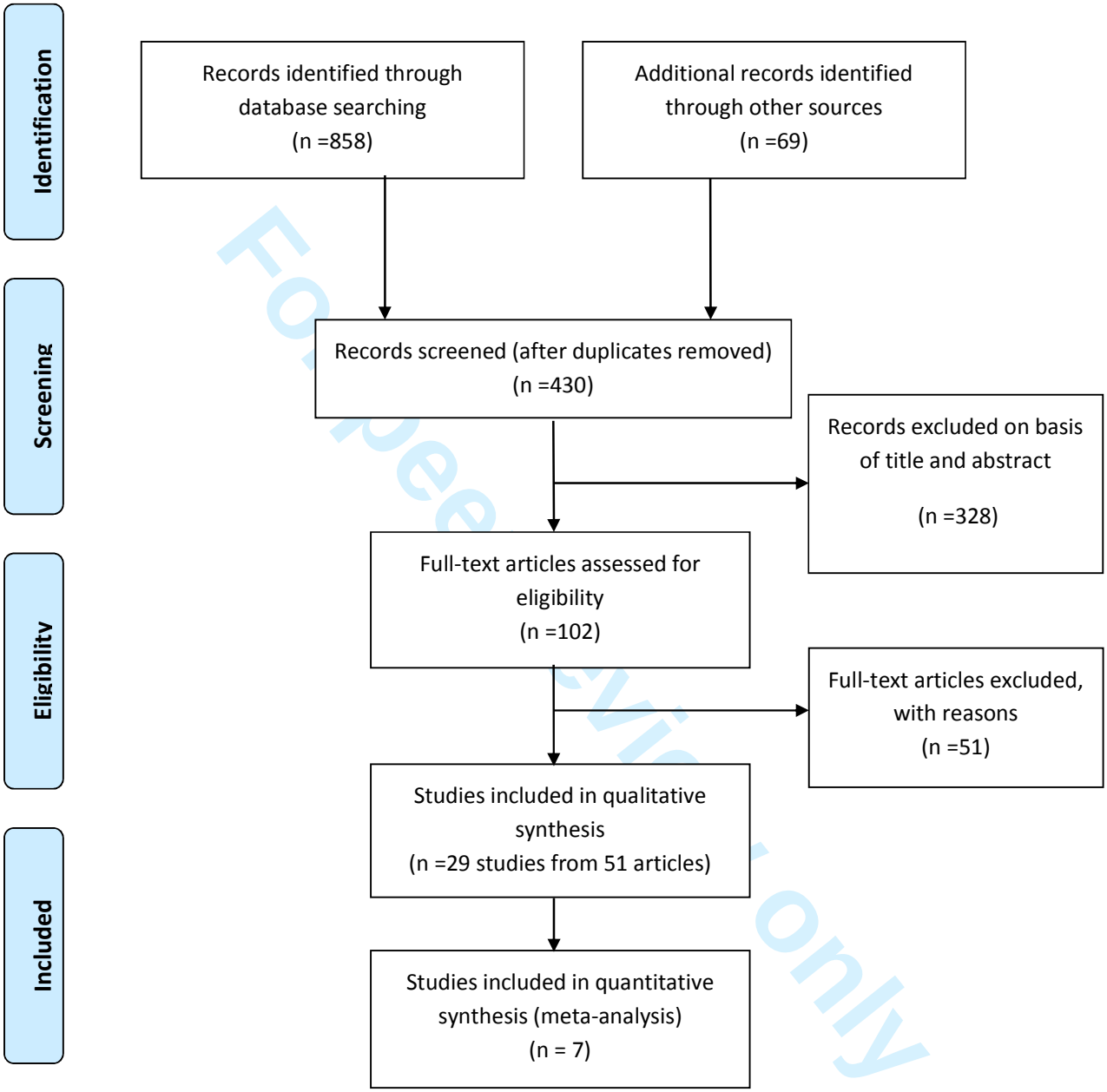

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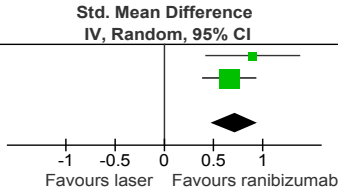
Figure 2 Ranibizumab 0.5mg alone versus laser alone

2.1 Mean change in BCVA

Study or Subgroup	Rani 0.5 mg Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	0.14	0.17	37	-0.01	0.16	38	24.1%	0.90 [0.42, 1.38]
RESTORE 2011	0.12	0.13	115	0.02	0.17	110	75.9%	0.66 [0.39, 0.93]
Total (95% CI)			**152**			**148**	**100.0%**	**0.72 [0.48, 0.95]**

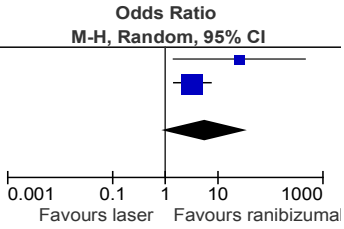
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 6.02 (P < 0.00001)



2.2 Proportion with >15 letter gain

Study or Subgroup	Rani 0.5 mg Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
READ-2 2009	9	37	0	38	28.0%	25.67 [1.43, 459.42]
RESTORE 2011	26	115	9	110	72.0%	3.28 [1.46, 7.37]
Total (95% CI)		**152**		**148**	**100.0%**	**5.83 [0.90, 37.86]**
Total events	35		9			

Heterogeneity: Tau² = 1.09; Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 1.85 (P = 0.06)



2.3 CMT

Study or Subgroup	Rani 0.5 mg Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	-103.73	126.76	37	-144.76	109.22	38	47.2%	0.34 [-0.11, 0.80]
RESTORE 2011	-118.7	115.07	115	-61.3	132.29	110	52.8%	-0.46 [-0.73, -0.20]
Total (95% CI)			**152**			**148**	**100.0%**	**-0.08 [-0.87, 0.71]**

Heterogeneity: Tau² = 0.29; Chi² = 8.96, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.20 (P = 0.84)

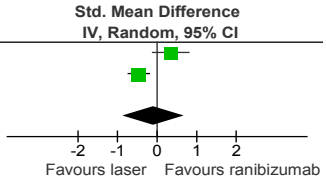
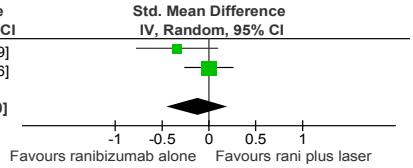


Figure 3 Ranibizumab 0.5mg plus laser versus ranibizumab 0.5mg alone

3.1 Mean change in BCVA

Study or Subgroup	Rani 0.5 plus laser Mean	SD	Total	Rani 0.5mg alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	0.08	0.18	42	0.14	0.17	42	36.5%	-0.34 [-0.77, 0.09]
RESTORE 2011	0.12	0.16	118	0.12	0.13	116	63.5%	0.00 [-0.26, 0.26]
Total (95% CI)			**160**			**158**	**100.0%**	**-0.12 [-0.44, 0.20]**

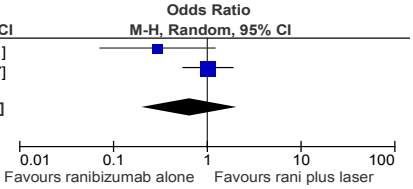
Heterogeneity: Tau² = 0.02; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 0.76 (P = 0.45)



3.2 Proportion with >15 letter gain

Study or Subgroup	Rani 0.5 plus laser Events	Total	Rani 0.5mg alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
READ-2 2009	3	40	8	37	36.3%	0.29 [0.07, 1.21]
RESTORE 2011	27	118	26	115	63.7%	1.02 [0.55, 1.87]
Total (95% CI)		**158**		**152**	**100.0%**	**0.65 [0.20, 2.09]**
Total events	30		34			

Heterogeneity: Tau² = 0.46; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.73 (P = 0.47)



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3.3 CMT

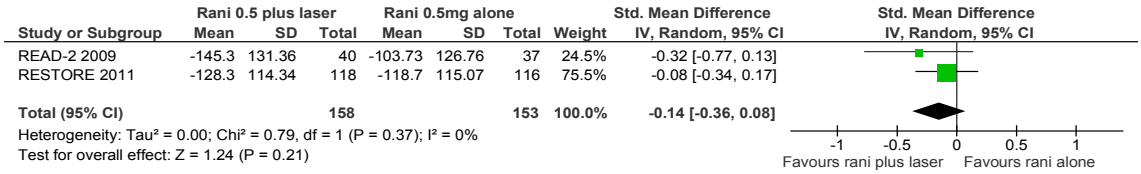
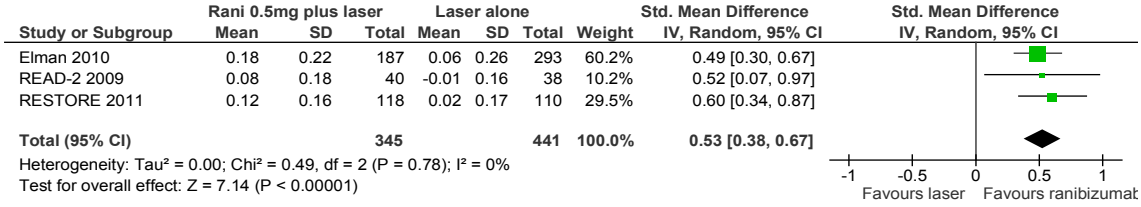
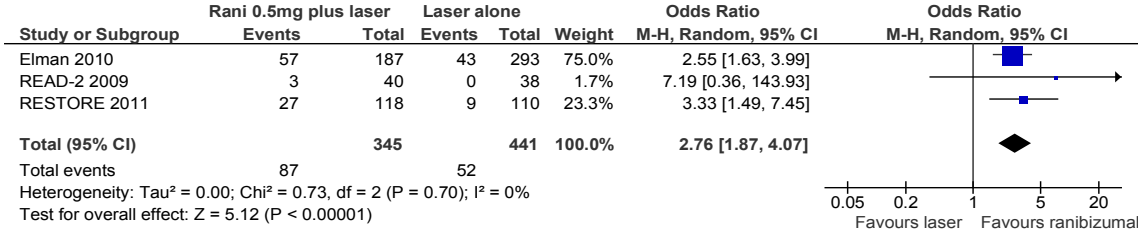


Figure 4 Ranibizumab 0.5mg plus laser versus laser alone

4.1 Mean change in BCVA



4.2 Proportion with >15 letter gain



4.3 CMT

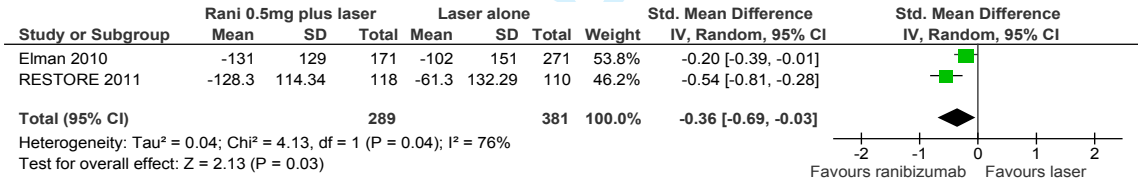


Figure 5 Pegaptanib 0.3mg versus sham injection

5.1 Proportion with >15 letter gain

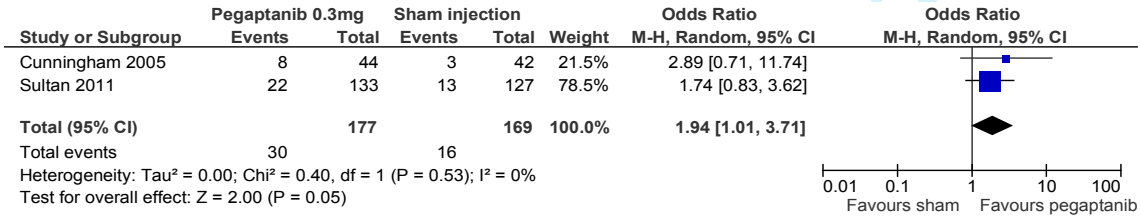


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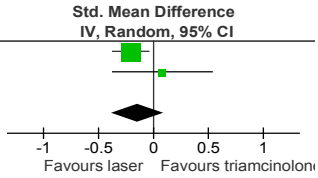
Figure 6 Triamcinolone 4mg versus laser alone

6.1 Mean change in BCVA

Study or Subgroup	Triamcinalone 4mg alone Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ip 2008	-0.06	0.44	254	0.02	0.34	330	78.2%	-0.21 [-0.37, -0.04]
Lam 2007	-0.7	10.7	38	-1.6	11.5	37	21.8%	0.08 [-0.37, 0.53]
Total (95% CI)			**292**			**367**	**100.0%**	**-0.14 [-0.38, 0.09]**

Heterogeneity: Tau² = 0.01; Chi² = 1.36, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.22 (P = 0.22)



6.2 Proportion with >15 letter gain

Study or Subgroup	Triamcinalone 4mg alone Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ip 2008	43	254	59	330	95.6%	0.94 [0.61, 1.44]
Lam 2007	2	38	2	37	4.4%	0.97 [0.13, 7.29]
Total (95% CI)		**292**		**367**	**100.0%**	**0.94 [0.61, 1.43]**
Total events	45		61			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)

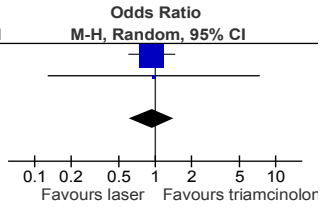
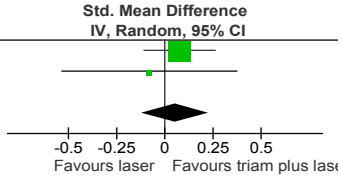


Figure 7 Triamcinolone 4mg plus laser versus laser alone

7.1 Mean change in BCVA

Study or Subgroup	Triam 4mg plus laser Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Elman 2010	0.08	0.26	186	0.06	0.26	293	85.9%	0.08 [-0.11, 0.26]
Lam 2007	0.7	10.7	38	1.6	11.5	37	14.1%	-0.08 [-0.53, 0.37]
Total (95% CI)			**224**			**330**	**100.0%**	**0.05 [-0.12, 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)



7.2 Proportion with >15 letter gain

Study or Subgroup	Triam 4mg plus laser Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Elman 2010	39	186	43	293	94.7%	1.54 [0.96, 2.49]
Lam 2007	2	38	2	37	5.3%	0.97 [0.13, 7.29]
Total (95% CI)		**224**		**330**	**100.0%**	**1.50 [0.94, 2.40]**
Total events	41		45			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)

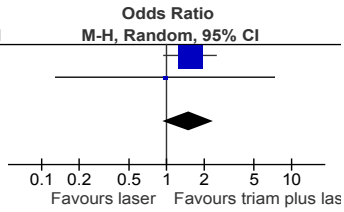


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Table 1: List of excluded studies

Study	Reason
Active comparator trials	
Cho 2010[86]	Single dose
DRCRN 2010 (Googe 2010)[87]	<6 mths f/u
Faghihi 2008[88]	Single dose
Figueroa 2008[89]	Single dose
Isaac 2012[90]	Single dose
Paccola 2008[91]	Single dose
Prager 2011[92]	<25 pts per arm
Ozturk 2011[93]	Non-RCT
Marey 2011[94]	<6 mths
Shahin 2010[95]	Single dose
Pegaptanib	
Loftus 2011[96]	Quality of life data.
Ranibizumab	
Ferrone 2011[97]	<25 pts per arm
Bevacizumab	
Solaiman 2010[98]	Single dose
DRCRN –Scott 2007[99]	<25 pts per arm
Lee 2011[100]	Non-RCT
Isaac 2012[90]	Single dose
Trimacinolone	
Audren 2006a[101]	Single dose (dosing study)
Audren 2006b[102]	Single dose
Avitabile 2005[103]	Mixed RVO and DMO
Bandello 2004[104]	Case report + PDR
Bonini 2005[105]	Single dose injection technique
Cellini 2008[106]	Single injection PSTI
Cardillo 2005[107]	Single injection PSTI
Chung 2008[108]	Single injection PSTI
Dehghan 2008[109]	Single dose
DRCRN -Chew 2007[110]	<25 pts per arm
Gil 2011[111]	<25 pts per arm
Entezari 2005[112]	<6 months
Hauser 2008[113]	Single dose
Jonas 2006[114]	Single dose
Joussen 2007[115]	Study protocol
Avci 2006[116]	Anaesthetic technique
Kang 2006[117]	Single dose
Kim 2008[118]	Single injection and CME
Lam 2007b[119]	Single injection
Lee 2009[120]	Single injection
Maia 2009[121]	Single dose
Massin 2004[122]	Single dose
Mohamed 2009[123]	Post-hoc analysis
Nakamura 2004[124]	Single dose
Spandau 2005[125]	Single dose
Tunc 2005[126]	<6 months

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Verma 2004[127]	Single dose
Wickremasinghe 2008[128]	Single dose
Yalcinbayir 2011[129]	Single dose
Dexamethasone	
Haller 2010[130]	<6 months
Haller 2009[131]	<25pts per arm
Kuppermann 2007 [132]	Mixture of macular oedema causes
Boyer 2011[133]	Non-randomised
Fluocinolone	
Campochiaro 2010[134]	<25pts per arm
Diclofenac	
Elbendary 2011 [71]	<35pts per arm

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Table 2: Ranibizumab trials

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
READ-2 Study (Nguyen 2009 / Nguyen 2010)[28,47] **USA** Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months, 2 year extension [no relevant outcomes as IVR received by all groups by that time, no safety outcomes for 2 year data]	**N:** 126 eyes of 126 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO, BCVA 20/40 to 20/320, CMT ≥250 µm, HbA1c ≥6% within 12 months before randomization; expectation that scatter laser photocoagulation not required for 6 months **Exclusion criteria:** contributing causes to reduced BCVA other than DMO, focal/grid laser within 3 months, intraocular steroid within 3 months, intraocular VEGF antagonist within 2 months **Age:** 62 years **Sex:** 52 to 69% female **Diabetes type:** not reported **HbA1c:** 7.39 to 7.77% **Baseline VA:** ETDRS letter score 24.85 to 28.35 **Baseline CMT:** excess foveal thickness 198.75 to 262.52 µm **Comorbidities:** not reported	**Group 1 (IVR, n=42 eyes):** IV injections of 0.5 mg ranibizumab at baseline, 1, 3, and 5 months **Group 2 (L, n=42 eyes):** focal/grid laser at baseline and 3 months if CMT ≥250 µm **Group 3 (IVRL, n=42 eyes):** IV injections of 0.5 mg ranibizumab at baseline and 3 months, followed by focal/grid laser treatment 1 week later **Regimen for all groups:** after 6 months, patients could receive IV injections of ranibizumab no more than every 2 months or focal/grid laser no more than every 3 months if CMT ≥250 µm **Laser** Modified ETDRS protocol was used	**At 6 months** **BCVA (ETDRS):** **BCVA (letters)** / **p** ***IVR*** +7.24 / 0.0003 vs L ***L*** -0.43 ***IVRL*** +3.80 / NS vs IVR or L **plus ≥3 lines** ***IVR*** 22% / <0.05 vs L ***L*** 0 ***IVRL*** 8% **CMT (OCT):** **CMT (µm)** / **p** ***IVR*** -106.3 / all <0.01 vs baseline, NS for elimination of ≥50% excess foveal thickness between groups ***L*** -82.8 ***IVRL*** -117.2
READ-3 Study (Do 2012) USA[50] **Design:** phase 2, 2-arm RCT **Follow-up:** 6 months	**N:** 152 eyes **Inclusion criteria:** NR **Exclusion criteria:** NR **Age:** NR **Sex:** NR **Diabetes type:** NR **HbA1c:** NR **Baseline VA:** Mean BCVA Snellen equivalent 20/63 in the 2.0 mg group and 20/80 in the 0.5 mg group **Baseline CST (central subfield thickness):** 432 µm in the 2.0 mg group and 441 µm in the 0.5 mg group **Comorbidities:** NR	**Group 1 (IVR2.0, n=NR):** monthly injections **Group 2 (IVR0.5, n=NR):** monthly injections After month 6, eyes evaluated and additional ranibizumab injections given on an as needed basis if DMO still present on OCT.	**At 6 months:** **BCVA** **Mean BCVA letters gain** / **p** ***IVR2.0*** +7.46 / NR ***IVR0.5*** +8.69 / NR **CST** **CST reduction** ***IVR2.0*** -163.86 µm / NR ***IVR0.5*** -169.27 µm / NR

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
RESOLVE Study (Massin 2010)[36] Multicenter international **Design:** 3-arm placebo-controlled RCT **Follow-up:** 12 months	**N:** 151 eyes of 151 patients **Inclusion criteria:** >18 years, type 1 or 2 DM, clinically significant DMO, BCVA 20/40 to 20/160, HbA1c <12%, decreased vision attributed to foveal thickening from DMO, laser photocoagulation could be safely withheld in the study eye for at least 3 months after randomization **Exclusion criteria:** unstable medical status, panretinal laser photocoagulation performed within 6 months before study entry, previous grid/laser photocoagulation except patients with only mild laser burns at least 1000 µm from the centre of the fovea performed >6 months previously **Age:** 63 to 65 (range 32 to 85) years **Sex:** 43.1 to 49.0% female **Diabetes type:** 96.1 to 98.0% type 2 DM **HbA1c:** 7.3 to 7.6 (range 5.3 to 11.1) % **Baseline VA:** ETDRS letter score 59.2 to 61.2 SD9.0 to 10.2 **Baseline CMT:** 448.9 to 459.5 SD102.8 to 120.1 µm **Comorbidities:** not reported	**Group 1 (IVR0.3, n=51 eyes):** 0.3 mg (0.05 ml) IV ranibizumab, 3 monthly injections (dose up to 0.6 mg, see below) **Group 2 (IVR0.5, n=51 eyes):** 0.5 mg IV (0.05 ml) ranibizumab, 3 monthly injections (dose up to 1.0 mg, see below) **Group 3 (C, n=49 eyes):** sham treatment, 3 monthly injections **Regimen for all groups:** after month 1, the injection dose could be doubled if CMT remained >300 µm or was >225 µm and reduction in retinal oedema from previous assessment was <50 µm; once injection volume was 0.1 ml it remained that for subsequent injections; if treatment had been withheld for >45 days, subsequent injections restarted at 0.05 ml; 68.6% of dose doubling with ranibizumab, 91.8% with sham; 34.7% of rescue laser photocoagulation in sham group, 4.9% in ranibizumab group	**At 12 months** **BCVA (ETDRS):** ***IVR0.3*** **BCVA (letters)** +11.8 SD6.6 **p** <0.0001 vs C ***IVR0.5*** +8.8 SD11.0 <0.0001 vs C ***C*** -1.4 SD14.2 **change ≥10 letters** ***IVR0.3*** gain 72.5% loss 0 <0.0001 vs C ***IVR0.5*** gain 49.0% loss 9.8% 0.001 vs C ***C*** gain 18.4% loss 24.5% **CMT (OCT):** ***IVR0.3*** **CMT (µm)** -200.7 SD122.2 **p** <0.0001 vs C ***IVR0.5*** -187.6 SD147.8 <0.0001 vs C ***C*** -48.4 SD153.4
RESTORE Study (Mitchell 2011/ Mitchell 2012)[24,49] Multicenter international **Design:** 3-arm RCT **Follow-up:** 12 months	**N:** 345 eyes of 345 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, HbA1c ≤10%, visual impairment due to DMO (eligible for laser treatment), stable medication for management of diabetes, BCVA ETDRS letter score 39 to 78 **Exclusion criteria:** concomitant eye conditions that could affect VA, active intraocular inflammation or infection, uncontrolled glaucoma in either eye, panretinal laser photocoagulation within 6 months or focal/grid laser photocoagulation within 3 months prior to study entry, history of stroke, hypertension. **Age:** 62.9 to 64.0 SD8.15 to 9.29 years **Sex:** 37.1 to 47.7% female **Diabetes type:** 86.4 to 88.8% type 2 DM **HbA1c:** not reported	**Group 1 (IVR, n=116 eyes):** 0.5 mg IV ranibizumab plus sham laser (median injections 7 (range 1 to 12), median sham laser treatments 2 (range 1 to 5)) **Group 2 (IVRL, n=118 eyes):** 0.5 mg IV ranibizumab plus active laser (median injections 7 (range 2 to 12), median laser treatments 1 (range 1 to 5)) **Group 3 (L, n=111 eyes):** laser treatment plus sham injections (median sham injections 7 (range 1 to 12), median laser treatments 2 (range 1 to 4)) **Regimen for all groups:** 3 initial monthly injections, followed by retreatment schedule; 1 injection per month if stable VA not reached;	**At 12 months** **BCVA (ETDRS):** ***IVR*** **BCVA (letters)** +6.1 SD6.43 **p** <0.0001 vs L ***IVRL*** +5.9 SD7.92 <0.0001 vs L ***L*** +0.8 SD8.56 **BCVA change categories** ***IVR*** plus ≥10: 37.4% loss ≥10: 3.5% <0.0001 vs L ***IVRL*** plus ≥10: 43.2% loss ≥10: 4.2% <0.0001 vs L ***L*** plus ≥10: 15.5% loss ≥10: 12.7% **CMT (OCT):**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	Baseline VA: ETDRS letter score 62.4 to 64.8 SD9.99 to 11.11 **Baseline CMT:** 412.4 to 426.6 SD118.01 to 123.95 **Comorbidities:** not reported	**Laser** retreatments in accordance with ETDRS guidelines at intervals no shorter than 3 months from previous treatment	**CMT (µm) / p** ***IVR*** -118.7 SD115.07 — 0.0002 vs L ***IVRL*** -128.3 SD114.34 — <0.0001 vs L ***L*** -61.3 SD132.29
REVEAL Study (Ohji 2012) Japan Multicenter[48] **Design:** phase III double-masked RCT **Follow-up:** 12 months	**N:** 396 patients **Inclusion criteria:** NR **Exclusion criteria:** NR **Age:** 61.1 years **Sex:** NR **Diabetes type:** 98.7% with type 2 diabetes **HbA1c:** 7.5% **Baseline VA:** 58.6 letters **Baseline CMT:** 421.9 µm **Comorbidities:** NR	**Group 1 (IVR 0.5 + sham laser, n=133):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA **Group 2 (IVR 0.5+ active laser, n=132):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA **Group 3 (sham injection + active laser, n=131):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA Active/sham laser photocoagulation performed according to ETDRS guidelines at ≥3 month intervals.	**At 12 months BCVA:** **Mean average change from baseline to month 1 to 12 / p** ***IVR + sham laser*** +5.9 — vs laser <0.0001 ***IVR + laser*** +5.7 — vs laser <0.0001 ***Laser + sham*** +1.4 **Mean change from baseline to month12 in BCVA and CRT** ***IVR + sham laser*** +6.6; -148.0 µm — vs C <0.0001 ***IVR + laser*** +6.4; -163.8 µm — vs C <0.0001 ***Laser + sham*** +1.8; -57.1 µm
RISE Study (Brown 2011/Nguyen 2012)[38,135] USA Multicenter **Design:** 3-arm double-blind sham-controlled RCT **Follow-up:** 24 months	**N:** 377 eyes of 377 patients **Inclusion criteria:** ≥18 years, type 1 or 2 diabetes, BCVA 20/40 to 20/320, DMO CMT ≥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 or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction **Age:** 61.7 to 62.8 SD8.9 to 10.0 (range 21 to 87) years **Sex:** 41.6 to 48% female	**Group 1 (IVR0.3, n=125 eyes):** 0.3 mg IV ranibizumab **Group 2 (IVR0.5, n=125 eyes):** 0.5 mg IV ranibizumab **Group 3 (C, n=127 eyes):** sham injection **Regimen for all groups:** monthly injections; need for macular rescue laser assessed monthly starting at month 3	**At 24 months BCVA:** **plus ≥15 letters / p** ***IVR0.3*** 44.8% — <0.0001 vs C ***IVR0.5*** 39.2% — =0.0002 vs C ***C*** 18.1% **Loss of <15 letters** ***IVR0.3*** 97.6% — =0.0086 vs C ***IVR0.5*** 97.6% — =0.0126 vs C ***C*** 89.8%

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	Diabetes type: type 1 or 2 **HbA1c:** 7.7% SD 1.4 to 1.5; ≤8% (65 to 68.3%); >8% (31.7% to 35%) **Baseline VA:** Mean ETDRS letter score 54.7 to 57.2; ≤20/200 (7.9 to 13.6%); >20/200 but <20/40 (72.4 to 72.8%); ≥20/40 (13.6 to 19.7%) **Baseline CMT:** 463.8 to 474.5 µm **Comorbidities:** History of smoking 46.4 to 51.2%		**Snellen equivalent of 20/40 or better** ***IVR0.3*** 60.0% <0.0001 vs C ***IVR0.5*** 63.2% <0.0001 vs C ***C*** 37.8% **Mean BCVA gain (letters)** ***IVR0.3*** +12.5 SD14.1 <0.0001 vs C ***IVR0.5*** +11.9 SD12.1 <0.0001 vs C ***C*** +2.6 SD13.9 **CFT:** **Mean change from baseline** **p** ***IVR0.3*** -250.6 SD212.2 <0.0001 vs C ***IVR0.5*** -253.1 SD183.7 <0.0001 vs C ***C*** -133.4 SD209.0
RIDE study (Boyer 2011/Nguyen 2012)[38,136] **USA** Multicentre **Design:** 3-arm double-blind sham-controlled RCT **Follow-up:** 24 months	**N:** 382 eyes **Inclusion criteria:** ≥18 years, type 1 or 2 diabetes, BCVA 20/40-20/320 and DMO CMT ≥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 or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction **Age:** 61.8 to 63.5 (range 22 to 91) years **Sex:** 37 to 49.1% female **Diabetes type:** type 1 or 2 **HbA1c:** 7.6 SD1.3 to 1.5; ≤8% (65.8 to 67.5%); >8% (32.5 to 34.2%) **Baseline VA:** Mean ETDRS letter score 56.9 to 57.5	**Group 1 (IVR0.3, n=125 eyes):** 0.3 mg IV ranibizumab **Group 2 (IVR0.5, n=127 eyes):** 0.5 mg IV ranibizumab **Group 3 (C, n=130 eyes):** sham injection **Regimen for all groups:** Patients were eligible for rescue macular laser starting at Month 3	**At 24 months** **BCVA:** **More than 15 letters** **p** ***IVR0.3*** 33.6% <0.0001 vs. C ***IVR0.5*** 45.7% <0.0001 vs. C ***C*** 12.3% **Less than 15 letters** ***IVR0.3*** 1.6% >0.05 vs C ***IVR0.5*** 3.9% <0.05 vs. C ***C*** 8.5% **Snellen equivalent of 20/40 or better** ***IVR0.3*** 54.4% =0.0002 vs C

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)		
	Baseline CMT: 447.4 to 482.6 µm **Comorbidities:** history of smoking 33.6 to 51.6%		***IVR0.5***	62.2%	<0.0001 vs C
			C	34.6%	
				Mean BCVA gain (letters)	
			IVR0.3	+10.9 SD10.4	<0.0001vs C
			IVR0.5	+12.0 SD14.9	<0.0001 vs. C
			C	+2.3 SD14.2	
			CMT:		
				Mean change from baseline	**p**
			IVR0.3	-259.8 SD169.3	<0.0001 vs C
			IVR0.5	-270.7 SD201.6	<0.0001 vs C
			C	-125.8 SD198.3	

Abbreviations: BCVA – best corrected visual acuity, CMT – central macular thickness, DM – diabetes mellitus, DMO – diabetic macular oedema, DP – diastolic pressure, DR – diabetic retinopathy, HR QoL – health-related quality of life, IOP – intraocular pressure, IQR – interquartile range, IV – intravitreal, NEI VFQ-25 – National Eye Institute Visual Function Questionnaire-25, NPDR – nonproliferative diabetic retinopathy, NR – not reported, OCT – optical coherence tomography, PDR – proliferative diabetic retinopathy, PRP – panretinal photocoagulation, RCT – randomized controlled trial, SD – standard deviation, SP – systolic pressure, VA – visual acuity, VEGF – vascular endothelia growth factor, vs – versus, CSME – clinically significant macular oedema, MLT/MPC – macular laser therapy/macular photocoagulation, IVR – intravitreal ranibizumab, IVB – intravitreal bevacizumab, IVP – intravitreal pegaptanib, IVVTE – intravitreal VEGF Trap Eye, C - control, DIL - dexamethasone followed by laser, DDS - dexamethasone, SRFA – fluocinolone, SOC – standard of care, IVT - intravitreal triamcinolone, L – laser, IVTL intravitreal triamcinolone plus laser **Notes:** injections are intravitreal unless otherwise noted

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Table 3: Bevacizumab studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
BOLT Study (Michaelides 2010/ Rajendram 2012)) [23,52,84] **UK** **Design:** 2-arm RCT **Follow-up:** 12 months	**N:** 80 eyes of 80 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, BCVA in the study eye 35 to 69 ETDRS letters at 4 m (≥6/60 or ≤6/12), center-involving clinically significant DMO with CMT ≥270 µm; media clarity, papillary dilation and cooperation sufficient for adequate fundus imaging; a least 1 prior macular laser therapy; IOP <30 mmHg; fellow eye BCVA ≥3/60; fellow eye received no anti-VEGF in past 3 months and no expectation of such therapy **Exclusion criteria:** (ocular for study eye) macular ischemia, macular oedema due to causes other than DMO, coexistent ocular disease affecting VA or DMO, any treatment for DMO in prior 3 months, PRP within 3 months prior to randomization or anticipated, PDR, HbA1c >11.0%, medical history of chronic renal failure; any thromboembolic event within 6 months prior to randomization, unstable angina, evidence of active ischemia on ECG; major surgery within 28 days of randomization or planned; participation in an investigational drug trial; systemic anti-VEGF or pro-VEGF treatment within 3 months of enrollment; pregnancy, lactation; intraocular surgery within 3 months of randomization; aphakia; uncontrolled glaucoma; significant external ocular disease **Age:** 64.2 SD8.8 years **Sex:** 31% female **Diabetes type:** 90% type 2 DM, 10% type 1 DM **HbA1c:** 7.5 to 7.6 SD1.2 to 1.4% **Baseline VA:** ETDRS letter score 54.6 to 55.7 SD8.6 to 9.7 **Baseline CMT:** 481 to 507 SD121 to 145 µm **Comorbidities:** 19% mild NPDR (level 35), 46% moderate NPDR (level 43), 19% moderately severe NPDR (level 47), 13% severe NPDR (level 53), 3% moderate PDR (level 65), 79 to 88% phakic	**Group 1 (MLT, n=38 eyes):** modified ETDRS macular laser therapy; reviewed every 4 months up to 52 weeks; retreatment performed if clinically indicated by ETDRS guidelines (median 4 laser treatments) **Group 2 (IVB, n=42 eyes):** 1.25 mg (0.05 ml) IV bevacizumab at baseline, 6 and 12 weeks; subsequent IVB injections (up to 52 weeks) guided by an OCT-based retreatment protocol (median 13 injections) **Laser** Modified ETDRS protocol, retreatment by ETDRS guidelines	**At 24 months** **BCVA (ETDRS):** **BCVA.mean (SD) p** ***MLT*** -0.5 (10.6) ***IVB*** +8.6 (9.1) 0.005 vs MLT **BCVA gain categories (letters)** ***MLT*** gaining ≥10: 7%; losing >15: 4% ***IVB*** gaining ≥10: 49% 0.001 vs MLT; losing >15: 32% 0.004 vs MLT **CMT (OCT):** **CMT (µm, quartiles) p** ***MLT*** -118 SD171 ***IVB*** -146 SD122 0.62 vs MLT •

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Lam 2009[35] **Hong Kong** **Design:** 2-arm RCT **Follow-up:** 6 months	**N:** 52 eyes of 52 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, clinically significant DMO (slit-lamp biomicroscopy, ETDRS criteria; leakage confirmed by fluorescein angiography, CMT ≥250 µm on OCT), BCVA ≥1.3 ETDRS logMAR units; only patients with diffuse DMO recruited **Exclusion criteria:** macular oedema due to reasons other than diabetes, significant media opacities, macular ischemia of ≥1 disk area, vitreomacular traction, PDR, aphakia, glaucoma or ocular hypertension, previous anti-VEGF treatment, intraocular surgery except uncomplicated cataract extraction (but > 6 months prior), focal DMO, any laser procedure within previous 4 months, subtenon or intravitreal triamcinolone injection within 6 months, pregnancy. **Age:** 65.3 SD8.9 years **Sex:** 46.2% female **Diabetes type:** not reported **HbA1c:** 7.5 SD1.0% **Baseline VA:** 0.61 SD0.29 logMAR **Baseline CMT:** 466 SD127 µm **Comorbidities:** not reported	**Group 1 (IVB1.25, n=26 eyes):** 1.25 mg bevacizumab (0.05 ml) **Group 2 (IVB2.5, n=26 eyes):** 2.5 mg bevacizumab (0.1 ml) **Regimen for all groups:** 3 monthly IV injections, topical 0.5% levofloxacin 4x/day for up to 2 weeks after each injection	**At 6 months** **BCVA (ETDRS chart):** ***IVB1.25*** BCVA (logMAR): 0.11 SD0.31 [+5.5 letters]; p: 0.018 vs baseline, NS vs IVB2.5 ***IVB2.5*** BCVA (logMAR): 0.13 SD0.26 [+6.5 letters]; p: 0.003 vs baseline **CMT (OCT):** ***IVB1.25*** CMT (µm): 96; p: 0.002 vs baseline, NS vs IVB2.5 ***IVB2.5*** CMT (µm): 74; p: 0.013 vs baseline Subgroups: • For patients with previous DMO treatment (mainly laser): no significant reduction in CMT at 6 months (452 µm at baseline to 416 µm at 6 months, p=0.22); no significant improvement in BCVA (0.66 logMAR at baseline to 0.56 logMAR at 6 months [+5 letters], p=0.074)
Faghihi 2010[53] **Iran** **Design:** 2-arm RCT **Follow-up:** 6 months	**N:** 80 eyes of 40 patients **Inclusion criteria:** Bilateral non-tractional CSME, 10/10> V.A≥ 1/10, Controlled blood pressure. **Exclusion criteria:** Advanced or advanced active PDR, Significant cataract, Glaucoma, History of recent vascular accident (e.g, MI, CVA), Previous treatment of CSME or PDR, or pharmacotherapy for CSME, macular ischemia and uncontrolled hypertension. **Age:** 57.7±8 years. **Sex:** 27.5% females **Diabetes type:** NR **HbA1c:** 8.42±1.82 g/dl **Baseline VA:** 0.326 to 0.409 (SD 0.279 to 0.332) **Baseline CMT:** 277 um to 287 um (SD 78 to 98) **Comorbidities:** not reported	**Group 1 (IVB, n= 40 eyes):** 1.25mg bevacizumab **Group 2 (IVB+MPC, n= 40 eyes):** 1.25mg bevacizumab **Regimen for all groups:** Eyes examined every two months and if evidence of CSME IVB was injected. mean of the number of IVB injections in IVB group and IVB+MPC group were 2.23±1.24 and 2.49±1.09 respectively.	**At 6 months** **Mean change in BCVA (ETDRS chart):** **IVB** BCVA (logMAR): 0.138; p: <0.05 vs baseline **IVB+MPC** BCVA (logMAR): 0.179; p: <0.05 vs baseline • no statistically significant difference between the two groups **CMT (OCT):** **IVB** CMT (µm): -39; p: <0.05 vs baseline **IVB+MPC** CMT (µm): -39; p: <0.05 vs baseline • no statistically significant difference between the two groups

Abbreviations: See table 2

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Table 4: Pegaptanib and aflibercept studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Pegaptanib			
Cunningham 2005 / Adamis 2006 [39,57] **USA** **Design:** 4-arm phase II RCT **Follow-up:** 36 weeks	**N:** 172 eyes of 172 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO involving the center of the macula with corresponding leakage from microaneurysms, retinal telangiectasis, or both; clear ocular media, BCVA letter scores between 68 and 25 in the study eye and at least 35 in the fellow eye; IOP ≤23 mmHg, focal photocoagulation could be safely deferred for 16 weeks; no ECG abnormalities, no major serological abnormalities **Exclusion criteria:** history of panretinal or focal photocoagulation; neodymium:yttrium–aluminum–garnet laser or peripheral retinal cryoablation in previous 6 months; any ocular abnormality interfering with VA assessment or fundus photography; vitreoretinal traction; vitreous incarceration; retinal vein occlusion involving the macula; atrophy/scarring/fibrosis or hard exudates involving the center of the macula; history of intraocular surgery within previous 12 months, myopia of ≥8 diopters, axial length of ≥25mm, likelihood of requiring panretinal photocoagulation within following 9 months; cataract surgery within 12 months; active ocular or periocular infection; previous therapeutic radiation to the eye, head, or neck;; known serious allergies to fluorescein dye; HbA1c ≥13%, pregnancy **Age:** 61.3 to 64.0 SD9.3 to 10.1 years **Sex:** 45 to 55% female **Diabetes type:** 5 to 10% IDDM **HbA1c:** 7.1 to 7.7 SD1.2 to 1.6 **Baseline VA:** letter score 55.0 to 57.1 SD9.1 to 11.5 **Baseline CMT:** 423.2 to 476.0 µm **Comorbidities:** not reported	**Group 1 (IVP0.3, n=44 eyes):** 0.3 mg IV pegaptanib (90 µl) (median 5 injections (range 1 to 6)) **Group 2 (IVP1, n=44 eyes):** 1 mg IV pegaptanib (90 µl) (median 6 injections (range 3 to 6)) **Group 3 (IVP3, n=42 eyes):** 3 mg IV pegaptanib (90 µl) (median 6 injections (range 1 to 6)) **Group 4 (C, n=42 eyes):** sham injection (median 5 injections (range 1 to 6)) **Regimen for all groups:** injections at baseline, week 6 and week 12; thereafter, additional injections administered every 6 weeks at the discretion of the investigators if judged indicated (maximum of 6 injections up to week 30); laser photocoagulation allowed after week 13 if judged indicated by the study-masked ophthalmologist (25% for IVP0.3, 30% for IVP1, 40% for IVP3, 48% for C)	**At 36 weeks** **BCVA:** **BCVA (letters)** / **p** ***IVP0.3*** +4.7 / 0.04 vs C ***IVP1*** +4.7 / 0.05 vs C ***IVP3*** +1.1 / NS vs C ***C*** -0.4 **plus ≥10 letters** ***IVP0.3*** 34% / 0.003 vs C ***IVP1*** 30% ***IVP3*** 14% ***C*** 10% **CMT (OCT):** **CMT (µm, 95% CI)** / **p** ***IVP0.3*** -68.0 (-118.9 to -9.88) / 0.02 vs C ***IVP1*** -22.7 (-76.9 to +33.8) / NS vs C ***IVP3*** -5.3 (-63.0 to +49.5) / NS vs C ***C*** +3.7 Subgroups: • of 16 participants with retinal neovascularization at baseline, 8 of 13 (62%) in the pegaptanib groups and 0 of 3 in the sham group had regression of neovascularization at 36 weeks
Sultan 2011[40] Multicenter international **Design:** 2-arm placebo-controlled RCT	**N:** 260 eyes of 260 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO involving the center of the macula not associated with ischemia, CMT ≥250 µm, BCVA letter score 65 to 35, IOP ≤21 mmHg, clear ocular media **Exclusion criteria:** any abnormality other than DMO affecting VA assessment, vitreomacular traction; yttrium-aluminium-garnet laser, peripheral retinal cryoablation, laser retinopexy for retinal tears, focal or	**Group 1 (IVP, n=133 eyes):** 0.3 mg IV pegaptanib sodium (mean number of injections 12.7 SD4.6) **Group 2 (C, n=127 eyes):** sham injection (mean number of injections 12.9 SD4.4)	**At 1 year** **BCVA (ETDRS):** **BCVA (letters)** / **p** ***IVP*** +5.2 / <0.05 vs C ***C*** +1.2 **plus ≥10**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Follow-up: 2 years (primary efficacy endpoint at 1 year)	grid photocoagulation within prior 16 weeks; panretinal photocoagulation <6 months before baseline or likely to be needed within 9 months; significant media opacities; intraocular surgery in prior 6 months; pathologic high myopia; prior radiation in region of study eye; history of severe cardiac or peripheral vascular disease, stroke in prior 12 months, major surgery in prior 1 month, treatment in prior 90 days with any investigational agent or with bevacizumab for any nonocular condition, HbA1c ≥10% or signs of uncontrolled diabetes, hypertension, known relevant allergies; pregnant or lactating **Age:** 62.3 to 62.5 SD9.3 to 10.2 years **Sex:** 39 to 46% female **Diabetes type:** 6.3 to 7.5% type 1 DM, 92.5 to 93.7% type 2 DM **HbA1c:** 42.5 to 45.9% <7.6%, 54.1 to 57.5% >7.6% **Baseline VA:** letter score 57.0 to 57.5 SD8.1 to 8.9 **Baseline CMT:** 441.6 to 464.6 SD135.5 to 148.5 µm **Comorbidities:** not reported	**Regimen for all groups:** injections every 6 weeks up to week 48 (9 injections); at investigator determination (ETDRS criteria), laser photocoagulation could be performed at week 18, with possible repeat treatment at a minimum of 17 weeks later (maximum 3 treatments per year) (laser treatments in 25.2% of IVP group and 45% of C group); in year 2, injections as judged necessary	**letters** ***IVP*** 36.8% 0.0047 vs C ***C*** 19.7% **Retinopathy:** **increase in degree by ≥2 steps** ***IVP*** 4.1% 0.047 vs C ***C*** 12.4% **decrease in degree by ≥2 steps** ***IVP*** 10.2% NS vs C ***C*** 3.1% **CMT (OCT):** **decrease in CMT** ***IVP*** ≥25%: 31.7% NS s C ≥50%: 14.6% ***C*** ≥25%: 23.7% ≥50%: 11.9% **At 2 years** **BCVA (ETDRS):** **BCVA (letters) p** ***IVP*** +6.1 <0.01 vs C ***C*** +1.3 **plus ≥10 letters** ***IVP*** 38.3% NS vs C ***C*** 30.0% **Retinopathy:** **increase in degree by ≥2 steps** ***IVP*** 6.3% NS vs C ***C*** 13.8% **decrease in degree by ≥2 steps** ***IVP*** 16.3% 0.03 vs C ***C*** 3.8% **CMT (OCT):** **decrease in CMT** ***IVP*** ≥25%: 40.4% NS vs C ≥50%: 19.2%

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
			C ≥25%: 44.6% ≥50%: 26.1% **QoL:** • NEI VFQ-25: between group differences not significant at 54 weeks; at 102 weeks, significantly greater improvement in composite score and subscales distance vision activities, social functioning and mental health with pegaptanib • EQ-5D: no significant differences between groups in EQ-5D scores at weeks 54 or 102

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td>Aflibercept</td><td></td><td></td><td></td></tr>
<tr><td>DA VINCI 2010 (Do 2011)
Multicenter[30,58]

Design: 5-arm phase II RCT
Follow-up: 24 weeks</td><td>N: 221 eyes of 221 patients
Inclusion criteria: aged >18 years and diagnosed with type 1 or 2 diabetes mellitus, with DMO involving the central macula defined as CRT (>250 um in the central subfield. Participants were required to have BCVA letter score at 4 m of 73 to 24. 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: history of vitreoretinal surgery; panretinal 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; proliferative diabetic retinopathy (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 visual acuity or require medical or surgical intervention during the study period: active iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT; history of idiopathicor autoimmune uveitis; structural damage to the center of the macula that is likely to preclude improvement in visual acuity after the resolution of macular oedema; uncontrolled glaucoma or previous filtration surgery; infectious blepharitis, keratitis, scleritis, or conjunctivitis; or current treatment for serious systemic infection: 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 (even if the eye met all other entry criteria); or an ocular condition in the fellow eye with a poorer prognosis than the study eye
Age: 60.7 to 64.0 years (SD 8.1 to 11.5)
Sex: % female 35.6% to 47.6%
Diabetes type: % type 2, 88.6% to 97.7%
HbA1c: 7.85 to 8.10 (SD 1.71 to 1.94)
Baseline VA: 57.6 to 59.9 (SD 10.1 to 12.5)
Baseline CMT: 426.1 um to 456.6 um (SD 111.8 to 152.4)
Co morbidities: history of any cardiac disease was twice as common in the VEGF Trap-Eye groups compared with the laser group.</td><td>Trial of VEGF Trap-Eye (VTE), randomized on a 1:1:1:1:1 basis
Group 1 (IVVTE1, n=44 eyes): IV VTE, 0.5 mg every 4 weeks
Group 2 (IVVTE2, n=44 eyes): IV VTE, 2 mg every 4 weeks
Group 3 (IVVTE3, n=42 eyes): IV VTE, 2 mg for 3 initial months then every 8 weeks
Group 4 (IVVTE4, n=45 eyes): IV VTE, 2 mg for 3 initial months then as needed
Group 5 (L, n=44 eyes): laser photocoagulation
Laser Modified ETDRS protocol</td><td>At 6 months
<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>IVVTE1</td><td>+8.6</td><td>0.005 vs L</td></tr><tr><td>IVVTE2</td><td>+11.4</td><td><0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>+8.5</td><td>0.008 vs L</td></tr><tr><td>IVVTE3</td><td>+10.3</td><td>0.0004 vs L</td></tr><tr><td>L</td><td>+2.5</td><td></td></tr><tr><td></td><td>plus ≥10 letters</td><td></td></tr><tr><td>IVVTE1</td><td>50%</td><td>NR</td></tr><tr><td>IVVTE2</td><td>64%</td><td>NR</td></tr><tr><td>IVVTE3</td><td>43%</td><td>NR</td></tr><tr><td>IVVTE3</td><td>58%</td><td>NR</td></tr><tr><td>L</td><td>32%</td><td>NR</td></tr><tr><td></td><td>CMT(um)</td><td></td></tr><tr><td>IVVTE1</td><td>-144.6</td><td>0.0002 vs L</td></tr><tr><td>IVVTE2</td><td>-194.5</td><td><0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>-127.3</td><td>0.007 vs L</td></tr><tr><td>IVVTE3</td><td>-153.3</td><td><0.0001 vs L</td></tr><tr><td>L</td><td>-67.9</td><td></td></tr></table>At 12 months
<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>IVVTE1</td><td>+11.0</td><td>≤0.0001 vs L</td></tr><tr><td>IVVTE2</td><td>+13.1</td><td>≤0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>+9.7</td><td>≤0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>+12.0</td><td>≤0.0001 vs L</td></tr><tr><td>L</td><td>-1.3</td><td></td></tr><tr><td></td><td>plus ≥15 letters</td><td></td></tr><tr><td>IVVTE1</td><td>40.9%</td><td>0.0031 vs L</td></tr><tr><td>IVVTE2</td><td>45.5%</td><td>0.0007 vs L</td></tr><tr><td>IVVTE3</td><td>23.8%</td><td>0.1608 vs L</td></tr><tr><td>IVVTE3</td><td>42.2%</td><td>0.0016 vs L</td></tr><tr><td>L</td><td>11.4%</td><td></td></tr></table></td></tr>
</table>

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)		
				plus ≥10 letters	
			IVVTE1	57%	0.0031 vs L
			IVVTE2	71%	0.0007 vs L
			IVVTE3	45%	0.1608 vs L
			IVVTE3	62%	0.0016 vs L
			L		
				CMT(µm)	
			IVVTE1	-165.4	< 0.0001 vs L
			IVVTE2	-227.4	< 0.0001 vs L
			IVVTE3	-187.8	< 0.0001 vs L
			IVVTE3	-180.3	< 0.0001 vs L
			L	-58.4	

Abbreviations: See table 2

Table 5: Dexamethasone and fluocinolone studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Dexamethasone			
Callanan 2011USA[44] **Design:** 2-arm RCT **Follow-up:** 12 months	**N:** 253 eyes of 253 patients **Inclusion criteria:** diffuse DMO, CMT ≥275 µm, BCVA ≥34 and ≤70 letters **Exclusion criteria:** not reported **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (DIL, n=126 eyes):** dexamethasone IV implant followed by laser photocoagulation after 1 month (mean 1.6 implants; 78.6% completion) **Group 2 (L, n=127 eyes):** laser alone (79.5% completion) **Regimen for all groups:** if needed, patients were retreated with the dexamethasone implant at months 6 or 9, and with laser at months 4, 7, and 10; mean 2.2 laser treatments per patient **Laser protocol** not reported	**At 12 months** **BCVA:** **plus ≥10 l tters** **p** ***DIL*** 28% NS vs L ***L*** 24% • patients in DIL group had significantly greater increases in BCVA from baseline than patients in the laser group ($p<0.05$) at months 1 to 9 only **CMT (OCT):** • patients in DIL group had significantly greater mean reductions from baseline in CMT at months 1 and 6 only ($p<0.001$)
Haller 2010[59] **USA** Multicenter	**N:** 171 eyes of 171 patients **Inclusion criteria:** ≥12 years, DMO persisting for ≥90 days after laser treatment or medical therapy, BCVA by ETDRS between 20/40 (67 letters) and 20/200 (35 letters) due to	**Group 1 (DDS350, n=57 eyes):** 350 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity	**At 90 days** **BCVA (ETDRS):** **plus ≥10 letters** **p** ***DDS350*** 21% [graph] NS vs C

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Design: 3-arm RCT **Follow-up:** 6 months (180 days), primary outcome 3 months (90 days)	clinically detectable DMO; analysis includes only eyes with DMO associated with DR **Exclusion criteria:** history of vitrectomy in the study eye; use of systemic, periocular, or intraocular steroids within 30 days of enrollment; moderate or severe glaucoma in the study eye; poorly controlled hypertension (SP >160 mmHg or DP >90 mmHg); poorly controlled diabetes (HbA1c >13%) **Age:** 62.9 to 63.8 years SD10.2 to 12.0 **Sex:** 45.6 to 49.1% female **Diabetes type:** not reported **HbA1c:** 7.3 to 7.6% **Baseline VA:** letter score 54.4 to 54.7 SD9.96 to 11.88 **Baseline CMT:** 417.5 to 446.5 µm SD123.7 to 155.9 **Comorbidities:** 19 to 21% prior cataract extraction	**Group 2 (DDS700, n=57 eyes):** 700 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity **Group 3 (C, n=57 eyes):** no treatment **Regimen for all groups:** eyes demonstrating a VA loss of ≥5 letters could be treated with any other therapy (including laser photocoagulation and IV triamcinolone) (n=4 with photocoagulation or IV triamcinolone in the C group, n=2 in the DDS350 group, none in the DDS700 group)	***DDS700*** 33% 0.007 vs C ***C*** 12% **CMT (OCT):** **CMT (µm) / p** ***DDS350*** -42.57 SD95.96 NS (p=0.07) vs C ***DDS700*** -132.27 SD160.86 <0.001 vs C ***C*** +30.21 SD82.12 **At 180 days** **BCVA (ETDRS):** **plus ≥10 letters / p** ***DDS350*** 20% [graph] NS vs C ***DDS700*** 33% [graph] NS vs C ***C*** 23% [graph]
Fluocinolone			
FAME Study (Campochiaro 2011/ Campochiaro 2012) [29,60] Multicenter international **Design:** 3-arm placebo-controlled RCT **Follow-up:** 24 months; abstract with 36 month outcomes	**N:** 956 eyes of 956 patients **Inclusion criteria:** DMO, CMT ≥250 µm despite at least 1 prior focal/grid macular laser photocoagulation treatment, BCVA ETDRS letter score between 19 and 68 (20/50 to 20/400) **Exclusion criteria:** glaucoma, ocular hypertension, IOP >21 mmHg, taking IOP lowering drops; laser treatment for DMO within 12 weeks of screening, any ocular surgery in the study eye within 12 weeks of screening; ocular or systemic steroid therapy; active ocular infection; pregnancy **Age:** 62.5 SD9.4 years **Sex:** 40.6% **Diabetes type:** 6.6% type 1 DM, 92% type 2 DM, 1.4% uncertain **HbA1c:** 7.8 SD1.59 % **Baseline VA:** ETDRS letter score 53.4 SD12.23 **Baseline CMT:** 469.0 SD164.78 µm **Comorbidities:** 47.1% cataract at baseline, 62.7 to 67.4% phakic	**Group 1 (SRFA0.2, n=375 eyes):** intravitreal insert releasing 0.2 µg/day fluocinolone acetonide (FA) (2, 3, or 4 treatments received by 21.3, 1.9 and 0.3%) **Group 2 (SRFA0.5, n=393 eyes):** intravitreal insert releasing 0.5 µg/day fluocinolone acetonide (2, 3, or 4 treatments received by 22.6, 2.5 and 0.3%) **Group 3 (C, n=185 eyes):** sham injection (2, 3, or 4 treatments received by 19.5, 2.7 and 1.6%) **Regimen for all groups:** patients could receive rescue focal/grid laser therapy any time after the first 6 weeks for persistent oedema (35.2 to 36.7% in FA groups, 58.9% control group, p<0.001); treatments were allowed every 3 months for persistent or recurrent oedema; patients eligible for another FA insert at 1 year if ≥5 letter	**At 24 months** **BCVA (ETDRS):** **BCVA (letters) / p** ***SRFA0.2*** +4.4 0.02 vs C ***SRFA0.5*** +5.4 0.017 vs C ***C*** +1.7 **plus ≥15 letters** ***SRFA0.2*** 29% 0.002 SRFA vs C ***SRFA0.5*** 29% ***C*** 16% Subgroups: • BCVA benefits only in pseudophakic eyes (cataract surgery before or during the study), in phakic eyes, BCVA letter score was reduced by 5 (high dose) and 9 (low dose) from baseline at 24 months **CMT (optical coherence tomography):** **CMT (µm) / p** ***SRFA0.2*** -167.8 0.005 vs C ***SRFA0.5*** -177.1 <0.001 vs C ***C*** -111.3

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td></td><td></td><td>reduction in BCVA or >50 µm CMT increase from best status</td><td>• effect maintained at 36 months

At 36 months
<table><tr><th></th><th>plus ≥15 letters</th><th></th></tr><tr><td>SRFA0.2/ 0.5</td><td>28.7%</td><td>0.018 SRFA vs C</td></tr><tr><td>C</td><td>18.9%</td><td></td></tr></table></td></tr>
<tr><td>Pearson 2011[43]
USA
Multicenter

Design: 2-arm RCT
Follow-up: 36 months</td><td>N: 196 patients
Inclusion criteria: persistent or recurrent unilateral or bilateral DMO with retinal thickening involving fixation of ≥1 disc area in size, ETDRS visual acuity of ≥20 letters (20/400) to ≤68 letters (20/50) and ≥1 macular laser treatment in the study eye more than 12 weeks prior to enrollment
Exclusion criteria: Ocular surgery within 3 months prior to enrolment, uncontrolled IOP within the past 12 months while on ≥1 antiglaucoma medication, IOP of ≥22 mmHg at screening while on ≥1 antiglaucoma medication, peripheral retinal detachment in the area of implantation or media opacity precluding diagnosis of status in the study eye
Age: 61.4-62.7 years
Sex: 41.7-42% female
Diabetes type: 62.3-70% on insulin
HbA1c: not reported
Baseline VA: not reported
Baseline CMT: not reported
Comorbidities: not reported</td><td>Group 1 (SRFA, n= 127): 0.5 mg sustained release fluocinolone acetonide intravitreal implant
Group 2 (SOC, n= 69): standard of care – either repeat laser or observation
Laser ETDRS protocol</td><td>At 3 years

BCVA:
<table><tr><th></th><th>gain ≥15 letters</th><th>p</th></tr><tr><td>SRFA</td><td>31%</td><td>NS</td></tr><tr><td>SOC</td><td>20%</td><td></td></tr><tr><th></th><th>loss ≥15 letters</th><th></th></tr><tr><td>SRFA</td><td>17%</td><td>NS</td></tr><tr><td>SOC</td><td>14%</td><td></td></tr></table>
CMT:
<table><tr><th></th><th>Mean change in baseline CMT</th><th>p</th></tr><tr><td>SRFA</td><td>-86</td><td>NS</td></tr><tr><td>SOC</td><td>-110</td><td></td></tr></table></td></tr>
</table>

Abbreviations: See table 2

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Table 6: Triamcinolone studies

<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr>
<td>DRCR Network 2008 (Ip 2008a / 2008b / Beck 2009 / Bressler 2009)[22,61,63,64]
USA
Multicenter

Design: 3-arm RCT
Follow-up: 2 years, additional 3 year follow-up</td>
<td>N: 840 eyes of 693 patients
Inclusion criteria: >18 years, type 1 or 2 DM, study eye: (1) BCVA (E-ETDRS) between 24 and 73 (20/320 and 20/40), (2) retinal thickening due to DMO involving the center of the macula main cause for visual loss, (3) CMT ≥250 µm, (4) no expectation of scatter photocoagulation within 4 months
Exclusion criteria: any prior treatment with IV corticosteroids, peribulbar steroid injection within prior 6 months, photocoagulation for DMO within prior 15 weeks, panretinal scatter photocoagulation within prior 4 months, pars plana vitrectomy, history of open-angle glaucoma or steroid-induced
IOP elevation requiring IOP-lowering treatment, and IOP ≥25 mmHg
Age: 63 SD9 years
Sex: 49% female
Diabetes type: 95% type 2 DM, 5% type 1 DM
HbA1c: 7.9 SD1.8%
Baseline VA: ETDRS letter score 59 SD11 (~20/63)
Baseline CMT: 24 SD130 µm
Comorbidities: 21% pseudophakic, 2% ocular hypertension, 7% mild NPDR, 13% moderate NPDR, 40% moderately severe NPDR, 11% severe NPDR, 23.5% mild to moderate, 3% high risk PDR</td>
<td>Group 1 (IVT1, n=256 eyes):
1 mg IV triamcinolone (3.5 treatments)
Group 2 (IVT4, n=254 eyes):
4 mg IV triamcinolone (3.1 treatments)
Group 3 (L, n=330 eyes):
focal/grid photocoagulation (2.9 treatments)
Regimen for all groups:
retreatment protocol: where indicated, retreatment was performed within 4 weeks after the follow-up visit and no sooner than 3.5 months from the time of last treatment; eyes were generally retreated unless:
(1) little or no oedema involving the center of the macula present and CMT ≤225 µm, (2) VA letter score ≥79 (20/25 or better), (3) substantial improvement in macular oedema since last treatment (e.g., ≥ 50% decrease in CMT), (4) clinically significant adverse effect from prior treatment, (5) additional treatment deemed futile (<5 letter improvement in VA letter score or lack of CMT reduction), and (6) for laser group, complete focal/grid photocoagulation already given, with no areas identified for which additional treatment was indicated
Laser Modified ETDRS protocol as used in prior DRCR.net protocols</td>
<td>At 2 years
BCVA (E-ETDRS):
<table>
<tr><th></th><th>BCVA (letters)</th><th>p</th></tr>
<tr><td>IVT1</td><td>-2 SD18</td><td>0.02 vs L
NS vs IVT4</td></tr>
<tr><td>IVT4</td><td>-3 SD22</td><td>0.002 vs L</td></tr>
<tr><td>L</td><td>+1 SD17</td><td></td></tr>
<tr><td></td><td>BCVA gain categories</td><td></td></tr>
<tr><td>IVT1</td><td>+10 or more: 25%
+9 to -9: 50%
-10 or more: 26%</td><td>0.03 vs L, NS vs IVT4</td></tr>
<tr><td>IVT4</td><td>+10 or more: 28%
+9 to -9: 44%
-10 or more: 28%</td><td>0.01 vs L</td></tr>
<tr><td>L</td><td>+10 or more: 31%
+9 to -9: 50%
-10 or more: 19%</td><td></td></tr>
</table>
Subgroups:
• similar results when considering only pseudophakic eyes or eyes with minimal cataract
• no substantially different results based on baseline VA, baseline CMT, history of focal/grid photocoagulation for DMO
• 3 year results consistent with 2 year results for BCVA and CMT

CMT (OCT):
<table>
<tr><th></th><th>CMT (µm)</th><th>p</th></tr>
<tr><td>IVT1</td><td>-86 SD167</td><td><0.001 vs L,
NS vs IVT4</td></tr>
<tr><td>IVT4</td><td>-77 SD160</td><td><0.001 vs L</td></tr>
<tr><td>L</td><td>-139 SD148</td><td></td></tr>
</table>
Progression of retinopathy:
<table>
<tr><th></th><th>2 yrs</th><th>3 yrs</th><th>p</th></tr>
<tr><td>IVT1</td><td>29%</td><td>35%</td><td></td></tr>
<tr><td>IVT4</td><td>21%</td><td>30%</td><td><0.05 vs L</td></tr>
</table>
</td>
</tr>
</table>

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			L 31% 37%
Gillies 2006 / 2007 / 2009 / Sutter 2004 [32,137-139] **Australia** **Design:** 2-arm placebo-controlled RCT **Follow-up:** 2 years, additional 3-year follow-up	**N:** 69 eyes of 43 patients **Inclusion criteria:** patients with persistent (≥3 months after adequate laser treatment) DMO involving the central fovea, BCVA in the affected eye ≤6/9 **Exclusion criteria:** uncontrolled glaucoma, loss of vision due to other causes, systemic treatment with >5 mg prednisolone (or equivalent) daily, intercurrent severe systemic disease, any condition affecting follow-up or documentation **Age:** 62.4 to 69.6 SD9.2 to 12.5 years **Sex:** 52% female **Diabetes type:** not reported **HbA1c:** 7.63 to 8.28 SD1.12 to 1.41 **Baseline VA:** ETDRS letter score 60.5 to 61.3 SD11.9 to 13.2 **Baseline CMT:** 439 to 444 SD101 to 125 µm **Comorbidities:** 25% pseudophakic	**Group 1 (IVT, n=34 eyes):** 4 mg (0.1 ml) IV triamcinolone acetonide (mean 2.6 injections over 2 years) **Group 2 (C, n=35 eyes):** placebo injection (subconjunctival saline injection) (mean 1.8 injections over 2 years) **Regimen for all groups:** retreatment considered at each visit as long as treatments were at least 6 months apart (retreatment if VA decreased ≥5 letters from previous peak value and persistent CMT >250 µm), if no improvement after 4 weeks, further laser treatment was applied (n=1 laser treatment in intervention group, n=16 in placebo group, p=0.0001) **Laser** ETDRS protocol	**At 2 years** **BCVA (ETDRS):** ***IVT*** +3.1 (0.01 vs C) ***C*** -2.9 **CVA gain categories** ***IVT*** +10 or more: 21%; +9 to -9: 70%; -10 or more: 9% (0.013 vs C) ***C*** +10 or more: 12%; +9 to -9: 62%; -10 or more: 25% **CMT (OCT):** ***IVT*** -125 (0.009 vs C, difference between groups 59 µm (95% CI 15, 104)) ***C*** -75
Gillies 2011[33] **Australia** **Design:** 2-arm RCT **Follow-up:** 24 months	**N:** 84 eyes of 54 patients **Inclusion criteria:** DMO involving the central fovea, CMT ≥250 µm, BCVA 17 to 70 letters (~20/40 to 20/400), laser treatment could be safely delayed for 6 weeks without significant adverse effects **Exclusion criteria:** uncontrolled glaucoma, controlled glaucoma but with a glaucomatous visual field defect, loss of vision resulting from other causes, systemic treatment with >5 mg prednisolone (or equivalent) daily, retinal laser treatment within 4 months, intraocular surgery within 6 months, concurrent severe systemic disease, any condition affecting follow-up or documentation **Age:** 65.4 to 66.9 SD8.9 to 9.5 years **Sex:** 38.1 to 47.6% female **Diabetes type:** not reported **HbA1c:** 7.81 to 8.02 SD1.44 to 1.63 % **Baseline VA:** letter score 55.2 to 55.5 SD11.3 to 12.5 **Baseline CMT:** 482.1 to 477.4 SD122.7 to 155.5 µm **Comorbidities:** not reported	**Group 1 (IVTL, n=42 eyes):** 4 mg (0.1 ml) IV triamcinolone acetonide followed by laser treatment (at least 1 retreatment in 2nd year in 69%) **Group 2 (L, n=42 eyes):** sham injection followed by laser treatment (at least 1 retreatment in 2nd year in 45%) **Regimen for all groups:** retreatment with injection followed by laser at discretion of chief investigator, with at least 6 weeks between treatments; no retreatment if: (1) investigator considered the macula nearly flat and CMT <300 µm; (2) VA was ≥79 letters (20/25) or VA had improved by ≥5 letters compared with the best VA after treatment or baseline acuity; (3) laser	**At 24 months** **BCVA (ETDRS):** ***I TL*** +0.76 (NS vs L) ***L*** -1.49 **BCVA gain categories** ***IVTL*** +10 or more: 36%; +9 to -9: 31%; -10 or more: 33% (0.049 vs L) ***L*** +10 or more: 17%; +9 to -9: 59%; -10 or more: 24% Subgroups: • BCVA outcome not significantly affected by cataract surgery **CMT (OCT):** **CMT (µm) p**

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		treatment was considered by the investigator as inappropriate or had no potential for improvement	***IVTL*** -137.1 NS vs L ***L*** -109.6
Kim 2010[45] **Korea** **Design:** 2-arm RCT **Follow-up:** 3 years	**N:** 86 eyes of 75 patients **Inclusion criteria:** diffuse DMO **Exclusion criteria:** not reported **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (IVT, n=38 eyes):** 4 mg IV triamcinolone (1.88 additional treatments, completion 68.1%) **Group 2 (IVTL, n=48 eyes):** macular laser photocoagulation 4 weeks after 4 mg IV triamcinolone (0.92 additional treatments, completion 77.1%) **Regimen for all groups:** additional treatment possible, criteria not mentioned **Laser protocol** not reported	**At 3 years** **BCVA:** not reported **Outcomes related to DMO:** **no DMO recurrence** **p** ***IVT*** 3.9% ***IVTL*** 24.3% 0.028 vs IVT **time DMO not present** ***IVT*** 10.33 months ***IVTL*** 19.88 months 0.027 vs IVT
Lam 2007[34] **Hong Kong** **Design:** 3-arm RCT **Follow-up:** 6 months (2 years planned)	**N:** 111 eyes of 111 patients **Inclusion criteria:** >18 years, type 1 or 2 DM, clinically significant DMO (ETDRS), CMT ≥250 µm **Exclusion criteria:** macular oedema due to causes other than diabetic maculopathy, signs of vitreomacular traction, proliferative diabetic retinopathy, aphakia, history of glaucoma or ocular hypertension, macular ischemia, any laser procedure within 3 months, ocular surgery within 6 months, significant media opacities **Age:** 64.7 to 67.2 SD8.2 to 10.3 years **Sex:** 42 to 59% female **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** ETDRS logMAR 0.64 to 0.72 SD0.34 to 0.36 **Baseline CMT:** 385 to 424 SD91 to 108 µm **Comorbidities:** 66 to 84% phakic eyes	**Group 1 (IVT, n=38 eyes):** 4 mg IV triamcinolone (no retreatments) **Group 2 (IVTL, n=36 eyes):** 4 mg IV triamcinolone followed by grid laser photocoagulation (ETDRS) (laser treatment once the macular oedema had reduced to <250 µm at the foveal center or at 1 to 2 months after injection, whichever was earlier) **Group 3 (L, n=37 eyes):** grid laser photocoagulation (n=3 retreatments) (no retreatments) **Regimen for all groups:** in case of recurrence or persistence of macular oedema, retreatment offered according to study group, at intervals no less than 4 months **Laser** ETDRS protocol	**At 6 months** **BCVA (ETDRS):** **BCVA improvement** **p** ***IVT*** -0.7 SD 10.7 log MAR plus ≥15 letters: 5% NS between groups ***IVTL*** -1.1 SD 10.8 log MAR plus ≥15 letters: 3% ***L*** -1.6 SD 11.5 log MAR plus ≥15 letters: 5% **CMT (OCT):** **CMT (µm)** **p** ***IVT*** 342 SD124 [-54] NS between groups, <0.01 vs baseline ***IVTL*** 307 SD181 [-116] <0.01 vs baseline ***L*** 350 SD169 [-35]

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<table>
<tr>
<td>Ockrim 2008 / Sivaprasad 2008 [42,62]
UK

Design: 2-arm RCT
Follow-up: 1 year</td>
<td>N: 88 eyes of 88 patients
Inclusion criteria: clinically significant DMO persisting ≥4 months, ≥1 previous laser treatment, BCVA 6/12 to 3/60, VA in fellow eye ≥3/60, duration visual loss <24 months
Exclusion criteria: significant macular ischemia, baseline IO >23 mmHg, glaucoma, coexistent renal disease, loss of VA due to other causes, previous vitrectomy, intraocular surgery within 3 months of study entry, previous inclusion in other DR trials, inability to return to follow-up, inability to give informed consent
Age: 62.3 to 64.8 SD7.5 to 10.1 years
Sex: 28.9 to 34.9% female
Diabetes type: 97.8 to 100% type 2 DM
HbA1c: 7 to 7.8 IQR6.5 to 8.7%
Baseline VA: ETDRS letter score 53.0 to 54.6 SD13.3 to 14.2
Baseline CMT: 410.4 to 413.4 SD127.8 to 134.1 µm
Comorbidities: 17.8 to 19.5% PDR, 13.3 to 18.6% pseudophakia, 15 to 17.8% posterior vitreous detachment</td>
<td>Group 1 (IVT, n=43 eyes): 4 mg IV triamcinolone (mean number of IVT injections 1.8 (range 1 to 3))
Group 2 (L, n=45 eyes): ETDRS laser photocoagulation (mean number of grid laser sessions 2.1 (range 1 to 3))
Regimen for all groups: patients retreated at 4 and 8 months if they had persistent macular oedema
Laser ETDRS protocol</td>
<td>At 12 months

BCVA (ETDRS):
<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>IVT</td><td>-0.2</td><td>NS vs L</td></tr><tr><td>L</td><td>+1.7</td><td></td></tr><tr><th></th><th>plus ≥15 letters</th><th></th></tr><tr><td>IVT</td><td>4.8%</td><td>NS vs L</td></tr><tr><td>L</td><td>12.2%</td><td></td></tr></table>
CMT (optical coherence tomography):
<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVT</td><td>-91.3</td><td>NS vs L</td></tr><tr><td>L</td><td>-63.7</td><td></td></tr></table></td>
</tr>
</table>

Abbreviations: See table 2

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Table 7: Trials assessing more than one drug

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Ahmadieh 2008[31] **Iran** **Design:** 3-arm placebo-controlled RCT **Follow-up:** 24 weeks	**N:** 115 eyes of 101 patients **Inclusion criteria:** eyes with clinically significant DMO unresponsive to previous macular laser photocoagulation (last session >3 months prior) **Exclusion criteria:** visual acuity ≥20/40; history of cataract surgery within past 6 months; prior intraocular injection or vitrectomy, glaucoma or ocular hypertension; PDR with high-risk characteristics; vitreous hemorrhage; significant media opacity; presence of traction on the macula; pregnancy; serum creatinine ≥3 mg/100 ml; monocular patients **Age:** 59.7 SD8.3 years (range 39 to 74) **Sex:** 50.5% female **Diabetes type:** not reported, 27.6% to 33.3% on insulin **HbA1c:** 9.35% to 10.06% **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** (percentage of eyes) 13.9% history of cataract surgery, 81.7% NPDR, 4.3% early PDR, 13.9% regressed PDR; no iris neovascularization	**Group 1 (IVB, n=41 eyes):** bevacizumab 1.25 mg (0.05 ml) **Group 2 (IVB/IVT, n=37 eyes):** combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone **Group 3 (C, n=37 eyes):** sham injection **Regimen for all groups:** 3 consecutive IV injections at 6-week intervals	**At 24 weeks** **BCVA (Snellen chart):** ***IVB*** -0.18 (-0.29, -0.08) [+9 letters (4, 14.5)] — 0.01 vs C, NS vs IVB/IVT ***IVB/ IVT*** -0.21 (-0.30, -0.12) [+10.5 letters (6, 15)] — 0.006 vs C ***C*** -0.03 (-0.08, 0.14) [+1.5 letters (-7, 4)] **CMT (OCT):** ***IVB*** -95.7 (-172.2, -19.3) — 0.012 vs C, NS vs IVB/IVT ***IVB/ IVT*** -92.1 (-154.4, -29.7) — 0.022 vs C ***C*** 34.9 (7.9, 61.9)
ATEMD 2011 (Oliveira Neto 2010 / 2011) [56] Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months **Note:** only 48.3% completion	**N:** 120 eyes of 120 patients **Inclusion criteria:** DMO, BCVA 20/40 to 20/400, CMT ≥275 µm **Exclusion criteria:** PDR, laser photocoagulation in previous 3 months, no IV corticosteroid or anti-VEGF in previous 3 months **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (IVB, n=NR eyes):** 1.25 mg (0.05 ml) of IV bevacizumab **Group 2 (IVT, n=NR eyes):** 4 mg (0.1 ml) of IV triamcinolone acetonide **Group 3 (IVB/IVT, n=NR eyes):** 1.25 mg (0.05 ml) of IV bevacizumab plus 4 mg (0.1 ml) of IV triamcinolone acetonide **Regimen for all groups:** monthly injections	**At 6 months** **BCVA:** • no significant difference between groups (between 1.7 and 2.3 lines gained in the different groups in 2010 report (n=18)) **CMT (OCT):** • CMT reduced in all 3 groups (between 17 and 33% reduction in the different groups in 2010 report (n=18)); no significant difference between groups
DRCR Network 2010 (Elman 2010, Elman 2011)[21,46] **USA** Multicenter	**N:** 854 eyes of 691 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM; study eye: (1) BCVA letter score 78 to 24 (20/32 to 20/320), (2) definite retinal thickening due to DMO assessed to be main cause of visual loss, (3) retinal thickness measured on time domain OCT ≥250 µm in central	**Group 1 (CPL, n=293 eyes):** sham injection plus prompt (within 3-10 days after injection) focal/grid photocoagulation **Group 2 (RPL, n=187 eyes):** 0.5 mg IV ranibizumab plus prompt focal/grid	**At 1 year** **BCVA (E-ETDRS Visual Acuity Test):** ***CPL*** +3 SD13 ***RPL*** +9 SD11 — <0.001 vs CPL

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Design: 4-arm placebo-controlled RCT **Follow-up:** 1-2 years; 2 years extension (Elman 2011) for consenting patients	subfield (2 study eyes per patient could be included if both were eligible at study entry) **Exclusion criteria:** (1) treatment for DMO within the prior 3 months, (2) panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, (3) major ocular surgery within the prior 4 months, (4) history of open-angle glaucoma or steroid-induced IOP elevation, requiring IOP-lowering treatment, (5) IOP ≥25 mmHg; systolic pressure >180 mmHg, diastolic pressure >110 mmHg; myocardial infarction, other cardiac event requiring hospitalization, cerebrovascular accident, transient ischemic attack, treatment for acute congestive heart failure within 4 months before randomization **Age:** median 62 to 64 years (25^{th}, 75^{th} centile 55 to 58, 69 to 70) **Sex:** 41 to 46% female **Diabetes type:** 6 to 9% type 1 DM, 89 to 92% type 2 DM, 2 to 3% uncertain **HbA1c:** median 7.3 to 7.5% (25^{th}, 75^{th} centile 6.5 to 6.7, 8.3 to 8.6) **Baseline VA:** letter score 63 SD12 (~20/63 SD2.4 lines) **Baseline CMT:** 405 SD134 µm **Comorbidities:** 60 to 67% prior treatment for DMO; 61 to 68% with NPDR, 26 to 36% with PDR or PDR scars	photocoagulation **Group 3 (RDL, n=188 eyes):** 0.5 mg IV ranibizumab plus deferred (≥24 weeks) focal/grid photocoagulation **Group 4 (TPL, n=186 eyes):** 4 mg IV triamcinolone plus prompt focal/grid photocoagulation **Regimen for all groups:** Baseline treatment 0.5 mg IV ranibizumab and 4 mg preservative free triamcinolone; study treatment every 4 weeks up to 12 weeks, then retreatment algorithm: 16 to 20 weeks, monthly retreatment unless 'success' criteria were met (visual acuity letter score ≥84 (20/20) or OCT central subfield thickness <250 µm); 24 to 48 weeks, patients subdivided (according to predefined criteria) into 'success', 'improvement', 'no improvement' or 'failure'; 'improvement' group continued treatment, other groups treated at investigator discretion; alternative treatment permitted if eye met criteria for 'failure' or 'futility'. In the case of retreatment, ranibizumab could be given as often as every 4 weeks, and triamcinolone every 16 weeks (with sham injections as often as every 4 weeks). Retreatment for focal/grid laser (after ≥13 weeks from previous treatment) if there was oedema involving or threatening the center of the macula and if complete laser had not been given; retreatment algorithms facilitated by web-based real-time data entry system. Median number of drug injections before 1 year visit was 8-9 for ranibizumab, 3 for triamcinolone, and 5 sham injections. Retreatment between 1 and 2 years	***RDL*** +9 SD12 <0.001 vs CPL ***TPL*** +4 SD13 NS vs CPL **BCVA gain categories (letters)** ***CPL*** +10 or more: 28%; +9 to -9: 59%; -10 or more: 13% ***RPL*** +10 or more: 50%; +9 to -9: 45%; -10 or more: 4% <0.001 vs CPL ***RDL*** +10 or more: 47%; +9 to -9: 51%; -10 or more: 3% <0.001 vs CPL ***TPL*** +10 or more: 33%; +9 to -9: 52%; -10 or more: 14% NS vs CPL Subgroups: • BCVA results in TPL group substantially better for pseudophakic eyes than for phakic eyes (comparable to results for RPL and RDL groups) (p not reported) • no difference in results according to prior treatment for DMO, baseline VA, baseline CMT, baseline level of retinopathy, focal or diffuse oedema **CMT (OCT):** ***CPL*** CMT (µm) -102 SD151; p ***RPL*** -131 SD129 <0.001 vs CPL ***RDL*** -137 SD136 <0.001 vs CPL ***TPL*** -127 SD140 <0.001 vs CPL Subgroups: • pattern of CMT decrease similar for groups with CMT <400 µm and ≥400 µm at baseline • Significantly more patients with severe NPDR or worse improved by 2 levels or more in the ranibizumab groups (28%, no significant change in the other groups) **At 2 years (expanded results, Elman 2011)** **BCVA (E-ETDRS Visual Acuity Test):**

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr>
<td></td>
<td></td>
<td>(Elman 2011): median injections 2 in RPL group, 3 in RDL group; in TPL group 68% of eyes received at least 1 injection; at least one focal/grid laser sessions between 1 and 2 years: 51% CPL, 40% RPL, 29% RDL, 52% TPL
Laser Modified ETDRS protocol as used in prior DRCR.net protocols</td>
<td>
<table>
<tr><th></th><th>BCVA (letters)</th><th>p</th></tr>
<tr><td>CPL (n=211)</td><td>+3 SD15</td><td></td></tr>
<tr><td>RPL (n=136)</td><td>+7 SD13</td><td>0.03 vs CPL</td></tr>
<tr><td>RDL (n=139)</td><td>+9 SD14</td><td><0.001 vs CPL</td></tr>
<tr><td>TPL (n=142)</td><td>+2 SD19</td><td>NS vs CPL</td></tr>
<tr><td colspan="3">BCVA gain categories (letters)</td></tr>
<tr><td>CPL</td><td>+10 or more: 36%
+9 to -9: 52%
-10 or more: 13%</td><td></td></tr>
<tr><td>RPL</td><td>+10 or more: 44%
+9 to -9: 49%
-10 or more: 7%</td><td>NS vs CPL</td></tr>
<tr><td>RDL</td><td>+10 or more: 49%
+9 to -9: 48%
-10 or more: 3%</td><td>0.01 vs CPL</td></tr>
<tr><td>TPL</td><td>+10 or more: 41%
+9 to -9: 40%
-10 or more: 19%</td><td>NS vs CPL</td></tr>
</table>
CMT (OCT):
<table>
<tr><th></th><th>CMT (µm)</th><th>p</th></tr>
<tr><td>CPL</td><td>-138 SD149</td><td></td></tr>
<tr><td>RPL</td><td>-141 SD155</td><td>0.003 vs CPL</td></tr>
<tr><td>RDL</td><td>-150 SD143</td><td>0.01 vs CPL</td></tr>
<tr><td>TPL</td><td>-107 SD145</td><td>NS vs CPL</td></tr>
</table>
</td>
</tr>
<tr>
<td>Jorge 201
Brazil[51]

Design: Prospective RCT
Follow-up: 24 and 48 weeks [To date, 73% and 56% of patients completed 24 and 48 weeks respectively]</td>
<td>N: 63 eyes of 47 patients
Inclusion criteria: Refractory cener-involving DMO
Exclusion criteria: NR
Age: NR
Sex: NR
Diabetes type: NR
HbA1c: NR
Baseline VA: NR
Baseline CMT: NR
Comorbidities: NR</td>
<td>Group 1 (IVB 1.5 mg, n=NR): injections at baseline and monthly if CSFT (central subfield thickness) measured by SDOCT (spectral domain OCT) >275 µm.
Group 2 (IVR 0.5 mg, n=NR) : injections at baseline and monthly if CSFT >275 µm.</td>
<td>At 48 weeks
BCVA
<table>
<tr><th></th><th>Mean BCVA reduction from baseline (logMAR)</th><th>p</th></tr>
<tr><td>IVB1.5</td><td>-0.21</td><td>vs baseline <0.05 at all-time points

vs IVR0.5: no significant difference at all time-points</td></tr>
<tr><td>IVR0.5</td><td>-0.21</td><td>vs baseline <0.05 at all time-points</td></tr>
</table>
</td>
</tr>
</table>

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
			vs IVB1.5: no significant difference at all time-points **CSFT** **Mean CSFT reduction from baseline** / **p** ***IVB1.5*** -129.6 µm — vs baseline <0.05 at all-time points; vs IVR0.5 no significant different at all-time points ***IVR0.5*** -137.9 µm — vs baseline <0.05 at all-time points; vs IVB1.5 no significant different at all-time points
Lim 2012[55] **Korea** **Design:** 3-arm RCT **Follow-up:** 12 months	**N: 111 eyes of 105 patients** **Inclusion criteria:** eyes with clinically significant DMO based on ETDRS and DMO with central macular thickness of at least 300 µm by optical coherence tomography (OCT). **Exclusion criteria:** unstable medical status, including glycemic control and blood pressure; any previous treatment for DMO, including intravitreal, sub-Tenon injection or macular photocoagulation, history of vitreoretinal surgery, uncontrolled glaucoma; proliferative diabetic retinopathy with active neovascularization, previous panretinal photocoagulation, presence of vitreomacular traction, history of systemic corticosteroids within 6 months, contraindications for bevacizumab or triamcinolone acetonide. **Age:** 60.4 SD 7.4 (range 48 to 70) years **Sex:** 52% female	**Group 1 (IVB/IVT, n=36):** IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks and IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of addition injection 1.28 **Group 2 (IVB, n=38):** IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks. Mean number of injections 2.54. **Group 3 (IVT, n=37):** IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of injections 1.04 **Unclear if rescue laser was available** **IVB injections were repeated if CMT appeared >300 µm on OCT in at least 6-weeks in all three groups**	At 12 months **BCVA (logMAR)** / **p** ***IVB/IVT*** -0.15 ***IVB*** -0.16 ***IVT*** -0.16 0.088 (between groups) **CMT (µm)** / **p** ***IVB/IVT*** -199 ***IVB*** -179 ***IVT*** -200 0.132 (between groups)

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td></td><td>Diabetes type: NR
HbA1c: 7.2 SD 1.2 to 7.4 SD1.2
Baseline VA: 0.62 SD 0.23 to 0.65 SD 0.28 logMAR
Baseline CMT: 447 SD 110 to 458 SD 92 µm
Comorbidities: NR</td><td></td><td></td></tr>
<tr><td>Soheilian 2007 / Soheilian 2009/ Soheilian 2011/ Soheilian 2012
[37,41,54,140]
Iran

Design: 3-arm RCT
Follow-up: 36 weeks

[Soheilian 2007 reports 12 week results of the same trial, these were not considered here]</td><td>N: 150 eyes of 129 patients
Inclusion criteria: eyes with clinically significant DMO (ETDRS criteria)
Exclusion criteria: previous panretinal of focal laser photocoagulation, prior ocular surgery or injection, history of glaucoma or ocular hypertension, VA ≥20/40 or <20/300, iris neovascularization, high risk PDR, significant media opacity, monocularity, pregnancy, serum creatinine ≥3 mg/dL, uncontrolled DM
Age: 61.2 SD6.1 years
Sex: 47.3% female
Diabetes type: not reported
HbA1c: not reported
Baseline VA: 0.55 to 0.73 SD0.26 to 0.28 logMAR
Baseline CMT: 300 to 359 SD118 to 149 µm
Comorbidities: 94% NPDR, 6% early PDR</td><td>Group 1 (IVB, n=50 eyes): IV injection of bevacizumab 1.25 mg (0.05 ml) (retreatment IVB 14 eyes)
Group 2 (IVB/IVT, n=50 eyes): IV injection of combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone (retreatment IVB/IVT 10 eyes)
Group 3 (MPC, n=50 eyes): focal or modified grid laser (retreatment MPC 3 eyes)
Regimen for all groups:
Retreatments performed at 12 week intervals as required</td><td>At 36 weeks

BCVA (Snellen chart):
<table><tr><th></th><th>BCVA (logMAR), SD</th><th>p</th></tr><tr><td>IVB</td><td>-0.28 SD0.25
[+14 SD12.5 letters]</td><td>0.053 vs IVB/IVT or MPC</td></tr><tr><td>IVB/ IVT</td><td>-0.04 SD0.33
[+2 SD16.5 letters]</td><td>NS vs MPC</td></tr><tr><td>MPC</td><td>+0.01 SD0.27
[-0.5 SD13.5 letters]</td><td></td></tr><tr><td></td><td>Snellen line changes</td><td></td></tr><tr><td>IVB</td><td>+2 lines or more: 37.0%
stable within 2 lines: 59.3%
-2 lines or more: 3.7%</td><td>NS between groups</td></tr><tr><td>IVB/ IVT</td><td>+2 lines or more: 25.0%
stable within 2 lines: 54.2%
-2 lines or more: 20.8%</td><td></td></tr><tr><td>MPC</td><td>+2 lines or more: 14.8%
stable within 2 lines: 66.7%
-2 lines or more: 18.5%</td><td></td></tr></table>
CMT (OCT):
<table><tr><th></th><th>CMT (µm), SD</th><th>p</th></tr><tr><td>IVB</td><td>-56 SD140</td><td>0.044 vs baseline, NS between groups</td></tr><tr><td>IVB/ IVT</td><td>-5 SD113</td><td></td></tr><tr><td>MPC</td><td>-8 SD67</td><td></td></tr></table>
Subgroups:
• larger CMT reduction in subgroup with ≥400 µm at baseline (36 weeks: IVB -27.2 SD34.8%, IVB/IVT -8.8 SD35.9%, MPC -15.1 SD14.6%, p<0.001 versus baseline in IVB and MPC groups only)</td></tr>
</table>

Abbreviations: See table 2

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Table 8: Ranibizumab safety data

	READ-2 study[28,47]	RESOLVE study[36]	RESTORE study[24]	RISE study[38]	RIDE study[38]
Number of patients	IVR: n=42; L: n=42; IVRL: n=42	IVR0.3: n=51; IVR0.5: n=51; C: n=49	IVR: n=116; IVRL: n=118; L: n=111	IVR0.3: 125; IVR0.5: 126; C: 123	IVR0.3: 125; IVR0.5: 124; C: 127
Ocular adverse events					
Eye pain	NR	IVR0.3: n=9 (18%); IVR0.5: n=9 (18%); C: n=10 (20%)	IVR: n=13 (11%); IVRL: n=10 (8%); L: n=12 (11%)	IVR0.3: 26%; IVR0.5: 21%; C: 19%	IVR0.3: 8%; IVR0.5: 12.9%; C: 7.1%
Conjunctival hyperaemia	NR	NR	IVR: n=9 (8%); IVRL: n=6 (5%); L: n=6 (5%)	NR	NR
Conjunctival haemorrhage	NR	IVR0.3: n=10 (20%); IVR0.5: n=13 (25%); C: n=7 (14%)	IVR: n=8 (7%); IVRL: n=10 (8%); L: n=0	IVR0.3: 54%; IVR0.5: 52%; C: 32%	IVR0.3: 40.8%; IVR0.5: 50.0%; C: 31.5%
IOP increase	NR	IVR0.3: n=6 (12%); IVR0.5: n=15 (29%); C: n=1 (2%)	IVR: n=1 (<1%); IVRL: n=1 (<1%);	IVR0.3: 20%; IVR0.5: 14%; C: 2%	IVR0.3:15.2%;IVR0.5: 18.5%; C: 11%
Vitreous haemorrhage	IVR: n=1 (2%); L: n=4 (10%); IVRL: n=3 (7%)	IVR0.3: n=1 (2%); IVR0.5: n=0; C: n=0	NR	IVR0.3: 3.2%; IVR0.5: 3.2%; C: 13%	IVR0.3: 0.8%; IVR0.5: 2.4%; C: 15%
Substantial worsening of DMO	L: n=1 (2%)		NR	NR	NR
Retinal ischaemia	NR	IVR0.3: n=0; IVR0.5: n=1 (2%); C: n=0	NR	NR	NR
Retinal artery occlusion	NR	IVR0.3: n=0; IVR0.5: n=1 (2%); C: n=0	NR	NR	NR
Endophthalmitis	NR	IVR0.3: n=1 (2%); IVR0.5: n=1 (2%); C: n=0	NR	IVR0.3: 0.8%; IVR0.5: 0; C: 0	IVR0.3 + IVR0.5: 1.2%; C: 0%
Retinal detachment	NR	IVR0.3: n=0; IVR0.5: n=0; C: n=1 (2%)	NR	IVR0.3: 0.8%; IVR0.5: 0; C: 0.8%	IVR0.3 + IVR0.5: 0.4%; C: 0%
Neovascularisation	NR	NR	NR	IVR0.3: 0; IVR0.5: 0; C: 0.8%	IVR0.3: 0.8%; IVR0.5: 0.8%; C: 5.5%
Traumatic cataract	NR	NR	NR	IVR0.3: 0.8%; IVR0.5: 0.8%; C: 0	IVR0.3 + IVR0.5: 0.4%; C: 0%
Uveitis	NR	NR	NR	NR	IVR0.3 + IVR0.5: 0.4%; C: 0%
Macular oedema	NR	NR	NR	IVR0.3: 16.8%; IVR0.5: 20.6%; C: 21.1%	IVR0.3: 19.2%; IVR0.5: 13.7%; C: 20.5%
Retinal exudates	NR	NR	NR	IVR0.3: 19.2%; IVR0.5: 17.5%; C: 20.3%	IVR0.3: 16.0%; IVR0.5: 15.3%; C: 11.0%
Retinal haemorrhage	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 12.7%; C: 20.3%	IVR0.3: 15.2%; IVR0.5: 22.6%; C: 18.9%

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Cataract	NR	NR	NR	IVR0.3: 16.8%; IVR0.5: 11.9%; C: 14.6%	IVR0.3: 20.0%; IVR0.5: 23.4%; C: 23.6%
Vitreous detachment	NR	NR	NR	IVR0.3: 13.6%; IVR0.5: 11.1%; C: 15.4%	IVR0.3: 8.8%; IVR0.5: 12.9%; C: 15.0%
Ocular hyperemia	NR	NR	NR	IVR0.3: 15.2%; IVR0.5: 11.1%; C: 10.6%	IVR0.3: 3.2%; IVR0.5: 3.2%; C: 7.9%
Vitreous floaters	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 14.3%; C: 5.7%	IVR0.3: 7.2%; IVR0.5: 8.1%; C: 3.1%
Eye irritation	NR	NR	NR	IVR0.3: 10.4%; IVR0.5: 9.5%; C: 6.5%	IVR0.3: 5.6%; IVR0.5: 5.6%; C: 3.1%
Foreign body sensation in eyes	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 7.1%; C: 4.1%	IVR0.3: 8.0%; IVR0.5: 2.4%; C: 5.5%
Systematic adverse events					
Arterial thromboembolic events	Stroke in 1 pt (2%) in IVRL group- not related to study drug	IVR0.3: n=0; IVR0.5: n=3 (6%); C: n=2 (4%)	IVR: n=6 (5%); IVRL: n=1 (<1%); L: n=1 (<1%)	IVR0.3: 3.2% (n=1 stroke); IVR0.5: 7.9% (n=5 strokes); C: 7.3% (n=2 strokes)	IVR0.3: 1.6% (stroke), 5.6% (heart attack); IVR0.5: 2.4% (stroke), 2.4% (heart attack); C: 1.6% (stroke), 5.6% (heart attack)
Hypertension	NR	IVR0.3: n=4 (8%); IVR0.5: n=5 ((10%); C: n=5 (10%)	IVR: n=9 (8%); IVRL: n=6 (5%); L: n=9 (8%)	Serious IVR0.3: 0.8%; IVR0.5: 3.2%; C: 0.8%	Serious IVR0.3: 1.6%; IVR0.5: 1.6%; C: 0%
Non-ocular haemorrhage	NR	IVR0.3: n=1 (2%); IVR0.5: n=1 (2%); C: n=0	IVR: n=1 (<1%); IVRL: n=0; L: n=1 (<1%)	NR	NR
Proteinuria	NR	NR	IVR: n=1 (<1%); IVRL: n=1 (<1%); L: n=0	NR	NR
Deaths	1 (2%) due to CVA in IVRL group	NR	IVR: n=2 (2%); IVRL: n=2 (2%); L: n=2 (2%)	IVR0.3: 2.4%; IVR0.5: 4.0%; C: 0.8%	IVR0.3: 3.2%; IVR0.5: 4.8%; C: 1.6%

NR – not reported, IVR – intra-vitreal ranibizumab, IVRL – intra-vitreal ranibizumab plus laser, C – control, L – laser, IOP –intra-ocular pressure, DMO – diabetic macular oedema,

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Table 9: Bevacizumab safety

	BOLT study[23,52]	Lam 2009[35]	Faghihi 2010[53]
Number of patients	MLT: n=38; IVB: n=42	IVB1.25, n=26; IVB2.5, n=26	IVB 1.25 n= 40 IVB 1.25 plus MLT n=40
Ocular adverse events			**Not reported**
Loss of _15 or _30 ETDRS letters	MLT: n=1 transient, 3 at 24 month analysis; IVB: n=4 transient	No significant ocular events (IOP increase, retinal tear, retinal detachment, endophthalmitis); no significant difference in change in cataract scores between groups	
Vitreous haemorrhage	MLT: n=1; IVB: n=0		
Eye pain/irritation/watering during or after injection	MLT:n= 0; IVB: n=8		
Red eye after injection	MLT: n=0; IVB: n=8		
Endophthalmitis	NR		
Transient IOP increase	≥30 mm Hg - MLT: 0; IVB: n=4≥ 45 mm Hg – MLT: n=1; IVB: n=1		
Floaters after injection	MLT: n= 0; IVB: n=2		
Corneal epithelial defect	MLT:n=0; IVB:n=1		
Vitreomacular traction with macular oedema	MLT: n=1; IVB: n=0		
Systematic adverse events			
Anaemia	MLT: n=1; IVB: n=0	no systematic adverse effects (1 patient in 1.25 mg group with foot gangrene requiring amputation due to worsening diabetic neuropathy, considered unrelated to treatment)	
Vomiting after FFA	MLT: n=1; IVB: n=0		
Uncontrolled hypertension	MLT:n=0; IVB: n=1		
Polymyalgia rheumatica	MLT:n=0; IVB: n=1		
Intermittent claudication	MLT:n=0; IVB: n=1		
Gastroenteritis	MLT:n=0; IVB: n=1		
Fall	MLT:n=2; IVB: n=0		
Urinary tract infection	MLT:n=0; IVB: n=1		
Chest infection	MLT:n=0; IVB: n=1		
Headaches, dizziness, tiredness	MLT:n=1; IVB: n=0		
Bell palsy	MLT:n=1; IVB: n=0		
Admission for diabetic foot ulcer	MLT:n=1; IVB: n=1		
Admission for cholecystectomy	MLT:n=0; IVB: n=1		
Admission for fall/loss of consciousness	MLT:n=1; IVB: n=0		
Angina–hospital admission	MLT:n=1; IVB: n=0		
Cerebrovascular accident	MLT:n=1; IVB: n=0		
Myocardial infarction	MLT:n=0; IVB: n=2		
Coronary artery bypass graft	MLT:n=0; IVB: n=1		
Dyspnea, chest pain–admitted for hospital observation	MLT:n=0; IVB: n=1		

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DEATH	NR		

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Table 10 Pegaptanib safety

	Cunningham 2005/Adamis 2006[39,57]	Sultan 2011[40]
Number of patients	IVP0.3, n=44 eyes; IVP1, n=44 eyes; IVP3, n=42 eyes	IVP, n=133 eyes; C, n=127 eyes
Ocular adverse events		
Eye pain	Pegaptanib: 31%; C: 17%	IVP: 11.1%; C: 7.0%
Vitreous haemorrhage	Pegaptanib: 22%; C: 7%	IVP: 6.3%; C: 7.7%
Punctuate keratitis	Pegaptanib: 18%; C: 17%	IVP: 11.8%; C: 6.3%
Cataract	Pegaptanib: 13%; C: 10%	IVP: 8.3%; C: 9.2%
Eye discharge	Pegaptanib: 11%; C: 10%	NR
Conjunctival haemorrhage	Pegaptanib: 10%; C: 0%	IVP: 22.2%; C: 14.1%
Vitreous opacities	Pegaptanib: 9%; C: 5%	NR
Blurred vision	Pegaptanib: 7%; C: 5%	NR
Other vitreous disorder	Pegaptanib: 7%; C: 0%	NR
Other visual disturbance	Pegaptanib: 7%; C: 0%	NR
Culture-negative endophthalmitis	Pegaptanib: n=1	NR
IOP increase	NR	IVP: 17.4%; C: 6.3%
Retinal haemorrhage	NR	IVP: 6.3%; C: 10.6%
Retinal exudates	NR	IVP: 6.3%; C: 5.6%
Conjunctivitis	NR	IVP: 5.6%; C: 4.2%
Lacrimation increased	NR	IVP: 5.6%; C: 2.8%
Diabetic retinal oedema	NR	IVP: 11.1%; C: 17.6%
Macular oedema	NR	IVP: 9.7%; C: 11.6%
Systemic adverse events		
Non-ocular hypertension	NR	IVP: 13.9%; C: 9.9%
Cardiac disorders	NR	IVP: 6.9%; C: 5.6%
DEATHS	NR	IVP: n=4

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Table 11: aflibercept safety

	DA VINCI 2010[30,58]
Number of patients	IVVTE (all doses) n=175, laser n = 44
Ocular adverse events	
Conjunctival hemorrhage	At 6 months: Laser 18.2%, IVVTE 18.9% At 12 months: Laser 18.2%, IVVTE 26.9%
IOP increase	At 6 months: Laser 2.3%, IVVTE 9.7% At 12 months: Laser 2.3%, IVVTE 9.7%
Eye pain	At 6 months: Laser 4.5%, IVVTE 8.6% At 12 months: Laser 4.5%, IVVTE 13.7%
Ocular hyperaemia	At 6 months: Laser 4.5%, IVVTE 6.3% At 12 months: Laser 4.5%, IVVTE 7.4%
Vitreous floaters	At 6 months: Laser 4.5%, IVVTE 5.1% At 12 months: Laser 4.5%, IVVTE 6.9%
Endophthalmitis	At 6 months: Laser 0%, IVVTE 1.1% At 12 months: Laser 0%, IVVTE 1.1%
Uveitis	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: Laser 0%, IVVTE 0.6%
Diabetic retinal oedema	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 2.3%, IVVTE 4.6%
Visual acuity reduced	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 2.3%, IVVTE 0%
Vitreous hemorrhage	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 6.8%, IVVTE 0%
Corneal abrasion	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: Laser 0%, IVVTE 4.6%
Retinal tear	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: NR
Systematic events	
Hypertension	At 6 months: Laser 6.8%, IVVTE 9.7% At 12 months: Laser 0%, IVVTE 1.7%
Myocardial infarction	At 6 months: Laser 0%, IVVTE 1.1% At 12 months: Laser 0%, IVVTE 1.7%
Cerebrovascular event	At 6 months: Laser 0%, IVVTE1.1% At 12 months: Laser 2.3%, IVVTE 1.7%
Death	At 6 months: Laser 0%, IVVTE 1.7% At 12 months: Laser 2.3%, IVVTE 4.0%

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Table 12: Dexamethasone safety

	Callanan 2011[44]	Haller 2010[59]
Number of patients		
Ocular adverse events		
IOP elevation	DIL: 20% ($p<0.001$); 1% ≥10 mm Hg L: 1.6% ; 0% ≥10 mm Hg	
Cataract	NR	NR
Anterior chamber cells	NR	DDS350: 29.1%; DDS700: 26.4%; C: 1.8%
Anterior chamber flare	NR	DDS350: 27.3%; DDS700: 20.8%; C: 8.8%
Vitreous haemorrhage	NR	DDS350: 20.0%; DDS700: 22.6%; C: 5.3%
Eye pain	NR	DDS350: 18.2%; DDS700: 9.4%; C: 3.5%
Vitreous disorder	NR	DDS350: 20.0%; DDS700: 15.1%; C: 3.5%
Increased IOP	NR	DDS350: 14.5%; DDS700: 9.4%; C: 0%
Conjunctival haemorrhage	NR	DDS350: 14.5%; DDS700: 7.5%; C: 0%
Vitreous floaters	NR	DDS350: 7.3%; DDS700: 17.0%; C: 0%
		No significant differences in: reduced VA, eye irritation, abnormal sensation in eye, macular oedema, eye pruritus, retinal hemorrhage, DR, nonocular events

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Table 13 Fluocinolone safety

	FAME study (Campochiaro 2011/2012)[29,60]	Pearson 2011[43]
Number of patients		
Ocular adverse events		
IOP at 12 months	NR	NR
Progression of cataract	NR	NR
Cataract	NR	SRFA: 55.9%; SOC: 21.7%
Transient vitreous floaters	NR	NR
Transient subconjunctival haemorrhage	NR	NR
Cataract surgery	SRFA0.2: 41.1% (74.9% of those without cataract surgery at baseline, 80.0% at 36 months); SRFA0.5: 50.9% (84.5% of those without cataract surgery at baseline, 87.2% at 36 months); C: 7% (23.1% of those without cataract surgery at baseline, 27.3% at 36 months)	NR
Glaucoma	SRFA0.2: 1.6%; SRFA0.5: 2.3%; C: 0.5%	NR
Increased IOP	SRFA0.2: 3.2%; SRFA0.5: 3.3%; C: 0%	SRFA: 69.3%; SOC: 11.6%
IOP >30 mmHg at any point during 36 months	SRFA0.2: 18.4%; SRFA0.5: 22.9%; C: 4.3%	NR
Trabeculectomy	SRFA0.2: 2.1%; SRFA0.5: 4.8%; C: 0%	NR
Other glaucoma surgery	SRFA0.2: 1.3%; SRFA0.5: 1.3%; C: 0.5%	NR
Trabeculoplasty	SRFA0.2: 0.8%; SRFA0.5: 2.3%; C: 0%	NR
Vitreous haemorrhage	NR	SRFA: 40.2%; SOC: 18.8%
Abnormal sensation in eye	NR	SRFA: 37%; SOC: 11.6%
Macular oedema	NR	SRFA: 34.6%
Eye pain	NR	SRFA: 26.8%; SOC: 15.9%
Eye irritation	NR	SRFA: 22%; SOC: 10.1%
Increased lacrimation	NR	SRFA: 22%; SOC: 8.7%
Photophobia	NR	SRFA: 21.3%; SOC: 21.7%
Blurred vision	NR	SRFA: 21.3%; SOC: 15.9%
Vitreous floaters	NR	SRFA: 21.3%; SOC: 8.7%
Systemic adverse events		
Serious cardiovascular events	SRFA0.2: 12.0%; SRFA0.5: 13.2%; C: 10.3%	
Pruritus	NR	SRFA: 38.6%; SOC: 21.7%
DEATHS	NR	NR

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Table 14: Triamcinolone safety

	DRCR Network 2008 (Ip 2008a / Ip 2008b / Beck 2009 / Bressler 2009) [22,61,63,64]	Gillies 2006 / 2007 / 2009 / Sutter 2004[32,137-139]	Gillies 2011[33]	Kim 2010[45]	Lam 2007[34]	Ockrim 2008 / Sivaprasad 2008[42,62]
Number of patients						
Ocular adverse events						
	At 2 years (or 3 years when indicated)	At 2 years	-	Not reported	-	At 12 months
IOP ≥30 mm Hg	IVT1: n=22; IVT4: n=53; L: n=3	NR	NR		NR	IVT: IOP significantly higher than in L group (18.2 mm Hg, range 12 to 26 mm Hg); no cases of glaucoma
IOP >22 mm Hg	NR	NR	NR		IVT: 37% (p=0.002 vs. L); IVTL: 36% (p=0.002 vs. L); L: 5%	NR
IOP ≥10 mm Hg from baseline	IVT1: n=41; IVT4: n=85; L: n=12	NR	NR		NR	NR
IOP ≥5 mm Hg	NR	IVT: 68% (p=0.007 vs. C); C: 10%	NR		NR	NR
IOP lowering medication used	IVT1: n=31; IVT4: n=76; L: n=25	IVT: 44% (p=0.0002 vs. C); C: 3%	IVTL: 64% (P<0.001); L: 24%		NR	NR
Cataract surgery	IVT1: 23% (of those phakic at baseline, 46% by 3 years (p<0.001 between all groups); IVT4: 51% (of those phakic at baseline, 83% by 3 years); L: 13% (of those phakic at baseline, 31% by 3 years)	IVT: 56% (of phakic eyes over 3 years, p<0.001 vs. C); C: 8% (of phakic eyes over 3 years)			NR	NR
Ptosis	NR	NR	NR		NR	NR
Retinal detachment	IVT1: n=2; IVT4: n=4; L: n=2	NR	NR		None	NR
Retinal vein occlusion	IVT1: n=1; IVT4: n=2; L: n=3	NR	NR		NR	NR
Retinal artery occlusion	IVT1: n=0; IVT4: n=0; L: n=1	NR	NR		NR	NR
Anterior ischemic optic neuropathy	IVT1: n=1; IVT4: n=0; L: n=0	NR	NR		NR	NR
Vitrectomy	IVT1: n=26; IVT4: n=19; L: n=31	NR	NR		NR	NR
Open angle glaucoma	IVT1: n=2; IVT4: n=7; L: n=2	NR	NR		NR	NR

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Glaucoma filtering surgery	IVT1: n=0; IVT4: n=2; L: n=0	NR	NR		NR	NR
Laser trabeculoplasty	IVT1: n=0; IVT4: n=1; L: n=0	IVT: n=2; C: n=0	IVTL: n=1		NR	NR
Ciliary body destruction	IVT1: n=0; IVT4: n=1; L: n=0	NR	NR		NR	NR
Endophthalmitis	IVT1: n=0; IVT4: n=;0 L: n=0	(Infectious) IVT: n=1; C: NR	(Culture-negative) IVTL: n=1		None	(sterile) IVT: n=1
pseudoendophthalmitis	IVT1: n=0; IVT4: n=;0 L: n=0	NR	NR		NR	NR
Chemosis	NR	NR	NR		NR	NR
% increase in cataract scores	NR	NR	NR		IVT: +1.0 SD1.1 (p=NS vs. L); IVTL: +1.3 SD1.9 (p=NS vs. L); L: +0.5 SD0.9	NR
Ocular hypertension (>21 mm Hg)	NR	NR	NR		NR	NR
Cataract progression	NR	NR	Phakic eyes, progression by ≥2 AREDS grade, IVTL: 64% (p<0.001); L: 11% (p<0.001)		NR	NR
Corneal decompensation	NR	IVT: NR; C: n=1	NR		NR	NR
Cataract surgery	NR	NR	IVTL: 61% (p<0.001); L: 0%		NR	IVT: n=2; L: n=1
Vitreous haemorrhage	NR	NR	NR		IVTL: n=1	
Lens opacity	NR	NR	NR		NR	Significantly greater change in lens opacity in IVT group than in L group (1.9)
DEATHS	N=33, unrelated to study treatment	IVT: n=1; C: n=2	IVTL: n=2; L: n=1		NR	NR

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Table 15 Safety data in trials assessing more than one drug

	Ahmadieh 2008[31]	ATEMD 2011 (Oliveira Neto 2011) [56]	DRCR Network 2010 (Elman 2010, Elman 2011)[21,46]	Lim 2012[55]	Soheilian 2007 / Soheilian 2009[37,41]
Number of patients					
	Ocular adverse events				
Mild anterior chamber reaction	IVB: 19.5% (n=8 eyes), resolved after one week of no treatment; IVB/IVT: 18.9% (n=7 eyes), resolved after one week of no treatment	NR	NR	NR	IVB: 20% (n=10 eyes), resolved after 1 week; IVB/IVT: 18% (n=9 eyes), resolved after 1 week
Marked anterior chamber reaction	IVB: n=1 (topical corticosteroid and cycloplegic drops)	NR	NR	NR	IVB: n=1 (topical corticosteroids and cycloplegic drops);
Progression of fibrous proliferation	IVB: n=1 with no sign of retinal traction	NR	NR	NR	IVB: n=1 with no sign of retinal traction;
Vitreous haemorrhage	IVB/IVT: n=1 after third injection (excluded from study)	NR	NR	NR	NR
IOP rise	IVB: 23, 22 and 28 mm Hg at 6, 12 and 18 weeks (anti-glaucoma drops)	NR	IOP elevation more frequent with triamcinolone + PL	IVB/IVT: 8.3% IVT: 10.8%	NR
IOP ≥10 mm Hg from baseline	NR	NR	CPL: n=16; RPL: n=10; RDL: n=5; TPL: n=70	NR	NR
IOP ≥30 mm Hg from baseline	NR	NR	CPL: n=3; RPL: n=2; RDL: n=4; TPL: n=46	NR	NR
Initiation of IOP lowering treatment at any visit	NR	NR	CPL: n=9; RPL: n=5; RDL: n=4; TPL: n=41	NR	NR
Iris neovascularization	None	NR	NR	NR	NR
Lens opactiy	None	NR	NR	NR	Severe lens opacity IVB/IVT: n=4 eyes; MPC: n=1 eye
Endophthalmitis	NR	NR	CPL: n=1; RPL: n=1; RDL: n=1; TPL: n=0	NR	None
Pseudoendophthalmitis	NR	NR	CPL: n=1; RPL: n=0; RDL: n=0; TPL: n=1	NR	NR
Ocular vascular event	NR	NR	CPL: n=1; RPL: n=1; RDL: n=0; TPL: n=2	NR	NR

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Retinal detachment	NR	NR	CPL: n=0; RPL: n=0; RDL: n=1; TPL: n=0	NR	None
Vitrectomy	NR	NR	CPL: n=7; RPL: n=0; RDL: n=3; TPL: n=0	NR	NR
Vitreous haemorrhage	NR	NR	CPL: n=15; RPL: n=3; RDL: n=4; TPL: n=2	NR	None
Cataract surgery	NR	NR	CPL: n=11 (of those phakic at baseline); RPL: n=6 (of those phakic at baseline); RDL: n=8 (of those phakic at baseline); TPL: n=19 (of those phakic at baseline)	NR	NR
Glaucoma surgery	NR	NR	NR	NR	NR
Retinal neovascularization	NR	NR	NR	NR	IVB: n=4 (all resolved); MPC: n=3 eyes (2 resolved)
Development of early PDR	NR	NR	NR	NR	IVB: n=1; IVB/IVT: n=4; MPC: n=3
Progression to high-risk PDR	NR	NR	NR	NR	IVB: n=4; IVB/IVT: n=3; MP: n=3
Ocular hypertension (≥23 mm HG)	NR	NR	NR	NR	IVB/IVT: 16% (n=8 of eyes), controlled medically in all except 1 that progressed to neovascular glaucoma
	Systemic adverse events				
Acute myocardial infarction		N=1, considered not to be related to the study drug	No specific systemic adverse events that could be attributed to chance		No significant blood pressure increase, no thromboembolic events
Deaths	C: n=1	N=1, considered not to be related to the study drug	CPL: n=8; RPL: n=5; RDL: n=3; TPL: n=2		IVB/IVT: n=2; MPC: n=2

NR – not reported, IVB – intra-vitreal bevacizumab, IVT- intravitreal triamcinolone, IVR – intra-vitreal ranibizumab, IVRL – intra-vitreal ranibizumab plus laser, C – control, L – laser, IOP –intra-ocular pressure, PDR – proliferative diabetic retinopathy, DMO – diabetic macular oedema,

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Table 16: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Anti-VEGFs							
Ranibizumab							
READ-2 Study [28,47]	Unclear	Unclear	Unclear	Yes (91.3% completion)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Juvenile Diabetes Research Foundation, Genentech Inc.
RESOLVE Study (Massin 2010)[36]	Yes	Yes	Yes (patients and outcome assessors)	Yes (82% completion in sham arm, 90.2% with ranibizumab)	Yes	Comparison groups similar at baseline; power analysis unclear	Novartis Pharma, Switzerland
RESTORE Study (Mitchell 2011)[24]	Yes	Unclear	Yes (patients, outcome assessors)	Yes (87.3 to 88.3% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Novartis Pharma, Switzerland
RISE and RIDE (Nguyen 2012)[38]	Yes	Yes	Yes (patients, treating physician masked to assigned dose of ranibizumab)	Yes (2 year study completed by 83.3% of patients in RISE and by 84.6% in RIDE)	Yes	Comparison groups similar at baseline; ITT analysis; power analysis carried out (power adequate for primary endpoint)	Genentech Inc.
Bevacizumab							
BOLT Study (Michaelides 2010)[23,52]	Yes	Unclear	Partial (outcome assessors, not patients)	Yes (97.5% completion)	Yes	Comparison groups similar at baseline (except laser group had longer duration of clinically significant DMO); power analysis carried out (power adequate for VA changes)	Moorfields Special Trustees, National Institute for Health Research
Faghihi 2010[53]	Yes	Unclear	Yes (patient	Yes (100% completion)	Yes	Comparable groups at baseline	Not specified

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Lam 2009[35]	Yes	Yes	Yes (patients and technicians assessing BCVA, OCT and IOP)	Yes (92.3% follow-up at 6 months)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	supported in part by the Action for Vision Eye Foundation Hong Kong (charity)
Pegaptanib							
Cunningham 2005 / Adamis 2006[39,57]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (95% completion)	Yes	Comparison groups similar at baseline; acknowledge lack of power to detect differences between doses of pegaptanib	Eyetech Pharmaceuticals Inc., New York, and Pfizer Inc., New York
Sultan 2011[40]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (69.9 to 73.8% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Pfizer Inc., New York
Aflibercept							
Da Vinci 2010 [30,58]	Unclear (predetermined randomization scheme)	Unclear	Yes (patients)	Yes (85% completion)	Yes	Comparison groups similar at baseline, power calculation completed	Regeneron Pharmaceuticals, Inc., New York
Steroids							
Dexamethasone							
Haller 2010[59]	Yes	Unclear	Yes (patients to dexamethasone dose, outcome assessors)	Yes (92% completion)	Yes	Comparison groups similar at baseline; power analysis carried out, but study not powered to detect differences in subgroups	Oculex Pharmaceuticals Inc.
Fluocinolone							
FAME Study (Campochiaro 2011)[29,60]	Unclear	Unclear	Partial (patients, masking of outcome assessment not mentioned)	Yes (drop-out rate 19.0 to 22.7%)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Alimera Sciences Inc., Atlanta, Georgia; Psivida Inc., Watertown, Massachusetts

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Pearson 2011[43]	Yes	Unclear	Third party masked design (patient and investigator not masked)	No losses to follow-up	Yes	Demographic characteristics were similar between implant and SOC groups; power calculation done, study adequately powered.	Bausch & Lomb Inc, Rochester, New York
Triamcinolone							
DRCR Network 2008 [22,61,63,64]	Yes	Unclear	Partial (patients to triamcinolone dose, outcome assessors not formally masked but generally not aware of participant's study group)	Yes (81 to 86% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services
Gillies 2006 / 2007 / 2009 / Sutter 2004[32,137-139]	Yes	Yes	Yes (patients, outcome assessors)	Yes (91% completion intervention, 83% control)	Yes	Comparison groups similar at baseline (but limited demographic data); power analysis carried out (power adequate for VA changes)	Sydney Eye Hospital Foundation and Juvenile Diabetes Research Foundation, New York
Gillies 2011[33]	Yes	Yes	Yes (patients, outcome assessors)	Yes (84.5% completion)	Yes	power analysis carried out (power adequate for VA changes)	National Health and Medical Research Council, Canberra, Australia, and the Sydney Eye Hospital Foundation, Sydney, Australia
Lam 2007[34]	Yes	Yes	Partial (outcome assessors)	No losses to follow-up	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	Action for Vision Foundation, Hong Kong
Ockrim 2008/Sviprasad 2008[42,62]	Yes	Unclear	Unclear	Yes (94% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Special Trustees of Moorfields Eye Hospital
Active comparator trials							

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Ahmadieh 2008[31]	Yes	Yes	Yes (patients and outcome assessors)	Unclear	Yes	CMT lower in control group at baseline ($p<0.05$), other baseline values similar; power analysis carried out (power adequate for CMT changes)	Not reported
DRCR Network [21,46]	Yes	Unclear	Yes (patients, except deferred laser group; outcome assessors); masking discontinued after the first year	Yes (1 year completion for 91-95% of eyes)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and Human Services; Ranibizumab provided by Genentech, triamcinolone provided by Allergan Inc.; companies also provided funds to defray the study's clinical site costs
Lim 2012[55]	Yes	Unclear	Yes (investigators only)	Yes (7.5% drop out after enrollment)	Yes	Groups similar at baseline. The bevacizumab group received more injections.	Not reported
Soheilian [37,41]	Yes	Yes	Yes (patients and outcome assessors)	Unclear (36 week completion for 76 to 88%)	Yes	CMT significantly lower and VA significantly better in MPC group at baseline, other baseline values similar; power analysis carried out (power adequate for VA changes)	Ophthalmic Research Centre, Labbafinejad Medical Center, Tehran

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	7

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figures 2-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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Current treatments in Diabetic Macular Oedema: systematic review and meta-analysis

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Title:

Current treatments in Diabetic Macular Oedema: systematic review and meta-analysis

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Protocol: This review was built upon several technology appraisals for NICE and therefore no protocol exists.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

No additional data available.

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Abstract (300 words max)

Objectives: The aim of this systematic review is to appraise the evidence for the use of anti-VEGF drugs and steroids in diabetic macular oedema (DMO) as assessed by change in best corrected visual acuity (BCVA), central macular thickness and adverse events

Data source: MEDLINE, Embase, Web of Science with Conference Proceedings and the Cochrane Library (inception to July 2012). Certain conference abstracts and drug regulatory websites were also searched.

Study eligibility criteria, participants and interventions: Randomised controlled trials were used to assess clinical effectiveness and observational trials were used for safety. Trials which assessed triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO were included.

Study appraisal and synthesis methods: Risk of bias was assessed using the cochrane risk of bias tool. Study results are narratively described and, where apprpriate, data was pooled using random effects meta-analysis.

Results: Anti-VEGF drugs are effective compared to both laser and placebo and seem to be more effective than steroids in improving BCVA. They have been shown to be safe in the short-term but require frequent injections. Studies assessing steroids (triamcinolone, dexamethasone, fluocinolone) have reported mixed results when compared with laser or placebo. Steroids have been associated with increased incidence of cataracts and intra-ocular pressure rise but require fewer injections, especially when steroid implants are used.

Limitations: The quality of included studies varied considerably. Five out of fourteen meta-analyses had moderate or high statistical heterogeneity.

Conclusions and implications of key findings: The anti-VEGFs, ranibizumab and bevacizumab, have consistently shown good clinical effectiveness without major unwanted side effects. Steroids results have been mixed and are usually associated with cataract formation and IOP increase.

Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision (≥20/40) and, thus, the search for new therapies needs to continue.

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Article focus

- To review the evidence for triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib and aflibercept in the treatment of diabetic macular oedema

Key messages

- The anti-VEGFs ranibizumab and bevacizumab, have consistently shown good clinical effectiveness in the short-term without major unwanted side effects
- Steroids results have been mixed and are usually associated with cataract formation and IOP increase

Strengthens and limitations

- A robust, detailed review of the literature has been undertaken and, when appropriate, data has been combined in meta-analysis
- The quality of studies included varied considerably.

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I - Introduction

Diabetic macular oedema (DMO) is a complication of diabetic retinopathy and a leading cause of blindness. The prevalence of DMO is likely to increase with more people suffering from diabetes.[1] Increasing DMO has significant implications for patients, healthcare providers and wider society. Laser has been the mainstay of treatment, but recently anti-vascular endothelial growth factor (anti-VEGF) drugs and steroids have been introduced as potential alternatives to laser photocoagulation.

a. Burden of disease

Diabetic retinopathy is present at the time of diagnosis of diabetes mellitus in 0-30% of individuals.[2] The incidence is estimated to be 2.3/100 person-years for the overall diabetic population and 4.5 for patients on insulin therapy.[3] There is good evidence that progression to DMO is associated with duration of disease[4-7], poor glycaemic control [8], and in type 2 diabetes, the need for insulin[9], though the need for insulin therapy is more a marker for duration, and poor control.

The number of people with DMO is likely to increase as diabetes becomes more common. Some reports have suggested a decrease in progression to severe visual loss between 1975-1985 and 1986-2008 in a combined population of type 1 and 2.[10] Regular screening for retinopathy and better glycaemic control are thought to have reduced the progression to severe visual loss. Diabetic retinopathy is associated with a reduced quality of life. Compared with all diabetic complications, blindness was perceived to be the third worst health state after a major stroke and amputation.[11]

In the US, the presence of DMO at diagnosis is associated with 29% additional costs within the first three years compared with individuals without retinopathy at diagnosis.[12] In 2010 the estimated healthcare costs for DMO in England were £92 million, with £65.6 million being spent on hospital treatment and related costs.[13]

Visual impairment results in increased welfare costs, early retirement, and costs of home help and carers.[14] In England in 2010 (total population 52.23 million) the estimated population with diabetes was 2.34 million; the above social costs were estimated to be £11.6 million for DMO.[13]

b. Overview of pathophysiology

DMO is caused mainly by disruption of the blood-retinal barrier. The complex pathway that leads to this disruption has been previously described in this journal.[15] Sustained hyperglycaemia causes a multi-factorial cascade of physiological processes, involving increased permeability, cytokine activation, altered blood flow, hypoxia and inflammation. Vascular endothelial growth factor-A (VEGF-A) is a major contributor to the inflammatory process and, in particular, to angiogenesis and permeability.[16] Hypoxia caused by microvascular disease stimulates release of VEGF-A to aid perfusion. There are six major isoforms of VEGF-A: 121, 145, 165, 183, 189 and 206. In addition to causing widespread microvascular injury, there is now evidence that hyperglycaemia results in preceding neuronal dysfunction, which may contribute to visual loss.[17]

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c. Overview of current treatments

Laser photocoagulation has been the mainstay of treatment for DMO. The landmark Diabetic Retinopathy Study[18] and the Early Treatment Diabetic Retinopathy Study (ETDRS)[19,20] demonstrated its clinical effectiveness. However, although laser photocoagulation was clearly effective in preserving vision, it was less successful in restoring it, once lost. Furthermore, patients with perifoveal ischaemia are not amenable to this form of therapy. In EDTRS, although laser was shown to reduce the risk of moderate visual loss (a loss of 3 ETDRS lines) by 50%, visual acuity improved in only 3% of patients.[20] However in some recent trials, laser has improved the proportion of patients with more than or equal to 10 letters by 7-31%.[21-24] In addition, laser is not without side effects. Foveal burns, visual field defects, retinal fibrosis and laser scars have been reported.[25] Over the following decade it became apparent that certain patients suffered severe visual loss despite aggressive treatment.[26]

Steroids and anti-VEGF drugs are newer treatments in DMO. Intravitreal corticosteroids have potent anti-inflammatory effects. Triamcinolone (Kenalog) is not licensed for eye use but has been used to treat DMO for over ten years. Triamcinolone (Trivaris), more recently, was licensed for eye use. The development of intravitreal implants has allowed sustained release formulations. Fluocinolone acetonide (Iluvien, Alimera Sciences) and dexamethasone (Ozudex, Allergan) are implants that have been introduced recently.

Anti-VEGF agents have shown efficacy compared with laser. Bevacizumab (Avastin, Genenetch /Roche) is a monoclonal antibody that targets all VEGF isoforms. Although being developed for colorectal cancer, it is widely used off-label, as an intravitreal treatment for macular oedema of different aetiologies. Ranibizumab (Lucentis, Genentech/Roche) is a fragment of the bevacizumab antibody (molecular weight of ranibizumab 48.4 KDa compared with 149 KDa for bevacizumab). It was designed specifically for use in the eye. Ranibizumab is considerably more expensive than bevacizumab (the estimated cost of ranibizumab is $2,000 per dose compared with $50 for bevacizumab).[27] Pegaptanib (Macugen, Eyetech Pharmaceuticals/Pfizer) is a PEGylated aptamer, with a high affinity to the VEGF isoform 165 and was approved for the treatment of exudative AMD in 2004. Aflibercept (Regeneron/Bayer HealthCare) is a recent addition to the anti-VEGF class that targets all forms of VEGF-A and placental growth factor.

d. Aim of the review

The aim of this review is to provide clinicians with an up-to-date overview of current intra-ocular drug treatments for DMO. It is hoped that the information contained herein will assist clinicians to present their patients with the best evidence supporting each treatment, including possible complications. In addition, this review may be helpful to policy makers. The review focuses on the current evidence for the use of anti-VEGF drugs and steroids to treat DMO, as assessed by change in best corrected visual acuity (BCVA) (mean and proportion with more than two lines improvement), central macular thickness (CMT), as determined by optical coherence tomography (OCT), and their adverse events.

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II - Evidence acquisition

A systematic literature search was performed. The databases searched included MEDLINE, Embase, Web of Science with Conference Proceedings and the Cochrane Library. The dates searched were from the inception of each database until July 2012

The search terms combined the following key words:

ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*

AND

diabetic macular oedema or diabetic macular edema or diabetic retinopathy or diabetic maculopathy

AND

(masked or sham or placebo OR control group or random*) OR (systematic review or meta-analysis) OR (risk or safety or adverse or harm or pharmacovigilance or side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic)

The meeting abstracts of the Association for Research in Vision and Ophthalmology, the American Diabetes Association (2002-2012) and the European Association for the Study of Diabetes were searched from 2002-2012.

In addition the web sites of the European Medicines Agency and the US Food and Drug Association were searched for data on registration status and safety. Clinicaltrials.gov and the EU Clinical Trials Register were searched in July 2012 for data on ongoing research.

Full details of the searches are shown in appendix 1.

Randomised controlled trials (RCT) were used to evaluate clinical effectiveness. Safety was assessed through both RCTs and observational studies.

RCTs were included provided that they 1) addressed the use of triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO, 2) had a minimum follow-up of six months, and 3) had a minimum of 25 eyes per study arm. Studies were excluded if they 1) evaluated laser only, 2) assessed the effect of the above mentioned treatments in macular oedema due to other retinal diseases (instead of DMO), 3) used only a single dose , 4) were combined with a surgical intervention or 5) published studies in languages other than English. There were no exclusions based on drug dose. Trials were excluded if they evaluated combined drug treatment with surgery or systemic treatment.

Search results were screened by two independent authors (JF and PR/DS). Data were extracted by one author (CC) and checked by a second (JF). Data extracted included inclusion/exclusion criteria, baseline demographics, BCVA expressed as a change in logMAR/ETDRS letters or proportion of

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participants with more than 2 or 3 lines BCVA improvement, CMT and adverse events. Risk of bias was assessed using the cochrane risk of bias tool.

Studies were assessed for similarity in study population, interventions (dose and frequency), outcomes and time to follow up, with a view to including similar studies in a meta-analysis. Conference abstracts were excluded from the meta-analysis because their quality and detailed methodology was not clear. A difference of six months was allowed between study follow-ups because of potential heterogeneity from disease progression and differences in the number of doses prescribed. If salient data were not reported, such as standard deviations, data were sought by personal communication with authors. Data were analysed using Review Manager software. If data from multiple time points were available, the primary end point data was used. Data were entered by one author (JF) and double-checked by a second (DS). Mean difference were calculated for change in BCVA and CMT and odds ratios were calculated for proportion of participants with more than 2 lines improvement. 95% confidence intervals were calculated for all outcomes. Statistical heterogeneity was measured through I^2 scores. A score of less than 30% was considered low heterogeneity, a score of more than 70% was considered high heterogeneity and scores between 30% and 70% were considered moderate. A random effects model was used throughout. The random effects model assumes variability between studies and therefore models uncertainty into the meta-analysis. Fixed assumes no variability. Generally speaking the random effects model results in wider confidence intervals.

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III - Results

The literature search identified 430 unique articles for possible inclusion, as shown in figure 1. 328 articles were excluded on the basis of title and abstract, leaving 102 full papers to be read. Fifty-one of these articles were excluded; the reasons for their exclusion are summarised in table 1. Fifty-one articles from 29 studies met the inclusion criteria and were included in the review; these are described in tables 3 to 16. Seven studies were suitable for meta-analysis.

a. Study quality

The quality of the included studies was, in general, good as is shown in table 2. (Note that the meeting abstracts were not quality assessed, due to lack of details reported on the methods). Most studies adequately described sequence generation, except in three studies where it was unclear.[28-30] However allocation concealment was poorly described throughout, with only eight reports addressing this issue appropriately. [31-38] Reporting of masking also varied. A number of studies masked patients using sham injection or sham laser.[21,24,29,31,33,36,39,40] [38]. Various studies reported that masking of patients was impossible. Assessors, where reported, were masked. In two studies incomplete outcomes were not addressed.[31,41] Baseline characteristics were consistent within study treatment arms. Administration of laser followed the ETDRS protocol, or a modified version, in all studies that described laser administration.[21-24,28,30,33,34,42,43] Two studies, both available only as meeting abstracts, did not report the laser administration details. [44,45]

b. Intravitreal anti-VEGFs

The characteristics of all published studies including design, inclusion/exclusion criteria, intervention, outcomes and their timing are shown in tables 3 to 8. Safety data for each drug is shown in tables 9 to 16.

1. Ranibizumab

Nine RCTs have evaluated ranibizumab as a potential new treatment for patients with DMO (table 3 and 8); seven were sponsored by industry, and two were an independent investigators-led.) [21,46](table 7). READ-2 was the first large RCT (n=126).[28,47] It compared ranibizumab (0.5 mg) alone, ranibizumab in combination with laser and laser alone. At six months BCVA had improved significantly in the ranibizumab alone group compared with laser alone or ranibizumab plus laser. Addition of laser to ranibizumab did not provide additional BCVA gain. REVEAL (n=396) compared ranibizumab (0.5mg) with ranibizumab plus laser and laser alone.[48] At 12 months both ranibizumab arms resulted in a statistically significantly better improvement in BCVA compared to laser alone. The addition of laser did not confer further benefit.

Within the past two years the results of RESOLVE[36], RESTORE[24], and RISE and RIDE[38] have been published in peer-reviewed journals. RESTORE (n=345) randomised similar groups as the READ-2 study (ranibizumab (0.5 mg) alone, laser alone and ranibizumab plus laser); outcomes were evaluated at 12 months. Ranibizumab improved mean BCVA, with laser providing no additional

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benefit. Two year extended follow-up suggested that these results continued.[49] RESOLVE (n=151) compared two doses of ranibizumab (0.3 mg and 0.5 mg) with sham injection. The greatest improvement in BCVA at 12 months was in the 0.3 mg group (11.8 letter gain) compared to the 0.5 mg group (8.8 letters gain) or sham injection (1.4 letter loss). In this study, rescue laser was allowed after three months of treatment, if BCVA had decreased by 10 letters or more, or if the investigator considered the macula not to be flat as assessed by OCT. Only 4.9% of the ranibizumab group required rescue laser, compared with 34.7% in the sham injection group.

READ-2 and RESTORE were suitable for pooling through meta-analysis and, when doing so, it was found that ranibizumab statistically significantly improved mean BCVA compared with laser (figure 2). In regards to the proportion of patients gaining more than or equal to 15 letters, individual trials showed a statistically significant difference between laser and ranibizumab but when these two trials were pooled using a random effects model the result was no longer statistically significant. When a fixed effects model was used the result was statistically significant (figure not shown). Adding laser to ranibizumab did not add any significant benefit (figure 3). In fact the mean change in BCVA and the proportion of patients with more than 15-letter gain favoured, although not statistically significantly so, ranibizumab alone compared with ranibizumab plus laser. This was probably a chance effect.

RISE (n=377) and RIDE (n=382) were identical in design. The study arms are similar to those in the RESOLVE study; 0.3 mg or 0.5 mg ranibizumab compared with sham. In the RISE study the proportion of patients with 15 or more letter gain was greatest in the 0.3 mg group at 24 months, whereas in the RIDE study this was greatest in the 0.5 mg group. In the DRCRN trial (n = 854), Elman and colleagues compared ranibizumab (0.5 mg) plus prompt (within 3-10 days post ranibizumab) or deferred ($\geq$ 24 weeks) laser with sham injection plus prompt laser, or triamcinolone (4m g, Trivaris) plus prompt laser (table 8). At one year both ranibizumab groups reported greater gains in mean BCVA change than triamcinolone or laser alone. Interestingly at 2 years (n= 628), the proportion of patients with 10 or more letter gain was not statistically significantly different between ranibizumab plus prompt laser and laser alone groups, but was statistically significant in the ranibizumab plus deferred laser compared with laser alone comparison. The reason for this is not clear.

READ-3 (n=152) has been published in abstract form and compared monthly injections of intravitreal ranibizumab high dose (2.0 mg) and low dose (0.5 mg).[50] At six months there was not a statistically significant difference in BCVA between groups.

One study (n=63), published in abstract form, was identified which directly compared monthly injections of ranibizumab (0.5 mg) with bevacizumab (1.5 mg).[51] At 48 weeks the authors found no statistically significant difference between bevacizumab and ranibizumab.

RESTORE, READ-2 and DRCRN (12 month data used) were suitable for pooling through meta-analysis to compare ranibizumab plus laser and laser alone (figure 4). Ranibizumab plus laser resulted in a statistically significantly greater change in mean BCVA, proportion of patients with more than 15 letter gain and CMT reduction versus laser alone.

Adverse events are shown in tables 9 and 16. Conjunctival hemorrhages were higher in the ranibizumab arms compared with laser (RESTORE) or no treatment (RESOLVE). In the RESOLVE, RISE and RIDE studies a considerably higher incidence of intra-ocular pressure (IOP) increase was

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reported in the ranibizumab arm compared to control. This increase in IOP was not demonstrated in the RESTOREstudy. There were no consistent differences in systemic adverse events between ranibizumab and laser or placebo.

2. Bevacizumab

Eight RCTs investigating the use of bevacizumab in DMO were identified (table 4 and 8). One RCT, the BOLT study (n=80), randomised patients to laser therapy or 1.25 mg intravitreal bevacizumab.[23,52] At 24 months, the mean change in BCVA and the proportion of patients who gained 10 ETDRS letters or more was statistically significantly higher in the bevacizumab arm than in the laser arm. Faghihi and colleagues (n=80), compared 1.25 mg bevacizumab (average 2.23 injections per patient) with 1.25 mg bevacizumab plus a single laser treatment (average 2.49 injections per patient).[53] After six months, the authors found both treatments to be effective at improving BCVA but neither treatment was found to result in a greater benefit.

Lam and colleagues (n=52) compared two doses of bevacizumab (1.25 mg and 2.5 mg) in patients with diffuse DMO.[35] Patients with focal DMO associated with localised retinal thickening were excluded. At 6 months, following 3 initial monthly injections (no treatment in the remaining 3 months), both groups showed a statistically significant increased mean BCVA compared with baseline vision, but there was no difference between doses.

Four trials have investigated the combination of bevacizumab and triamcinolone. Ahmadieh and colleagues (n=115), compared combined bevacizumab (three 1.25 mg injections at six week intervals) plus triamcinolone (2 mg baseline injection only, Triamhexal) with bevacizumab alone (three 1.25 mg at six week intervals) and sham injection in patients who had DMO unresponsive (definition not reported) to previous laser (last session more than three months prior).[31] The combination arm and bevacizumab alone arm improved mean BCVA more than sham injection. For BCVA the combination of bevacizumab plus triamcinolone was non-statistically significantly better than bevacizumab alone.

Soheilian and colleagues (n=150) compared combined bevacizumab (1.25 mg) plus triamcinolone (2 mg) with bevacizumab alone and laser alone in patients who were laser naïve.[37,41] At 36 weeks, bevacizumab alone improved BCVA more than either combination therapy or laser, although the difference was not statistically significant. Extended follow up at 24 months showed that there was no statistically significant difference between groups for BCVA, however the direction of effect favour the bevacizumab and combination arms more than the laser.[54]

Lim and colleagues (n=111) also evaluated the combination of bevacizumab plus triamcinolone when compared with bevacizumab alone or triamacinolone alone.[55] At 12 months the authors found no statistically significant difference between groups for BCVA or CMT.

The Efficacy Study of Triamcinolone and Bevacizumab Intravitreal for Treatment of Diabetic Macular Oedema (ATEMD) study, currently only published in abstract form, compared combined therapy with bevacizumab (1.25 mg) and triamcinolone (4 mg) with each of these alone.[56] At six months they found no statistically significant difference between groups. One study comparing bevacizumab with ranibizumab is discussed above.[51] No bevacizumab trials were suitable for meta-analysis because treatment arms were not comparable among included studies.

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Adverse events are shown in tables 10 and 16.There was a low frequency of adverse events reported in the included trials. A higher incidence of mild anterior chamber reaction was reported in bevacizumab groups compared with controls. The incidence of IOP increase was comparable between bevacizumab and laser. Soheilian and colleagues, were the only authors to report the incidence of lens opacity.[37,41] No patients in the bevacizumab alone group were found to have lens opacities but in four patients (8%) in the bevacizumab plus triamcinolone group this finding was observed over the 36 week follow-up period.

3. Pegaptanib

Two studies have evaluated pegaptanib in DMO and both compared it with sham injection (table 5). Cunningham and colleagues compare three doses of pegaptanib (0.3 mg, 1 mg and 3 mg) and sham injection in laser naive patients (n=172).[39,57] At six months patients in the 0.3 mg and 1 mg groups performed statistically significantly better than those in either 3mg or sham groups. Six injections (median) were administered in the 0.3 mg and 1 mg group, whereas only five (median) injections were administered in the 3 mg group.

The second trial (n=260), reported by Sultan and colleagues in 2011, compared pegaptanib (0.3 mg) and sham injection. At two years, the pegaptanib group showed a statistically significantly greater improvement in mean BCVA compared with sham.[40] However there was no statistically significant difference in the proportion of patients with an improvement of 10 letters or more. Patients were allowed rescue laser at the assessors' discretion (25.2% of patients in the pegaptanib group and 45% of patients in the sham group received rescue treatment). In regards to meta-analysis, data were only available to combine these trials for proportion of patients with more than 15 letter gain. Although individually neither trial demonstrated a statistically significant difference favouring pegaptanib over sham (figure 5), when pooled together in meta-analysis a statistically significant difference in favour of pegaptanib was found (OR 1.94, 95%CI 1.01 to 3.71).

Adverse events for pegaptanib are shown in table 11. There was a higher incidence of eye pain compared to control (31% versus 17%). [39,57] Cataract formation was similar between pegaptanib and control groups. There was a higher incidence of IOP increase in the pegaptanib arm compared to control (17.4% versus 6.3%).[40]

4. Other anti-VEGF

Aflibercept has been evaluated in the Da Vinci study (n=219)[30,58] (table 5). Four regimens of aflibercept (0.5 mg 4 weekly, 2 mg 4 weekly, 2 mg monthly for three months then every 8 weeks, and 2 mg monthly for three months followed by treatment as required) were compared with laser. At six months, all aflibercept arms had a statistically better BCVA and CMT change than the laser arm. The regimen that resulted in greatest BCVA gain and CMT reduction was 2 mg every 4 weeks, however statistical significance between aflibercept arms was not reported. One year extended follow-up showed that all aflibercept arms were found to have a statistically significantly better BCVA compared to laser.[58]

Adverse events are shown in table 12. There was a higher incidence of IOP increase and eye pain in the aflibercept group compared with laser. Other adverse events were too infrequent to draw meaningful conclusions. The incidence of cataracts was not reported.

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c. Steroids

1. Dexamethasone

Two included trials assessed the use of dexamethasone to treat DMO (table 6); Haller 2010 (full text available)[59] and Callanan (available to date only in an abstract form).[44] Haller 2010 (n=171) compared two doses of dexamethasone, administered as an intravitreal implant (350 µm and 700 µm) through a 20-gauge transscleral incision, with no treatment. At 90 days only the 700 µm group showed a statistically significant higher proportion of patients with 10 or more letter gain compared to no treatment (33% compared with 12%, p = 0.007). The 350 µm group showed a non-statistically significant improvement compared with laser alone (21% compared with 12%). At 180 days there was no statistically significant difference between either the dexamethasone group and no treatment group. The treatment effect appeared to peak at three months.

The second trial, by Callanan and colleagues (n=253), compared dexamethasone (dose not reported) plus laser with laser alone. Although a greater improvement in mean BCVA was seen at 1-9 months in the dexamethasone plus laser group compared with laser alone, there was no statistically significant difference at 12 months. A mean of 1.6 implants were used over the 12 month period.

These trials were not suitable for meta-analysis since one study is only available in abstract form.

Adverse events are shown in table 13. In the 350 µm and 700 µm groups compared with no treatment, there was a higher incidence of anterior chamber cells (29.1/26.4% compared with 1.8%), anterior chamber flare (27.3/20.8% compared with 8.8%), vitreous hemorrhage (20/22.6% compared with 5.3%) and increased IOP (14.5/9.4% compared with 0%). However there was no statistically significant difference in the cataract formation between the groups at 12 months. [59] Callanan and colleagues reported an increase in IOP in the dexamethasone plus laser group compared with laser alone (20% compared with 1.6%).[44]

2. Fluocinolone

Two trials assessed fluocinolone implant for DMO (table 6). The FAME study (n=956) compared two doses of fluocinolone (0.2 µg/day and 0.5 µg/day) with sham injection in patients with at least one prior laser treatment.[29] Approximately 25% of patients in each group had more than one prior laser treatment. At 24 months both doses of fluocinolone showed a statistically significant improvement in mean BCVA compared to sham. There was a modest difference between fluocinolone groups. Rescue laser was given after the first six weeks for persistent oedema and was allowed every three months. 35-37% of patients in the fluocinolone group and 59% in the sham injection group required rescue laser. Extended follow-up at 36 months showed that the both fluocinolone arms continued to result in a statistically significant benefit compared with sham.[60]

Pearson and colleagues (n=196) compared fluocinolone (0.59 mg) with standard of care, either laser or no treatment.[43] At three years there was no statistically significant difference in the proportion of patients with 15 letters gain or more (31% fluocinolone compared with 20% standard of care) between groups and proportion of patients losing 15 letters or more in the fluocinolone group (17% compared with 14%). Increased incidence of cataracts may have contributed to this difference.

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These trials were not suitable for meta-analysis.

Adverse events are shown in table 14. Pearson and colleagues reported a higher incidence of cataracts at three years in the fluocinolone group compared with standard of care (55.9% compared with 21.7%).In the extended report of the FAME study there was a considerably higher incidence of cataract surgery in phakic eyes in the 0.2 µg/day and 0.5µg/day fluocinolone groups (80.0% and 87.2% compared with 27.3%) and increased IOP at any point (37% and 46% compared with 12%).

Following the demonstration in the FAME trial that a lower dose was about as good as higher ones, the higher doses are unlikely to be used.

3. Triamcinolone

Ten trials evaluating triamcinolone were identified (table 7 and 8). All trials evaluated intravitreal administration of triamcinolone, there were no trials evaluating posterior or anterior sub-tenon injections. Two trials used Trivaris[21,61], two trials used Kenacort [32,33], one trial used Kenalog[62], one trial used Trimahexal [31] and four trials did not report the type of triamcinolone used.[34,37].[45,56] Three doses were assessed in the included studies (1 mg, 4 mg and 8 mg) and triamcinolone has been combined with laser or bevacizumab.

Ip and colleagues (n=840) were the only authors to evaluate triamcinolone 1mg (Trivaris).[22,61,63,64] They found a statistically significant improvement in mean BCVA at two years in the laser group compared with the triamcinolone group and no significant difference between 1 mg compared with 4 mg.

Several trials compared 4 mg intravitreal triamcinolone. Ip and colleagues (n=840) found that laser therapy resulted in a greater improvement in mean BCVA at two years compared to 4 mg triamcinolone (Trivaris). [22,61,63,64] Lam and colleagues (n=111), found no statistically significant difference between laser and triamcinolone at six months (triamcinolone type not reported).[34] When these two trials were pooled through meta-analysis, the treatment effect favoured laser but differences were not statistically significant (figure 6). Ockrim and colleagues (n=88) compared 4 mg intravitreal triamcinolone (Kenalog) with laser alone.[62] At 12 months they found no statistically significant BCVA improvement between the triamcinolone and laser groups. Gillies and colleagues (n=69) compared 4 mg of triamcinolone (Kenacort) with sham injection.[32] Mean BCVA improved statistically significantly with triamcinolone at 24 months compared with sham injection (3.1 letters gain compared with 2.9 letters loss, p = 0.01).

Lam and colleagues (n=111) compared triamcinolone 4 mg alone with 4 mg of triamcinolone plus laser or laser alone.[34] At six months the authors found no difference in BCVA between any of the groups. Elman and colleagues (n=854) compared 4 mg of triamcinolone (Trivaris) plus laser with ranibizumab plus prompt (within 3-10 days) or deferred (more than 24 week) laser and laser alone.[21] At two years they found a statistically significant difference in mean BCVA between ranibizumab plus prompt/deferred laser compared with laser alone (7 letters gain/9 letters gain compared with 3 letters gain), but no difference with triamcinolone plus laser compared with laser alone (2 letters gain compared with 3 letters gain). Oliveira-Neto and colleagues (n=120) compared 4 mg triamcinolone alone (triamcinolone type not reported) with 4 mg plus 1.25 mg bevacizumab.[56] At six months they found no statistically significant difference between groups.

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The Elman and Lam studies were suitable for meta-analysis, which showed non-statistically significant improvements in mean BCVA and the proportions of patients with more or equal than 15 letter gain in the triamcinolone plus laser group compared with laser alone (figure 7).

Adverse events are shown in table 15 and 16. Triamcinolone was associated with consistently higher incidences of IOP increase and cataracts. Gilles and colleagues reported a cataract rate of over 50% by three years in patients treated with triamcinolone.

d. Other pertinent studies

Only one study in abstract form directly compared bevacizumab with ranibizumab.[51] Bevacizumab and ranibizumab have been compared through indirect comparison of five trials.[65] There was no evidence of a difference between the drugs, however wide credible intervals meant that superiority of either drug could not be excluded.

Two-year results of the CATT (Comparison of AMD Treatment Trials) and one year results of the IVAN (Inhibit VEGF in Age-related choroidal Neovascularisation), recently published, have demonstrated a good safety profile of anti-VEGF therapies when used to treat patients with age-related macular degeneration.[66,67] The CATT study randomised 1208 patients with AMD to monthly or as required injection of either ranibizumab or bevacizumab. At 1 year the mean BCVA was similar in both groups (8.0 letter gain in bevacizumab and 8.5 in ranibizumab). Over two years, the rates of deaths, myocardial infarction and stroke did not differ between ranibizumab and bevacizumab treatment groups. However, there was a higher rate of serious adverse events in the bevacizumab compared with the ranibizumab group. This increased event rate was driven mainly by hospitalisations, (RR 1.29, 95%CI 1.01 to 1.66). However the hospitalisations were not caused by known adverse events of bevacizumab. Arterio-thrombotic events and heart failure occurred in less than 2% of participants in the IVAN, and there were more often observed in the ranibizumab group than in the bevacizumab group (p = 0.03). Further data from other ongoing clinical trials may provide more insight on the safety or anti-VEGF treatment and possible differences on this respect among available drugs.

Campbell and colleagues conducted a population based nested case-control study of 91,378 older adults with a history of physician diagnosed retinal disease.[68] The authors found that neither ranibizumab nor bevacizumab were associated with significant risks of ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism."

A recent systematic review specifically assessing adverse events in anti-VEGF drugs found a low incidence of serious (below 1 in 100) and non-serious ocular events (below 1 in 500) from ranibizumab, bevacizumab and pegaptanib.[69]

Fung and colleagues used an internet-based survey of clinicians to assess the safety of bevacizumab.[70] The survey covered over 5000 patients and found that bevacizumab was associated with an infrequent incidence of adverse events (all less than 0.21%).

One study which assessed diclofenac did not meet the inclusion criteria (follow-up for only 12 weeks).[71] The authors randomised 32 patients to either intravitreal diclofenac or triamcinolone

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and found that both diclofenac and triamcinolone reduced CMT, but a statistically significant visual improvement was observed only in the triamcinolone group.

Sfikakis and colleagues undertook a 30-week randomised crossover trial comparing infliximab and placebo.[72] The study failed to meet our inclusion criteria (only 11 patients included). The authors found that infliximab resulted in a 28.6% improvement in vision compared with 4.3% with placebo. The improvement seen with placebo could be due to a "carry over effect", seen in cross over trials.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was primarily a study to see if the lipid-lowering agent fenofibrate, could reduce macrovascular and microvascular events in type 2 diabetes.[73] However a substudy within FIELD recruited 1012 patients to a retinopathy study. The primary outcome in the main study was need for laser therapy (3.4% on fenofibrate versus 4.9% on placebo) but the substudy used retinal photography to assess progression of retinopathy or development of macular oedema. The hazard ratio at six years for DMO was 0.69 (95%CI 0.54 to 0.87) in the fenofibrate group compared to placebo.

Ruboxistaurin is another oral agent which has been assessed for the treatment of DMO. Aiello and colleagues randomised 686 patients to receive placebo or one of three doses of ruboxistaurin. [74,75] There was no statistically significant difference in delay to sight-threatening DMO in any ruboxistaurin group compared to placebo. The authors suggest that differences in laser treatment between groups may have contributed to the non-significant finding.

e. Assessment of heterogeneity within meta-analysis

Heterogeneity was assessed methodologically and statistically. Methodological heterogeneity was assessed by comparing study population, interventions, outcome measures and follow-up. Studies that were not methodologically comparable were excluded from the meta-analysis. For example bevacizumab trials were not pooled because Soheilian and colleagues included patients who were laser naïve[37] and Ahmadieh and colleagues included patients who were unresponsive to laser.[31] Some analyses were also excluded because sufficient details were not reported in the studies. For example several studies failed to report standard deviations.[35,39]

Statistical heterogeneity was assessed through I^2 scores. High statistical heterogeneity was found in two analyses (2.3, 4.3). Therefore these results should be interpreted with due caution. Moderate heterogeneity was found in three analyses (2.2, 3.1, 3.2). Low heterogeneity was found in the remaining eight analyses.

f. Ongoing trials

There are numerous on-going studies listed in appendix 2. The most salient studies include a study to compare ranibizumab and bevacizumab (Schmidt-Erfurth), a study investigating rescue ranibizumab treatment for patients who have failed on bevacizumab (Chaudhry), a study evaluating two algorithms for ranibizumab, 'treat and extend' and 'as required' (RETAIN), further studies of

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Trap-eye (VIVID and VISTA) and trials which are examining the use of NSAIDs, such as diclofenac and nepafenac (NEVANAC and Soheilian).

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IV – Discussion

It appears that anti-VEGF treatment is effective in DMO, especially ranibizumab and bevacizumab. Meta-analysis of available short-term data (up to 2 years) suggests that ranibizumab is superior to laser and that adding laser to ranibizumab treatment does not confer additional benefit. Steroid treatment has demonstrated mixed success and, almost uniformly, increased incidence of cataracts and increased IOP. The licence for fluocinolone takes note of this and it is positioned as a treatment when others have failed.

a. Strengths and limitations of the review

There are a number of strengths of this review. A robust systematic review methodology was used. Reliability was improved by excluding trials with small sample sizes or short follow up. Since a number of trials included similar intervention arms, consistent treatment effects further improve reliability. Validity was improved by assessing the quality of trials using the Cochrane risk of bias tables. Including abstracts from ARVO provided up to date results. Pooling results through meta-analysis provided further evidence. The random effects model was used throughout to allow for heterogeneity among studies.

This review, however, has limitations. Although the inclusion of abstracts provides a more up to date results, the studies contained in these abstracts could not be assessed for risk of bias and should therefore be interpreted with caution. In addition, reporting of quality assessment criteria was variable. Allocation concealment was especially poorly reported. There was only one study which compared different anti-VEGFs[51] and none that compared steroids (fluocinolone vs dexamethasone vs. triamcinolone). Therefore it is difficult to assess the effectiveness within drug classes. As with any meta-analysis questions of heterogeneity arise. Follow-up periods varied among studies. A difference of six months was allowed for studies to be pooled for meta-analysis but this could have still resulted in heterogeneity. High statistical heterogeneity was found in a quarter of analyses. Furthermore because of the low number of trials included, publication bias could not be assessed by funnel plot analysis. The manufacturers funded most of the trials for ranibizumab, pegaptanib, dexamethasone and fluocinolone, whereas trials for bevacizumab and triamcinolone were generally funded by non-pharmaceutical organisations. Generally, the non-commercial studies had smaller numbers, perhaps because of funding restraints.

It is important to note that there may be differences in laser treatment protocol between studies. This applies to trials which combine drug treatments with laser or include laser as a comparator. All studies referred to the ETDRS protocol [19,20] or a modified version of it. In the ETDRS, once the diagnosis of clinically significant macular oedema was made, an angiogram was obtained to identified "treatable lesions". "Treatable lesions" included discrete points of retinal hyperfluorescence or leakage (most of these are often microaneurisms), areas of diffuse leakage within the retina related to microaneurisms, intraretinal microvascular abnormalities, diffusely leaking retinal capillary bed and retinal avascular zones. In the ETDRS protocol, treatment of lesions closer than 500 microns from the centre of the macula was not required initially; however if vision was less than 20/40 and the oedema and leakage persisted, treatment up to 300 microns from the

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centre of the macula was recommended unless there was capillary dropout; in the latter case treatment was not recommended as it may lead to further loss of perifoveal capillaries

However in routine clinical practice clinicians generally use lighter and less intense treatment than specified in the ETDRS protocol.[76] In addition, some centres do not use fluorescein angiography (unlike the ETDRS study[19]) to guide treatment. The exact adherence to the ETDRS protocol within studies is unclear. For example, in the BOLT study a modified ETDRS protocol was used. One of the aims of the protocol was "not darkening/whitening of microaneuysms", which is not consistent with the ETDRS protocol.

b. Interpretation of the results

The anti-VEGF drugs appear to be clinically effective in treating DMO in short-term studies (up to 2 years). Ranibizumab has the most robust evidence base and has shown superiority compared to laser and sham injection in all trials and meta-analyses, except for the proportion of patients with 10 or more letter gain in the DRCR.net study published by Elman and colleagues at two years follow up.[46] Adding laser to ranibizumab conferred no benefit. Bevacizumab has also been shown to be superior to laser. Three doses have been used (1.25 mg, 1.5 mg and 2.5 mg). The higher dose does not appear to add further benefit, and most studies in the literature use 1.25 mg. Addition of triamcinolone to bevacizumab did not provide further benefits. Pegaptanib has only been compared to sham injection. Mean change in BCVA favoured pegaptanib, but only through meta-analysis did the proportion of patients with more than 15 letter gain favour pegaptanib. Further published data are required before drawing conclusions on aflibercept. However although the anti-VEGF drugs are a significant advance, they fail to improve BCVA by 10 or more letters in half or more patients, and so they do not provide a complete answer to DMO.

Steroid treatments have inconsistent results and are undoubtedly associated with increased IOP and cataract. The effects of dexamethasone appear to peak at three months. At six months there was no significant difference compared with laser. This might imply that earlier re-treatment is needed if the beneficial effect is to be maintained, but increasing the number of treatments would likely increase the associated complications, especially with the relatively large needle size. The addition of laser did not appear to add further benefit. There was no significant difference in cataract formation at six months with dexamethasone compared to observation but it is likely that a higher incidence of cataracts would be seen with longer follow-up. Significantly more patients suffered increased IOP in the dexamethasone group compared with observation. Fluocinolone has been shown to be effective compared with sham injection (FAME)[29,60], however when compared to standard of care (laser or observation at clinician's discretion) there was no significant difference in the proportion of patients with a 15 letter or more gain. Both studies reported higher incidence of cataract formation in the fluocinolone group, over 80% at three years at the higher dose. Results for triamcinolone are inconsistent. Ip and colleagues found that laser was more effective[61], others have found no statistically significant difference. Triamcinolone combined with laser, however, seemed to have similar efficacy as ranibizumab combined with laser in pseudophakic eyes.[21,46] Triamcinolone is more effective than sham injection. Triamcinolone has consistently been associated with increased incidence of cataract and raised IOP.

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Steroids and laser therapy may affect CMT in a different manner from anti-VEGF drugs. For example, when ranibizumab alone is compared with ranibizumab plus laser, ranibizumab alone appears to be more effective in terms of mean change in BCVA and proportion of patients with more than 15 letters gain. However ranibizumab plus laser is more effective at reducing CMT. Furthermore when triamcinolone plus laser is compared with ranibizumab plus laser, ranibizumab plus laser appears to be more effective in terms of change in BCVA and proportion of patients with more than 15 letters gain, but triamcinolone plus laser is more effective at reducing CMT. The reasons for this are unclear. There is a weak correlation between CMT and BCVA. However the long term benefits of reducing CMT are currently unknown.

No large observational studies were identified that compared anti-VEGF drugs. Fung and colleagues, using an internet based survey, found the incidence of adverse events in bevacizumab to be low.[70] One small outbreak of sterile endophthalmitis was reported with a single batch of bevacizumab in Canada, emphasising the need for sterility when preparing aliquots.[77] Curtis and colleagues carried out a very large retrospective cohort study in 146,942 patients aged 65 and over with age-related macular degeneration (AMD).[78] Their aim was to examine the cardiovascular outcomes in patients treated with the four options: photodynamic therapy (PDT), pegaptanib, bevacizumab and ranibizumab. The authors reported that one of their comparisons showed an increase in overall mortality and stroke risk with bevacizumab compared to ranibizumab, with hazard ratios 0.86 (95%CI 0.75 to 0.98) and 0.78 (0.64 to 0.96) respectively. However because of the very large cost differences between bevacizumab and ranibizumab, the authors noted that selection bias might be operating, with poorer people (with poorer health) more likely to be treated with bevacizumab. They therefore carried out another analysis using only ophthalmological clinics which used only one drug, to avoid selection bias. This analysis showed no significant difference: overall mortality hazard ratio for ranibizumab 1.10 (95%CI 0.85 to 1.141); MI 0.87 (0.53 to 1.14); stroke 0.87 (0.61 to 1.24).

Gower and colleagues analysed 77,886 anti-VEGF injections from Medicare data (46% ranibizumab and 54% bevacizumab).[79] Results have only been published in abstract form. The authors found an increased risk of overall mortality and cerebrovascular events in the bevacizumab group (HR 1.11 99%CI 1.01 to 1.23 and 1.57, 1.04 to 2.37 respectively). There was no statistically significant increased risk in the ranibizumab group. The authors acknowledge that a limitation of the study is a failure to adjust for important confounding factors (such as smoking, hypertension and hyperlipidaemia). Considering the cost difference, it is likely that patients treated with bevacizumab would have been in a lower socio-economic class and therefore would be at high risk of mortality and vascular disease.

c. Implications for clinicians

The anti-VEGF drugs appear to be a significant advance in the treatment of DMO and are regarded now as the treatment of choice for patients affected by this condition. Studies assessing the effectiveness of steroids have reported mixed results. The high rates of cataract and increased IOP are a drawback. Triamcinolone combined with laser may be a good option for pseudophakic patients and may be more cost-effective than treatment with ranibizumab. However the need for fewer administrations, potentially one every three years with fluocinolone, is advantageous. From an administration perspective, some patients might prefer infrequent steroid injections with a sizeable

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risk of cataract, and a small, but existent, risk of glaucoma, to frequent anti-VEGF injections, even if the potential gain may not be fully comparable. Steroids may be also considered for patients that do not adequately respond to anti-VEGFs. Currently, the role of laser in the treatment of DMO is debatable. Short term data from available trials have demonstrated the superiority of anti-VEGF with regards to laser treatment and have failed to demonstrate a benefit of combining both treatment approaches. It is possible that some ophthalmologists may still opt to offer laser treatment to patients with very focal areas of leakage.

Currently there is more evidence for the effectiveness of ranibizumab and bevacizumab than for pegaptanib and VEGF-trap eye. The results of direct head to head trials of ranibizumab and bevacizumab are awaited. Bevacizumab is not licensed for intraocular use but costs considerably less than other forms of therapy. Ranibizumab is licensed and more expensive, but its use is supported by large manufacturer funded trials demonstrating its clinical effectiveness. In the UK, the General Medical Council recommends that unlicensed medications should only be prescribed if "an alternative, licensed medicine would not meet the patient's needs" and there is "a sufficient evidence base and/or experience of using the medication to demonstrate its safety and efficacy".[80] The FDA says that when using a drug "off-label" clinicians "have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sounded medical evidence, and to maintain records of the product's use and effects".[81] Patients should be fully aware of the use of any unlicensed medication and consent to any safety or efficacy uncertainties.

The place of intravitreal steroids needs consideration now that we have the anti-VEGFs drugs, as does the role of laser. The anti-VEGFs drugs may now be the first-line treatment in place of laser, with laser being used selectively for focal lesions, and in sequence after anti-VEGF therapy once the retinal thickness has been reduced. However it should be noted that about half of patients do not get good results with anti-VEGFs. In RESTORE, only 50% of patients had gains in VA of 10 or more letters. So the anti-VEGFs are "game-changers" but their impact should not be over-estimated.

In those who do not respond to anti-VEGFs or laser, there remains a place for steroids, despite their high adverse effect rates. The European licence for fluocinolone recognises this, by stating that it should be used when other therapies have not had sufficient effect.[82] The commonest adverse effect is cataract, but that is very common in people with diabetes, and many are already pseudophakic when treatment of DMO is required.

Vitreoretinal surgery for the treatment of DMO was not included in our review. Laidlaw reviewed the literature and only found evidence for vitrectomy when there was signs of clinical or OCT traction.[83] However even in these cases, the evidence was not strong.

d. Implications for policy makers

In the UK, the National Institute of Health and Clinical Excellence (NICE) has recently made the decision not to recommend ranibizumab for the treatment of DMO.[84] NICE concluded that ranibizumab, although clinically effective, was not cost-effective compared to laser therapy. Bevacizumab is less than a tenth of the cost of ranibizumab. Bevacizumab is unlikely to be licensed.

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This beckons the question as to whether policy makers should recommend cheaper unlicensed medications over a more expensive licensed alternative when efficacy and side effects appear similar.

e. Unanswered questions

Several unanswered questions remain. Studies evaluating the effectiveness of ranibizumab compared with bevacizumab are needed. Although the anti-VEGFs are clinically effective and a major step forward in the management of DMO, it has to be noted that they have little effect in a large number of patients. Generally speaking, the proportion of patients who have demonstrated 10 or more letter gain using anti-VEGFs is between 30-50% in the trials that demonstrate greatest effectiveness. Most of these patients would not achieve the 20/40 visual acuity required for driving. More effective treatments, or combinations of treatments, are required.

There is a lack of specific evidence for the use of anti-VEGF drugs or steroids in patients with macular ischemia secondary to DMO. A number of trials excluded patients with macular ischemia.[23,34,35,40,53,62] The RESTORE trial included patients with macular ischemia and undertook a subgroup analysis.[24] The authors compared patients with (n=34) and without (n=35) macular ischemia at baseline. They found that those without macular ischemia responded better to ranibizumab (mean average change in BCVA at 12 months 7.2 letters gain compared with 6.3 letters). Larger trials are needed to assess the use of anti-VEGF drugs and steroids in patients with macular ischemia.

The duration of treatment is as yet uncertain. Most of the included studies use a retreatment protocol based on clinical need or OCT results. For example, in the BOLT study patients received a median of 9 injections of bevacizumab over 24 months.[23,85] However, it is not yet known how frequent long-term maintenance injections will be needed for and whether laser treatment in sequence could potentially reduce the number of anti-VEGF injections required. Other treatment strategies to apply laser, such as using laser power at sub-threshold levels, may prove more effective.[86] Future trials should use active comparators which are used in routine clinical practice and avoid placebo controlled trials.

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V - Conclusion

This review evaluated current treatments for DMO. Undoubtedly, the use of anti-VEGFs heralds a new era for patients who suffer from DMO. Currently, the anti-VEGFs ranibizumab and bevacizumab, have consistently shown good clinical effectiveness without major unwanted side effects. Steroids results have been mixed and are usually associated with cataract formation and IOP increase. Based on the short term data available, adding laser therapy to anti-VEGFs does not appear to confer additional benefit.

Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision (≥20/40) and, thus, the search for new therapies to prevent and manage DMO needs to continue.

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Contribution of authors

JF screened titles, checked data extraction, performed the meta-analysis and drafted manuscript. NL conceived the idea, interpreted the results and provided clinical expertise throughout. PR performed the literature search, updated the searches, screened titles and managed the references. CC extracted data from the studies. DS screened titles and checked the meta-analysis. NW designed the review and supervised the running of the study. All authors contributed to the final draft.

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Reference List

1. Holman N, Forouhi NG, Goyder E, et al. The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: estimates of total diabetes prevalence for England, 2010-2030. *Diabet Med* 2011;28:575-82.

2. Williams R, Airey M, Baxter H, et al. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond)* 2004;18:963-83.

3. Henricsson M, Sellman A, Tyrberg M, et al. Progression to proliferative retinopathy and macular oedema requiring treatment. Assessment of the alternative classification of the Wisconsin Study. *Acta Ophthalmol Scand* 1999;77:218-23.

4. Chen E, Looman M, Laouri M, et al. Burden of illness of diabetic macular edema: literature review. *Curr Med Res Opin* 2010;26:1587-97.

5. Hirai FE, Knudtson MD, Klein BE, et al. Clinically significant macular edema and survival in type 1 and type 2 diabetes. *Am J Ophthalmol* 2008;145:700-6.

6. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;105:1801-15.

7. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology* 2009;116:497-503.

8. Knudsen LL, Lervang HH, Lundbye-Christensen S, et al. The North Jutland County Diabetic Retinopathy Study (NCDRS) 2. Non-ophthalmic parameters and clinically significant macular oedema. *Br J Ophthalmol* 2007;91:1593-5.

9. Thomas RL, Dunstan F, Luzio SD, et al. Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. *BMJ* 2012;344:e874.

10. Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. *Diabetes Care* 2009;32:2307-13.

11. Huang ES, Brown SE, Ewigman BG, et al. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care* 2007;30:2478-83.

12. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. *Arch Ophthalmol* 2008;126:1748-54.

13. Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. *Br J Ophthalmol* 2012;96:345-9.

14. Happich M, Reitberger U, Breitscheidel L, et al. The economic burden of diabetic retinopathy in Germany in 2002. *Graefes Arch Clin Exp Ophthalmol* 2008;246:151-9.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

15. Bhagat N, Grigorian RA, Tutela A, et al. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol* 2009;54:1-32.

16. Murata T, Ishibashi T, Khalil A, et al. Vascular endothelial growth factor plays a role in hyperpermeability of diabetic retinal vessels. *Ophthalmic Res* 1995;27:48-52.

17. Barile GR, Pachydaki SI, Tari SR, et al. The RAGE axis in early diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2005;46:2916-24.

18. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383-96.

19. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796-806.

20. Early Treatment Diabetic Retinopathy Study research group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology* 1987;94:761-74.

21. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064-77.

22. Ip MS, Bressler SB, Antoszyk AN, et al. A randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema: baseline features. *Retina* 2008;28:919-30.

23. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology* 2010;117:1078-86.

24. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615-25.

25. Lovestam-Adrian M, Agardh E. Photocoagulation of diabetic macular oedema--complications and visual outcome. *Acta Ophthalmol Scand* 2000;78:667-71.

26. Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema. Long-term visual results. *Ophthalmology* 1991;98:1594-602.

27. Nwanze CC, Akinwale A, Adelman RA. Bevacizumab vs. Ranibizumab in Preserving or Improving Vision in Patients with Wet, Age-Related Macular Degeneration: A Cost-effectiveness Review. *Clinical Medicine Insights: Therapeutics* 2012;4:29-38.

28. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2010;117:2146-51.

29. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology* 2011;118:626-35.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

30. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology* 2011;118:1819-26.

31. Ahmadieh H, Ramezani A, Shoeibi N, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol* 2008;246:483-9.

32. Gillies MC, Sutter FK, Simpson JM, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. *Ophthalmology* 2006;113:1533-8.

33. Gillies MC, McAllister IL, Zhu M, et al. Intravitreal triamcinolone prior to laser treatment of diabetic macular edema: 24-month results of a randomized controlled trial. *Ophthalmology* 2011;118:866-72.

34. Lam DS, Chan CK, Mohamed S, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: six-month outcomes. *Ophthalmology* 2007;114:2162-7.

35. Lam DS, Lai TY, Lee VY, et al. Efficacy of 1.25 MG versus 2.5 MG intravitreal bevacizumab for diabetic macular edema: six-month results of a randomized controlled trial. *Retina* 2009;29:292-9.

36. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care* 2010;33:2399-405.

37. Soheilian M, Ramezani A, Bijanzadeh B, et al. Intravitreal bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. *Retina* 2007;27:1187-95.

38. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119:789-801.

39. Cunningham ET, Jr., Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 2005;112:1747-57.

40. Sultan MB, Zhou D, Loftus J, et al. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology* 2011;118:1107-18.

41. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;116:1142-50.

42. Sivaprasad S, Ockrim Z, Massaoutis P, et al. Posterior hyaloid changes following intravitreal triamcinolone and macular laser for diffuse diabetic macular edema. *Retina* 2008;28:1435-42.

43. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology* 2011;118:1580-7.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

44. Callanan D, Gupta S, Ciulla TA, et al. Efficacy and safety of combination therapy with dexamethasone intravitreal implant (DEX Implant) plus laser photocoagulation versus monotherapy with laser for treatment of diffuse diabetic macular edema (DDME) [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 3968.

45. Kim Y, Kang S, Yi CH. Three-year follow-up of intravitreal triamcinolone acetonide injection and macular laser photocoagulation for diffuse diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 11-4-2010;51:E-Abstract 4260.

46. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609-14.

47. Nguyen QD, Shah SM, Heier JS, et al. Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2009;116:2175-81.

48. Ohji M, Ishibashi T, Sr., REVEAL study group. Efficacy and safety of ranibizumab 0.5 Mg as monotherapy or adjunctive to laser versus laser monotherapy in Asian patients with visual impairment due to diabetic macular edema: 12-month results of the REVEAL Study [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 4664.

49. Mitchell P, RESTORE extension study group. 2-year safety and efficacy outcome of ranibizumab 0.5 mg in patients with visual impairment due to diabetic macular edema (DME): an interim analysis of the RESTORE extension study [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 4667.

50. Do DV, Campochiaro PA, Boyer DS, et al. 6 month results of the READ 3 Study: Ranibizumab for Edema of the mAcula in Diabetes [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 5282.

51. Jorge R, Nepomuceno AB, Takaki E, et al. A prospective randomized trial of intravitreal bevacizumab versus ranibizumab for the management of refractory diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 347.

52. Michaelides M, Fraser-Bell S, Hamilton R, et al. Macular perfusion determined by fundus fluorescein angiography at the 4-month time point in a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (Bolt Study): Report 1. *Retina* 2010;30:781-6.

53. Faghihi H, Esfahani MR, Harandi ZA, et al. Intravitreal bevacizumab vs. combination of intravitreal bevacizumab plus macular photocoagulation in clinically significant diabetic macular edema: 6 months results of a randomized clinical trial. *Iranian J of Ophthalmol* 2010;22:21-6.

54. Soheilian M, Garfami KH, Ramezani A, et al. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. *Retina* 2012;32:314-21.

55. 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;227:100-6.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

56. Oliveira Neto HL, Andrade RE, Casella M, et al. A randomized clinical trial to compare the efficacy and safety of isolated or combined intravitreal injection of triamcinolone acetonide and bevacizumab for diabetic macular edema ATEMD protocol - A Brazilian clinical trial [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 5331.

57. Adamis AP, Altaweel M, Bressler NM, et al. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology* 2006;113:23-8.

58. Do DV, Nguyen QD, Boyer D, et al. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 24-4-2012.

59. Haller JA, Kuppermann BD, Blumenkranz MS, et al. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol* 2010;128:289-96.

60. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 Years in patients with diabetic macular edema. *Ophthalmology* 21-6-2012.

61. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* 2009;127:245-51.

62. Ockrim ZK, Sivaprasad S, Falk S, et al. Intravitreal triamcinolone versus laser photocoagulation for persistent diabetic macular oedema. *Br J Ophthalmol* 2008;92:795-9.

63. Bressler NM, Edwards AR, Beck RW, et al. Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. *Arch Ophthalmol* 2009;127:1566-71.

64. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447-9.

65. Ford J, Elders A, Shyangdan D, et al. The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison. *BMJ* 2012;in press.

66. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;119:1399-411.

67. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388-98.

68. Campbell RJ, Gill SS, Bronskill SE, et al. Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study. *BMJ* 2012;345:e4203.

69. Van der Reis MI, La Heij EC, De Jong-Hesse Y, et al. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. *Retina-the Journal of Retinal and Vitreous Diseases* 2011;31:1449-69.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

70. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006;90:1344-9.

71. Elbendary AM, Shahin MM. Intravitreal diclofenac versus intravitreal triamcinolone acetonide in the treatment of diabetic macular edema. *Retina* 2011;31:2058-64.

72. Sfikakis PP, Grigoropoulos V, Emfietzoglou I, et al. Infliximab for diabetic macular edema refractory to laser photocoagulation: a randomized, double-blind, placebo-controlled, crossover, 32-week study. *Diabetes Care* 2010;33:1523-8.

73. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 17-11-2007;370:1687-97.

74. PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty-month results of the randomized PKC-DMES clinical trial. *Arch Ophthalmol* 2007;125:318-24.

75. PKC-DMES Study Group. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy. *Ophthalmology* 2006;113:2221-30.

76. Fong DS, Strauber SF, Aiello LP, et al. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Arch Ophthalmol* 2007;125:469-80.

77. Health Canada. Reports of eye inflammation, endophthalmitis, and Toxic Anterior Segment Syndrome (TASS) following off-label intravitreal use of Avastin (bevacizumab). 2008 [cited 2012 Oct 24];Available from: URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_4_hpc-cps-eng.php

78. Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol* 2010;128:1273-9.

79. Gower EW, Cassard S, Chu L, et al. Adverse event rates following intravitreal injection of Avastin or Lucentis for treating age-related macular degeneration [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 6644.

80. General Medical Council. Prescribing medicines for use outside the terms of their licence (off-label). 2012 [cited 2012 Oct 24];Available from: URL: http://www.gmc-uk.org/guidance/ethical_guidance/prescriptions_faqs.asp#10

81. U.S.Food and Drug Administration. Off-Label" and investigational use of marketed drugs, biologics, and medical devices - Information Sheet. 2011 [cited 2012 Oct 24];Available from: URL: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm

82. Alimera Sciences. Alimera Sciences' ILUVIEN® Receives Marketing Authorization in France for the Treatment of Chronic Diabetic Macular Edema. 2012 [cited 2012 Oct 24];Available from: URL: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=692876

83. Laidlaw DA. Vitrectomy for diabetic macular oedema. *Eye* 2008;22:1337-41.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

84. National Institute for Health and Clinical Excellence. Ranibizumab for the treatment of diabetic macular oedema:TA237. 2011 [cited 2012 Oct 24];Available from: URL: http://publications.nice.org.uk/ranibizumab-for-the-treatment-of-diabetic-macular-oedema-ta237

85. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema: 24-Month Data: Report 3. *Arch Ophthalmol* 9-4-2012.

86. Sivaprasad S, Dorin G. Subthreshold diode laser micropulse photocoagulation for the treatment of diabetic macular edema. *Expert Review of Medical Devices* 2012;9:189-97.

87. Cho WB, Moon JW, Kim HC. Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy. *Br J Ophthalmol* 2010;94:858-63.

88. Googe J, Brucker AJ, Bressler NM, et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011;31:1009-27.

89. Faghihi H, Roohipoor R, Mohammadi SF, et al. Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema. *Eur J Ophthalmol* 2008;18:941-8.

90. Figueroa MS, Contreras I, Noval S. Surgical and anatomical outcomes of pars plana vitrectomy for diffuse nontractional diabetic macular edema. *Retina* 2008;28:420-6.

91. Isaac DL, Abud MB, Frantz KA, et al. Comparing intravitreal triamcinolone acetonide and bevacizumab injections for the treatment of diabetic macular oedema: a randomized double-blind study. *Acta Ophthalmol* 2012;90:56-60.

92. Paccola L, Costa RA, Folgosa MS, et al. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). *Br J Ophthalmol* 2008;92:76-80.

93. Prager SG, Kriechbaum K, Mylonas G, et al. Comparison of intravitreally applied bevacizumab and triamcinolone on diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 11-4-2010;51:E-Abstract 4262.

94. Ozturk BT, Kerimoglu H, Bozkurt B, et al. Comparison of intravitreal bevacizumab and ranibizumab treatment for diabetic macular edema. *J Ocul Pharmacol Ther* 2011;27:373-7.

95. Marey HM, Ellakwa AF. Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. *Clin Ophthalmol* 2011;5:1011-6.

96. Shahin MM, El-Lakkany RS. A prospective, randomized comparison of intravitreal triamcinolone acetonide versus intravitreal bevacizumab (avastin) in diffuse diabetic macular edema. *Middle East Afr J Ophthalmol* 2010;17:250-3.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

97. Loftus JV, Sultan MB, Pleil AM, et al. Changes in vision- and health-related quality of life in patients with diabetic macular edema treated with pegaptanib sodium or sham. *Investigative Ophthalmology & Visual Science* 2011;52:7498-505.

98. Ferrone PJ, Jonisch J. Ranibizumab dose comparison for the treatment of diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 2011;52:E-Abstract 5333.

99. Solaiman KA, Diab MM, Abo-Elenin M. Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. *Retina* 2010;30:1638-45.

100. Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards AR, et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;114:1860-7.

101. Lee SJ, Kim ET, Moon YS. Intravitreal bevacizumab alone versus combined with macular photocoagulation in diabetic macular edema. *Korean J Ophthalmol* 2011;25:299-304.

102. Audren F, Lecleire-Collet A, Erginay A, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular edema: phase 2 trial comparing 4 mg vs 2 mg. *Am J Ophthalmol* 2006;142:794-9.

103. Audren F, Erginay A, Haouchine B, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. *Acta Ophthalmol Scand* 2006;84:624-30.

104. Avitabile T, Longo A, Reibaldi A. Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema. *Am J Ophthalmol* 2005;140:695-702.

105. Bandello F, Pognuz DR, Pirracchio A, et al. Intravitreal triamcinolone acetonide for florid proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2004;242:1024-7.

106. Bonini MA, Jorge R, Barbosa JC, et al. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: A randomized clinical trial. *Invest Ophthalmol Vis Sci* 2005;46:3845-9.

107. Cellini M, Pazzaglia A, Zamparini E, et al. Intravitreal vs. subtenon triamcinolone acetonide for the treatment of diabetic cystoid macular edema. *BMC Ophthalmol* 2008;8:5TN.

108. Cardillo JA, Melo LA, Jr., Costa RA, et al. Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. *Ophthalmology* 2005;112:1557-63.

109. Chung EJ, Freeman WR, Azen SP, et al. Comparison of combination posterior sub-tenon triamcinolone and modified grid laser treatment with intravitreal triamcinolone treatment in patients with diffuse diabetic macular edema. *Yonsei Medi J* 31-12-2008;49:955-64.

110. Dehghan MH, Ahmadieh H, Ramezani A, et al. A randomized, placebo-controlled clinical trial of intravitreal triamcinolone for refractory diabetic macular edema. *Int Ophthalmol* 2008;28:7-17.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

111. Diabetic Retinopathy Clinical Research Network, Chew E, Strauber S, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. *Ophthalmology* 2007;114:1190-6.

112. Gil AL, Azevedo MJ, Tomasetto GG, et al. Treatment of diffuse diabetic maculopathy with intravitreal triamcinolone and laser photocoagulation: randomized clinical trial with morphological and functional evaluation. *Arquivos Brasileiros de Oftalmologia* 2011;74:343-7.

113. Entezari M, Ahmadieh H, Dehghan MH, et al. Posterior sub-tenon triamcinolone for refractory diabetic macular edema: a randomized clinical trial. *Eur J Ophthalmol* 2005;15:746-50.

114. Hauser D, Bukelman A, Pokroy R, et al. Intravitreal triamcinolone for diabetic macular edema: comparison of 1, 2, and 4 mg. *Retina* 2008;28:825-30.

115. Jonas JB, Kamppeter BA, Harder B, et al. Intravitreal triamcinolone acetonide for diabetic macular edema: A prospective, randomized study. *J Ocul Pharmacol Ther* 2006;22:200-7.

116. Joussen AM, Weiss C, Bauer D, et al. Triamcinolone versus inner-limiting membrane peeling in persistent diabetic macular edema (TIME study): design issues and implications. *Graefes Arch Clin Exp Ophthalmol* 2007;245:1781-7.

117. Kaderli B, Avci R. Comparison of topical and subconjunctival anesthesia in intravitreal injection administrations. *Eur J Ophthalmol* 2006;16:718-21.

118. Kang SW, Sa HS, Cho HY, et al. Macular grid photocoagulation after intravitreal triamcinolone acetonide for diffuse diabetic macular edema. *Arch Ophthalmol* 2006;124:653-8.

119. Kim JE, Pollack JS, Miller DG, et al. ISIS-DME: a prospective, randomized, dose-escalation intravitreal steroid injection study for refractory diabetic macular edema. *Retina* 2008;28:735-40.

120. Lam DS, Chan CK, Mohamed S, et al. A prospective randomised trial of different doses of intravitreal triamcinolone for diabetic macular oedema. *Br J Ophthalmol* 2007;91:199-203.

121. Lee HY, Lee SY, Park JS. Comparison of photocoagulation with combined intravitreal triamcinolone for diabetic macular edema. *Korean J Ophthalmol* 2009;23:153-8.

122. Maia OO, Jr., Takahashi BS, Costa RA, et al. Combined laser and intravitreal triamcinolone for proliferative diabetic retinopathy and macular edema: one-year results of a randomized clinical trial. *Am J Ophthalmol* 2009;147:291-7.

123. Massin P, Audren F, Haouchine B, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. *Ophthalmology* 2004;111:218-24.

124. Mohamed S, Leung GM, Chan CK, et al. Factors associated with variability in response of diabetic macular oedema after intravitreal triamcinolone. *Clin Experiment Ophthalmol* 2009;37:602-8.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

125. Nakamura A, Shimada Y, Horio N, et al. Vitrectomy for diabetic macular edema with posterior subtenon injection of triamcinolone acetonide. [Japanese]. *Folia Ophthalmol Japonica* 2004;55:958-62.

126. Spandau UH, Derse M, Schmitz-Valckenberg P, et al. Dosage dependency of intravitreal triamcinolone acetonide as treatment for diabetic macular oedema. *Br J Ophthalmol* 2005;89:999-1003.

127. Tunc M, Onder HI, Kaya M. Posterior sub-Tenon's capsule triamcinolone injection combined with focal laser photocoagulation for diabetic macular edema. *Ophthalmology* 2005;112:1086-91.

128. Verma LK, Vivek MB, Kumar A, et al. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. *J Ocul Pharmacol Ther* 2004;20:277-84.

129. Wickremasinghe SS, Rogers SL, Gillies MC, et al. Retinal vascular caliber changes after intravitreal triamcinolone treatment for diabetic macular edema. *Invest Ophthalmol Vis Sci* 2008;49:4707-11.

130. Yalcinbayir O, Gelisken O, Kaderli B, et al. Intravitreal versus sub-Tenon posterior triamcinolone injection in bilateral diffuse diabetic macular edema. *Ophthalmologica* 2011;225:222-7.

131. Haller JA, Bandello F, Belfort R, Jr., et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010;117:1134-46.

132. Haller JA, Dugel P, Weinberg DV, et al. Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema. *Retina* 2009;29:46-51.

133. Kuppermann BD, Blumenkranz MS, Haller JA, et al. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol* 2007;125:309-17.

134. Boyer DS, Faber D, Gupta S, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina* 2011;31:915-23.

135. Campochiaro PA, Hafiz G, Shah SM, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology* 2010;117:1393-9.

136. Gillies MC, Islam FM, Zhu M, et al. Efficacy and safety of multiple intravitreal triamcinolone injections for refractory diabetic macular oedema. *Br J Ophthalmol* 2007;91:1323-6.

137. Gillies MC, Simpson JM, Gaston C, et al. Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. *Ophthalmology* 2009;116:2182-7.

138. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a **prospective,** randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology* 2004;111:2044-9.

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139. Brown DM, Nguyen QD, Rubio RG, et al. Ranibizumab for Diabetic Macular Edema (DME): 24-Month Efficacy and Safety Results of RISE - a Phase 3 Randomized Controlled Trial [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 6647.

140. Boyer D, Sy J, Rundle AC, et al. Ranibizumab (Anti-VEGF) for vision loss due to diabetic macular edema - results of two phase III randomized trials [abstract]. *71st Scientific Sessions June 24 - 28, 2011, San Diego Convention Center - San Diego, California* 2011;Abstract No, 133-LBOR.

141. Soheilian M, Ramezani A, Yaseri M, et al. Initial macular thickness and response to treatment in diabetic macular edema. *Retina* 2011;31:1564-73.

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Appendix 1: Methods of the literature search

Searches for clinical trials

Ovid MEDLINE 1948-July week 2, 2012 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012

1. Diabetic Retinopathy/dt [Drug Therapy]
2. Macular Edema/dt [Drug Therapy]
3. (diabet* adj2 macular adj (edema or oedema)).tw.
4. (diabet* adj2 maculopathy).tw.
5. (diabet* adj2 retinopathy).tw.
6. 1 or 2 or 3 or 4 or 5
7. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).tw.
8. exp Vascular Endothelial Growth Factor A/
9. exp Fluocinolone Acetonide/
10. exp Triamcinolone/
11. 7 or 8 or 9 or 10
12. 6 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. (masked or sham or placebo or control group or random*).tw.
16. 13 or 14 or 15
17. 12 and 16
18. (case reports or editorial or letter or review).pt.
19. 17 not 18
20. limit 19 to humans

Embase 1947 to 2012 Week 27

1. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).m_titl.

2. (diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy).m_titl.
3. 1 and 2
4. random*.tw.
5. 3 and 4

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Cochrane Central Register of Controlled Trials, Issue 7 of 12, July 2012

ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor* in Record Title and diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy in Record Title

Web of Science® – with Conference Proceedings (updated 2012-07-12)

Title=(ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*) AND Title=(diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy) AND Title=(random*)

Searches for systematic reviews

Ovid MEDLINE(R) Daily Update July 11, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012

1. Diabetic Retinopathy/dt [Drug Therapy]
2. Macular Edema/dt [Drug Therapy]
3. (diabet* adj2 macular adj (edema or oedema)).tw.
4. (diabet* adj2 maculopathy).tw.
5. (diabet* adj2 retinopathy).tw.
6. 1 or 2 or 3 or 4 or 5
7. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).tw.
8. exp Vascular Endothelial Growth Factor A/
9. exp Fluocinolone Acetonide/
10. exp Triamcinolone/
11. 7 or 8 or 9 or 10
12. 6 and 11
13. (systematic review or meta-analysis or pubmed or medline).tw.
14. meta-analysis.pt.
15. cochrane.af.
16. 13 or 14 or 15
17. 12 and 16

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Cochrane Database of Systematic Reviews and Technology Assessments Database, Cochrane Library July Issue, 2012

"ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor* in Record Title and diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy in Record Title

Searches for safety and adverse events

Ovid MEDLINE(R) Daily Update July 11, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012 ; Embase 1980to 2012 week 27

1. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or aflibercept or vegf trap-eye or macugen or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).m_titl.
2. (diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy).m_titl.
3. 1 and 2
4. (risk or safety or adverse or harm or pharmacovigilance).tw.
5. (side-effect* or precaution* or warning* or contraindication$ or contra-indication* or tolerability or toxic*).tw.
6. 4 or 5
7. 3 and 6

Searches of the annual meeting abstracts (for trials, reviews and safety studies)

- ARVO (Association for Research in Vision and Ophthalmology) (2002 to 2012)
- ADA (American Diabetes Association) (2002-2012)
- EASD (European Association for the Study of Diabetes) (2002-2012)

Other searches

Web sites of the following

- Drugs@FDA: FDA Approved Drug Products
- European Medicines Association
- ClinicalTrials.gov
- EU Clinical Trials Register

National Institute for Health and Clinical Excellence

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Appendix 2: Ongoing Trials in ClinicalTrials.gov

- Schmidt-Erfurth and colleagues are comparing ranibizumab and bevacizumab in DME (NCT00545870)
- TRIASTIN study is comparing ranibizumab, triamcinolone and sham injection (NCT00682539)
- Maturi and colleagues are comparing bevacizumab plus dexamethasone with bevacizumab alone (NCT01309451)
- IBeTA study (Jorge and colleagues) is comparing bevacizumab (1.5mg) plus laser, triamcinolone (4mg) plus laser with laser alone (NCT00997191)
- Chaudhry and colleagues are evaluating ranibizumab in patients who have failed with 3-6 injections of bevacizumab (NCT01253694)
- MIDME study (Pfizer) is comparing pegaptanib 0.3mg with sham injection. NCT01175070
- Figueira and colleagues are comparing pegaptanib plus laser with laser alone (NCT01281098)
- RESPOND (Novartis) is comparing ranibizumab (0.5mg) alone with ranibizumab plus laser or laser alone (NCT01135914)
- RETAIN (Novartis) study is comparing two different ranibizumab algorithms; "treat and extend" versus as needed (NCT01171976)
- RED-ES (Novartis) is comparing ranibizumab with laser in patients with visual impairment due to DME (NCT00901186)
- READ 3 study (Do and colleagues) are comparing two doses of ranibizumab 0.5 mg and 2 mg (NCT01077401)
- VIVID-DME and VISTA DME studies (Bayer) are comparing aflibercept with laser. (NCT01331681 and NCT01363440)
- Gillies and colleagues are comparing bevacizumab with dexamethasone (NCT01298076)
- Soheilian and colleagues are performing a phase I study looking at the use of diclofenac compared with bevacizumab in DME (NCT00999791)
- López-Miranda and colleagues are comparing the use of bevacizumab before and after laser therapy (NCT00804206)
- NEVANAC study is comparing triamcinolone alone with triamcinolone plus nepafenac (NSAID) (NCT00780780)
- Elman and colleagues are comparing laser alone, laser combined with an intravitreal injection of triamcinolone, laser combined with an intravitreal injection of ranibizumab, or intravitreal injection of ranibizumab alone (NCT00444600)
- BRDME (Schlingemann and collagues) study is comparing the use of bevacizumab and ranibizumab in the treatment of patients with DME (OCT central area thickness > 275 µm) (NCT01635790)
- Wiley and colleagues are comparing bevacizumab and ranibizumab in patients with DME in at least one eye(NCT01610557)
- Protocol T study (Wells and colleagues) is comparing effectiveness of a aflibercept, bevacizumab, and ranibizumab for DME (NCT01627249)
- Allergan funded study comparing safety and efficacy of 700 µg dexamethasone implant against 0.5 mg ranibizumab in patients with DME (NCT01492400)
- Pfizer funded study comparing effectiveness of 0.3 mg pegaptanib against sham injection (NCT01100307)

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- Allergan funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 µg and 350 µg) against sham in patients with DME (NCT00168389)
- Allergan funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 µg and 350 µg) against sham in patients with DME (NCT00168337)

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Figure 1 - PRISMA

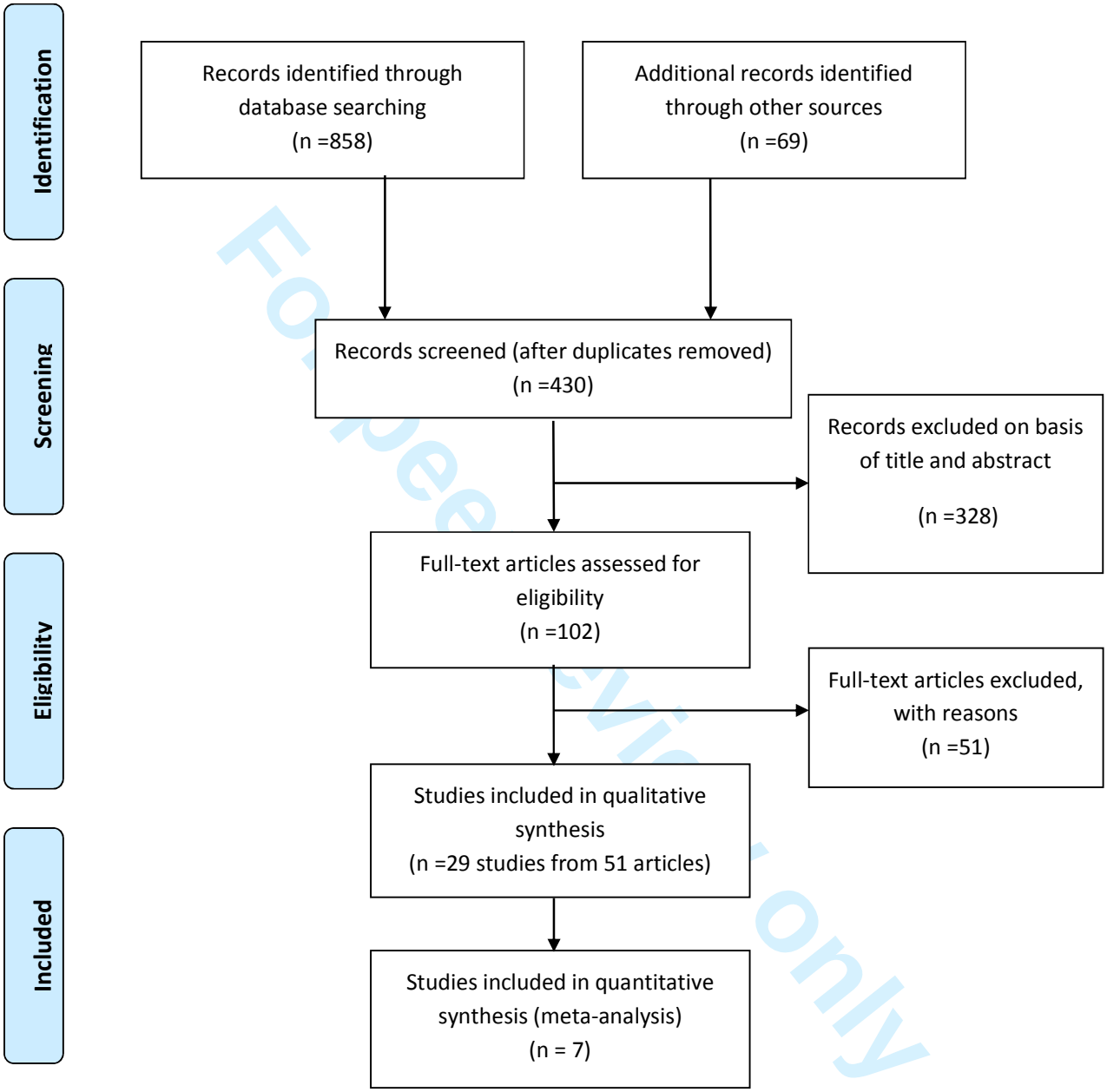

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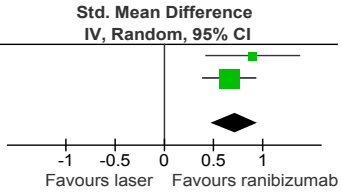
Figure 2 Ranibizumab 0.5mg alone versus laser alone

2.1 Mean change in BCVA

Study or Subgroup	Rani 0.5 mg Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	0.14	0.17	37	-0.01	0.16	38	24.1%	0.90 [0.42, 1.38]
RESTORE 2011	0.12	0.13	115	0.02	0.17	110	75.9%	0.66 [0.39, 0.93]
Total (95% CI)			**152**			**148**	**100.0%**	**0.72 [0.48, 0.95]**

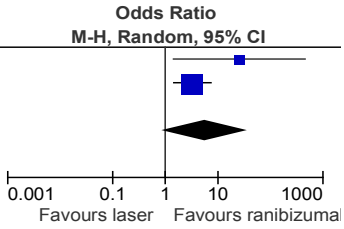
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 6.02 (P < 0.00001)



2.2 Proportion with >15 letter gain

Study or Subgroup	Rani 0.5 mg Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
READ-2 2009	9	37	0	38	28.0%	25.67 [1.43, 459.42]
RESTORE 2011	26	115	9	110	72.0%	3.28 [1.46, 7.37]
Total (95% CI)		**152**		**148**	**100.0%**	**5.83 [0.90, 37.86]**
Total events	35		9			

Heterogeneity: Tau² = 1.09; Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 1.85 (P = 0.06)



2.3 CMT

Study or Subgroup	Rani 0.5 mg Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	-103.73	126.76	37	-144.76	109.22	38	47.2%	0.34 [-0.11, 0.80]
RESTORE 2011	-118.7	115.07	115	-61.3	132.29	110	52.8%	-0.46 [-0.73, -0.20]
Total (95% CI)			**152**			**148**	**100.0%**	**-0.08 [-0.87, 0.71]**

Heterogeneity: Tau² = 0.29; Chi² = 8.96, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.20 (P = 0.84)

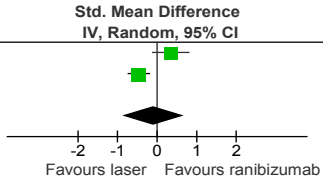
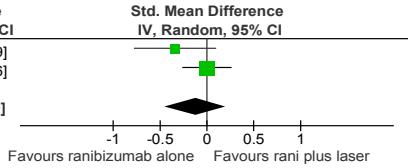


Figure 3 Ranibizumab 0.5mg plus laser versus ranibizumab 0.5mg alone

3.1 Mean change in BCVA

Study or Subgroup	Rani 0.5 plus laser Mean	SD	Total	Rani 0.5mg alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	0.08	0.18	42	0.14	0.17	42	36.5%	-0.34 [-0.77, 0.09]
RESTORE 2011	0.12	0.16	118	0.12	0.13	116	63.5%	0.00 [-0.26, 0.26]
Total (95% CI)			**160**			**158**	**100.0%**	**-0.12 [-0.44, 0.20]**

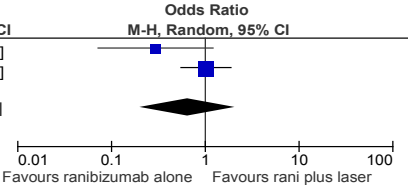
Heterogeneity: Tau² = 0.02; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 0.76 (P = 0.45)



3.2 Proportion with >15 letter gain

Study or Subgroup	Rani 0.5 plus laser Events	Total	Rani 0.5mg alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
READ-2 2009	3	40	8	37	36.3%	0.29 [0.07, 1.21]
RESTORE 2011	27	118	26	115	63.7%	1.02 [0.55, 1.87]
Total (95% CI)		**158**		**152**	**100.0%**	**0.65 [0.20, 2.09]**
Total events	30		34			

Heterogeneity: Tau² = 0.46; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.73 (P = 0.47)



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3.3 CMT

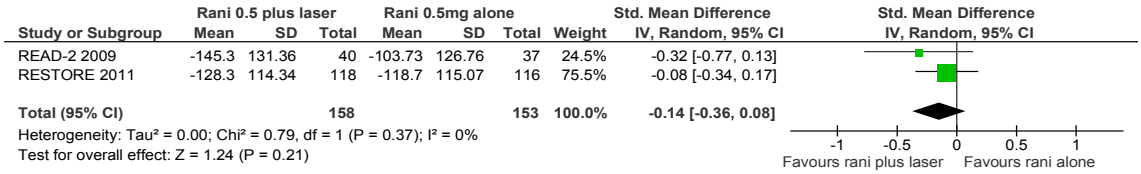
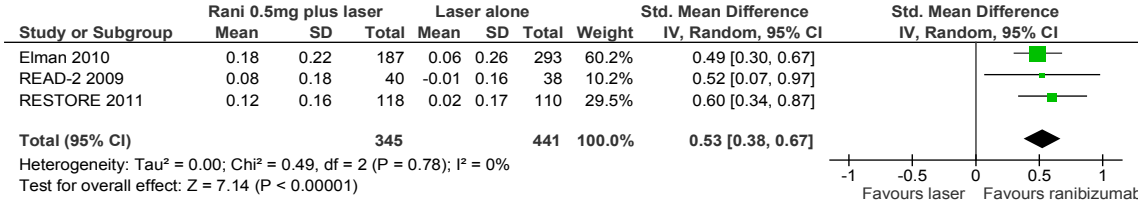
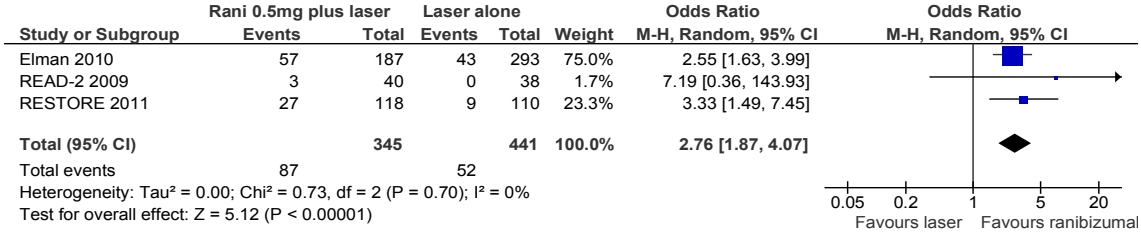


Figure 4 Ranibizumab 0.5mg plus laser versus laser alone

4.1 Mean change in BCVA



4.2 Proportion with >15 letter gain



4.3 CMT

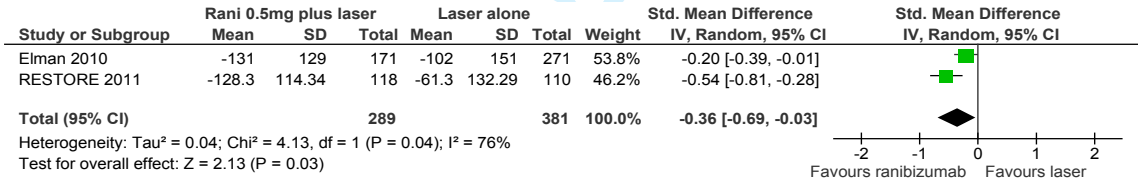


Figure 5 Pegaptanib 0.3mg versus sham injection

5.1 Proportion with >15 letter gain

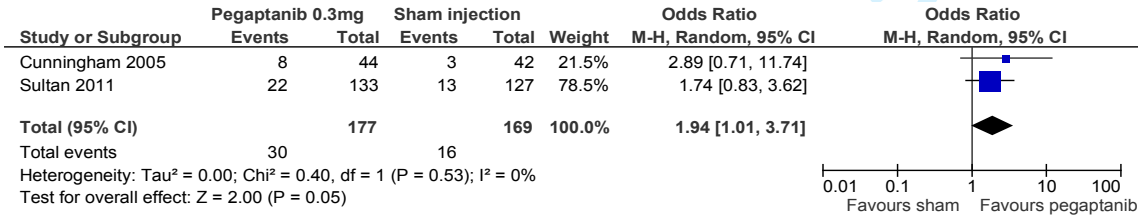


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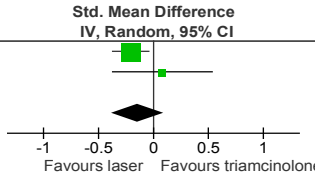
Figure 6 Triamcinolone 4mg versus laser alone

6.1 Mean change in BCVA

Study or Subgroup	Triamcinalone 4mg alone Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ip 2008	-0.06	0.44	254	0.02	0.34	330	78.2%	-0.21 [-0.37, -0.04]
Lam 2007	-0.7	10.7	38	-1.6	11.5	37	21.8%	0.08 [-0.37, 0.53]
Total (95% CI)			**292**			**367**	**100.0%**	**-0.14 [-0.38, 0.09]**

Heterogeneity: Tau² = 0.01; Chi² = 1.36, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.22 (P = 0.22)



6.2 Proportion with >15 letter gain

Study or Subgroup	Triamcinalone 4mg alone Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ip 2008	43	254	59	330	95.6%	0.94 [0.61, 1.44]
Lam 2007	2	38	2	37	4.4%	0.97 [0.13, 7.29]
Total (95% CI)		**292**		**367**	**100.0%**	**0.94 [0.61, 1.43]**
Total events	45		61			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)

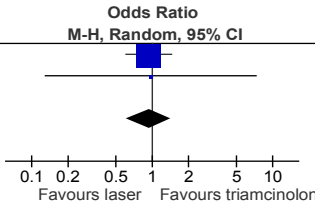
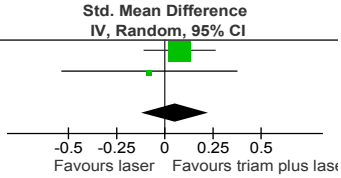


Figure 7 Triamcinolone 4mg plus laser versus laser alone

7.1 Mean change in BCVA

Study or Subgroup	Triam 4mg plus laser Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Elman 2010	0.08	0.26	186	0.06	0.26	293	85.9%	0.08 [-0.11, 0.26]
Lam 2007	0.7	10.7	38	1.6	11.5	37	14.1%	-0.08 [-0.53, 0.37]
Total (95% CI)			**224**			**330**	**100.0%**	**0.05 [-0.12, 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)



7.2 Proportion with >15 letter gain

Study or Subgroup	Triam 4mg plus laser Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Elman 2010	39	186	43	293	94.7%	1.54 [0.96, 2.49]
Lam 2007	2	38	2	37	5.3%	0.97 [0.13, 7.29]
Total (95% CI)		**224**		**330**	**100.0%**	**1.50 [0.94, 2.40]**
Total events	41		45			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)

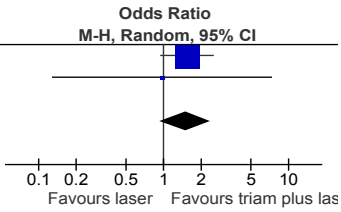


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Table 1: List of excluded studies

Study	Reason
Active comparator trials	
Cho 2010[87]	Single dose
DRCRN 2010 (Googe 2010)[88]	<6 mths f/u
Faghihi 2008[89]	Single dose
Figueroa 2008[90]	Single dose
Isaac 2012[91]	Single dose
Paccola 2008[92]	Single dose
Prager 2011[93]	<25 pts per arm
Ozturk 2011[94]	Non-RCT
Marey 2011[95]	<6 mths
Shahin 2010[96]	Single dose
Pegaptanib	
Loftus 2011[97]	Quality of life data.
Ranibizumab	
Ferrone 2011[98]	<25 pts per arm
Bevacizumab	
Solaiman 2010[99]	Single dose
DRCRN –Scott 2007[100]	<25 pts per arm
Lee 2011[101]	Non-RCT
Isaac 2012[91]	Single dose
Trimacinolone	
Audren 2006a[102]	Single dose (dosing study)
Audren 2006b[103]	Single dose
Avitabile 2005[104]	Mixed RVO and DMO
Bandello 2004[105]	Case report + PDR
Bonini 2005[106]	Single dose injection technique
Cellini 2008[107]	Single injection PSTI
Cardillo 2005[108]	Single injection PSTI
Chung 2008[109]	Single injection PSTI
Dehghan 2008[110]	Single dose
DRCRN -Chew 2007[111]	<25 pts per arm
Gil 2011[112]	<25 pts per arm
Entezari 2005[113]	<6 months
Hauser 2008[114]	Single dose
Jonas 2006[115]	Single dose
Joussen 2007[116]	Study protocol
Avci 2006[117]	Anaesthetic technique
Kang 2006[118]	Single dose
Kim 2008[119]	Single injection and CME
Lam 2007b[120]	Single injection
Lee 2009[121]	Single injection
Maia 2009[122]	Single dose
Massin 2004[123]	Single dose
Mohamed 2009[124]	Post-hoc analysis
Nakamura 2004[125]	Single dose
Spandau 2005[126]	Single dose
Tunc 2005[127]	<6 months

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Verma 2004[128]	Single dose
Wickremasinghe 2008[129]	Single dose
Yalcinbayir 2011[130]	Single dose
Dexamethasone	
Haller 2010[131]	<6 months
Haller 2009[132]	<25pts per arm
Kuppermann 2007 [133]	Mixture of macular oedema causes
Boyer 2011[134]	Non-randomised
Fluocinolone	
Campochiaro 2010[135]	<25pts per arm
Diclofenac	
Elbendary 2011 [71]	<35pts per arm

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Table 2: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Anti-VEGFs							
Ranibizumab							
READ-2 Study [28,47]	Unclear	Unclear	Unclear	Yes (91.3% completion)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Juvenile Diabetes Research Foundation, Genentech Inc.
RESOLVE Study (Massin 2010)[36]	Yes	Yes	Yes (patients and outcome assessors)	Yes (82% completion in sham arm, 90.2% with ranibizumab)	Yes	Comparison groups similar at baseline; power analysis unclear	Novartis Pharma, Switzerland
RESTORE Study (Mitchell 2011)[24]	Yes	Unclear	Yes (patients, outcome assessors)	Yes (87.3 to 88.3% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Novartis Pharma, Switzerland
RISE and RIDE (Nguyen 2012)[38]	Yes	Yes	Yes (patients, treating physician masked to assigned dose of ranibizumab)	Yes (2 year study completed by 83.3% of patients in RISE and by 84.6% in RIDE)	Yes	Comparison groups similar at baseline; ITT analysis; power analysis carried out (power adequate for primary endpoint)	Genentech Inc.
Bevacizumab							
BOLT Study (Michaelides 2010)[23,52]	Yes	Unclear	Partial (outcome assessors, not patients)	Yes (97.5% completion)	Yes	Comparison groups similar at baseline (except laser group had longer duration of clinically significant DMO); power analysis carried out (power adequate for VA changes)	Moorfields Special Trustees, National Institute for Health Research
Faghihi 2010[53]	Yes	Unclear	Yes (patient	Yes (100% completion)	Yes	Comparable groups at baseline	Not specified

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Lam 2009[35]	Yes	Yes	Yes (patients and technicians assessing BCVA, OCT and IOP)	Yes (92.3% follow-up at 6 months)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	supported in part by the Action for Vision Eye Foundation Hong Kong (charity)
Pegaptanib							
Cunningham 2005 / Adamis 2006[39,57]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (95% completion)	Yes	Comparison groups similar at baseline; acknowledge lack of power to detect differences between doses of pegaptanib	Eyetech Pharmaceuticals Inc., New York, and Pfizer Inc., New York
Sultan 2011[40]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (69.9 to 73.8% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Pfizer Inc., New York
Aflibercept							
Da Vinci 2010 [30,58]	Unclear (predetermined randomization scheme)	Unclear	Yes (patients)	Yes (85% completion)	Yes	Comparison groups similar at baseline, power calculation completed	Regeneron Pharmaceuticals, Inc., New York
Steroids							
Dexamethasone							
Haller 2010[59]	Yes	Unclear	Yes (patients to dexamethasone dose, outcome assessors)	Yes (92% completion)	Yes	Comparison groups similar at baseline; power analysis carried out, but study not powered to detect differences in subgroups	Oculex Pharmaceuticals Inc.
Fluocinolone							
FAME Study (Campochiaro 2011)[29,60]	Unclear	Unclear	Partial (patients, masking of outcome assessment not mentioned)	Yes (drop-out rate 19.0 to 22.7%)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Alimera Sciences Inc., Atlanta, Georgia; Psivida Inc., Watertown, Massachusetts

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Pearson 2011[43]	Yes	Unclear	Third party masked design (patient and investigator not masked)	No losses to follow-up	Yes	Demographic characteristics were similar between implant and SOC groups; power calculation done, study adequately powered.	Bausch & Lomb Inc, Rochester, New York
Triamcinolone							
DRCR Network 2008 [22,61,63,64]	Yes	Unclear	Partial (patients to triamcinolone dose, outcome assessors not formally masked but generally not aware of participant's study group)	Yes (81 to 86% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services
Gillies 2006 / 2007 / 2009 / Sutter 2004[32,136-138]	Yes	Yes	Yes (patients, outcome assessors)	Yes (91% completion intervention, 83% control)	Yes	Comparison groups similar at baseline (but limited demographic data); power analysis carried out (power adequate for VA changes)	Sydney Eye Hospital Foundation and Juvenile Diabetes Research Foundation, New York
Gillies 2011[33]	Yes	Yes	Yes (patients, outcome assessors)	Yes (84.5% completion)	Yes	power analysis carried out (power adequate for VA changes)	National Health and Medical Research Council, Canberra, Australia, and the Sydney Eye Hospital Foundation, Sydney, Australia
Lam 2007[34]	Yes	Yes	Partial (outcome assessors)	No losses to follow-up	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	Action for Vision Foundation, Hong Kong
Ockrim 2008/Sviprasad 2008[42,62]	Yes	Unclear	Unclear	Yes (94% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Special Trustees of Moorfields Eye Hospital
Active comparator trials							

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Ahmadieh 2008[31]	Yes	Yes	Yes (patients and outcome assessors)	Unclear	Yes	CMT lower in control group at baseline ($p<0.05$), other baseline values similar; power analysis carried out (power adequate for CMT changes)	Not reported
DRCR Network [21,46]	Yes	Unclear	Yes (patients, except deferred laser group; outcome assessors); masking discontinued after the first year	Yes (1 year completion for 91-95% of eyes)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and Human Services; Ranibizumab provided by Genentech, triamcinolone provided by Allergan Inc.; companies also provided funds to defray the study's clinical site costs
Lim 2012[55]	Yes	Unclear	Yes (investigators only)	Yes (7.5% drop out after enrollment)	Yes	Groups similar at baseline. The bevacizumab group received more injections.	Not reported
Soheilian [37,41]	Yes	Yes	Yes (patients and outcome assessors)	Unclear (36 week completion for 76 to 88%)	Yes	CMT significantly lower and VA significantly better in MPC group at baseline, other baseline values similar; power analysis carried out (power adequate for VA changes)	Ophthalmic Research Centre, Labbafinejad Medical Center, Tehran

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Table 3: Ranibizumab trials

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
READ-2 Study (Nguyen 2009 / Nguyen 2010)[28,47] **USA** Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months, 2 year extension [no relevant outcomes as IVR received by all groups by that time, no safety outcomes for 2 year data]	**N:** 126 eyes of 126 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO, BCVA 20/40 to 20/320, CMT ≥250 µm, HbA1c ≥6% within 12 months before randomization; expectation that scatter laser photocoagulation not required for 6 months **Exclusion criteria:** contributing causes to reduced BCVA other than DMO, focal/grid laser within 3 months, intraocular steroid within 3 months, intraocular VEGF antagonist within 2 months **Age:** 62 years **Sex:** 52 to 69% female **Diabetes type:** not reported **HbA1c:** 7.39 to 7.77% **Baseline VA:** ETDRS letter score 24.85 to 28.35 **Baseline CMT:** excess foveal thickness 198.75 to 262.52 µm **Comorbidities:** not reported	**Group 1 (IVR, n=42 eyes):** IV injections of 0.5 mg ranibizumab at baseline, 1, 3, and 5 months **Group 2 (L, n=42 eyes):** focal/grid laser at baseline and 3 months if CMT ≥250 µm **Group 3 (IVRL, n=42 eyes):** IV injections of 0.5 mg ranibizumab at baseline and 3 months, followed by focal/grid laser treatment 1 week later **Regimen for all groups:** after 6 months, patients could receive IV injections of ranibizumab no more than every 2 months or focal/grid laser no more than every 3 months if CMT ≥250 µm **Laser** Modified ETDRS protocol was used	**At 6 months** **BCVA (ETDRS):** ***IVR*** +7.24 (**BCVA (letters)**); 0.0003 vs L (**p**) ***L*** -0.43 ***IVRL*** +3.80; NS vs IVR or L **plus ≥3 lines** ***IVR*** 22%; <0.05 vs L ***L*** 0 ***IVRL*** 8% **CMT (OCT):** ***IVR*** -106.3 (**CMT (µm)**); all <0.01 vs baseline, NS for elimination of ≥50% excess foveal thickness between groups (**p**) ***L*** -82.8 ***IVRL*** -117.2
READ-3 Study (Do 2012) **USA**[50] **Design:** phase 2, 2-arm RCT **Follow-up:** 6 months	**N:** 152 eyes **Inclusion criteria:** NR **Exclusion criteria:** NR **Age:** NR **Sex:** NR **Diabetes type:** NR **HbA1c:** NR **Baseline VA:** Mean BCVA Snellen equivalent 20/63 in the 2.0 mg group and 20/80 in the 0.5 mg group **Baseline CST (central subfield thickness):** 432 µm in the 2.0 mg group and 441 µm in the 0.5 mg group **Comorbidities:** NR	**Group 1 (IVR2.0, n=NR):** monthly injections **Group 2 (IVR0.5, n=NR):** monthly injections After month 6, eyes evaluated and additional ranibizumab injections given on an as needed basis if DMO still present on OCT.	**At 6 months:** **BCVA** ***IVR2.0*** +7.46 (**Mean BCVA letters gain**); NR (**p**) ***IVR0.5*** +8.69; NR **CST** ***IVR2.0*** -163.86 µm (**CST reduction**); NR ***IVR0.5*** -169.27 µm; NR

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
RESOLVE Study (Massin 2010)[36] Multicenter international **Design:** 3-arm placebo-controlled RCT **Follow-up:** 12 months	**N:** 151 eyes of 151 patients **Inclusion criteria:** >18 years, type 1 or 2 DM, clinically significant DMO, BCVA 20/40 to 20/160, HbA1c <12%, decreased vision attributed to foveal thickening from DMO, laser photocoagulation could be safely withheld in the study eye for at least 3 months after randomization **Exclusion criteria:** unstable medical status, panretinal laser photocoagulation performed within 6 months before study entry, previous grid/laser photocoagulation except patients with only mild laser burns at least 1000 µm from the centre of the fovea performed >6 months previously **Age:** 63 to 65 (range 32 to 85) years **Sex:** 43.1 to 49.0% female **Diabetes type:** 96.1 to 98.0% type 2 DM **HbA1c:** 7.3 to 7.6 (range 5.3 to 11.1) % **Baseline VA:** ETDRS letter score 59.2 to 61.2 SD9.0 to 10.2 **Baseline CMT:** 448.9 to 459.5 SD102.8 to 120.1 µm **Comorbidities:** not reported	**Group 1 (IVR0.3, n=51 eyes):** 0.3 mg (0.05 ml) IV ranibizumab, 3 monthly injections (dose up to 0.6 mg, see below) **Group 2 (IVR0.5, n=51 eyes):** 0.5 mg IV (0.05 ml) ranibizumab, 3 monthly injections (dose up to 1.0 mg, see below) **Group 3 (C, n=49 eyes):** sham treatment, 3 monthly injections **Regimen for all groups:** after month 1, the injection dose could be doubled if CMT remained >300 µm or was >225 µm and reduction in retinal oedema from previous assessment was <50 µm; once injection volume was 0.1 ml it remained that for subsequent injections; if treatment had been withheld for >45 days, subsequent injections restarted at 0.05 ml; 68.6% of dose doubling with ranibizumab, 91.8% with sham; 34.7% of rescue laser photocoagulation in sham group, 4.9% in ranibizumab group	**At 12 months** **BCVA (ETDRS):** ***IVR0.3*** **BCVA (letters)** +11.8 SD6.6 **p** <0.0001 vs C ***IVR0.5*** +8.8 SD11.0 <0.0001 vs C ***C*** -1.4 SD14.2 **change ≥10 letters** ***IVR0.3*** gain 72.5% loss 0 <0.0001 vs C ***IVR0.5*** gain 49.0% loss 9.8% 0.001 vs C ***C*** gain 18.4% loss 24.5% **CMT (OCT):** ***IVR0.3*** **CMT (µm)** -200.7 SD122.2 **p** <0.0001 vs C ***IVR0.5*** -187.6 SD147.8 <0.0001 vs C ***C*** -48.4 SD153.4
RESTORE Study (Mitchell 2011/ Mitchell 2012)[24,49] Multicenter international **Design:** 3-arm RCT **Follow-up:** 12 months	**N:** 345 eyes of 345 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, HbA1c ≤10%, visual impairment due to DMO (eligible for laser treatment), stable medication for management of diabetes, BCVA ETDRS letter score 39 to 78 **Exclusion criteria:** concomitant eye conditions that could affect VA, active intraocular inflammation or infection, uncontrolled glaucoma in either eye, panretinal laser photocoagulation within 6 months or focal/grid laser photocoagulation within 3 months prior to study entry, history of stroke, hypertension. **Age:** 62.9 to 64.0 SD8.15 to 9.29 years **Sex:** 37.1 to 47.7% female **Diabetes type:** 86.4 to 88.8% type 2 DM **HbA1c:** not reported	**Group 1 (IVR, n=116 eyes):** 0.5 mg IV ranibizumab plus sham laser (median injections 7 (range 1 to 12), median sham laser treatments 2 (range 1 to 5)) **Group 2 (IVRL, n=118 eyes):** 0.5 mg IV ranibizumab plus active laser (median injections 7 (range 2 to 12), median laser treatments 1 (range 1 to 5)) **Group 3 (L, n=111 eyes):** laser treatment plus sham injections (median sham injections 7 (range 1 to 12), median laser treatments 2 (range 1 to 4)) **Regimen for all groups:** 3 initial monthly injections, followed by retreatment schedule; 1 injection per month if stable VA not reached;	**At 12 months** **BCVA (ETDRS):** ***IVR*** **BCVA (letters)** +6.1 SD6.43 **p** <0.0001 vs L ***IVRL*** +5.9 SD7.92 <0.0001 vs L ***L*** +0.8 SD8.56 **BCVA change categories** ***IVR*** plus ≥10: 37.4% loss ≥10: 3.5% <0.0001 vs L ***IVRL*** plus ≥10: 43.2% loss ≥10: 4.2% <0.0001 vs L ***L*** plus ≥10: 15.5% loss ≥10: 12.7% **CMT (OCT):**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	Baseline VA: ETDRS letter score 62.4 to 64.8 SD9.99 to 11.11 **Baseline CMT:** 412.4 to 426.6 SD118.01 to 123.95 **Comorbidities:** not reported	**Laser** retreatments in accordance with ETDRS guidelines at intervals no shorter than 3 months from previous treatment	**CMT (µm)** / **p** ***IVR*** -118.7 SD115.07 / 0.0002 vs L ***IVRL*** -128.3 SD114.34 / <0.0001 vs L ***L*** -61.3 SD132.29
REVEAL Study (Ohji 2012) Japan Multicenter[48] **Design:** phase III double-masked RCT **Follow-up:** 12 months	**N:** 396 patients **Inclusion criteria:** NR **Exclusion criteria:** NR **Age:** 61.1 years **Sex:** NR **Diabetes type:** 98.7% with type 2 diabetes **HbA1c:** 7.5% **Baseline VA:** 58.6 letters **Baseline CMT:** 421.9 µm **Comorbidities:** NR	**Group 1 (IVR 0.5 + sham laser, n=133):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA **Group 2 (IVR 0.5+ active laser, n=132):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA **Group 3 (sham injection + active laser, n=131):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA Active/sham laser photocoagulation performed according to ETDRS guidelines at ≥3 month intervals.	**At 12 months BCVA:** **Mean average change from baseline to month 1 to 12** / **p** ***IVR + sham laser*** +5.9 / vs laser <0.0001 ***IVR + laser*** +5.7 / vs laser <0.0001 ***Laser + sham*** +1.4 **Mean change from baseline to month12 in BCVA and CRT** ***IVR + sham laser*** +6.6; -148.0 µm / vs C <0.0001 ***IVR + laser*** +6.4; -163.8 µm / vs C <0.0001 ***Laser + sham*** +1.8; -57.1 µm
RISE Study (Brown 2011/Nguyen 2012)[38,139] USA Multicenter **Design:** 3-arm double-blind sham-controlled RCT **Follow-up:** 24 months	**N:** 377 eyes of 377 patients **Inclusion criteria:** ≥18 years, type 1 or 2 diabetes, BCVA 20/40 to 20/320, DMO CMT ≥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 or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction **Age:** 61.7 to 62.8 SD8.9 to 10.0 (range 21 to 87) years **Sex:** 41.6 to 48% female	**Group 1 (IVR0.3, n=125 eyes):** 0.3 mg IV ranibizumab **Group 2 (IVR0.5, n=125 eyes):** 0.5 mg IV ranibizumab **Group 3 (C, n=127 eyes):** sham injection **Regimen for all groups:** monthly injections; need for macular rescue laser assessed monthly starting at month 3	**At 24 months BCVA:** **plus ≥15 letters** / **p** ***IVR0.3*** 44.8% / <0.0001 vs C ***IVR0.5*** 39.2% / =0.0002 vs C ***C*** 18.1% **Loss of <15 letters** ***IVR0.3*** 97.6% / =0.0086 vs C ***IVR0.5*** 97.6% / =0.0126 vs C ***C*** 89.8%

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	Diabetes type: type 1 or 2 **HbA1c:** 7.7% SD 1.4 to 1.5; ≤8% (65 to 68.3%); >8% (31.7% to 35%) **Baseline VA:** Mean ETDRS letter score 54.7 to 57.2; ≤20/200 (7.9 to 13.6%); >20/200 but <20/40 (72.4 to 72.8%); ≥20/40 (13.6 to 19.7%) **Baseline CMT:** 463.8 to 474.5 µm **Comorbidities:** History of smoking 46.4 to 51.2%		**Snellen equivalent of 20/40 or better** ***IVR0.3*** 60.0% <0.0001 vs C ***IVR0.5*** 63.2% <0.0001 vs C ***C*** 37.8% **Mean BCVA gain (letters)** ***IVR0.3*** +12.5 SD14.1 <0.0001 vs C ***IVR0.5*** +11.9 SD12.1 <0.0001 vs C ***C*** +2.6 SD13.9 **CFT:** **Mean change from baseline** **p** ***IVR0.3*** -250.6 SD212.2 <0.0001 vs C ***IVR0.5*** -253.1 SD183.7 <0.0001 vs C ***C*** -133.4 SD209.0
RIDE study (Boyer 2011/Nguyen 2012)[38,140] **USA** Multicentre **Design:** 3-arm double-blind sham-controlled RCT **Follow-up:** 24 months	**N:** 382 eyes **Inclusion criteria:** ≥18 years, type 1 or 2 diabetes, BCVA 20/40-20/320 and DMO CMT ≥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 or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction **Age:** 61.8 to 63.5 (range 22 to 91) years **Sex:** 37 to 49.1% female **Diabetes type:** type 1 or 2 **HbA1c:** 7.6 SD1.3 to 1.5; ≤8% (65.8 to 67.5%); >8% (32.5 to 34.2%) **Baseline VA:** Mean ETDRS letter score 56.9 to 57.5	**Group 1 (IVR0.3, n=125 eyes):** 0.3 mg IV ranibizumab **Group 2 (IVR0.5, n=127 eyes):** 0.5 mg IV ranibizumab **Group 3 (C, n=130 eyes):** sham injection **Regimen for all groups:** Patients were eligible for rescue macular laser starting at Month 3	**At 24 months** **BCVA:** **More than 15 letters** **p** ***IVR0.3*** 33.6% <0.0001 vs. C ***IVR0.5*** 45.7% <0.0001 vs. C ***C*** 12.3% **Less than 15 letters** ***IVR0.3*** 1.6% >0.05 vs C ***IVR0.5*** 3.9% <0.05 vs. C ***C*** 8.5% **Snellen equivalent of 20/40 or better** ***IVR0.3*** 54.4% =0.0002 vs C

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)		
	Baseline CMT: 447.4 to 482.6 µm **Comorbidities:** history of smoking 33.6 to 51.6%		***IVR0.5***	62.2%	<0.0001 vs C
			C	34.6%	
				Mean BCVA gain (letters)	
			IVR0.3	+10.9 SD10.4	<0.0001vs C
			IVR0.5	+12.0 SD14.9	<0.0001 vs. C
			C	+2.3 SD14.2	
			CMT:		
				Mean change from baseline	**p**
			IVR0.3	-259.8 SD169.3	<0.0001 vs C
			IVR0.5	-270.7 SD201.6	<0.0001 vs C
			C	-125.8 SD198.3	

Abbreviations: BCVA – best corrected visual acuity, CMT – central macular thickness, DM – diabetes mellitus, DMO – diabetic macular oedema, DP – diastolic pressure, DR – diabetic retinopathy, HR QoL – health-related quality of life, IOP – intraocular pressure, IQR – interquartile range, IV – intravitreal, NEI VFQ-25 – National Eye Institute Visual Function Questionnaire-25, NPDR – nonproliferative diabetic retinopathy, NR – not reported, OCT – optical coherence tomography, PDR – proliferative diabetic retinopathy, PRP – panretinal photocoagulation, RCT – randomized controlled trial, SD – standard deviation, SP – systolic pressure, VA – visual acuity, VEGF – vascular endothelia growth factor, vs – versus, CSME – clinically significant macular oedema, MLT/MPC – macular laser therapy/macular photocoagulation, IVR – intravitreal ranibizumab, IVB – intravitreal bevacizumab, IVP – intravitreal pegaptanib, IVVTE – intravitreal VEGF Trap Eye, C - control, DIL - dexamethasone followed by laser, DDS - dexamethasone, SRFA – fluocinolone, SOC – standard of care, IVT - intravitreal triamcinolone, L – laser, IVTL intravitreal triamcinolone plus laser **Notes:** injections are intravitreal unless otherwise noted

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Table 4: Bevacizumab studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
BOLT Study (Michaelides 2010/ Rajendram 2012)) [23,52,85] **UK** **Design:** 2-arm RCT **Follow-up:** 12 months	**N:** 80 eyes of 80 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, BCVA in the study eye 35 to 69 ETDRS letters at 4 m (≥6/60 or ≤6/12), center-involving clinically significant DMO with CMT ≥270 µm; media clarity, papillary dilation and cooperation sufficient for adequate fundus imaging; a least 1 prior macular laser therapy; IOP <30 mmHg; fellow eye BCVA ≥3/60; fellow eye received no anti-VEGF in past 3 months and no expectation of such therapy **Exclusion criteria:** (ocular for study eye) macular ischemia, macular oedema due to causes other than DMO, coexistent ocular disease affecting VA or DMO, any treatment for DMO in prior 3 months, PRP within 3 months prior to randomization or anticipated, PDR, HbA1c >11.0%, medical history of chronic renal failure; any thromboembolic event within 6 months prior to randomization, unstable angina, evidence of active ischemia on ECG; major surgery within 28 days of randomization or planned; participation in an investigational drug trial; systemic anti-VEGF or pro-VEGF treatment within 3 months of enrollment; pregnancy, lactation; intraocular surgery within 3 months of randomization; aphakia; uncontrolled glaucoma; significant external ocular disease **Age:** 64.2 SD8.8 years **Sex:** 31% female **Diabetes type:** 90% type 2 DM, 10% type 1 DM **HbA1c:** 7.5 to 7.6 SD1.2 to 1.4% **Baseline VA:** ETDRS letter score 54.6 to 55.7 SD8.6 to 9.7 **Baseline CMT:** 481 to 507 SD121 to 145 µm **Comorbidities:** 19% mild NPDR (level 35), 46% moderate NPDR (level 43), 19% moderately severe NPDR (level 47), 13% severe NPDR (level 53), 3% moderate PDR (level 65), 79 to 88% phakic	**Group 1 (MLT, n=38 eyes):** modified ETDRS macular laser therapy; reviewed every 4 months up to 52 weeks; retreatment performed if clinically indicated by ETDRS guidelines (median 4 laser treatments) **Group 2 (IVB, n=42 eyes):** 1.25 mg (0.05 ml) IV bevacizumab at baseline, 6 and 12 weeks; subsequent IVB injections (up to 52 weeks) guided by an OCT-based retreatment protocol (median 13 injections) **Laser** Modified ETDRS protocol, retreatment by ETDRS guidelines	**At 24 months** **BCVA (ETDRS):** **BCVA.mean (SD) p** ***MLT*** -0.5 (10.6) ***IVB*** +8.6 (9.1) 0.005 vs MLT **BCVA gain categories (letters)** ***MLT*** gaining ≥10: 7%; losing >15: 4% ***IVB*** gaining ≥10: 49% 0.001 vs MLT; losing >15: 32% 0.004 vs MLT **CMT (OCT):** **CMT (µm, quartiles) p** ***MLT*** -118 SD171 ***IVB*** -146 SD122 0.62 vs MLT •

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td>Lam 2009[35]
Hong Kong

Design: 2-arm RCT
Follow-up: 6 months</td><td>N: 52 eyes of 52 patients
Inclusion criteria: ≥18 years, type 1 or 2 DM, clinically significant DMO (slit-lamp biomicroscopy, ETDRS criteria; leakage confirmed by fluorescein angiography, CMT ≥250 µm on OCT), BCVA ≥1.3 ETDRS logMAR units; only patients with diffuse DMO recruited
Exclusion criteria: macular oedema due to reasons other than diabetes, significant media opacities, macular ischemia of ≥1 disk area, vitreomacular traction, PDR, aphakia, glaucoma or ocular hypertension, previous anti-VEGF treatment, intraocular surgery except uncomplicated cataract extraction (but > 6 months prior), focal DMO, any laser procedure within previous 4 months, subtenon or intravitreal triamcinolone injection within 6 months, pregnancy.
Age: 65.3 SD8.9 years
Sex: 46.2% female
Diabetes type: not reported
HbA1c: 7.5 SD1.0%
Baseline VA: 0.61 SD0.29 logMAR
Baseline CMT: 466 SD127 µm
Comorbidities: not reported</td><td>Group 1 (IVB1.25, n=26 eyes): 1.25 mg bevacizumab (0.05 ml)
Group 2 (IVB2.5, n=26 eyes): 2.5 mg bevacizumab (0.1 ml)
Regimen for all groups: 3 monthly IV injections, topical 0.5% levofloxacin 4x/day for up to 2 weeks after each injection</td><td>At 6 months
BCVA (ETDRS chart):
<table><tr><th></th><th>BCVA (logMAR)</th><th>p</th></tr><tr><td>IVB1.25</td><td>0.11 SD0.31 [+5.5 letters]</td><td>0.018 vs baseline, NS vs IVB2.5</td></tr><tr><td>IVB2.5</td><td>0.13 SD0.26 [+6.5 letters]</td><td>0.003 vs baseline</td></tr></table>CMT (OCT):
<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVB1.25</td><td>96</td><td>0.002 vs baseline, NS vs IVB2.5</td></tr><tr><td>IVB2.5</td><td>74</td><td>0.013 vs baseline</td></tr></table>Subgroups:
For patients with previous DMO treatment (mainly laser): no significant reduction in CMT at 6 months (452 µm at baseline to 416 µm at 6 months, p=0.22); no significant improvement in BCVA (0.66 logMAR at baseline to 0.56 logMAR at 6 months [+5 letters], p=0.074)</td></tr>
<tr><td>Faghihi 2010[53]
Iran

Design: 2-arm RCT
Follow-up: 6 months</td><td>N: 80 eyes of 40 patients
Inclusion criteria: Bilateral non-tractional CSME, 10/10> V.A≥ 1/10, Controlled blood pressure.
Exclusion criteria: Advanced or advanced active PDR, Significant cataract, Glaucoma, History of recent vascular accident (e.g, MI, CVA), Previous treatment of CSME or PDR, or pharmacotherapy for CSME, macular ischemia and uncontrolled hypertension.
Age: 57.7±8 years.
Sex: 27.5% females
Diabetes type: NR
HbA1c: 8.42±1.82 g/dl
Baseline VA: 0.326 to 0.409 (SD 0.279 to 0.332)
Baseline CMT: 277 um to 287 um (SD 78 to 98)
Comorbidities: not reported</td><td>Group 1 (IVB, n= 40 eyes): 1.25mg bevacizumab
Group 2 (IVB+MPC, n= 40 eyes): 1.25mg bevacizumab
Regimen for all groups: Eyes examined every two months and if evidence of CSME IVB was injected. mean of the number of IVB injections in IVB group and IVB+MPC group were 2.23±1.24 and 2.49±1.09 respectively.</td><td>At 6 months
Mean change in BCVA (ETDRS chart):
<table><tr><th></th><th>BCVA (logMAR)</th><th>p</th></tr><tr><td>IVB</td><td>0.138</td><td><0.05 vs baseline</td></tr><tr><td>IVB+MPC</td><td>0.179</td><td><0.05 vs baseline</td></tr></table>
no statistically significant difference between the two groups
CMT (OCT):
<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVB</td><td>-39</td><td><0.05 vs baseline</td></tr><tr><td>IVB+MPC</td><td>-39</td><td><0.05 vs baseline</td></tr></table>
no statistically significant difference between the two groups</td></tr>
</table>

Abbreviations: See table 2

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Table 5: Pegaptanib and aflibercept studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Pegaptanib			
Cunningham 2005 / Adamis 2006 [39,57] **USA** **Design:** 4-arm phase II RCT **Follow-up:** 36 weeks	**N:** 172 eyes of 172 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO involving the center of the macula with corresponding leakage from microaneurysms, retinal telangiectasis, or both; clear ocular media, BCVA letter scores between 68 and 25 in the study eye and at least 35 in the fellow eye; IOP ≤23 mmHg, focal photocoagulation could be safely deferred for 16 weeks; no ECG abnormalities, no major serological abnormalities **Exclusion criteria:** history of panretinal or focal photocoagulation; neodymium:yttrium–aluminum–garnet laser or peripheral retinal cryoablation in previous 6 months; any ocular abnormality interfering with VA assessment or fundus photography; vitreoretinal traction; vitreous incarceration; retinal vein occlusion involving the macula; atrophy/scarring/fibrosis or hard exudates involving the center of the macula; history of intraocular surgery within previous 12 months, myopia of ≥8 diopters, axial length of ≥25mm, likelihood of requiring panretinal photocoagulation within following 9 months; cataract surgery within 12 months; active ocular or periocular infection; previous therapeutic radiation to the eye, head, or neck;; known serious allergies to fluorescein dye; HbA1c ≥13%, pregnancy **Age:** 61.3 to 64.0 SD9.3 to 10.1 years **Sex:** 45 to 55% female **Diabetes type:** 5 to 10% IDDM **HbA1c:** 7.1 to 7.7 SD1.2 to 1.6 **Baseline VA:** letter score 55.0 to 57.1 SD9.1 to 11.5 **Baseline CMT:** 423.2 to 476.0 µm **Comorbidities:** not reported	**Group 1 (IVP0.3, n=44 eyes):** 0.3 mg IV pegaptanib (90 µl) (median 5 injections (range 1 to 6)) **Group 2 (IVP1, n=44 eyes):** 1 mg IV pegaptanib (90 µl) (median 6 injections (range 3 to 6)) **Group 3 (IVP3, n=42 eyes):** 3 mg IV pegaptanib (90 µl) (median 6 injections (range 1 to 6)) **Group 4 (C, n=42 eyes):** sham injection (median 5 injections (range 1 to 6)) **Regimen for all groups:** injections at baseline, week 6 and week 12; thereafter, additional injections administered every 6 weeks at the discretion of the investigators if judged indicated (maximum of 6 injections up to week 30); laser photocoagulation allowed after week 13 if judged indicated by the study-masked ophthalmologist (25% for IVP0.3, 30% for IVP1, 40% for IVP3, 48% for C)	**At 36 weeks** **BCVA:** **BCVA (letters)** / **p** ***IVP0.3*** +4.7 / 0.04 vs C ***IVP1*** +4.7 / 0.05 vs C ***IVP3*** +1.1 / NS vs C ***C*** -0.4 **plus ≥10 letters** ***IVP0.3*** 34% / 0.003 vs C ***IVP1*** 30% ***IVP3*** 14% ***C*** 10% **CMT (OCT):** **CMT (µm, 95% CI)** / **p** ***IVP0.3*** -68.0 (-118.9 to -9.88) / 0.02 vs C ***IVP1*** -22.7 (-76.9 to +33.8) / NS vs C ***IVP3*** -5.3 (-63.0 to +49.5) / NS vs C ***C*** +3.7 Subgroups: • of 16 participants with retinal neovascularization at baseline, 8 of 13 (62%) in the pegaptanib groups and 0 of 3 in the sham group had regression of neovascularization at 36 weeks
Sultan 2011[40] Multicenter international **Design:** 2-arm placebo-controlled RCT	**N:** 260 eyes of 260 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO involving the center of the macula not associated with ischemia, CMT ≥250 µm, BCVA letter score 65 to 35, IOP ≤21 mmHg, clear ocular media **Exclusion criteria:** any abnormality other than DMO affecting VA assessment, vitreomacular traction; yttrium-aluminium-garnet laser, peripheral retinal cryoablation, laser retinopexy for retinal tears, focal or	**Group 1 (IVP, n=133 eyes):** 0.3 mg IV pegaptanib sodium (mean number of injections 12.7 SD4.6) **Group 2 (C, n=127 eyes):** sham injection (mean number of injections 12.9 SD4.4)	**At 1 year** **BCVA (ETDRS):** **BCVA (letters)** / **p** ***IVP*** +5.2 / <0.05 vs C ***C*** +1.2 **plus ≥10**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Follow-up: 2 years (primary efficacy endpoint at 1 year)	grid photocoagulation within prior 16 weeks; panretinal photocoagulation <6 months before baseline or likely to be needed within 9 months; significant media opacities; intraocular surgery in prior 6 months; pathologic high myopia; prior radiation in region of study eye; history of severe cardiac or peripheral vascular disease, stroke in prior 12 months, major surgery in prior 1 month, treatment in prior 90 days with any investigational agent or with bevacizumab for any nonocular condition, HbA1c ≥10% or signs of uncontrolled diabetes, hypertension, known relevant allergies; pregnant or lactating **Age:** 62.3 to 62.5 SD9.3 to 10.2 years **Sex:** 39 to 46% female **Diabetes type:** 6.3 to 7.5% type 1 DM, 92.5 to 93.7% type 2 DM **HbA1c:** 42.5 to 45.9% <7.6%, 54.1 to 57.5% >7.6% **Baseline VA:** letter score 57.0 to 57.5 SD8.1 to 8.9 **Baseline CMT:** 441.6 to 464.6 SD135.5 to 148.5 µm **Comorbidities:** not reported	**Regimen for all groups:** injections every 6 weeks up to week 48 (9 injections); at investigator determination (ETDRS criteria), laser photocoagulation could be performed at week 18, with possible repeat treatment at a minimum of 17 weeks later (maximum 3 treatments per year) (laser treatments in 25.2% of IVP group and 45% of C group); in year 2, injections as judged necessary	**letters** ***IVP*** 36.8% 0.0047 vs C ***C*** 19.7% **Retinopathy:** **increase in degree by ≥2 steps** ***IVP*** 4.1% 0.047 vs C ***C*** 12.4% **decrease in degree by ≥2 steps** ***IVP*** 10.2% NS vs C ***C*** 3.1% **CMT (OCT):** **decrease in CMT** ***IVP*** ≥25%: 31.7% NS s C ≥50%: 14.6% ***C*** ≥25%: 23.7% ≥50%: 11.9% **At 2 years** **BCVA (ETDRS):** **BCVA (letters) p** ***IVP*** +6.1 <0.01 vs C ***C*** +1.3 **plus ≥10 letters** ***IVP*** 38.3% NS vs C ***C*** 30.0% **Retinopathy:** **increase in degree by ≥2 steps** ***IVP*** 6.3% NS vs C ***C*** 13.8% **decrease in degree by ≥2 steps** ***IVP*** 16.3% 0.03 vs C ***C*** 3.8% **CMT (OCT):** **decrease in CMT** ***IVP*** ≥25%: 40.4% NS vs C ≥50%: 19.2%

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
			C ≥25%: 44.6% ≥50%: 26.1% **QoL:** • NEI VFQ-25: between group differences not significant at 54 weeks; at 102 weeks, significantly greater improvement in composite score and subscales distance vision activities, social functioning and mental health with pegaptanib • EQ-5D: no significant differences between groups in EQ-5D scores at weeks 54 or 102

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Aflibercept			
DA VINCI 2010 (Do 2011) Multicenter[30,58] **Design:** 5-arm phase II RCT **Follow-up:** 24 weeks	**N:** 221 eyes of 221 patients **Inclusion criteria:** aged >18 years and diagnosed with type 1 or 2 diabetes mellitus, with DMO involving the central macula defined as CRT (>250 um in the central subfield. Participants were required to have BCVA letter score at 4 m of 73 to 24. 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:** history of vitreoretinal surgery; panretinal 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; proliferative diabetic retinopathy (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 visual acuity or require medical or surgical intervention during the study period: active iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT; history of idiopathicor autoimmune uveitis; structural damage to the center of the macula that is likely to preclude improvement in visual acuity after the resolution of macular oedema; uncontrolled glaucoma or previous filtration surgery; infectious blepharitis, keratitis, scleritis, or conjunctivitis; or current treatment for serious systemic infection: 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 (even if the eye met all other entry criteria); or an ocular condition in the fellow eye with a poorer prognosis than the study eye **Age:** 60.7 to 64.0 years (SD 8.1 to 11.5) **Sex:** % female 35.6% to 47.6% **Diabetes type:** % type 2, 88.6% to 97.7% **HbA1c:** 7.85 to 8.10 (SD 1.71 to 1.94) **Baseline VA:** 57.6 to 59.9 (SD 10.1 to 12.5) **Baseline CMT:** 426.1 um to 456.6 um (SD 111.8 to 152.4) **Co morbidities:** history of any cardiac disease was twice as common in the VEGF Trap-Eye groups compared with the laser group.	Trial of VEGF Trap-Eye (VTE), randomized on a 1:1:1:1:1 basis **Group 1 (IVVTE1, n=44 eyes):** IV VTE, 0.5 mg every 4 weeks **Group 2 (IVVTE2, n=44 eyes):** IV VTE, 2 mg every 4 weeks **Group 3 (IVVTE3, n=42 eyes):** IV VTE, 2 mg for 3 initial months then every 8 weeks **Group 4 (IVVTE4, n=45 eyes):** IV VTE, 2 mg for 3 initial months then as needed **Group 5 (L, n=44 eyes):** laser photocoagulation **Laser** Modified ETDRS protocol	**At 6 months** **BCVA (letters) / p** ***IVVTE1*** **+8.6** 0.005 vs L ***IVVTE2*** +11.4 <0.0001 vs L ***IVVTE3*** +8.5 0.008 vs L ***IVVTE3*** +10.3 0.0004 vs L ***L*** +2.5 **plus ≥10 letters** ***IVVTE1*** 50% NR ***IVVTE2*** 64% NR ***IVVTE3*** 43% NR ***IVVTE3*** 58% NR ***L*** 32% NR **CMT(um)** ***IVVTE1*** -144.6 0.0002 vs L ***IVVTE2*** -194.5 <0.0001 vs L ***IVVTE3*** -127.3 0.007 vs L ***IVVTE3*** -153.3 <0.0001 vs L ***L*** -67.9 **At 12 months** **BCVA (letters) / p** ***IVVTE1*** +11.0 ≤0.0001 vs L ***IVVTE2*** +13.1 ≤0.0001 vs L ***IVVTE3*** +9.7 ≤0.0001 vs L ***IVVTE3*** +12.0 ≤0.0001 vs L ***L*** -1.3 **plus ≥15 letters** ***IVVTE1*** 40.9% 0.0031 vs L ***IVVTE2*** 45.5% 0.0007 vs L ***IVVTE3*** 23.8% 0.1608 vs L ***IVVTE3*** 42.2% 0.0016 vs L ***L*** 11.4%

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)		
				plus ≥10 letters	
			IVVTE1	57%	0.0031 vs L
			IVVTE2	71%	0.0007 vs L
			IVVTE3	45%	0.1608 vs L
			IVVTE3	62%	0.0016 vs L
			L		
				CMT(µm)	
			IVVTE1	-165.4	< 0.0001 vs L
			IVVTE2	-227.4	< 0.0001 vs L
			IVVTE3	-187.8	< 0.0001 vs L
			IVVTE3	-180.3	< 0.0001 vs L
			L	-58.4	

Abbreviations: See table 2

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Table 6: Dexamethasone and fluocinolone studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Dexamethasone			
Callanan 2011USA[44] **Design:** 2-arm RCT **Follow-up:** 12 months	**N:** 253 eyes of 253 patients **Inclusion criteria:** diffuse DMO, CMT ≥275 µm, BCVA ≥34 and ≤70 letters **Exclusion criteria:** not reported **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (DIL, n=126 eyes):** dexamethasone IV implant followed by laser photocoagulation after 1 month (mean 1.6 implants; 78.6% completion) **Group 2 (L, n=127 eyes):** laser alone (79.5% completion) **Regimen for all groups:** if needed, patients were retreated with the dexamethasone implant at months 6 or 9, and with laser at months 4, 7, and 10; mean 2.2 laser treatments per patient **Laser protocol** not reported	**At 12 months** **BCVA:** **plus ≥10 l tters** — **p** ***DIL*** — 28% — NS vs L ***L*** — 24% • patients in DIL group had significantly greater increases in BCVA from baseline than patients in the laser group (p<0.05) at months 1 to 9 only **CMT (OCT):** • patients in DIL group had significantly greater mean reductions from baseline in CMT at months 1 and 6 only (p<0.001)
Haller 2010[59] **USA** Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months (180 days), primary outcome 3 months (90 days)	**N:** 171 eyes of 171 patients **Inclusion criteria:** ≥12 years, DMO persisting for ≥90 days after laser treatment or medical therapy, BCVA by ETDRS between 20/40 (67 letters) and 20/200 (35 letters) due to clinically detectable DMO; analysis includes only eyes with DMO associated with DR **Exclusion criteria:** history of vitrectomy in the study eye; use of systemic, periocular, or intraocular steroids within 30 days of enrollment; moderate or severe glaucoma in the study eye; poorly controlled hypertension (SP >160 mmHg or DP >90 mmHg); poorly controlled diabetes (HbA1c >13%) **Age:** 62.9 to 63.8 years SD10.2 to 12.0 **Sex:** 45.6 to 49.1% female **Diabetes type:** not reported **HbA1c:** 7.3 to 7.6% **Baseline VA:** letter score 54.4 to 54.7 SD9.96 to 11.88 **Baseline CMT:** 417.5 to 446.5 µm SD123.7 to 155.9 **Comorbidities:** 19 to 21% prior cataract extraction	**Group 1 (DDS350, n=57 eyes):** 350 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity **Group 2 (DDS700, n=57 eyes):** 700 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity **Group 3 (C, n=57 eyes):** no treatment **Regimen for all groups:** eyes demonstrating a VA loss of ≥5 letters could be treated with any other therapy (including laser photocoagulation and IV triamcinolone) (n=4 with photocoagulation or IV triamcinolone in the C group, n=2 in the DDS350 group, none in the DDS700 group)	**At 90 days** **BCVA (ETDRS):** **plus ≥10 letters** — **p** ***DDS350*** — 21% [graph] — NS vs C ***DDS700*** — 33% — 0.007 vs C ***C*** — 12% **CMT (OCT):** **CMT (µm)** — **p** ***DDS350*** — -42.57 SD95.96 — NS (p=0.07) vs C ***DDS700*** — -132.27 SD160.86 — <0.001 vs C ***C*** — +30.21 SD82.12 **At 180 days** **BCVA (ETDRS):** **plus ≥10 letters** — **p** ***DDS350*** — 20% [graph] — NS vs C ***DDS700*** — 33% [graph] — NS vs C ***C*** — 23% [graph]
Fluocinolone			

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
FAME Study (Campochiaro 2011/ Campochiaro 2012) [29,60] Multicenter international **Design:** 3-arm placebo-controlled RCT **Follow-up:** 24 months; abstract with 36 month outcomes	**N:** 956 eyes of 956 patients **Inclusion criteria:** DMO, CMT ≥250 µm despite at least 1 prior focal/grid macular laser photocoagulation treatment, BCVA ETDRS letter score between 19 and 68 (20/50 to 20/400) **Exclusion criteria:** glaucoma, ocular hypertension, IOP >21 mmHg, taking IOP lowering drops; laser treatment for DMO within 12 weeks of screening, any ocular surgery in the study eye within 12 weeks of screening; ocular or systemic steroid therapy; active ocular infection; pregnancy **Age:** 62.5 SD9.4 years **Sex:** 40.6% **Diabetes type:** 6.6% type 1 DM, 92% type 2 DM, 1.4% uncertain **HbA1c:** 7.8 SD1.59 % **Baseline VA:** ETDRS letter score 53.4 SD12.23 **Baseline CMT:** 469.0 SD164.78 µm **Comorbidities:** 47.1% cataract at baseline, 62.7 to 67.4% phakic	**Group 1 (SRFA0.2, n=375 eyes):** intravitreal insert releasing 0.2 µg/day fluocinolone acetonide (FA) (2, 3, or 4 treatments received by 21.3, 1.9 and 0.3%) **Group 2 (SRFA0.5, n=393 eyes):** intravitreal insert releasing 0.5 µg/day fluocinolone acetonide (2, 3, or 4 treatments received by 22.6, 2.5 and 0.3%) **Group 3 (C, n=185 eyes):** sham injection (2, 3, or 4 treatments received by 19.5, 2.7 and 1.6%) **Regimen for all groups:** patients could receive rescue focal/grid laser therapy any time after the first 6 weeks for persistent oedema (35.2 to 36.7% in FA groups, 58.9% control group, p<0.001); treatments were allowed every 3 months for persistent or recurrent oedema; patients eligible for another FA insert at 1 year if ≥5 letter reduction in BCVA or >50 µm CMT increase from best status	**At 24 months** **BCVA (ETDRS):** **BCVA (letters) / p** ***SRFA0.2*** +4.4 / 0.02 vs C ***SRFA0.5*** +5.4 / 0.017 vs C ***C*** +1.7 **plus ≥15 letters** ***SRFA0.2*** 29% / 0.002 SRFA vs C ***SRFA0.5*** 29% ***C*** 16% Subgroups: • BCVA benefits only in pseudophakic eyes (cataract surgery before or during the study), in phakic eyes, BCVA letter score was reduced by 5 (high dose) and 9 (low dose) from baseline at 24 months **CMT (optical coherence tomography):** **CMT (µm) / p** ***SRFA0.2*** -167.8 / 0.005 vs C ***SRFA0.5*** -177.1 / <0.001 vs C ***C*** -111.3 • effect maintained at 36 months **At 36 months** **plus ≥15 letters** ***SRFA0.2/ 0.5*** 28.7% / 0.018 SRFA vs C ***C*** 18.9%
Pearson 2011[43] **USA** Multicenter **Design:** 2-arm RCT **Follow-up:** 36 months	**N:** 196 patients **Inclusion criteria:** persistent or recurrent unilateral or bilateral DMO with retinal thickening involving fixation of ≥1 disc area in size, ETDRS visual acuity of ≥20 letters (20/400) to ≤68 letters (20/50) and ≥1 macular laser treatment in the study eye more than 12 weeks prior to enrollment **Exclusion criteria:** Ocular surgery within 3 months prior to enrolment, uncontrolled IOP within the past 12 months while on ≥1 antiglaucoma medication, IOP of ≥22 mmHg at screening while on ≥1 antiglaucoma medication, peripheral retinal detachment in the area of implantation or media	**Group 1 (SRFA, n= 127):** 0.5 mg sustained release fluocinolone acetonide intravitreal implant **Group 2 (SOC, n= 69):** standard of care – either repeat laser or observation **Laser** ETDRS protocol	**At 3 years** **BCVA:** **gain ≥15 letters / p** ***SRFA*** 31% / NS ***SOC*** 20% **loss ≥15 letters** ***SRFA*** 17% / NS ***SOC*** 14% **CMT:**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	opacity precluding diagnosis of status in the study eye **Age:** 61.4-62.7 years **Sex:** 41.7-42% female **Diabetes type:** 62.3-70% on insulin **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported		**Mean change in baseline CMT** / **p** ***SRFA*** -86 / **NS** ***SOC*** -110

Abbreviations: See table 2

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Table 7: Triamcinolone studies

<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr>
<td>DRCR Network 2008 (Ip 2008a / 2008b / Beck 2009 / Bressler 2009)[22,61,63,64]
USA
Multicenter

Design: 3-arm RCT
Follow-up: 2 years, additional 3 year follow-up</td>
<td>N: 840 eyes of 693 patients
Inclusion criteria: >18 years, type 1 or 2 DM, study eye: (1) BCVA (E-ETDRS) between 24 and 73 (20/320 and 20/40), (2) retinal thickening due to DMO involving the center of the macula main cause for visual loss, (3) CMT ≥250 µm, (4) no expectation of scatter photocoagulation within 4 months
Exclusion criteria: any prior treatment with IV corticosteroids, peribulbar steroid injection within prior 6 months, photocoagulation for DMO within prior 15 weeks, panretinal scatter photocoagulation within prior 4 months, pars plana vitrectomy, history of open-angle glaucoma or steroid-induced
IOP elevation requiring IOP-lowering treatment, and IOP ≥25 mmHg
Age: 63 SD9 years
Sex: 49% female
Diabetes type: 95% type 2 DM, 5% type 1 DM
HbA1c: 7.9 SD1.8%
Baseline VA: ETDRS letter score 59 SD11 (~20/63)
Baseline CMT: 24 SD130 µm
Comorbidities: 21% pseudophakic, 2% ocular hypertension, 7% mild NPDR, 13% moderate NPDR, 40% moderately severe NPDR, 11% severe NPDR, 23.5% mild to moderate, 3% high risk PDR</td>
<td>Group 1 (IVT1, n=256 eyes):
1 mg IV triamcinolone (3.5 treatments)
Group 2 (IVT4, n=254 eyes):
4 mg IV triamcinolone (3.1 treatments)
Group 3 (L, n=330 eyes):
focal/grid photocoagulation (2.9 treatments)
Regimen for all groups:
retreatment protocol: where indicated, retreatment was performed within 4 weeks after the follow-up visit and no sooner than 3.5 months from the time of last treatment; eyes were generally retreated unless:
(1) little or no oedema involving the center of the macula present and CMT ≤225 µm, (2) VA letter score ≥79 (20/25 or better), (3) substantial improvement in macular oedema since last treatment (e.g., ≥ 50% decrease in CMT), (4) clinically significant adverse effect from prior treatment, (5) additional treatment deemed futile (<5 letter improvement in VA letter score or lack of CMT reduction), and (6) for laser group, complete focal/grid photocoagulation already given, with no areas identified for which additional treatment was indicated
Laser Modified ETDRS protocol as used in prior DRCR.net protocols</td>
<td>At 2 years
BCVA (E-ETDRS):
<table>
<tr><th></th><th>BCVA (letters)</th><th>p</th></tr>
<tr><td>IVT1</td><td>-2 SD18</td><td>0.02 vs L
NS vs IVT4</td></tr>
<tr><td>IVT4</td><td>-3 SD22</td><td>0.002 vs L</td></tr>
<tr><td>L</td><td>+1 SD17</td><td></td></tr>
<tr><td></td><td>BCVA gain categories</td><td></td></tr>
<tr><td>IVT1</td><td>+10 or more: 25%
+9 to -9: 50%
-10 or more: 26%</td><td>0.03 vs L, NS vs IVT4</td></tr>
<tr><td>IVT4</td><td>+10 or more: 28%
+9 to -9: 44%
-10 or more: 28%</td><td>0.01 vs L</td></tr>
<tr><td>L</td><td>+10 or more: 31%
+9 to -9: 50%
-10 or more: 19%</td><td></td></tr>
</table>
Subgroups:
• similar results when considering only pseudophakic eyes or eyes with minimal cataract
• no substantially different results based on baseline VA, baseline CMT, history of focal/grid photocoagulation for DMO
• 3 year results consistent with 2 year results for BCVA and CMT

CMT (OCT):
<table>
<tr><th></th><th>CMT (µm)</th><th>p</th></tr>
<tr><td>IVT1</td><td>-86 SD167</td><td><0.001 vs L,
NS vs IVT4</td></tr>
<tr><td>IVT4</td><td>-77 SD160</td><td><0.001 vs L</td></tr>
<tr><td>L</td><td>-139 SD148</td><td></td></tr>
</table>
Progression of retinopathy:
<table>
<tr><th></th><th>2 yrs</th><th>3 yrs</th><th>p</th></tr>
<tr><td>IVT1</td><td>29%</td><td>35%</td><td></td></tr>
<tr><td>IVT4</td><td>21%</td><td>30%</td><td><0.05 vs L</td></tr>
</table>
</td>
</tr>
</table>

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			L 31% 37%
Gillies 2006 / 2007 / 2009 / Sutter 2004 [32,136-138] **Australia** **Design:** 2-arm placebo-controlled RCT **Follow-up:** 2 years, additional 3-year follow-up	**N:** 69 eyes of 43 patients **Inclusion criteria:** patients with persistent (≥3 months after adequate laser treatment) DMO involving the central fovea, BCVA in the affected eye ≤6/9 **Exclusion criteria:** uncontrolled glaucoma, loss of vision due to other causes, systemic treatment with >5 mg prednisolone (or equivalent) daily, intercurrent severe systemic disease, any condition affecting follow-up or documentation **Age:** 62.4 to 69.6 SD9.2 to 12.5 years **Sex:** 52% female **Diabetes type:** not reported **HbA1c:** 7.63 to 8.28 SD1.12 to 1.41 **Baseline VA:** ETDRS letter score 60.5 to 61.3 SD11.9 to 13.2 **Baseline CMT:** 439 to 444 SD101 to 125 µm **Comorbidities:** 25% pseudophakic	**Group 1 (IVT, n=34 eyes):** 4 mg (0.1 ml) IV triamcinolone acetonide (mean 2.6 injections over 2 years) **Group 2 (C, n=35 eyes):** placebo injection (subconjunctival saline injection) (mean 1.8 injections over 2 years) **Regimen for all groups:** retreatment considered at each visit as long as treatments were at least 6 months apart (retreatment if VA decreased ≥5 letters from previous peak value and persistent CMT >250 µm), if no improvement after 4 weeks, further laser treatment was applied (n=1 laser treatment in intervention group, n=16 in placebo group, p=0.0001) **Laser** ETDRS protocol	**At 2 years** **BCVA (ETDRS):** ***IVT*** +3.1 (0.01 vs C) ***C*** -2.9 **CVA gain categories** ***IVT*** +10 or more: 21%; +9 to -9: 70%; -10 or more: 9% (0.013 vs C) ***C*** +10 or more: 12%; +9 to -9: 62%; -10 or more: 25% **CMT (OCT):** ***IVT*** -125 (0.009 vs C, difference between groups 59 µm (95% CI 15, 104)) ***C*** -75
Gillies 2011[33] **Australia** **Design:** 2-arm RCT **Follow-up:** 24 months	**N:** 84 eyes of 54 patients **Inclusion criteria:** DMO involving the central fovea, CMT ≥250 µm, BCVA 17 to 70 letters (~20/40 to 20/400), laser treatment could be safely delayed for 6 weeks without significant adverse effects **Exclusion criteria:** uncontrolled glaucoma, controlled glaucoma but with a glaucomatous visual field defect, loss of vision resulting from other causes, systemic treatment with >5 mg prednisolone (or equivalent) daily, retinal laser treatment within 4 months, intraocular surgery within 6 months, concurrent severe systemic disease, any condition affecting follow-up or documentation **Age:** 65.4 to 66.9 SD8.9 to 9.5 years **Sex:** 38.1 to 47.6% female **Diabetes type:** not reported **HbA1c:** 7.81 to 8.02 SD1.44 to 1.63 % **Baseline VA:** letter score 55.2 to 55.5 SD11.3 to 12.5 **Baseline CMT:** 482.1 to 477.4 SD122.7 to 155.5 µm **Comorbidities:** not reported	**Group 1 (IVTL, n=42 eyes):** 4 mg (0.1 ml) IV triamcinolone acetonide followed by laser treatment (at least 1 retreatment in 2nd year in 69%) **Group 2 (L, n=42 eyes):** sham injection followed by laser treatment (at least 1 retreatment in 2nd year in 45%) **Regimen for all groups:** retreatment with injection followed by laser at discretion of chief investigator, with at least 6 weeks between treatments; no retreatment if: (1) investigator considered the macula nearly flat and CMT <300 µm; (2) VA was ≥79 letters (20/25) or VA had improved by ≥5 letters compared with the best VA after treatment or baseline acuity; (3) laser	**At 24 months** **BCVA (ETDRS):** ***I TL*** +0.76 (NS vs L) ***L*** -1.49 **BCVA gain categories** ***IVTL*** +10 or more: 36%; +9 to -9: 31%; -10 or more: 33% (0.049 vs L) ***L*** +10 or more: 17%; +9 to -9: 59%; -10 or more: 24% Subgroups: • BCVA outcome not significantly affected by cataract surgery **CMT (OCT):** **CMT (µm) p**

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		treatment was considered by the investigator as inappropriate or had no potential for improvement	***IVTL*** -137.1 NS vs L ***L*** -109.6
Kim 2010[45] **Korea** **Design:** 2-arm RCT **Follow-up:** 3 years	**N:** 86 eyes of 75 patients **Inclusion criteria:** diffuse DMO **Exclusion criteria:** not reported **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (IVT, n=38 eyes):** 4 mg IV triamcinolone (1.88 additional treatments, completion 68.1%) **Group 2 (IVTL, n=48 eyes):** macular laser photocoagulation 4 weeks after 4 mg IV triamcinolone (0.92 additional treatments, completion 77.1%) **Regimen for all groups:** additional treatment possible, criteria not mentioned **Laser protocol** not reported	**At 3 years** **BCVA:** not reported **Outcomes related to DMO:** **no DMO recurrence** **p** ***IVT*** 3.9% ***IVTL*** 24.3% 0.028 vs IVT **time DMO not present** ***IVT*** 10.33 months ***IVTL*** 19.88 months 0.027 vs IVT
Lam 2007[34] **Hong Kong** **Design:** 3-arm RCT **Follow-up:** 6 months (2 years planned)	**N:** 111 eyes of 111 patients **Inclusion criteria:** >18 years, type 1 or 2 DM, clinically significant DMO (ETDRS), CMT ≥250 µm **Exclusion criteria:** macular oedema due to causes other than diabetic maculopathy, signs of vitreomacular traction, proliferative diabetic retinopathy, aphakia, history of glaucoma or ocular hypertension, macular ischemia, any laser procedure within 3 months, ocular surgery within 6 months, significant media opacities **Age:** 64.7 to 67.2 SD8.2 to 10.3 years **Sex:** 42 to 59% female **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** ETDRS logMAR 0.64 to 0.72 SD0.34 to 0.36 **Baseline CMT:** 385 to 424 SD91 to 108 µm **Comorbidities:** 66 to 84% phakic eyes	**Group 1 (IVT, n=38 eyes):** 4 mg IV triamcinolone (no retreatments) **Group 2 (IVTL, n=36 eyes):** 4 mg IV triamcinolone followed by grid laser photocoagulation (ETDRS) (laser treatment once the macular oedema had reduced to <250 µm at the foveal center or at 1 to 2 months after injection, whichever was earlier) **Group 3 (L, n=37 eyes):** grid laser photocoagulation (n=3 retreatments) (no retreatments) **Regimen for all groups:** in case of recurrence or persistence of macular oedema, retreatment offered according to study group, at intervals no less than 4 months **Laser** ETDRS protocol	**At 6 months** **BCVA (ETDRS):** **BCVA improvement** **p** ***IVT*** -0.7 SD 10.7 log MAR plus ≥15 letters: 5% NS between groups ***IVTL*** -1.1 SD 10.8 log MAR plus ≥15 letters: 3% ***L*** -1.6 SD 11.5 log MAR plus ≥15 letters: 5% **CMT (OCT):** **CMT (µm)** **p** ***IVT*** 342 SD124 [-54] NS between groups, <0.01 vs baseline ***IVTL*** 307 SD181 [-116] <0.01 vs baseline ***L*** 350 SD169 [-35]

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<table>
<tr>
<td>Ockrim 2008 / Sivaprasad 2008 [42,62]
UK

Design: 2-arm RCT
Follow-up: 1 year</td>
<td>N: 88 eyes of 88 patients
Inclusion criteria: clinically significant DMO persisting ≥4 months, ≥1 previous laser treatment, BCVA 6/12 to 3/60, VA in fellow eye ≥3/60, duration visual loss <24 months
Exclusion criteria: significant macular ischemia, baseline IO >23 mmHg, glaucoma, coexistent renal disease, loss of VA due to other causes, previous vitrectomy, intraocular surgery within 3 months of study entry, previous inclusion in other DR trials, inability to return to follow-up, inability to give informed consent
Age: 62.3 to 64.8 SD7.5 to 10.1 years
Sex: 28.9 to 34.9% female
Diabetes type: 97.8 to 100% type 2 DM
HbA1c: 7 to 7.8 IQR6.5 to 8.7%
Baseline VA: ETDRS letter score 53.0 to 54.6 SD13.3 to 14.2
Baseline CMT: 410.4 to 413.4 SD127.8 to 134.1 µm
Comorbidities: 17.8 to 19.5% PDR, 13.3 to 18.6% pseudophakia, 15 to 17.8% posterior vitreous detachment</td>
<td>Group 1 (IVT, n=43 eyes): 4 mg IV triamcinolone (mean number of IVT injections 1.8 (range 1 to 3))
Group 2 (L, n=45 eyes): ETDRS laser photocoagulation (mean number of grid laser sessions 2.1 (range 1 to 3))
Regimen for all groups: patients retreated at 4 and 8 months if they had persistent macular oedema
Laser ETDRS protocol</td>
<td>At 12 months

BCVA (ETDRS):
<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>IVT</td><td>-0.2</td><td>NS vs L</td></tr><tr><td>L</td><td>+1.7</td><td></td></tr><tr><th></th><th>plus ≥15 letters</th><th></th></tr><tr><td>IVT</td><td>4.8%</td><td>NS vs L</td></tr><tr><td>L</td><td>12.2%</td><td></td></tr></table>
CMT (optical coherence tomography):
<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVT</td><td>-91.3</td><td>NS vs L</td></tr><tr><td>L</td><td>-63.7</td><td></td></tr></table></td>
</tr>
</table>

Abbreviations: See table 2

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Table 8: Trials assessing more than one drug

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Ahmadieh 2008[31] **Iran** **Design:** 3-arm placebo-controlled RCT **Follow-up:** 24 weeks	**N:** 115 eyes of 101 patients **Inclusion criteria:** eyes with clinically significant DMO unresponsive to previous macular laser photocoagulation (last session >3 months prior) **Exclusion criteria:** visual acuity ≥20/40; history of cataract surgery within past 6 months; prior intraocular injection or vitrectomy, glaucoma or ocular hypertension; PDR with high-risk characteristics; vitreous hemorrhage; significant media opacity; presence of traction on the macula; pregnancy; serum creatinine ≥3 mg/100 ml; monocular patients **Age:** 59.7 SD8.3 years (range 39 to 74) **Sex:** 50.5% female **Diabetes type:** not reported, 27.6% to 33.3% on insulin **HbA1c:** 9.35% to 10.06% **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** (percentage of eyes) 13.9% history of cataract surgery, 81.7% NPDR, 4.3% early PDR, 13.9% regressed PDR; no iris neovascularization	**Group 1 (IVB, n=41 eyes):** bevacizumab 1.25 mg (0.05 ml) **Group 2 (IVB/IVT, n=37 eyes):** combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone **Group 3 (C, n=37 eyes):** sham injection **Regimen for all groups:** 3 consecutive IV injections at 6-week intervals	**At 24 weeks** **BCVA (Snellen chart):** ***IVB*** -0.18 (-0.29, -0.08) [+9 letters (4, 14.5)] — 0.01 vs C, NS vs IVB/IVT ***IVB/ IVT*** -0.21 (-0.30, -0.12) [+10.5 letters (6, 15)] — 0.006 vs C ***C*** -0.03 (-0.08, 0.14) [+1.5 letters (-7, 4)] **CMT (OCT):** ***IVB*** -95.7 (-172.2, -19.3) — 0.012 vs C, NS vs IVB/IVT ***IVB/ IVT*** -92.1 (-154.4, -29.7) — 0.022 vs C ***C*** 34.9 (7.9, 61.9)
ATEMD 2011 (Oliveira Neto 2010 / 2011) [56] Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months **Note:** only 48.3% completion	**N:** 120 eyes of 120 patients **Inclusion criteria:** DMO, BCVA 20/40 to 20/400, CMT ≥275 µm **Exclusion criteria:** PDR, laser photocoagulation in previous 3 months, no IV corticosteroid or anti-VEGF in previous 3 months **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (IVB, n=NR eyes):** 1.25 mg (0.05 ml) of IV bevacizumab **Group 2 (IVT, n=NR eyes):** 4 mg (0.1 ml) of IV triamcinolone acetonide **Group 3 (IVB/IVT, n=NR eyes):** 1.25 mg (0.05 ml) of IV bevacizumab plus 4 mg (0.1 ml) of IV triamcinolone acetonide **Regimen for all groups:** monthly injections	**At 6 months** **BCVA:** • no significant difference between groups (between 1.7 and 2.3 lines gained in the different groups in 2010 report (n=18)) **CMT (OCT):** • CMT reduced in all 3 groups (between 17 and 33% reduction in the different groups in 2010 report (n=18)); no significant difference between groups
DRCR Network 2010 (Elman 2010, Elman 2011)[21,46] **USA** Multicenter	**N:** 854 eyes of 691 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM; study eye: (1) BCVA letter score 78 to 24 (20/32 to 20/320), (2) definite retinal thickening due to DMO assessed to be main cause of visual loss, (3) retinal thickness measured on time domain OCT ≥250 µm in central	**Group 1 (CPL, n=293 eyes):** sham injection plus prompt (within 3-10 days after injection) focal/grid photocoagulation **Group 2 (RPL, n=187 eyes):** 0.5 mg IV ranibizumab plus prompt focal/grid	**At 1 year** **BCVA (E-ETDRS Visual Acuity Test):** ***CPL*** +3 SD13 ***RPL*** +9 SD11 — <0.001 vs CPL

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Design: 4-arm placebo-controlled RCT **Follow-up:** 1-2 years; 2 years extension (Elman 2011) for consenting patients	subfield (2 study eyes per patient could be included if both were eligible at study entry) **Exclusion criteria:** (1) treatment for DMO within the prior 3 months, (2) panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, (3) major ocular surgery within the prior 4 months, (4) history of open-angle glaucoma or steroid-induced IOP elevation, requiring IOP-lowering treatment, (5) IOP ≥25 mmHg; systolic pressure >180 mmHg, diastolic pressure >110 mmHg; myocardial infarction, other cardiac event requiring hospitalization, cerebrovascular accident, transient ischemic attack, treatment for acute congestive heart failure within 4 months before randomization **Age:** median 62 to 64 years (25^{th}, 75^{th} centile 55 to 58, 69 to 70) **Sex:** 41 to 46% female **Diabetes type:** 6 to 9% type 1 DM, 89 to 92% type 2 DM, 2 to 3% uncertain **HbA1c:** median 7.3 to 7.5% (25^{th}, 75^{th} centile 6.5 to 6.7, 8.3 to 8.6) **Baseline VA:** letter score 63 SD12 (~20/63 SD2.4 lines) **Baseline CMT:** 405 SD134 µm **Comorbidities:** 60 to 67% prior treatment for DMO; 61 to 68% with NPDR, 26 to 36% with PDR or PDR scars	photocoagulation **Group 3 (RDL, n=188 eyes):** 0.5 mg IV ranibizumab plus deferred (≥24 weeks) focal/grid photocoagulation **Group 4 (TPL, n=186 eyes):** 4 mg IV triamcinolone plus prompt focal/grid photocoagulation **Regimen for all groups:** Baseline treatment 0.5 mg IV ranibizumab and 4 mg preservative free triamcinolone; study treatment every 4 weeks up to 12 weeks, then retreatment algorithm: 16 to 20 weeks, monthly retreatment unless 'success' criteria were met (visual acuity letter score ≥84 (20/20) or OCT central subfield thickness <250 µm); 24 to 48 weeks, patients subdivided (according to predefined criteria) into 'success', 'improvement', 'no improvement' or 'failure'; 'improvement' group continued treatment, other groups treated at investigator discretion; alternative treatment permitted if eye met criteria for 'failure' or 'futility'. In the case of retreatment, ranibizumab could be given as often as every 4 weeks, and triamcinolone every 16 weeks (with sham injections as often as every 4 weeks). Retreatment for focal/grid laser (after ≥13 weeks from previous treatment) if there was oedema involving or threatening the center of the macula and if complete laser had not been given; retreatment algorithms facilitated by web-based real-time data entry system. Median number of drug injections before 1 year visit was 8-9 for ranibizumab, 3 for triamcinolone, and 5 sham injections. Retreatment between 1 and 2 years	***RDL*** +9 SD12 <0.001 vs CPL ***TPL*** +4 SD13 NS vs CPL **BCVA gain categories (letters)** ***CPL*** +10 or more: 28%; +9 to -9: 59%; -10 or more: 13% ***RPL*** +10 or more: 50%; +9 to -9: 45%; -10 or more: 4% <0.001 vs CPL ***RDL*** +10 or more: 47%; +9 to -9: 51%; -10 or more: 3% <0.001 vs CPL ***TPL*** +10 or more: 33%; +9 to -9: 52%; -10 or more: 14% NS vs CPL Subgroups: • BCVA results in TPL group substantially better for pseudophakic eyes than for phakic eyes (comparable to results for RPL and RDL groups) (p not reported) • no difference in results according to prior treatment for DMO, baseline VA, baseline CMT, baseline level of retinopathy, focal or diffuse oedema **CMT (OCT):** ***CPL*** CMT (µm): -102 SD151; p: ***RPL*** -131 SD129 <0.001 vs CPL ***RDL*** -137 SD136 <0.001 vs CPL ***TPL*** -127 SD140 <0.001 vs CPL Subgroups: • pattern of CMT decrease similar for groups with CMT <400 µm and ≥400 µm at baseline • Significantly more patients with severe NPDR or worse improved by 2 levels or more in the ranibizumab groups (28%, no significant change in the other groups) **At 2 years (expanded results, Elman 2011)** **BCVA (E-ETDRS Visual Acuity Test):**

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr>
<td></td>
<td></td>
<td>(Elman 2011): median injections 2 in RPL group, 3 in RDL group; in TPL group 68% of eyes received at least 1 injection; at least one focal/grid laser sessions between 1 and 2 years: 51% CPL, 40% RPL, 29% RDL, 52% TPL
Laser Modified ETDRS protocol as used in prior DRCR.net protocols</td>
<td>
<table>
<tr><th></th><th>BCVA (letters)</th><th>p</th></tr>
<tr><td>CPL (n=211)</td><td>+3 SD15</td><td></td></tr>
<tr><td>RPL (n=136)</td><td>+7 SD13</td><td>0.03 vs CPL</td></tr>
<tr><td>RDL (n=139)</td><td>+9 SD14</td><td><0.001 vs CPL</td></tr>
<tr><td>TPL (n=142)</td><td>+2 SD19</td><td>NS vs CPL</td></tr>
<tr><td colspan="3">BCVA gain categories (letters)</td></tr>
<tr><td>CPL</td><td>+10 or more: 36%
+9 to -9: 52%
-10 or more: 13%</td><td></td></tr>
<tr><td>RPL</td><td>+10 or more: 44%
+9 to -9: 49%
-10 or more: 7%</td><td>NS vs CPL</td></tr>
<tr><td>RDL</td><td>+10 or more: 49%
+9 to -9: 48%
-10 or more: 3%</td><td>0.01 vs CPL</td></tr>
<tr><td>TPL</td><td>+10 or more: 41%
+9 to -9: 40%
-10 or more: 19%</td><td>NS vs CPL</td></tr>
</table>
CMT (OCT):
<table>
<tr><th></th><th>CMT (µm)</th><th>p</th></tr>
<tr><td>CPL</td><td>-138 SD149</td><td></td></tr>
<tr><td>RPL</td><td>-141 SD155</td><td>0.003 vs CPL</td></tr>
<tr><td>RDL</td><td>-150 SD143</td><td>0.01 vs CPL</td></tr>
<tr><td>TPL</td><td>-107 SD145</td><td>NS vs CPL</td></tr>
</table>
</td>
</tr>
<tr>
<td>Jorge 201
Brazil[51]

Design: Prospective RCT
Follow-up: 24 and 48 weeks [To date, 73% and 56% of patients completed 24 and 48 weeks respectively]</td>
<td>N: 63 eyes of 47 patients
Inclusion criteria: Refractory cener-involving DMO
Exclusion criteria: NR
Age: NR
Sex: NR
Diabetes type: NR
HbA1c: NR
Baseline VA: NR
Baseline CMT: NR
Comorbidities: NR</td>
<td>Group 1 (IVB 1.5 mg, n=NR): injections at baseline and monthly if CSFT (central subfield thickness) measured by SDOCT (spectral domain OCT) >275 µm.
Group 2 (IVR 0.5 mg, n=NR) : injections at baseline and monthly if CSFT >275 µm.</td>
<td>
At 48 weeks
BCVA
<table>
<tr><th></th><th>Mean BCVA reduction from baseline (logMAR)</th><th>p</th></tr>
<tr><td>IVB1.5</td><td>-0.21</td><td>vs baseline <0.05 at all-time points

vs IVR0.5: no significant difference at all time-points</td></tr>
<tr><td>IVR0.5</td><td>-0.21</td><td>vs baseline <0.05 at all time-points</td></tr>
</table>
</td>
</tr>
</table>

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td></td><td></td><td></td><td>vs IVB1.5: no significant difference at all time-points

CSFT
<table><tr><th></th><th>Mean CSFT reduction from baseline</th><th>p</th></tr><tr><td>IVB1.5</td><td>-129.6 µm</td><td>vs baseline <0.05 at all-time points

vs IVR0.5 no significant different at all-time points</td></tr><tr><td>IVR0.5</td><td>-137.9 µm</td><td>vs baseline <0.05 at all-time points

vs IVB1.5 no significant different at all-time points</td></tr></table></td></tr>
<tr><td>Lim 2012[55]
Korea

Design: 3-arm RCT
Follow-up: 12 months</td><td>N: 111 eyes of 105 patients
Inclusion criteria: eyes with clinically significant DMO based on ETDRS and DMO with central macular thickness of at least 300 µm by optical coherence tomography (OCT).
Exclusion criteria: unstable medical status, including glycemic control and blood pressure; any previous treatment for DMO, including intravitreal, sub-Tenon injection or macular photocoagulation, history of vitreoretinal surgery, uncontrolled glaucoma; proliferative diabetic retinopathy with active neovascularization, previous panretinal photocoagulation, presence of vitreomacular traction, history of systemic corticosteroids within 6 months, contraindications for bevacizumab or triamcinolone acetonide.
Age: 60.4 SD 7.4 (range 48 to 70) years
Sex: 52% female</td><td>Group 1 (IVB/IVT, n=36): IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks and IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of addition injection 1.28
Group 2 (IVB, n=38): IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks. Mean number of injections 2.54.
Group 3 (IVT, n=37): IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of injections 1.04

Unclear if rescue laser was available

IVB injections were repeated if CMT appeared >300 µm on OCT in at least 6-weeks in all three groups</td><td>At 12 months
<table><tr><th></th><th>BCVA (logMAR)</th><th>p</th></tr><tr><td>IVB/IVT</td><td>-0.15</td><td rowspan="3">0.088 (between groups)</td></tr><tr><td>IVB</td><td>-0.16</td></tr><tr><td>IVT</td><td>-0.16</td></tr></table><table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVB/IVT</td><td>-199</td><td rowspan="3">0.132 (between groups)</td></tr><tr><td>IVB</td><td>-179</td></tr><tr><td>IVT</td><td>-200</td></tr></table></td></tr>
</table>

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td></td><td>Diabetes type: NR
HbA1c: 7.2 SD 1.2 to 7.4 SD1.2
Baseline VA: 0.62 SD 0.23 to 0.65 SD 0.28 logMAR
Baseline CMT: 447 SD 110 to 458 SD 92 µm
Comorbidities: NR</td><td></td><td></td></tr>
<tr><td>Soheilian 2007 / Soheilian 2009/ Soheilian 2011/ Soheilian 2012
[37,41,54,141]
Iran

Design: 3-arm RCT
Follow-up: 36 weeks

[Soheilian 2007 reports 12 week results of the same trial, these were not considered here]</td><td>N: 150 eyes of 129 patients
Inclusion criteria: eyes with clinically significant DMO (ETDRS criteria)
Exclusion criteria: previous panretinal of focal laser photocoagulation, prior ocular surgery or injection, history of glaucoma or ocular hypertension, VA ≥20/40 or <20/300, iris neovascularization, high risk PDR, significant media opacity, monocularity, pregnancy, serum creatinine ≥3 mg/dL, uncontrolled DM
Age: 61.2 SD6.1 years
Sex: 47.3% female
Diabetes type: not reported
HbA1c: not reported
Baseline VA: 0.55 to 0.73 SD0.26 to 0.28 logMAR
Baseline CMT: 300 to 359 SD118 to 149 µm
Comorbidities: 94% NPDR, 6% early PDR</td><td>Group 1 (IVB, n=50 eyes): IV injection of bevacizumab 1.25 mg (0.05 ml) (retreatment IVB 14 eyes)
Group 2 (IVB/IVT, n=50 eyes): IV injection of combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone (retreatment IVB/IVT 10 eyes)
Group 3 (MPC, n=50 eyes): focal or modified grid laser (retreatment MPC 3 eyes)
Regimen for all groups:
Retreatments performed at 12 week intervals as required</td><td>At 36 weeks

BCVA (Snellen chart):
<table>
<tr><th></th><th>BCVA (logMAR), SD</th><th>p</th></tr>
<tr><td>IVB</td><td>-0.28 SD0.25
[+14 SD12.5 letters]</td><td>0.053 vs IVB/IVT or MPC</td></tr>
<tr><td>IVB/ IVT</td><td>-0.04 SD0.33
[+2 SD16.5 letters]</td><td>NS vs MPC</td></tr>
<tr><td>MPC</td><td>+0.01 SD0.27
[-0.5 SD13.5 letters]</td><td></td></tr>
<tr><td></td><td>Snellen line changes</td><td></td></tr>
<tr><td>IVB</td><td>+2 lines or more: 37.0%
stable within 2 lines: 59.3%
-2 lines or more: 3.7%</td><td>NS between groups</td></tr>
<tr><td>IVB/ IVT</td><td>+2 lines or more: 25.0%
stable within 2 lines: 54.2%
-2 lines or more: 20.8%</td><td></td></tr>
<tr><td>MPC</td><td>+2 lines or more: 14.8%
stable within 2 lines: 66.7%
-2 lines or more: 18.5%</td><td></td></tr>
</table>
CMT (OCT):
<table>
<tr><th></th><th>CMT (µm), SD</th><th>p</th></tr>
<tr><td>IVB</td><td>-56 SD140</td><td>0.044 vs baseline, NS between groups</td></tr>
<tr><td>IVB/ IVT</td><td>-5 SD113</td><td></td></tr>
<tr><td>MPC</td><td>-8 SD67</td><td></td></tr>
</table>
Subgroups:
• larger CMT reduction in subgroup with ≥400 µm at baseline (36 weeks: IVB -27.2 SD34.8%, IVB/IVT -8.8 SD35.9%, MPC -15.1 SD14.6%, p<0.001 versus baseline in IVB and MPC groups only)</td></tr>
</table>

Abbreviations: See table 2

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Table 9: Ranibizumab safety data

	READ-2 study[28,47]	RESOLVE study[36]	RESTORE study[24]	RISE study[38]	RIDE study[38]
Number of patients	IVR: n=42; L: n=42; IVRL: n=42	IVR0.3: n=51; IVR0.5: n=51; C: n=49	IVR: n=116; IVRL: n=118; L: n=111	IVR0.3: 125; IVR0.5: 126; C: 123	IVR0.3: 125; IVR0.5: 124; C: 127
Ocular adverse events					
Eye pain	NR	IVR0.3: n=9 (18%); IVR0.5: n=9 (18%); C: n=10 (20%)	IVR: n=13 (11%); IVRL: n=10 (8%); L: n=12 (11%)	IVR0.3: 26%; IVR0.5: 21%; C: 19%	IVR0.3: 8%; IVR0.5: 12.9%; C: 7.1%
Conjunctival hyperaemia	NR	NR	IVR: n=9 (8%); IVRL: n=6 (5%); L: n=6 (5%)	NR	NR
Conjunctival haemorrhage	NR	IVR0.3: n=10 (20%); IVR0.5: n=13 (25%); C: n=7 (14%)	IVR: n=8 (7%); IVRL: n=10 (8%); L: n=0	IVR0.3: 54%; IVR0.5: 52%; C: 32%	IVR0.3: 40.8%; IVR0.5: 50.0%; C: 31.5%
IOP increase	NR	IVR0.3: n=6 (12%); IVR0.5: n=15 (29%); C: n=1 (2%)	IVR: n=1 (<1%); IVRL: n=1 (<1%);	IVR0.3: 20%; IVR0.5: 14%; C: 2%	IVR0.3:15.2%;IVR0.5: 18.5%; C: 11%
Vitreous haemorrhage	IVR: n=1 (2%); L: n=4 (10%); IVRL: n=3 (7%)	IVR0.3: n=1 (2%); IVR0.5: n=0; C: n=0	NR	IVR0.3: 3.2%; IVR0.5: 3.2%; C: 13%	IVR0.3: 0.8%; IVR0.5: 2.4%; C: 15%
Substantial worsening of DMO	L: n=1 (2%)		NR	NR	NR
Retinal ischaemia	NR	IVR0.3: n=0; IVR0.5: n=1 (2%); C: n=0	NR	NR	NR
Retinal artery occlusion	NR	IVR0.3: n=0; IVR0.5: n=1 (2%); C: n=0	NR	NR	NR
Endophthalmitis	NR	IVR0.3: n=1 (2%); IVR0.5: n=1 (2%); C: n=0	NR	IVR0.3: 0.8%; IVR0.5: 0; C: 0	IVR0.3 + IVR0.5: 1.2%; C: 0%
Retinal detachment	NR	IVR0.3: n=0; IVR0.5: n=0; C: n=1 (2%)	NR	IVR0.3: 0.8%; IVR0.5: 0; C: 0.8%	IVR0.3 + IVR0.5: 0.4%; C: 0%
Neovascularisation	NR	NR	NR	IVR0.3: 0; IVR0.5: 0; C: 0.8%	IVR0.3: 0.8%; IVR0.5: 0.8%; C: 5.5%
Traumatic cataract	NR	NR	NR	IVR0.3: 0.8%; IVR0.5: 0.8%; C: 0	IVR0.3 + IVR0.5: 0.4%; C: 0%
Uveitis	NR	NR	NR	NR	IVR0.3 + IVR0.5: 0.4%; C: 0%
Macular oedema	NR	NR	NR	IVR0.3: 16.8%; IVR0.5: 20.6%; C: 21.1%	IVR0.3: 19.2%; IVR0.5: 13.7%; C: 20.5%
Retinal exudates	NR	NR	NR	IVR0.3: 19.2%; IVR0.5: 17.5%; C: 20.3%	IVR0.3: 16.0%; IVR0.5: 15.3%; C: 11.0%
Retinal haemorrhage	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 12.7%; C: 20.3%	IVR0.3: 15.2%; IVR0.5: 22.6%; C: 18.9%

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Cataract	NR	NR	NR	IVR0.3: 16.8%; IVR0.5: 11.9%; C: 14.6%	IVR0.3: 20.0%; IVR0.5: 23.4%; C: 23.6%
Vitreous detachment	NR	NR	NR	IVR0.3: 13.6%; IVR0.5: 11.1%; C: 15.4%	IVR0.3: 8.8%; IVR0.5: 12.9%; C: 15.0%
Ocular hyperemia	NR	NR	NR	IVR0.3: 15.2%; IVR0.5: 11.1%; C: 10.6%	IVR0.3: 3.2%; IVR0.5: 3.2%; C: 7.9%
Vitreous floaters	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 14.3%; C: 5.7%	IVR0.3: 7.2%; IVR0.5: 8.1%; C: 3.1%
Eye irritation	NR	NR	NR	IVR0.3: 10.4%; IVR0.5: 9.5%; C: 6.5%	IVR0.3: 5.6%; IVR0.5: 5.6%; C: 3.1%
Foreign body sensation in eyes	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 7.1%; C: 4.1%	IVR0.3: 8.0%; IVR0.5: 2.4%; C: 5.5%
Systematic adverse events					
Arterial thromboembolic events	Stroke in 1 pt (2%) in IVRL group- not related to study drug	IVR0.3: n=0; IVR0.5: n=3 (6%); C: n=2 (4%)	IVR: n=6 (5%); IVRL: n=1 (<1%); L: n=1 (<1%)	IVR0.3: 3.2% (n=1 stroke); IVR0.5: 7.9% (n=5 strokes); C: 7.3% (n=2 strokes)	IVR0.3: 1.6% (stroke), 5.6% (heart attack); IVR0.5: 2.4% (stroke), 2.4% (heart attack); C: 1.6% (stroke), 5.6% (heart attack)
Hypertension	NR	IVR0.3: n=4 (8%); IVR0.5: n=5 ((10%); C: n=5 (10%)	IVR: n=9 (8%); IVRL: n=6 (5%); L: n=9 (8%)	Serious IVR0.3: 0.8%; IVR0.5: 3.2%; C: 0.8%	Serious IVR0.3: 1.6%; IVR0.5: 1.6%; C: 0%
Non-ocular haemorrhage	NR	IVR0.3: n=1 (2%); IVR0.5: n=1 (2%); C: n=0	IVR: n=1 (<1%); IVRL: n=0; L: n=1 (<1%)	NR	NR
Proteinuria	NR	NR	IVR: n=1 (<1%); IVRL: n=1 (<1%); L: n=0	NR	NR
Deaths	1 (2%) due to CVA in IVRL group	NR	IVR: n=2 (2%); IVRL: n=2 (2%); L: n=2 (2%)	IVR0.3: 2.4%; IVR0.5: 4.0%; C: 0.8%	IVR0.3: 3.2%; IVR0.5: 4.8%; C: 1.6%

NR – not reported, IVR – intra-vitreal ranibizumab, IVRL – intra-vitreal ranibizumab plus laser, C – control, L – laser, IOP –intra-ocular pressure, DMO – diabetic macular oedema,

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Table 10: Bevacizumab safety

	BOLT study[23,52]	Lam 2009[35]	Faghihi 2010[53]
Number of patients	MLT: n=38; IVB: n=42	IVB1.25, n=26; IVB2.5, n=26	IVB 1.25 n= 40 IVB 1.25 plus MLT n=40
Ocular adverse events			**Not reported**
Loss of _15 or _30 ETDRS letters	MLT: n=1 transient, 3 at 24 month analysis; IVB: n=4 transient	No significant ocular events (IOP increase, retinal tear, retinal detachment, endophthalmitis); no significant difference in change in cataract scores between groups	
Vitreous haemorrhage	MLT: n=1; IVB: n=0		
Eye pain/irritation/watering during or after injection	MLT:n= 0; IVB: n=8		
Red eye after injection	MLT: n=0; IVB: n=8		
Endophthalmitis	NR		
Transient IOP increase	≥30 mm Hg - MLT: 0; IVB: n=4≥ 45 mm Hg – MLT: n=1; IVB: n=1		
Floaters after injection	MLT: n= 0; IVB: n=2		
Corneal epithelial defect	MLT:n=0; IVB:n=1		
Vitreomacular traction with macular oedema	MLT: n=1; IVB: n=0		
Systematic adverse events			
Anaemia	MLT: n=1; IVB: n=0	no systematic adverse effects (1 patient in 1.25 mg group with foot gangrene requiring amputation due to worsening diabetic neuropathy, considered unrelated to treatment)	
Vomiting after FFA	MLT: n=1; IVB: n=0		
Uncontrolled hypertension	MLT:n=0; IVB: n=1		
Polymyalgia rheumatica	MLT:n=0; IVB: n=1		
Intermittent claudication	MLT:n=0; IVB: n=1		
Gastroenteritis	MLT:n=0; IVB: n=1		
Fall	MLT:n=2; IVB: n=0		
Urinary tract infection	MLT:n=0; IVB: n=1		
Chest infection	MLT:n=0; IVB: n=1		
Headaches, dizziness, tiredness	MLT:n=1; IVB: n=0		
Bell palsy	MLT:n=1; IVB: n=0		
Admission for diabetic foot ulcer	MLT:n=1; IVB: n=1		
Admission for cholecystectomy	MLT:n=0; IVB: n=1		
Admission for fall/loss of consciousness	MLT:n=1; IVB: n=0		
Angina–hospital admission	MLT:n=1; IVB: n=0		
Cerebrovascular accident	MLT:n=1; IVB: n=0		
Myocardial infarction	MLT:n=0; IVB: n=2		
Coronary artery bypass graft	MLT:n=0; IVB: n=1		
Dyspnea, chest pain–admitted for hospital observation	MLT:n=0; IVB: n=1		

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DEATH	NR		

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Table 11: Pegaptanib safety

	Cunningham 2005/Adamis 2006[39,57]	Sultan 2011[40]
Number of patients	IVP0.3, n=44 eyes; IVP1, n=44 eyes; IVP3, n=42 eyes	IVP, n=133 eyes; C, n=127 eyes
Ocular adverse events		
Eye pain	Pegaptanib: 31%; C: 17%	IVP: 11.1%; C: 7.0%
Vitreous haemorrhage	Pegaptanib: 22%; C: 7%	IVP: 6.3%; C: 7.7%
Punctuate keratitis	Pegaptanib: 18%; C: 17%	IVP: 11.8%; C: 6.3%
Cataract	Pegaptanib: 13%; C: 10%	IVP: 8.3%; C: 9.2%
Eye discharge	Pegaptanib: 11%; C: 10%	NR
Conjunctival haemorrhage	Pegaptanib: 10%; C: 0%	IVP: 22.2%; C: 14.1%
Vitreous opacities	Pegaptanib: 9%; C: 5%	NR
Blurred vision	Pegaptanib: 7%; C: 5%	NR
Other vitreous disorder	Pegaptanib: 7%; C: 0%	NR
Other visual disturbance	Pegaptanib: 7%; C: 0%	NR
Culture-negative endophthalmitis	Pegaptanib: n=1	NR
IOP increase	NR	IVP: 17.4%; C: 6.3%
Retinal haemorrhage	NR	IVP: 6.3%; C: 10.6%
Retinal exudates	NR	IVP: 6.3%; C: 5.6%
Conjunctivitis	NR	IVP: 5.6%; C: 4.2%
Lacrimation increased	NR	IVP: 5.6%; C: 2.8%
Diabetic retinal oedema	NR	IVP: 11.1%; C: 17.6%
Macular oedema	NR	IVP: 9.7%; C: 11.6%
Systemic adverse events		
Non-ocular hypertension	NR	IVP: 13.9%; C: 9.9%
Cardiac disorders	NR	IVP: 6.9%; C: 5.6%
DEATHS	NR	IVP: n=4

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Table 12: aflibercept safety

	DA VINCI 2010[30,58]
Number of patients	IVVTE (all doses) n=175, laser n = 44
Ocular adverse events	
Conjunctival hemorrhage	At 6 months: Laser 18.2%, IVVTE 18.9% At 12 months: Laser 18.2%, IVVTE 26.9%
IOP increase	At 6 months: Laser 2.3%, IVVTE 9.7% At 12 months: Laser 2.3%, IVVTE 9.7%
Eye pain	At 6 months: Laser 4.5%, IVVTE 8.6% At 12 months: Laser 4.5%, IVVTE 13.7%
Ocular hyperaemia	At 6 months: Laser 4.5%, IVVTE 6.3% At 12 months: Laser 4.5%, IVVTE 7.4%
Vitreous floaters	At 6 months: Laser 4.5%, IVVTE 5.1% At 12 months: Laser 4.5%, IVVTE 6.9%
Endophthalmitis	At 6 months: Laser 0%, IVVTE 1.1% At 12 months: Laser 0%, IVVTE 1.1%
Uveitis	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: Laser 0%, IVVTE 0.6%
Diabetic retinal oedema	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 2.3%, IVVTE 4.6%
Visual acuity reduced	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 2.3%, IVVTE 0%
Vitreous hemorrhage	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 6.8%, IVVTE 0%
Corneal abrasion	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: Laser 0%, IVVTE 4.6%
Retinal tear	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: NR
Systematic events	
Hypertension	At 6 months: Laser 6.8%, IVVTE 9.7% At 12 months: Laser 0%, IVVTE 1.7%
Myocardial infarction	At 6 months: Laser 0%, IVVTE 1.1% At 12 months: Laser 0%, IVVTE 1.7%
Cerebrovascular event	At 6 months: Laser 0%, IVVTE1.1% At 12 months: Laser 2.3%, IVVTE 1.7%
Death	At 6 months: Laser 0%, IVVTE 1.7% At 12 months: Laser 2.3%, IVVTE 4.0%

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Table 13: Dexamethasone safety

	Callanan 2011[44]	Haller 2010[59]
Number of patients		
Ocular adverse events		
IOP elevation	DIL: 20% ($p<0.001$); 1% ≥10 mm Hg L: 1.6% ; 0% ≥10 mm Hg	
Cataract	NR	NR
Anterior chamber cells	NR	DDS350: 29.1%; DDS700: 26.4%; C: 1.8%
Anterior chamber flare	NR	DDS350: 27.3%; DDS700: 20.8%; C: 8.8%
Vitreous haemorrhage	NR	DDS350: 20.0%; DDS700: 22.6%; C: 5.3%
Eye pain	NR	DDS350: 18.2%; DDS700: 9.4%; C: 3.5%
Vitreous disorder	NR	DDS350: 20.0%; DDS700: 15.1%; C: 3.5%
Increased IOP	NR	DDS350: 14.5%; DDS700: 9.4%; C: 0%
Conjunctival haemorrhage	NR	DDS350: 14.5%; DDS700: 7.5%; C: 0%
Vitreous floaters	NR	DDS350: 7.3%; DDS700: 17.0%; C: 0%
		No significant differences in: reduced VA, eye irritation, abnormal sensation in eye, macular oedema, eye pruritus, retinal hemorrhage, DR, nonocular events

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Table 14: Fluocinolone safety

	FAME study (Campochiaro 2011/2012)[29,60]	Pearson 2011[43]
Number of patients		
Ocular adverse events		
IOP at 12 months	NR	NR
Progression of cataract	NR	NR
Cataract	NR	SRFA: 55.9%; SOC: 21.7%
Transient vitreous floaters	NR	NR
Transient subconjunctival haemorrhage	NR	NR
Cataract surgery	SRFA0.2: 41.1% (74.9% of those without cataract surgery at baseline, 80.0% at 36 months); SRFA0.5: 50.9% (84.5% of those without cataract surgery at baseline, 87.2% at 36 months); C: 7% (23.1% of those without cataract surgery at baseline, 27.3% at 36 months)	NR
Glaucoma	SRFA0.2: 1.6%; SRFA0.5: 2.3%; C: 0.5%	NR
Increased IOP	SRFA0.2: 3.2%; SRFA0.5: 3.3%; C: 0%	SRFA: 69.3%; SOC: 11.6%
IOP >30 mmHg at any point during 36 months	SRFA0.2: 18.4%; SRFA0.5: 22.9%; C: 4.3%	NR
Trabeculectomy	SRFA0.2: 2.1%; SRFA0.5: 4.8%; C: 0%	NR
Other glaucoma surgery	SRFA0.2: 1.3%; SRFA0.5: 1.3%; C: 0.5%	NR
Trabeculoplasty	SRFA0.2: 0.8%; SRFA0.5: 2.3%; C: 0%	NR
Vitreous haemorrhage	NR	SRFA: 40.2%; SOC: 18.8%
Abnormal sensation in eye	NR	SRFA: 37%; SOC: 11.6%
Macular oedema	NR	SRFA: 34.6%
Eye pain	NR	SRFA: 26.8%; SOC: 15.9%
Eye irritation	NR	SRFA: 22%; SOC: 10.1%
Increased lacrimation	NR	SRFA: 22%; SOC: 8.7%
Photophobia	NR	SRFA: 21.3%; SOC: 21.7%
Blurred vision	NR	SRFA: 21.3%; SOC: 15.9%
Vitreous floaters	NR	SRFA: 21.3%; SOC: 8.7%
Systemic adverse events		
Serious cardiovascular events	SRFA0.2: 12.0%; SRFA0.5: 13.2%; C: 10.3%	
Pruritus	NR	SRFA: 38.6%; SOC: 21.7%
DEATHS	NR	NR

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Table 15: Triamcinolone safety

	DRCR Network 2008 (Ip 2008a / Ip 2008b / Beck 2009 / Bressler 2009) [22,61,63,64]	Gillies 2006 / 2007 / 2009 / Sutter 2004[32,136-138]	Gillies 2011[33]	Kim 2010[45]	Lam 2007[34]	Ockrim 2008 / Sivaprasad 2008[42,62]
Number of patients						
Ocular adverse events						
	At 2 years (or 3 years when indicated)	At 2 years	-	Not reported	-	At 12 months
IOP ≥30 mm Hg	IVT1: n=22; IVT4: n=53; L: n=3	NR	NR		NR	IVT: IOP significantly higher than in L group (18.2 mm Hg, range 12 to 26 mm Hg); no cases of glaucoma
IOP >22 mm Hg	NR	NR	NR		IVT: 37% (p=0.002 vs. L); IVTL: 36% (p=0.002 vs. L); L: 5%	NR
IOP ≥10 mm Hg from baseline	IVT1: n=41; IVT4: n=85; L: n=12	NR	NR		NR	NR
IOP ≥5 mm Hg	NR	IVT: 68% (p=0.007 vs. C); C: 10%	NR		NR	NR
IOP lowering medication used	IVT1: n=31; IVT4: n=76; L: n=25	IVT: 44% (p=0.0002 vs. C); C: 3%	IVTL: 64% (P<0.001); L: 24%		NR	NR
Cataract surgery	IVT1: 23% (of those phakic at baseline, 46% by 3 years (p<0.001 between all groups); IVT4: 51% (of those phakic at baseline, 83% by 3 years); L: 13% (of those phakic at baseline, 31% by 3 years)	IVT: 56% (of phakic eyes over 3 years, p<0.001 vs. C); C: 8% (of phakic eyes over 3 years)			NR	NR
Ptosis	NR	NR	NR		NR	NR
Retinal detachment	IVT1: n=2; IVT4: n=4; L: n=2	NR	NR		None	NR
Retinal vein occlusion	IVT1: n=1; IVT4: n=2; L: n=3	NR	NR		NR	NR
Retinal artery occlusion	IVT1: n=0; IVT4: n=0; L: n=1	NR	NR		NR	NR
Anterior ischemic optic neuropathy	IVT1: n=1; IVT4: n=0; L: n=0	NR	NR		NR	NR
Vitrectomy	IVT1: n=26; IVT4: n=19; L: n=31	NR	NR		NR	NR
Open angle glaucoma	IVT1: n=2; IVT4: n=7; L: n=2	NR	NR		NR	NR

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Glaucoma filtering surgery	IVT1: n=0; IVT4: n=2; L: n=0	NR	NR		NR	NR
Laser trabeculoplasty	IVT1: n=0; IVT4: n=1; L: n=0	IVT: n=2; C: n=0	IVTL: n=1		NR	NR
Ciliary body destruction	IVT1: n=0; IVT4: n=1; L: n=0	NR	NR		NR	NR
Endophthalmitis	IVT1: n=0; IVT4: n=;0 L: n=0	(Infectious) IVT: n=1; C: NR	(Culture-negative) IVTL: n=1		None	(sterile) IVT: n=1
pseudoendophthalmitis	IVT1: n=0; IVT4: n=;0 L: n=0	NR	NR		NR	NR
Chemosis	NR	NR	NR		NR	NR
% increase in cataract scores	NR	NR	NR		IVT: +1.0 SD1.1 (p=NS vs. L); IVTL: +1.3 SD1.9 (p=NS vs. L); L: +0.5 SD0.9	NR
Ocular hypertension (>21 mm Hg)	NR	NR	NR		NR	NR
Cataract progression	NR	NR	Phakic eyes, progression by ≥2 AREDS grade, IVTL: 64% (p<0.001); L: 11% (p<0.001)		NR	NR
Corneal decompensation	NR	IVT: NR; C: n=1	NR		NR	NR
Cataract surgery	NR	NR	IVTL: 61% (p<0.001); L: 0%		NR	IVT: n=2; L: n=1
Vitreous haemorrhage	NR	NR	NR		IVTL: n=1	
Lens opacity	NR	NR	NR		NR	Significantly greater change in lens opacity in IVT group than in L group (1.9)
DEATHS	N=33, unrelated to study treatment	IVT: n=1; C: n=2	IVTL: n=2; L: n=1		NR	NR

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Table 16: Safety data in trials assessing more than one drug

	Ahmadieh 2008[31]	ATEMD 2011 (Oliveira Neto 2011) [56]	DRCR Network 2010 (Elman 2010, Elman 2011)[21,46]	Lim 2012[55]	Soheilian 2007 / Soheilian 2009[37,41]
Number of patients					
	Ocular adverse events				
Mild anterior chamber reaction	IVB: 19.5% (n=8 eyes), resolved after one week of no treatment; IVB/IVT: 18.9% (n=7 eyes), resolved after one week of no treatment	NR	NR	NR	IVB: 20% (n=10 eyes), resolved after 1 week; IVB/IVT: 18% (n=9 eyes), resolved after 1 week
Marked anterior chamber reaction	IVB: n=1 (topical corticosteroid and cycloplegic drops)	NR	NR	NR	IVB: n=1 (topical corticosteroids and cycloplegic drops);
Progression of fibrous proliferation	IVB: n=1 with no sign of retinal traction	NR	NR	NR	IVB: n=1 with no sign of retinal traction;
Vitreous haemorrhage	IVB/IVT: n=1 after third injection (excluded from study)	NR	NR	NR	NR
IOP rise	IVB: 23, 22 and 28 mm Hg at 6, 12 and 18 weeks (anti-glaucoma drops)	NR	IOP elevation more frequent with triamcinolone + PL	IVB/IVT: 8.3% IVT: 10.8%	NR
IOP ≥10 mm Hg from baseline	NR	NR	CPL: n=16; RPL: n=10; RDL: n=5; TPL: n=70	NR	NR
IOP ≥30 mm Hg from baseline	NR	NR	CPL: n=3; RPL: n=2; RDL: n=4; TPL: n=46	NR	NR
Initiation of IOP lowering treatment at any visit	NR	NR	CPL: n=9; RPL: n=5; RDL: n=4; TPL: n=41	NR	NR
Iris neovascularization	None	NR	NR	NR	NR
Lens opactiy	None	NR	NR	NR	Severe lens opacity IVB/IVT: n=4 eyes; MPC: n=1 eye
Endophthalmitis	NR	NR	CPL: n=1; RPL: n=1; RDL: n=1; TPL: n=0	NR	None
Pseudoendophthalmitis	NR	NR	CPL: n=1; RPL: n=0; RDL: n=0; TPL: n=1	NR	NR
Ocular vascular event	NR	NR	CPL: n=1; RPL: n=1; RDL: n=0; TPL: n=2	NR	NR

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Retinal detachment	NR	NR	CPL: n=0; RPL: n=0; RDL: n=1; TPL: n=0	NR	None
Vitrectomy	NR	NR	CPL: n=7; RPL: n=0; RDL: n=3; TPL: n=0	NR	NR
Vitreous haemorrhage	NR	NR	CPL: n=15; RPL: n=3; RDL: n=4; TPL: n=2	NR	None
Cataract surgery	NR	NR	CPL: n=11 (of those phakic at baseline); RPL: n=6 (of those phakic at baseline); RDL: n=8 (of those phakic at baseline); TPL: n=19 (of those phakic at baseline)	NR	NR
Glaucoma surgery	NR	NR	NR	NR	NR
Retinal neovascularization	NR	NR	NR	NR	IVB: n=4 (all resolved); MPC: n=3 eyes (2 resolved)
Development of early PDR	NR	NR	NR	NR	IVB: n=1; IVB/IVT: n=4; MPC: n=3
Progression to high-risk PDR	NR	NR	NR	NR	IVB: n=4; IVB/IVT: n=3; MP: n=3
Ocular hypertension (≥23 mm HG)	NR	NR	NR	NR	IVB/IVT: 16% (n=8 of eyes), controlled medically in all except 1 that progressed to neovascular glaucoma
	Systemic adverse events				
Acute myocardial infarction		N=1, considered not to be related to the study drug	No specific systemic adverse events that could be attributed to chance		No significant blood pressure increase, no thromboembolic events
Deaths	C: n=1	N=1, considered not to be related to the study drug	CPL: n=8; RPL: n=5; RDL: n=3; TPL: n=2		IVB/IVT: n=2; MPC: n=2

NR – not reported, IVB – intra-vitreal bevacizumab, IVT- intravitreal triamcinolone, IVR – intra-vitreal ranibizumab, IVRL – intra-vitreal ranibizumab plus laser, C – control, L – laser, IOP –intra-ocular pressure, PDR – proliferative diabetic retinopathy, DMO – diabetic macular oedema,

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Title:

Current treatments in Diabetic Macular Oedema: systematic review and meta-analysis

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

No additional data available.

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Abstract (300 words max)

Objectives: The aim of this systematic review is to appraise the evidence for the use of anti-VEGF drugs and steroids in diabetic macular oedema (DMO) as assessed by change in best corrected visual acuity (BCVA), central macular thickness and adverse events

Data source: MEDLINE, Embase, Web of Science with Conference Proceedings and the Cochrane Library (inception to July 2012). Certain conference abstracts and drug regulatory websites were also searched.

Study eligibility criteria, participants and interventions: Randomised controlled trials were used to assess clinical effectiveness and observational trials were used for safety. Trials which assessed triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO were included.

Study appraisal and synthesis methods: Risk of bias was assessed using the cochrane risk of bias tool. Study results are narratively described and, where apprpriate, data was pooled using random effects meta-analysis.

Results: Anti-VEGF drugs are effective compared to both laser and placebo and seem to be more effective than steroids in improving BCVA. They have been shown to be safe in the short-term but require frequent injections. Studies assessing steroids (triamcinolone, dexamethasone, fluocinolone) have reported mixed results when compared with laser or placebo. Steroids have been associated with increased incidence of cataracts and intra-ocular pressure rise but require fewer injections, especially when steroid implants are used.

Limitations: The quality of included studies varied considerably. Five out of fourteen meta-analyses had moderate or high statistical heterogeneity.

Conclusions and implications of key findings: The anti-VEGFs, ranibizumab and bevacizumab, have consistently shown good clinical effectiveness without major unwanted side effects. Steroids results have been mixed and are usually associated with cataract formation and IOP increase.

Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision ($\geq$20/40) and, thus, the search for new therapies needs to continue.

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Article focus

- To review the evidence for triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib and aflibercept in the treatment of diabetic macular oedema

Key messages

- The anti-VEGFs ranibizumab and bevacizumab, have consistently shown good clinical effectiveness in the short-term without major unwanted side effects
- Steroids results have been mixed and are usually associated with cataract formation and IOP increase

Strengthens and limitations

- A robust, detailed review of the literature has been undertaken and, when appropriate, data has been combined in meta-analysis
- The quality of studies included varied considerably.

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I - Introduction

Diabetic macular oedema (DMO) is a complication of diabetic retinopathy and a leading cause of blindness. The prevalence of DMO is likely to increase with more people suffering from diabetes.[1] Increasing DMO has significant implications for patients, healthcare providers and wider society. Laser has been the mainstay of treatment, but recently anti-vascular endothelial growth factor (anti-VEGF) drugs and steroids have been introduced as potential alternatives to laser photocoagulation.

a. Burden of disease

Diabetic retinopathy is present at the time of diagnosis of diabetes mellitus in 0-30% of individuals.[2] The incidence is estimated to be 2.3/100 person-years for the overall diabetic population and 4.5 for patients on insulin therapy.[3] There is good evidence that progression to DMO is associated with duration of disease[4-7], poor glycaemic control [8], and in type 2 diabetes, the need for insulin[9], though the need for insulin therapy is more a marker for duration, and poor control.

The number of people with DMO is likely to increase as diabetes becomes more common. Some reports have suggested a decrease in progression to severe visual loss between 1975-1985 and 1986-2008 in a combined population of type 1 and 2.[10] Regular screening for retinopathy and better glycaemic control are thought to have reduced the progression to severe visual loss. Diabetic retinopathy is associated with a reduced quality of life. Compared with all diabetic complications, blindness was perceived to be the third worst health state after a major stroke and amputation.[11]

In the US, the presence of DMO at diagnosis is associated with 29% additional costs within the first three years compared with individuals without retinopathy at diagnosis.[12] In 2010 the estimated healthcare costs for DMO in England were £92 million, with £65.6 million being spent on hospital treatment and related costs.[13]

Visual impairment results in increased welfare costs, early retirement, and costs of home help and carers.[14] In England in 2010 (total population 52.23 million) the estimated population with diabetes was 2.34 million; the above social costs were estimated to be £11.6 million for DMO.[13]

b. Overview of pathophysiology

DMO is caused mainly by disruption of the blood-retinal barrier. The complex pathway that leads to this disruption has been previously described in this journal.[15] Sustained hyperglycaemia causes a multi-factorial cascade of physiological processes, involving increased permeability, cytokine activation, altered blood flow, hypoxia and inflammation. Vascular endothelial growth factor-A (VEGF-A) is a major contributor to the inflammatory process and, in particular, to angiogenesis and permeability.[16] Hypoxia caused by microvascular disease stimulates release of VEGF-A to aid perfusion. There are six major isoforms of VEGF-A: 121, 145, 165, 183, 189 and 206. In addition to causing widespread microvascular injury, there is now evidence that hyperglycaemia results in preceding neuronal dysfunction, which may contribute to visual loss.[17]

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c. Overview of current treatments

Laser photocoagulation has been the mainstay of treatment for DMO. The landmark Diabetic Retinopathy Study[18] and the Early Treatment Diabetic Retinopathy Study (ETDRS)[19,20] demonstrated its clinical effectiveness. However, although laser photocoagulation was clearly effective in preserving vision, it was less successful in restoring it, once lost. Furthermore, patients with perifoveal ischaemia are not amenable to this form of therapy. In EDTRS, although laser was shown to reduce the risk of moderate visual loss (a loss of 3 ETDRS lines) by 50%, visual acuity improved in only 3% of patients.[20] However in some recent trials, laser has improved the proportion of patients with more than or equal to 10 letters by 7-31%.[21-24] In addition, laser is not without side effects. Foveal burns, visual field defects, retinal fibrosis and laser scars have been reported.[25] Over the following decade it became apparent that certain patients suffered severe visual loss despite aggressive treatment.[26]

Steroids and anti-VEGF drugs are newer treatments in DMO. Intravitreal corticosteroids have potent anti-inflammatory effects. Triamcinolone (Kenalog) is not licensed for eye use but has been used to treat DMO for over ten years. Triamcinolone (Trivaris), more recently, was licensed for eye use. The development of intravitreal implants has allowed sustained release formulations. Fluocinolone acetonide (Iluvien, Alimera Sciences) and dexamethasone (Ozudex, Allergan) are implants that have been introduced recently.

Anti-VEGF agents have shown efficacy compared with laser. Bevacizumab (Avastin, Genenetch /Roche) is a monoclonal antibody that targets all VEGF isoforms. Although being developed for colorectal cancer, it is widely used off-label, as an intravitreal treatment for macular oedema of different aetiologies. Ranibizumab (Lucentis, Genentech/Roche) is a fragment of the bevacizumab antibody (molecular weight of ranibizumab 48.4 KDa compared with 149 KDa for bevacizumab). It was designed specifically for use in the eye. Ranibizumab is considerably more expensive than bevacizumab (the estimated cost of ranibizumab is $2,000 per dose compared with $50 for bevacizumab).[27] Pegaptanib (Macugen, Eyetech Pharmaceuticals/Pfizer) is a PEGylated aptamer, with a high affinity to the VEGF isoform 165 and was approved for the treatment of exudative AMD in 2004. Aflibercept (Regeneron/Bayer HealthCare) is a recent addition to the anti-VEGF class that targets all forms of VEGF-A and placental growth factor.

d. Aim of the review

The aim of this review is to provide clinicians with an up-to-date overview of current intra-ocular drug treatments for DMO. It is hoped that the information contained herein will assist clinicians to present their patients with the best evidence supporting each treatment, including possible complications. In addition, this review may be helpful to policy makers. The review focuses on the current evidence for the use of anti-VEGF drugs and steroids to treat DMO, as assessed by change in best corrected visual acuity (BCVA) (mean and proportion with more than two lines improvement), central macular thickness (CMT), as determined by optical coherence tomography (OCT), and their adverse events.

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II - Evidence acquisition

A systematic literature search was performed. The databases searched included MEDLINE, Embase, Web of Science with Conference Proceedings and the Cochrane Library. The dates searched were from the inception of each database until July 2012

The search terms combined the following key words:

ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*

AND

diabetic macular oedema or diabetic macular ~~o~~edema or diabetic retinopathy or diabetic maculopathy

AND

(masked or sham or placebo OR control group or random*) OR (systematic review or meta-analysis) OR (risk or safety or adverse or harm or pharmacovigilance or side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic)

The meeting abstracts of the Association for Research in Vision and Ophthalmology, the American Diabetes Association (2002-2012) and the European Association for the Study of Diabetes were searched from 2002-2012.

In addition the web sites of the European Medicines Agency and the US Food and Drug Association were searched for data on registration status and safety. Clinicaltrials.gov and the EU Clinical Trials Register were searched in July 2012 for data on ongoing research.

Full details of the searches are shown in appendix 1.

Randomised controlled trials (RCT) were used to evaluate clinical effectiveness. Safety was assessed through both RCTs and observational studies.

RCTs were included provided that they 1) addressed the use of triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO, 2) had a minimum follow-up of six months, and 3) had a minimum of 25 eyes per study arm. Studies were excluded if they 1) evaluated laser only, 2) assessed the effect of the above mentioned treatments in macular oedema due to other retinal diseases (instead of DMO), 3) used only a single dose , 4) were combined with a surgical intervention or 5) published studies in languages other than English. There were no exclusions based on drug dose. Trials were excluded if they evaluated combined drug treatment with surgery or systemic treatment.

Search results were screened by two independent authors (JF and PR/DS). Data were extracted by one author (CC) and checked by a second (JF). Data extracted included inclusion/exclusion criteria, baseline demographics, BCVA expressed as a change in logMAR/ETDRS letters or proportion of

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participants with more than 2 or 3 lines BCVA improvement, CMT and adverse events. Risk of bias was assessed using the cochrane risk of bias tool.

Studies were assessed for similarity in study population, interventions (dose and frequency), outcomes and time to follow up, with a view to including similar studies in a meta-analysis. ~~Only full text articles were included~~ Conference abstracts were excluded from ~~in~~ the meta-analysis because their quality and detailed methodology was not clear. A difference of six months was allowed between study follow-ups because of potential heterogeneity from disease progression and differences in the number of doses ~~. If~~prescribed. If salient data were not reported, such as standard deviations, data were sought by personal communication with authors. Data were analysed using Review Manager software. If data from multiple time points were available, the primary end point data was used. Data were entered by one author (JF) and double-checked by a second (DS). Mean difference were calculated for change in BCVA and CMT and odds ratios were calculated for proportion of participants with more than 2 lines improvement. ~~, with~~ 95% confidence intervals were calculated for all outcomes. Statistical heterogeneity was measured through I^2 scores. A score of less than 30% was considered low heterogeneity, a score of more than 70% was considered high heterogeneity and scores between 30% and 70% were considered moderate. A random effects model was used throughout. The random effects model assumes variability between studies and therefore models uncertainty into the meta-analysis. Fixed assumes no variability. Generally speaking the random effects model results in wider confidence intervals. ~~.~~

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III - Results

The literature search identified 430 unique articles for possible inclusion, as shown in figure 1. 328 articles were excluded on the basis of title and abstract, leaving 102 full papers to be read. Fifty-one of these articles were excluded; the reasons for their exclusion are summarised in table 1. Fifty-one articles from 29 studies met the inclusion criteria and were included in the review; these are described in tables ~~2~~3 to 1~~5~~6. Seven studies were suitable for meta-analysis.

a. Study quality

The quality of the included studies was, in general, good as is shown in table 2~~16~~. (Note that the meeting abstracts were not quality assessed, due to lack of details reported on the methods). Most studies adequately described sequence generation, except in three studies where it was unclear.[28-30] However allocation concealment was poorly described throughout, with only eight reports addressing this issue appropriately. [31-38] Reporting of masking also varied. A number of studies masked patients using sham injection or sham laser.[21,24,29,31,33,36,39,40] [38]. Various studies reported that masking of patients was impossible. Assessors, where reported, were masked. In two studies incomplete outcomes were not addressed.[31,41] Baseline characteristics were consistent within study treatment arms. Administration of laser followed the ETDRS protocol, or a modified version, in all studies that described laser administration.[21-24,28,30,33,34,42,43] Two studies, both available only as meeting abstracts, did not report the laser administration details. [44,45]

b. Intravitreal anti-VEGFs

The characteristics of all published studies including design, inclusion/exclusion criteria, intervention, outcomes and their timing are shown in tables 3~~2~~ to 8~~7~~. Safety data for each drug is shown in tables 9~~8~~ to 16~~15~~.

1. Ranibizumab

Nine RCTs have evaluated ranibizumab as a potential new treatment for patients with DMO (table 3~~2~~ and 8~~7~~); seven were sponsored by industry, and two were an independent investigators-led.) [21,46](table 7). READ-2 was the first large RCT (n=126).[28,47] It compared ranibizumab (0.5 mg) alone, ranibizumab in combination with laser and laser alone. At six months BCVA had improved significantly in the ranibizumab alone group compared with laser alone or ranibizumab plus laser. Addition of laser to ranibizumab did not provide additional BCVA gain. REVEAL (n=396) compared ranibizumab (0.5mg) with ranibizumab plus laser and laser alone.[48] At 12 months both ranibizumab arms resulted in a statistically significantly better improvement in BCVA compared to laser alone. The addition of laser did not confer further benefit.

Within the past two years the results of RESOLVE[36], RESTORE[24], and RISE and RIDE[38] have been published in peer-reviewed journals. RESTORE (n=345) randomised similar groups as the READ-2 study (ranibizumab (0.5 mg) alone, laser alone and ranibizumab plus laser); outcomes were evaluated at 12 months. Ranibizumab improved mean BCVA, with laser providing no additional

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benefit. Two year extended follow-up suggested that these results continued.[49] RESOLVE (n=151) compared two doses of ranibizumab (0.3 mg and 0.5 mg) with sham injection. The greatest improvement in BCVA at 12 months was in the 0.3 mg group (11.8 letter gain) compared to the 0.5 mg group (8.8 letters gain) or sham injection (1.4 letter loss). In this study, rescue laser was allowed after three months of treatment, if BCVA had decreased by 10 letters or more, or if the investigator considered the macula not to be flat as assessed by OCT. Only 4.9% of the ranibizumab group required rescue laser, compared with 34.7% in the sham injection group.

READ-2 and RESTORE were suitable for pooling through meta-analysis and, when doing so, it was found that ranibizumab statistically significantly improved mean BCVA compared with laser (figure 2). In regards to the proportion of patients gaining more than or equal to 15 letters, individual trials showed a statistically significant difference between laser and ranibizumab but when these two trials were pooled using a random effects model the result was no longer statistically significant. When a fixed effects model was used the result was statistically significant (figure not shown). ~~The random effects model assumes variability between studies and therefore models uncertainty into the meta-analysis. Fixed assumes no variability. Generally speaking the random effects model results in wider confidence intervals.~~ Adding laser to ranibizumab did not add any significant benefit (figure 3). In fact the mean change in BCVA and the proportion of patients with more than 15-letter gain favoured, although not statistically significantly so, ranibizumab alone compared with ranibizumab plus laser. This was probably a chance effect.

RISE (n=377) and RIDE (n=382) were identical in design. The study arms are similar to those in the RESOLVE study; 0.3 mg or 0.5 mg ranibizumab compared with sham. In the RISE study the proportion of patients with 15 or more letter gain was greatest in the 0.3 mg group at 24 months, whereas in the RIDE study this was greatest in the 0.5 mg group. In the DRCRN trial (n = 854), Elman and colleagues compared ranibizumab (0.5 mg) plus prompt (within 3-10 days post ranibizumab) or deferred (≥ 24 weeks) laser with sham injection plus prompt laser, or triamcinolone (4m g, Trivaris) plus prompt laser (table 8~~7~~). At one year both ranibizumab groups reported greater gains in mean BCVA change than triamcinolone or laser alone. Interestingly at 2 years (n= 628), the proportion of patients with 10 or more letter gain was not statistically significantly different between ranibizumab plus prompt laser and laser alone groups, but was statistically significant in the ranibizumab plus deferred laser compared with laser alone comparison. The reason for this is not clear.

READ-3 (n=152) has been published in abstract form and compared monthly injections of intravitreal ranibizumab high dose (2.0 mg) and low dose (0.5 mg).[50] At six months there was not a statistically significant difference in BCVA between groups.

One study (n=63), published in abstract form, was identified which directly compared monthly injections of ranibizumab (0.5 mg) with bevacizumab (1.5 mg).[51] At 48 weeks the authors found no statistically significant difference between bevacizumab and ranibizumab.

RESTORE, READ-2 and DRCRN (12 month data used) were suitable for pooling through meta-analysis to compare ranibizumab plus laser and laser alone (figure 4). Ranibizumab plus laser resulted in a statistically significantly greater change in mean BCVA, proportion of patients with more than 15 letter gain and CMT reduction versus laser alone.

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Adverse events are shown in tables 98 and 165. Conjunctival hemorrhages were higher in the ranibizumab arms compared with laser (RESTORE) or no treatment (RESOLVE). In the RESOLVE, RISE and RIDE studies a considerably higher incidence of intra-ocular pressure (IOP) increase was reported in the ranibizumab arm compared to control. This increase in IOP was not demonstrated in the RESTOREstudy. There were no consistent differences in systemic adverse events between ranibizumab and laser or placebo.

2. Bevacizumab

Eight RCTs investigating the use of bevacizumab in DMO were identified (table 43 and 87). One RCT, the BOLT study (n=80), randomised patients to laser therapy or 1.25 mg intravitreal bevacizumab.[23,52] At 24 months, the mean change in BCVA and the proportion of patients who gained 10 ETDRS letters or more was statistically significantly higher in the bevacizumab arm than in the laser arm. Faghihi and colleagues (n=80), compared 1.25 mg bevacizumab (average 2.23 injections per patient) with 1.25 mg bevacizumab plus a single laser treatment (average 2.49 injections per patient).[53] After six months, the authors found both treatments to be effective at improving BCVA but neither treatment was found to result in a greater benefit.

Lam and colleagues (n=52) compared two doses of bevacizumab (1.25 mg and 2.5 mg) in patients with diffuse DMO.[35] Patients with focal DMO associated with localised retinal thickening were excluded. At 6 months, following 3 initial monthly injections (no treatment in the remaining 3 months), both groups showed a statistically significant increased mean BCVA compared with baseline vision, but there was no difference between doses.

Four trials have investigated the combination of bevacizumab and triamcinolone. Ahmadieh and colleagues (n=115), compared combined bevacizumab (three 1.25 mg injections at six week intervals) plus triamcinolone (2 mg baseline injection only, Triamhexal) with bevacizumab alone (three 1.25 mg at six week intervals) and sham injection in patients who had DMO unresponsive (definition not reported) to previous laser (last session more than three months prior).[31] The combination arm and bevacizumab alone arm improved mean BCVA more than sham injection. For BCVA the combination of bevacizumab plus triamcinolone was non-statistically significantly better than bevacizumab alone.

Soheilian and colleagues (n=150) compared combined bevacizumab (1.25 mg) plus triamcinolone (2 mg) with bevacizumab alone and laser alone in patients who were laser naïve.[37,41] At 36 weeks, bevacizumab alone improved BCVA more than either combination therapy or laser, although the difference was not statistically significant. Extended follow up at 24 months showed that there was no statistically significant difference between groups for BCVA, however the direction of effect favour the bevacizumab and combination arms more than the laser.[54]

Lim and colleagues (n=111) also evaluated the combination of bevacizumab plus triamcinolone when compared with bevacizumab alone or triamacinolone alone.[55] At 12 months the authors found no statistically significant difference between groups for BCVA or CMT.

The Efficacy Study of Triamcinolone and Bevacizumab Intravitreal for Treatment of Diabetic Macular Oedema (ATEMD) study, currently only published in abstract form, compared combined therapy with bevacizumab (1.25 mg) and triamcinolone (4 mg) with each of these alone.[56] At six months

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they found no statistically significant difference between groups. One study comparing bevacizumab with ranibizumab is discussed above.[51] No bevacizumab trials were suitable for meta-analysis because treatment arms were not comparable among included studies.

Adverse events are shown in tables 109 and 165.There was a low frequency of adverse events reported in the included trials. A higher incidence of mild anterior chamber reaction was reported in bevacizumab groups compared with controls. The incidence of IOP increase was comparable between bevacizumab and laser. Soheilian and colleagues, were the only authors to report the incidence of lens opacity.[37,41] No patients in the bevacizumab alone group were found to have lens opacities but in four patients (8%) in the bevacizumab plus triamcinolone group this finding was observed over the 36 week follow-up period.

3. Pegaptanib

Two studies have evaluated pegaptanib in DMO and both compared it with sham injection (table 54). Cunningham and colleagues compare three doses of pegaptanib (0.3 mg, 1 mg and 3 mg) and sham injection in laser naive patients (n=172).[39,57] At six months patients in the 0.3 mg and 1 mg groups performed statistically significantly better than those in either 3mg or sham groups. Six injections (median) were administered in the 0.3 mg and 1 mg group, whereas only five (median) injections were administered in the 3 mg group.

The second trial (n=260), reported by Sultan and colleagues in 2011, compared pegaptanib (0.3 mg) and sham injection. At two years, the pegaptanib group showed a statistically significantly greater improvement in mean BCVA compared with sham.[40] However there was no statistically significant difference in the proportion of patients with an improvement of 10 letters or more. Patients were allowed rescue laser at the assessors' discretion (25.2% of patients in the pegaptanib group and 45% of patients in the sham group received rescue treatment). In regards to meta-analysis, data were only available to combine these trials for proportion of patients with more than 15 letter gain. Although individually neither trial demonstrated a statistically significant difference favouring pegaptanib over sham (figure 5), when pooled together in meta-analysis a statistically significant difference in favour of pegaptanib was found (OR 1.94, 95%CI 1.01 to 3.71).

Adverse events for pegaptanib are shown in table 110. There was a higher incidence of eye pain compared to control (31% versus 17%). [39,57] Cataract formation was similar between pegaptanib and control groups. There was a higher incidence of IOP increase in the pegaptanib arm compared to control (17.4% versus 6.3%).[40]

4. Other anti-VEGF

Aflibercept has been evaluated in the Da Vinci study (n=219)[30,58] (table 54). Four regimens of aflibercept (0.5 mg 4 weekly, 2 mg 4 weekly, 2 mg monthly for three months then every 8 weeks, and 2 mg monthly for three months followed by treatment as required) were compared with laser. At six months, all aflibercept arms had a statistically better BCVA and CMT change than the laser arm. The regimen that resulted in greatest BCVA gain and CMT reduction was 2 mg every 4 weeks, however statistical significance between aflibercept arms was not reported. One year extended follow-up showed that all aflibercept arms were found to have a statistically significantly better BCVA compared to laser.[58]

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Adverse events are shown in table 12~~1~~. There was a higher incidence of IOP increase and eye pain in the aflibercept group compared with laser. Other adverse events were too infrequent to draw meaningful conclusions. The incidence of cataracts was not reported.

c. Steroids

1. Dexamethasone

Two included trials assessed the use of dexamethasone to treat DMO (table 6~~5~~); Haller 2010 (full text available)[59] and Callanan (available to date only in an abstract form).[44] Haller 2010 (n=171) compared two doses of dexamethasone, administered as an intravitreal implant (350 µm and 700 µm) through a 20-gauge transscleral incision, with no treatment. At 90 days only the 700 µm group showed a statistically significant higher proportion of patients with 10 or more letter gain compared to no treatment (33% compared with 12%, p = 0.007). The 350 µm group showed a non-statistically significant improvement compared with laser alone (21% compared with 12%). At 180 days there was no statistically significant difference between either the dexamethasone group and no treatment group. The treatment effect appeared to peak at three months.

The second trial, by Callanan and colleagues (n=253), compared dexamethasone (dose not reported) plus laser with laser alone. Although a greater improvement in mean BCVA was seen at 1-9 months in the dexamethasone plus laser group compared with laser alone, there was no statistically significant difference at 12 months. A mean of 1.6 implants were used over the 12 month period.

These trials were not suitable for meta-analysis since one study is only available in abstract form.

Adverse events are shown in table 13~~2~~. In the 350 µm and 700 µm groups compared with no treatment, there was a higher incidence of anterior chamber cells (29.1/26.4% compared with 1.8%), anterior chamber flare (27.3/20.8% compared with 8.8%), vitreous hemorrhage (20/22.6% compared with 5.3%) and increased IOP (14.5/9.4% compared with 0%). However there was no statistically significant difference in the cataract formation between the groups at 12 months. [59] Callanan and colleagues reported an increase in IOP in the dexamethasone plus laser group compared with laser alone (20% compared with 1.6%).[44]

2. Fluocinolone

Two trials assessed fluocinolone implant for DMO (table 6~~5~~). The FAME study (n=956) compared two doses of fluocinolone (0.2 µg/day and 0.5 µg/day) with sham injection in patients with at least one prior laser treatment.[29] Approximately 25% of patients in each group had more than one prior laser treatment. At 24 months both doses of fluocinolone showed a statistically significant improvement in mean BCVA compared to sham. There was a modest difference between fluocinolone groups. Rescue laser was given after the first six weeks for persistent oedema and was allowed every three months. 35-37% of patients in the fluocinolone group and 59% in the sham injection group required rescue laser. Extended follow-up at 36 months showed that the both fluocinolone arms continued to result in a statistically significant benefit compared with sham.[60]

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Pearson and colleagues (n=196) compared fluocinolone (0.59 mg) with standard of care, either laser or no treatment.[43] At three years there was no statistically significant difference in the proportion of patients with 15 letters gain or more (31% fluocinolone compared with 20% standard of care) between groups and proportion of patients losing 15 letters or more in the fluocinolone group (17% compared with 14%). Increased incidence of cataracts may have contributed to this difference.

These trials were not suitable for meta-analysis.

Adverse events are shown in table 143. Pearson and colleagues reported a higher incidence of cataracts at three years in the fluocinolone group compared with standard of care (55.9% compared with 21.7%).In the extended report of the FAME study there was a considerably higher incidence of cataract surgery in phakic eyes in the 0.2 µg/day and 0.5µg/day fluocinolone groups (80.0% and 87.2% compared with 27.3%) and increased IOP at any point (37% and 46% compared with 12%).

Following the demonstration in the FAME trial that a lower dose was about as good as higher ones, the higher doses are unlikely to be used.

3. Triamcinolone

Ten trials evaluating triamcinolone were identified (table 76 and 87). All trials evaluated intravitreal administration of triamcinolone, there were no trials evaluating posterior or anterior sub-tenon injections. Two trials used Trivaris[21,61], two trials used Kenacort [32,33], one trial used Kenalog[62], one trial used Trimahexal [31] and four trials did not report the type of triamcinolone used.[34,37].[45,56] Three doses were assessed in the included studies (1 mg, 4 mg and 8 mg) and triamcinolone has been combined with laser or bevacizumab.

Ip and colleagues (n=840) were the only authors to evaluate triamcinolone 1mg (Trivaris).[22,61,63,64] They found a statistically significant improvement in mean BCVA at two years in the laser group compared with the triamcinolone group and no significant difference between 1 mg compared with 4 mg.

Several trials compared 4 mg intravitreal triamcinolone. Ip and colleagues (n=840) found that laser therapy resulted in a greater improvement in mean BCVA at two years compared to 4 mg triamcinolone (Trivaris). [22,61,63,64] Lam and colleagues (n=111), found no statistically significant difference between laser and triamcinolone at six months (triamcinolone type not reported).[34] When these two trials were pooled through meta-analysis, the treatment effect favoured laser but differences were not statistically significant (figure 6). Ockrim and colleagues (n=88) compared 4 mg intravitreal triamcinolone (Kenalog) with laser alone.[62] At 12 months they found no statistically significant BCVA improvement between the triamcinolone and laser groups. Gillies and colleagues (n=69) compared 4 mg of triamcinolone (Kenacort) with sham injection.[32] Mean BCVA improved statistically significantly with triamcinolone at 24 months compared with sham injection (3.1 letters gain compared with 2.9 letters loss, p = 0.01).

Lam and colleagues (n=111) compared triamcinolone 4 mg alone with 4 mg of triamcinolone plus laser or laser alone.[34] At six months the authors found no difference in BCVA between any of the groups. Elman and colleagues (n=854) compared 4 mg of triamcinolone (Trivaris) plus laser with ranibizumab plus prompt (within 3-10 days) or deferred (more than 24 week) laser and laser alone.[21] At two years they found a statistically significant difference in mean BCVA between

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ranibizumab plus prompt/deferred laser compared with laser alone (7 letters gain/9 letters gain compared with 3 letters gain), but no difference with triamcinolone plus laser compared with laser alone (2 letters gain compared with 3 letters gain). Oliveira-Neto and colleagues (n=120) compared 4 mg triamcinolone alone (triamcinolone type not reported) with 4 mg plus 1.25 mg bevacizumab.[56] At six months they found no statistically significant difference between groups.

The Elman and Lam studies were suitable for meta-analysis, which showed non-statistically significant improvements in mean BCVA and the proportions of patients with more or equal than 15 letter gain in the triamcinolone plus laser group compared with laser alone (figure 7).

Adverse events are shown in table ~~14~~ 15 and 1~~6~~5. Triamcinolone was associated with consistently higher incidences of IOP increase and cataracts. Gilles and colleagues reported a cataract rate of over 50% by three years in patients treated with triamcinolone.

d. Other pertinent studies

Only one study in abstract form directly compared bevacizumab with ranibizumab.[51] Bevacizumab and ranibizumab have been compared through indirect comparison of five trials.[65] There was no evidence of a difference between the drugs, however wide credible intervals meant that superiority of either drug could not be excluded.

Two-year results of the CATT (Comparison of AMD Treatment Trials) and one year results of the IVAN (Inhibit VEGF in Age-related choroidal Neovascularisation), recently published, have demonstrated a good safety profile of anti-VEGF therapies when used to treat patients with age-related macular degeneration.[66,67] The CATT study randomised 1208 patients with AMD to monthly or as required injection of either ranibizumab or bevacizumab. At 1 year the mean BCVA was similar in both groups (8.0 letter gain in bevacizumab and 8.5 in ranibizumab). Over two years, the rates of deaths, myocardial infarction and stroke did not differ between ranibizumab and bevacizumab treatment groups. However, there was a higher rate of serious adverse events in the bevacizumab compared with the ranibizumab group. This increased event rate was driven mainly by hospitalisations, (RR 1.29, 95%CI 1.01 to 1.66). However the hospitalisations were not caused by known adverse events of bevacizumab. Arterio-thrombotic events and heart failure occurred in less than 2% of participants in the IVAN, and there were more often observed in the ranibizumab group than in the bevacizumab group (p = 0.03). Further data from other ongoing clinical trials may provide more insight on the safety or anti-VEGF treatment and possible differences on this respect among available drugs.

Campbell and colleagues conducted a population based nested case-control study of 91,378 older adults with a history of physician diagnosed retinal disease.[68] The authors found that neither ranibizumab nor bevacizumab were associated with significant risks of ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism."

A recent systematic review specifically assessing adverse events in anti-VEGF drugs found a low incidence of serious (below 1 in 100) and non-serious ocular events (below 1 in 500) from ranibizumab, bevacizumab and pegaptanib.[69]

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Fung and colleagues used an internet-based survey of clinicians to assess the safety of bevacizumab.[70] The survey covered over 5000 patients and found that bevacizumab was associated with an infrequent incidence of adverse events (all less than 0.21%).

One study which assessed diclofenac did not meet the inclusion criteria (follow-up for only 12 weeks).[71] The authors randomised 32 patients to either intravitreal diclofenac or triamcinolone and found that both diclofenac and triamcinolone reduced CMT, but a statistically significant visual improvement was observed only in the triamcinolone group.

Sfikakis and colleagues undertook a 30-week randomised crossover trial comparing infliximab and placebo.[72] The study failed to meet our inclusion criteria (only 11 patients included). The authors found that infliximab resulted in a 28.6% improvement in vision compared with 4.3% with placebo. The improvement seen with placebo could be due to a "carry over effect", seen in cross over trials.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was primarily a study to see if the lipid-lowering agent fenofibrate, could reduce macrovascular and microvascular events in type 2 diabetes.[73] However a substudy within FIELD recruited 1012 patients to a retinopathy study. The primary outcome in the main study was need for laser therapy (3.4% on fenofibrate versus 4.9% on placebo) but the substudy used retinal photography to assess progression of retinopathy or development of macular oedema. The hazard ratio at six years for DMO was 0.69 (95%CI 0.54 to 0.87) in the fenofibrate group compared to placebo.

Ruboxistaurin is another oral agent which has been assessed for the treatment of DMO. Aiello and colleagues randomised 686 patients to receive placebo or one of three doses of ruboxistaurin. [74,75] There was no statistically significant difference in delay to sight-threatening DMO in any ruboxistaurin group compared to placebo. The authors suggest that differences in laser treatment between groups may have contributed to the non-significant finding.

e. Assessment of heterogeneity within meta-analysis

Heterogeneity was assessed methodologically and statistically. Methodological heterogeneity was assessed by comparing study population, interventions, outcome measures and follow-up. Studies that were not methodologically comparable were excluded from the meta-analysis. For example bevacizumab trials were not pooled because Soheilian and colleagues included patients who were laser naïve[37] and Ahmadieh and colleagues included patients who were unresponsive to laser.[31] Some analyses were also excluded because sufficient details were not reported in the studies. For example several studies failed to report standard deviations.[35,39]

Statistical heterogeneity was assessed through I^2 scores. High statistical heterogeneity was found in two analyses (2.3, 4.3). Therefore these results should be interpreted with due caution. Moderate heterogeneity was found in three analyses (2.2, 3.1, 3.2). Low heterogeneity was found in the remaining eight analyses.

f. Ongoing trials

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There are numerous on-going studies listed in appendix 2. The most salient studies include a study to compare ranibizumab and bevacizumab (Schmidt-Erfurth), a study investigating rescue ranibizumab treatment for patients who have failed on bevacizumab (Chaudhry), a study evaluating two algorithms for ranibizumab, 'treat and extend' and 'as required' (RETAIN), further studies of Trap-eye (VIVID and VISTA) and trials which are examining the use of NSAIDs, such as diclofenac and nepafenac (NEVANAC and Soheilian).

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IV – Discussion

It appears that anti-VEGF treatment is effective in DMO, especially ranibizumab and bevacizumab. Meta-analysis of available short-term data (up to 2 years) suggests that ranibizumab is superior to laser and that adding laser to ranibizumab treatment does not confer additional benefit. Steroid treatment has demonstrated mixed success and, almost uniformly, increased incidence of cataracts and increased IOP. The licence for fluocinolone takes note of this and it is positioned as a treatment when others have failed.

a. Strengths and limitations of the review

There are a number of strengths of this review. A robust systematic review methodology was used. Reliability was improved by excluding trials with small sample sizes or short follow up. Since a number of trials included similar intervention arms, consistent treatment effects further improve reliability. Validity was improved by assessing the quality of trials using the Cochrane risk of bias tables. Including abstracts from ARVO provided up to date results. Pooling results through meta-analysis provided further evidence. The random effects model was used throughout to allow for heterogeneity among studies.

This review, however, has limitations. Although the inclusion of abstracts provides a more up to date results, the studies contained in these abstracts could not be assessed for risk of bias and should therefore be interpreted with caution. In addition, reporting of quality assessment criteria was variable. Allocation concealment was especially poorly reported. There was only one study which compared different anti-VEGFs[51] and none that compared steroids (fluocinolone vs dexamethasone vs. triamcinolone). Therefore it is difficult to assess the effectiveness within drug classes. As with any meta-analysis questions of heterogeneity arise. Follow-up periods varied among studies. A difference of six months was allowed for studies to be pooled for meta-analysis but this could have still resulted in heterogeneity. High statistical heterogeneity was found in a quarter of analyses. Furthermore because of the low number of trials included, publication bias could not be assessed by funnel plot analysis. The manufacturers funded most of the trials for ranibizumab, pegaptanib, dexamethasone and fluocinolone, whereas trials for bevacizumab and triamcinolone were generally funded by non-pharmaceutical organisations. Generally, the non-commercial studies had smaller numbers, perhaps because of funding restraints.

It is important to note that there may be differences in laser treatment protocol between studies. This applies to trials which combine drug treatments with laser or include laser as a comparator. All studies referred to the ETDRS protocol [19,20] or a modified version of it. In the ETDRS, once the diagnosis of clinically significant macular oedema was made, an angiogram was obtained to identified "treatable lesions". "Treatable lesions" included discrete points of retinal hyperfluorescence or leakage (most of these are often microaneurisms), areas of diffuse leakage within the retina related to microaneurisms, intraretinal microvascular abnormalities, diffusely leaking retinal capillary bed and retinal avascular zones. In the ETDRS protocol, treatment of lesions closer than 500 microns from the centre of the macula was not required initially; however if vision was less than 20/40 and the oedema and leakage persisted, treatment up to 300 microns from the

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centre of the macula was recommended unless there was capillary dropout; in the latter case treatment was not recommended as it may lead to further loss of perifoveal capillaries

However in routine clinical practice clinicians generally use lighter and less intense treatment than specified in the ETDRS protocol.[76] In addition, some centres do not use fluorescein angiography (unlike the ETDRS study[19]) to guide treatment. The exact adherence to the ETDRS protocol within studies is unclear. For example, in the BOLT study a modified ETDRS protocol was used. One of the aims of the protocol was "not darkening/whitening of microaneuysms", which is not consistent with the ETDRS protocol.

b. Interpretation of the results

The anti-VEGF drugs appear to be clinically effective in treating DMO in short-term studies (up to 2 years). Ranibizumab has the most robust evidence base and has shown superiority compared to laser and sham injection in all trials and meta-analyses, except for the proportion of patients with 10 or more letter gain in the DRCR.net study published by Elman and colleagues at two years follow up.[46] Adding laser to ranibizumab conferred no benefit. Bevacizumab has also been shown to be superior to laser. Three doses have been used (1.25 mg, 1.5 mg and 2.5 mg). The higher dose does not appear to add further benefit, and most studies in the literature use 1.25 mg. Addition of triamcinolone to bevacizumab did not provide further benefits. Pegaptanib has only been compared to sham injection. Mean change in BCVA favoured pegaptanib, but only through meta-analysis did the proportion of patients with more than 15 letter gain favour pegaptanib. Further published data are required before drawing conclusions on aflibercept. However although the anti-VEGF drugs are a significant advance, they fail to improve BCVA by 10 or more letters in half or more patients, and so they do not provide a complete answer to DMO.

Steroid treatments have inconsistent results and are undoubtedly associated with increased IOP and cataract. The effects of dexamethasone appear to peak at three months. At six months there was no significant difference compared with laser. This might imply that earlier re-treatment is needed if the beneficial effect is to be maintained, but increasing the number of treatments would likely increase the associated complications, especially with the relatively large needle size. The addition of laser did not appear to add further benefit. There was no significant difference in cataract formation at six months with dexamethasone compared to observation but it is likely that a higher incidence of cataracts would be seen with longer follow-up. Significantly more patients suffered increased IOP in the dexamethasone group compared with observation. Fluocinolone has been shown to be effective compared with sham injection (FAME)[29,60], however when compared to standard of care (laser or observation at clinician's discretion) there was no significant difference in the proportion of patients with a 15 letter or more gain. Both studies reported higher incidence of cataract formation in the fluocinolone group, over 80% at three years at the higher dose. Results for triamcinolone are inconsistent. Ip and colleagues found that laser was more effective[61], others have found no statistically significant difference. Triamcinolone combined with laser, however, seemed to have similar efficacy as ranibizumab combined with laser in pseudophakic eyes.[21,46] Triamcinolone is more effective than sham injection. Triamcinolone has consistently been associated with increased incidence of cataract and raised IOP.

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Steroids and laser therapy may affect CMT in a different manner from anti-VEGF drugs. For example, when ranibizumab alone is compared with ranibizumab plus laser, ranibizumab alone appears to be more effective in terms of mean change in BCVA and proportion of patients with more than 15 letters gain. However ranibizumab plus laser is more effective at reducing CMT. Furthermore when triamcinolone plus laser is compared with ranibizumab plus laser, ranibizumab plus laser appears to be more effective in terms of change in BCVA and proportion of patients with more than 15 letters gain, but triamcinolone plus laser is more effective at reducing CMT. The reasons for this are unclear. There is a weak correlation between CMT and BCVA. However the long term benefits of reducing CMT are currently unknown.

No large observational studies were identified that compared anti-VEGF drugs. Fung and colleagues, using an internet based survey, found the incidence of adverse events in bevacizumab to be low.[70] One small outbreak of sterile endophthalmitis was reported with a single batch of bevacizumab in Canada, emphasising the need for sterility when preparing aliquots.[77] Curtis and colleagues carried out a very large retrospective cohort study in 146,942 patients aged 65 and over with age-related macular degeneration (AMD).[78] Their aim was to examine the cardiovascular outcomes in patients treated with the four options: photodynamic therapy (PDT), pegaptanib, bevacizumab and ranibizumab. The authors reported that one of their comparisons showed an increase in overall mortality and stroke risk with bevacizumab compared to ranibizumab, with hazard ratios 0.86 (95%CI 0.75 to 0.98) and 0.78 (0.64 to 0.96) respectively. However because of the very large cost differences between bevacizumab and ranibizumab, the authors noted that selection bias might be operating, with poorer people (with poorer health) more likely to be treated with bevacizumab. They therefore carried out another analysis using only ophthalmological clinics which used only one drug, to avoid selection bias. This analysis showed no significant difference: overall mortality hazard ratio for ranibizumab 1.10 (95%CI 0.85 to 1.141); MI 0.87 (0.53 to 1.14); stroke 0.87 (0.61 to 1.24).

Gower and colleagues analysed 77,886 anti-VEGF injections from Medicare data (46% ranibizumab and 54% bevacizumab).[79] Results have only been published in abstract form. The authors found an increased risk of overall mortality and cerebrovascular events in the bevacizumab group (HR 1.11 99%CI 1.01 to 1.23 and 1.57, 1.04 to 2.37 respectively). There was no statistically significant increased risk in the ranibizumab group. The authors acknowledge that a limitation of the study is a failure to adjust for important confounding factors (such as smoking, hypertension and hyperlipidaemia). Considering the cost difference, it is likely that patients treated with bevacizumab would have been in a lower socio-economic class and therefore would be at high risk of mortality and vascular disease.

c. Implications for clinicians

The anti-VEGF drugs appear to be a significant advance in the treatment of DMO and are regarded now as the treatment of choice for patients affected by this condition. Studies assessing the effectiveness of steroids have reported mixed results. The high rates of cataract and increased IOP are a drawback. Triamcinolone combined with laser may be a good option for pseudophakic patients and may be more cost-effective than treatment with ranibizumab. However the need for fewer administrations, potentially one every three years with fluocinolone, is advantageous. From an administration perspective, some patients might prefer infrequent steroid injections with a sizeable

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risk of cataract, and a small, but existent, risk of glaucoma, to frequent anti-VEGF injections, even if the potential gain may not be fully comparable. Steroids may be also considered for patients that do not adequately respond to anti-VEGFs. Currently, the role of laser in the treatment of DMO is debatable. Short term data from available trials have demonstrated the superiority of anti-VEGF with regards to laser treatment and have failed to demonstrate a benefit of combining both treatment approaches. It is possible that some ophthalmologists may still opt to offer laser treatment to patients with very focal areas of leakage.

Currently there is more evidence for the effectiveness of ranibizumab and bevacizumab than for pegaptanib and VEGF-trap eye. The results of direct head to head trials of ranibizumab and bevacizumab are awaited. Bevacizumab is not licensed for intraocular use but costs considerably less than other forms of therapy. Ranibizumab is licensed and more expensive, but its use is supported by large manufacturer funded trials demonstrating its clinical effectiveness. In the UK, the General Medical Council recommends that unlicensed medications should only be prescribed if "an alternative, licensed medicine would not meet the patient's needs" and there is "a sufficient evidence base and/or experience of using the medication to demonstrate its safety and efficacy".[80] The FDA says that when using a drug "off-label" clinicians "have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sounded medical evidence, and to maintain records of the product's use and effects".[81] Patients should be fully aware of the use of any unlicensed medication and consent to any safety or efficacy uncertainties.

The place of intravitreal steroids needs consideration now that we have the anti-VEGFs drugs, as does the role of laser. The anti-VEGFs drugs may now be the first-line treatment in place of laser, with laser being used selectively for focal lesions, and in sequence after anti-VEGF therapy once the retinal thickness has been reduced. However it should be noted that about half of patients do not get good results with anti-VEGFs. In RESTORE, only 50% of patients had gains in VA of 10 or more letters. So the anti-VEGFs are "game-changers" but their impact should not be over-estimated.

In those who do not respond to anti-VEGFs or laser, there remains a place for steroids, despite their high adverse effect rates. The European licence for fluocinolone recognises this, by stating that it should be used when other therapies have not had sufficient effect.[82] The commonest adverse effect is cataract, but that is very common in people with diabetes, and many are already pseudophakic when treatment of DMO is required.

Vitreoretinal surgery for the treatment of DMO was not included in our review. Laidlaw reviewed the literature and only found evidence for vitrectomy when there was signs of clinical or OCT traction.[83] However even in these cases, the evidence was not strong.

d. Implications for policy makers

In the UK, the National Institute of Health and Clinical Excellence (NICE) has recently made the decision not to recommend ranibizumab for the treatment of DMO.[84] NICE concluded that ranibizumab, although clinically effective, was not cost-effective compared to laser therapy. Bevacizumab is less than a tenth of the cost of ranibizumab. Bevacizumab is unlikely to be licensed.

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This beckons the question as to whether policy makers should recommend cheaper unlicensed medications over a more expensive licensed alternative when efficacy and side effects appear similar.

e. Unanswered questions

Several unanswered questions remain. Studies evaluating the effectiveness of ranibizumab compared with bevacizumab are needed. Although the anti-VEGFs are clinically effective and a major step forward in the management of DMO, it has to be noted that they have little effect in a large number of patients. Generally speaking, the proportion of patients who have demonstrated 10 or more letter gain using anti-VEGFs is between 30-50% in the trials that demonstrate greatest effectiveness. Most of these patients would not achieve the 20/40 visual acuity required for driving. More effective treatments, or combinations of treatments, are required.

There is a lack of specific evidence for the use of anti-VEGF drugs or steroids in patients with macular ischemia secondary to DMO. A number of trials excluded patients with macular ischemia.[23,34,35,40,53,62] The RESTORE trial included patients with macular ischemia and undertook a subgroup analysis.[24] The authors compared patients with (n=34) and without (n=35) macular ischemia at baseline. They found that those without macular ischemia responded better to ranibizumab (mean average change in BCVA at 12 months 7.2 letters gain compared with 6.3 letters). Larger trials are needed to assess the use of anti-VEGF drugs and steroids in patients with macular ischemia.

The duration of treatment is as yet uncertain. Most of the included studies use a retreatment protocol based on clinical need or OCT results. For example, in the BOLT study patients received a median of 9 injections of bevacizumab over 24 months.[23,85] However, it is not yet known how frequent long-term maintenance injections will be needed for and whether laser treatment in sequence could potentially reduce the number of anti-VEGF injections required. Other treatment strategies to apply laser, such as using laser power at sub-threshold levels, may prove more effective.[86] Future trials should use active comparators which are used in routine clinical practice and avoid placebo controlled trials.

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V - Conclusion

This review evaluated current treatments for DMO. Undoubtedly, the use of anti-VEGFs heralds a new era for patients who suffer from DMO. Currently, the anti-VEGFs ranibizumab and bevacizumab, have consistently shown good clinical effectiveness without major unwanted side effects. Steroids results have been mixed and are usually associated with cataract formation and IOP increase. Based on the short term data available, adding laser therapy to anti-VEGFs does not appear to confer additional benefit.

Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision (≥20/40) and, thus, the search for new therapies to prevent and manage DMO needs to continue.

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Contribution of authors

JF screened titles, checked data extraction, performed the meta-analysis and drafted manuscript. NL conceived the idea, interpreted the results and provided clinical expertise throughout. PR performed the literature search, updated the searches, screened titles and managed the references. CC extracted data from the studies. DS screened titles and checked the meta-analysis. NW designed the review and supervised the running of the study. All authors contributed to the final draft.

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Reference List

1. Holman N, Forouhi NG, Goyder E, et al. The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: estimates of total diabetes prevalence for England, 2010-2030. *Diabet Med* 2011;28:575-82.
2. Williams R, Airey M, Baxter H, et al. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond)* 2004;18:963-83.
3. Henricsson M, Sellman A, Tyrberg M, et al. Progression to proliferative retinopathy and macular oedema requiring treatment. Assessment of the alternative classification of the Wisconsin Study. *Acta Ophthalmol Scand* 1999;77:218-23.
4. Chen E, Looman M, Laouri M, et al. Burden of illness of diabetic macular edema: literature review. *Curr Med Res Opin* 2010;26:1587-97.
5. Hirai FE, Knudtson MD, Klein BE, et al. Clinically significant macular edema and survival in type 1 and type 2 diabetes. *Am J Ophthalmol* 2008;145:700-6.
6. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;105:1801-15.
7. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology* 2009;116:497-503.
8. Knudsen LL, Lervang HH, Lundbye-Christensen S, et al. The North Jutland County Diabetic Retinopathy Study (NCDRS) 2. Non-ophthalmic parameters and clinically significant macular oedema. *Br J Ophthalmol* 2007;91:1593-5.
9. Thomas RL, Dunstan F, Luzio SD, et al. Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. *BMJ* 2012;344:e874.
10. Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. *Diabetes Care* 2009;32:2307-13.
11. Huang ES, Brown SE, Ewigman BG, et al. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care* 2007;30:2478-83.
12. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. *Arch Ophthalmol* 2008;126:1748-54.
13. Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. *Br J Ophthalmol* 2012;96:345-9.
14. Happich M, Reitberger U, Breitscheidel L, et al. The economic burden of diabetic retinopathy in Germany in 2002. *Graefes Arch Clin Exp Ophthalmol* 2008;246:151-9.

For peer review only

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15. Bhagat N, Grigorian RA, Tutela A, et al. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol* 2009;54:1-32.

16. Murata T, Ishibashi T, Khalil A, et al. Vascular endothelial growth factor plays a role in hyperpermeability of diabetic retinal vessels. *Ophthalmic Res* 1995;27:48-52.

17. Barile GR, Pachydaki SI, Tari SR, et al. The RAGE axis in early diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2005;46:2916-24.

18. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383-96.

19. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796-806.

20. Early Treatment Diabetic Retinopathy Study research group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology* 1987;94:761-74.

21. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064-77.

22. Ip MS, Bressler SB, Antoszyk AN, et al. A randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema: baseline features. *Retina* 2008;28:919-30.

23. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology* 2010;117:1078-86.

24. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615-25.

25. Lovestam-Adrian M, Agardh E. Photocoagulation of diabetic macular oedema--complications and visual outcome. *Acta Ophthalmol Scand* 2000;78:667-71.

26. Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema. Long-term visual results. *Ophthalmology* 1991;98:1594-602.

27. Nwanze CC, Akinwale A, Adelman RA. Bevacizumab vs. Ranibizumab in Preserving or Improving Vision in Patients with Wet, Age-Related Macular Degeneration: A Cost-effectiveness Review. *Clinical Medicine Insights: Therapeutics* 2012;4:29-38.

28. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2010;117:2146-51.

29. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology* 2011;118:626-35.

For peer review only

30. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology* 2011;118:1819-26.

31. Ahmadieh H, Ramezani A, Shoeibi N, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol* 2008;246:483-9.

32. Gillies MC, Sutter FK, Simpson JM, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. *Ophthalmology* 2006;113:1533-8.

33. Gillies MC, McAllister IL, Zhu M, et al. Intravitreal triamcinolone prior to laser treatment of diabetic macular edema: 24-month results of a randomized controlled trial. *Ophthalmology* 2011;118:866-72.

34. Lam DS, Chan CK, Mohamed S, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: six-month outcomes. *Ophthalmology* 2007;114:2162-7.

35. Lam DS, Lai TY, Lee VY, et al. Efficacy of 1.25 MG versus 2.5 MG intravitreal bevacizumab for diabetic macular edema: six-month results of a randomized controlled trial. *Retina* 2009;29:292-9.

36. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care* 2010;33:2399-405.

37. Soheilian M, Ramezani A, Bijanzadeh B, et al. Intravitreal bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. *Retina* 2007;27:1187-95.

38. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119:789-801.

39. Cunningham ET, Jr., Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 2005;112:1747-57.

40. Sultan MB, Zhou D, Loftus J, et al. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology* 2011;118:1107-18.

41. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;116:1142-50.

42. Sivaprasad S, Ockrim Z, Massaoutis P, et al. Posterior hyaloid changes following intravitreal triamcinolone and macular laser for diffuse diabetic macular edema. *Retina* 2008;28:1435-42.

43. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology* 2011;118:1580-7.

For peer review only

44. Callanan D, Gupta S, Ciulla TA, et al. Efficacy and safety of combination therapy with dexamethasone intravitreal implant (DEX Implant) plus laser photocoagulation versus monotherapy with laser for treatment of diffuse diabetic macular edema (DDME) [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 3968.

45. Kim Y, Kang S, Yi CH. Three-year follow-up of intravitreal triamcinolone acetonide injection and macular laser photocoagulation for diffuse diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 11-4-2010;51:E-Abstract 4260.

46. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609-14.

47. Nguyen QD, Shah SM, Heier JS, et al. Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2009;116:2175-81.

48. Ohji M, Ishibashi T, Sr., REVEAL study group. Efficacy and safety of ranibizumab 0.5 Mg as monotherapy or adjunctive to laser versus laser monotherapy in Asian patients with visual impairment due to diabetic macular edema: 12-month results of the REVEAL Study [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 4664.

49. Mitchell P, RESTORE extension study group. 2-year safety and efficacy outcome of ranibizumab 0.5 mg in patients with visual impairment due to diabetic macular edema (DME): an interim analysis of the RESTORE extension study [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 4667.

50. Do DV, Campochiaro PA, Boyer DS, et al. 6 month results of the READ 3 Study: Ranibizumab for Edema of the mAcula in Diabetes [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 5282.

51. Jorge R, Nepomuceno AB, Takaki E, et al. A prospective randomized trial of intravitreal bevacizumab versus ranibizumab for the management of refractory diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 26-3-2012;53:E-Abstract 347.

52. Michaelides M, Fraser-Bell S, Hamilton R, et al. Macular perfusion determined by fundus fluorescein angiography at the 4-month time point in a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (Bolt Study): Report 1. *Retina* 2010;30:781-6.

53. Faghihi H, Esfahani MR, Harandi ZA, et al. Intravitreal bevacizumab vs. combination of intravitreal bevacizumab plus macular photocoagulation in clinically significant diabetic macular edema: 6 months results of a randomized clinical trial. *Iranian J of Ophthalmol* 2010;22:21-6.

54. Soheilian M, Garfami KH, Ramezani A, et al. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. *Retina* 2012;32:314-21.

55. 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;227:100-6.

For peer review only

56. Oliveira Neto HL, Andrade RE, Casella M, et al. A randomized clinical trial to compare the efficacy and safety of isolated or combined intravitreal injection of triamcinolone acetonide and bevacizumab for diabetic macular edema ATEMD protocol - A Brazilian clinical trial [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 5331.

57. Adamis AP, Altaweel M, Bressler NM, et al. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology* 2006;113:23-8.

58. Do DV, Nguyen QD, Boyer D, et al. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 24-4-2012.

59. Haller JA, Kuppermann BD, Blumenkranz MS, et al. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol* 2010;128:289-96.

60. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 Years in patients with diabetic macular edema. *Ophthalmology* 21-6-2012.

61. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* 2009;127:245-51.

62. Ockrim ZK, Sivaprasad S, Falk S, et al. Intravitreal triamcinolone versus laser photocoagulation for persistent diabetic macular oedema. *Br J Ophthalmol* 2008;92:795-9.

63. Bressler NM, Edwards AR, Beck RW, et al. Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. *Arch Ophthalmol* 2009;127:1566-71.

64. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447-9.

65. Ford J, Elders A, Shyangdan D, et al. The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison. *BMJ* 2012;in press.

66. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;119:1399-411.

67. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388-98.

68. Campbell RJ, Gill SS, Bronskill SE, et al. Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study. *BMJ* 2012;345:e4203.

69. Van der Reis MI, La Heij EC, De Jong-Hesse Y, et al. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. *Retina-the Journal of Retinal and Vitreous Diseases* 2011;31:1449-69.

For peer review only

70. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006;90:1344-9.

71. Elbendary AM, Shahin MM. Intravitreal diclofenac versus intravitreal triamcinolone acetonide in the treatment of diabetic macular edema. *Retina* 2011;31:2058-64.

72. Sfikakis PP, Grigoropoulos V, Emfietzoglou I, et al. Infliximab for diabetic macular edema refractory to laser photocoagulation: a randomized, double-blind, placebo-controlled, crossover, 32-week study. *Diabetes Care* 2010;33:1523-8.

73. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 17-11-2007;370:1687-97.

74. PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty-month results of the randomized PKC-DMES clinical trial. *Arch Ophthalmol* 2007;125:318-24.

75. PKC-DMES Study Group. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy. *Ophthalmology* 2006;113:2221-30.

76. Fong DS, Strauber SF, Aiello LP, et al. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Arch Ophthalmol* 2007;125:469-80.

77. Health Canada. Reports of eye inflammation, endophthalmitis, and Toxic Anterior Segment Syndrome (TASS) following off-label intravitreal use of Avastin (bevacizumab). 2008 [cited 2012 Oct 24];Available from: URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_4_hpc-cps-eng.php

78. Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol* 2010;128:1273-9.

79. Gower EW, Cassard S, Chu L, et al. Adverse event rates following intravitreal injection of Avastin or Lucentis for treating age-related macular degeneration [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 6644.

80. General Medical Council. Prescribing medicines for use outside the terms of their licence (off-label). 2012 [cited 2012 Oct 24];Available from: URL: http://www.gmc-uk.org/guidance/ethical_guidance/prescriptions_faqs.asp#10

81. U.S.Food and Drug Administration. Off-Label" and investigational use of marketed drugs, biologics, and medical devices - Information Sheet. 2011 [cited 2012 Oct 24];Available from: URL: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm

82. Alimera Sciences. Alimera Sciences' ILUVIEN® Receives Marketing Authorization in France for the Treatment of Chronic Diabetic Macular Edema. 2012 [cited 2012 Oct 24];Available from: URL: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=692876

83. Laidlaw DA. Vitrectomy for diabetic macular oedema. *Eye* 2008;22:1337-41.

For peer review only

84. National Institute for Health and Clinical Excellence. Ranibizumab for the treatment of diabetic macular oedema:TA237. 2011 [cited 2012 Oct 24];Available from: URL: http://publications.nice.org.uk/ranibizumab-for-the-treatment-of-diabetic-macular-oedema-ta237

85. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema: 24-Month Data: Report 3. *Arch Ophthalmol* 9-4-2012.

86. Sivaprasad S, Dorin G. Subthreshold diode laser micropulse photocoagulation for the treatment of diabetic macular edema. *Expert Review of Medical Devices* 2012;9:189-97.

87. Cho WB, Moon JW, Kim HC. Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy. *Br J Ophthalmol* 2010;94:858-63.

88. Googe J, Brucker AJ, Bressler NM, et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011;31:1009-27.

89. Faghihi H, Roohipoor R, Mohammadi SF, et al. Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema. *Eur J Ophthalmol* 2008;18:941-8.

90. Figueroa MS, Contreras I, Noval S. Surgical and anatomical outcomes of pars plana vitrectomy for diffuse nontractional diabetic macular edema. *Retina* 2008;28:420-6.

91. Isaac DL, Abud MB, Frantz KA, et al. Comparing intravitreal triamcinolone acetonide and bevacizumab injections for the treatment of diabetic macular oedema: a randomized double-blind study. *Acta Ophthalmol* 2012;90:56-60.

92. Paccola L, Costa RA, Folgosa MS, et al. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). *Br J Ophthalmol* 2008;92:76-80.

93. Prager SG, Kriechbaum K, Mylonas G, et al. Comparison of intravitreally applied bevacizumab and triamcinolone on diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 11-4-2010;51:E-Abstract 4262.

94. Ozturk BT, Kerimoglu H, Bozkurt B, et al. Comparison of intravitreal bevacizumab and ranibizumab treatment for diabetic macular edema. *J Ocul Pharmacol Ther* 2011;27:373-7.

95. Marey HM, Ellakwa AF. Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. *Clin Ophthalmol* 2011;5:1011-6.

96. Shahin MM, El-Lakkany RS. A prospective, randomized comparison of intravitreal triamcinolone acetonide versus intravitreal bevacizumab (avastin) in diffuse diabetic macular edema. *Middle East Afr J Ophthalmol* 2010;17:250-3.

For peer review only

97. Loftus JV, Sultan MB, Pleil AM, et al. Changes in vision- and health-related quality of life in patients with diabetic macular edema treated with pegaptanib sodium or sham. *Investigative Ophthalmology & Visual Science* 2011;52:7498-505.

98. Ferrone PJ, Jonisch J. Ranibizumab dose comparison for the treatment of diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 2011;52:E-Abstract 5333.

99. Solaiman KA, Diab MM, Abo-Elenin M. Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. *Retina* 2010;30:1638-45.

100. Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards AR, et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;114:1860-7.

101. Lee SJ, Kim ET, Moon YS. Intravitreal bevacizumab alone versus combined with macular photocoagulation in diabetic macular edema. *Korean J Ophthalmol* 2011;25:299-304.

102. Audren F, Lecleire-Collet A, Erginay A, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular edema: phase 2 trial comparing 4 mg vs 2 mg. *Am J Ophthalmol* 2006;142:794-9.

103. Audren F, Erginay A, Haouchine B, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. *Acta Ophthalmol Scand* 2006;84:624-30.

104. Avitabile T, Longo A, Reibaldi A. Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema. *Am J Ophthalmol* 2005;140:695-702.

105. Bandello F, Pognuz DR, Pirracchio A, et al. Intravitreal triamcinolone acetonide for florid proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2004;242:1024-7.

106. Bonini MA, Jorge R, Barbosa JC, et al. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: A randomized clinical trial. *Invest Ophthalmol Vis Sci* 2005;46:3845-9.

107. Cellini M, Pazzaglia A, Zamparini E, et al. Intravitreal vs. subtenon triamcinolone acetonide for the treatment of diabetic cystoid macular edema. *BMC Ophthalmol* 2008;8:5TN.

108. Cardillo JA, Melo LA, Jr., Costa RA, et al. Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. *Ophthalmology* 2005;112:1557-63.

109. Chung EJ, Freeman WR, Azen SP, et al. Comparison of combination posterior sub-tenon triamcinolone and modified grid laser treatment with intravitreal triamcinolone treatment in patients with diffuse diabetic macular edema. *Yonsei Medi J* 31-12-2008;49:955-64.

110. Dehghan MH, Ahmadieh H, Ramezani A, et al. A randomized, placebo-controlled clinical trial of intravitreal triamcinolone for refractory diabetic macular edema. *Int Ophthalmol* 2008;28:7-17.

For peer review only

111. Diabetic Retinopathy Clinical Research Network, Chew E, Strauber S, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. *Ophthalmology* 2007;114:1190-6.

112. Gil AL, Azevedo MJ, Tomasetto GG, et al. Treatment of diffuse diabetic maculopathy with intravitreal triamcinolone and laser photocoagulation: randomized clinical trial with morphological and functional evaluation. *Arquivos Brasileiros de Oftalmologia* 2011;74:343-7.

113. Entezari M, Ahmadieh H, Dehghan MH, et al. Posterior sub-tenon triamcinolone for refractory diabetic macular edema: a randomized clinical trial. *Eur J Ophthalmol* 2005;15:746-50.

114. Hauser D, Bukelman A, Pokroy R, et al. Intravitreal triamcinolone for diabetic macular edema: comparison of 1, 2, and 4 mg. *Retina* 2008;28:825-30.

115. Jonas JB, Kamppeter BA, Harder B, et al. Intravitreal triamcinolone acetonide for diabetic macular edema: A prospective, randomized study. *J Ocul Pharmacol Ther* 2006;22:200-7.

116. Joussen AM, Weiss C, Bauer D, et al. Triamcinolone versus inner-limiting membrane peeling in persistent diabetic macular edema (TIME study): design issues and implications. *Graefes Arch Clin Exp Ophthalmol* 2007;245:1781-7.

117. Kaderli B, Avci R. Comparison of topical and subconjunctival anesthesia in intravitreal injection administrations. *Eur J Ophthalmol* 2006;16:718-21.

118. Kang SW, Sa HS, Cho HY, et al. Macular grid photocoagulation after intravitreal triamcinolone acetonide for diffuse diabetic macular edema. *Arch Ophthalmol* 2006;124:653-8.

119. Kim JE, Pollack JS, Miller DG, et al. ISIS-DME: a prospective, randomized, dose-escalation intravitreal steroid injection study for refractory diabetic macular edema. *Retina* 2008;28:735-40.

120. Lam DS, Chan CK, Mohamed S, et al. A prospective randomised trial of different doses of intravitreal triamcinolone for diabetic macular oedema. *Br J Ophthalmol* 2007;91:199-203.

121. Lee HY, Lee SY, Park JS. Comparison of photocoagulation with combined intravitreal triamcinolone for diabetic macular edema. *Korean J Ophthalmol* 2009;23:153-8.

122. Maia OO, Jr., Takahashi BS, Costa RA, et al. Combined laser and intravitreal triamcinolone for proliferative diabetic retinopathy and macular edema: one-year results of a randomized clinical trial. *Am J Ophthalmol* 2009;147:291-7.

123. Massin P, Audren F, Haouchine B, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. *Ophthalmology* 2004;111:218-24.

124. Mohamed S, Leung GM, Chan CK, et al. Factors associated with variability in response of diabetic macular oedema after intravitreal triamcinolone. *Clin Experiment Ophthalmol* 2009;37:602-8.

For peer review only

125. Nakamura A, Shimada Y, Horio N, et al. Vitrectomy for diabetic macular edema with posterior subtenon injection of triamcinolone acetonide. [Japanese]. *Folia Ophthalmol Japonica* 2004;55:958-62.

126. Spandau UH, Derse M, Schmitz-Valckenberg P, et al. Dosage dependency of intravitreal triamcinolone acetonide as treatment for diabetic macular oedema. *Br J Ophthalmol* 2005;89:999-1003.

127. Tunc M, Onder HI, Kaya M. Posterior sub-Tenon's capsule triamcinolone injection combined with focal laser photocoagulation for diabetic macular edema. *Ophthalmology* 2005;112:1086-91.

128. Verma LK, Vivek MB, Kumar A, et al. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. *J Ocul Pharmacol Ther* 2004;20:277-84.

129. Wickremasinghe SS, Rogers SL, Gillies MC, et al. Retinal vascular caliber changes after intravitreal triamcinolone treatment for diabetic macular edema. *Invest Ophthalmol Vis Sci* 2008;49:4707-11.

130. Yalcinbayir O, Gelisken O, Kaderli B, et al. Intravitreal versus sub-Tenon posterior triamcinolone injection in bilateral diffuse diabetic macular edema. *Ophthalmologica* 2011;225:222-7.

131. Haller JA, Bandello F, Belfort R, Jr., et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010;117:1134-46.

132. Haller JA, Dugel P, Weinberg DV, et al. Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema. *Retina* 2009;29:46-51.

133. Kuppermann BD, Blumenkranz MS, Haller JA, et al. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol* 2007;125:309-17.

134. Boyer DS, Faber D, Gupta S, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina* 2011;31:915-23.

135. Campochiaro PA, Hafiz G, Shah SM, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology* 2010;117:1393-9.

136. Gillies MC, Islam FM, Zhu M, et al. Efficacy and safety of multiple intravitreal triamcinolone injections for refractory diabetic macular oedema. *Br J Ophthalmol* 2007;91:1323-6.

137. Gillies MC, Simpson JM, Gaston C, et al. Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. *Ophthalmology* 2009;116:2182-7.

138. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a **prospective,** randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology* 2004;111:2044-9.

For peer review only

139. Brown DM, Nguyen QD, Rubio RG, et al. Ranibizumab for Diabetic Macular Edema (DME): 24-Month Efficacy and Safety Results of RISE - a Phase 3 Randomized Controlled Trial [abstract]. *Invest Ophthalmol Vis Sci* 22-4-2011;52:E-Abstract 6647.

140. Boyer D, Sy J, Rundle AC, et al. Ranibizumab (Anti-VEGF) for vision loss due to diabetic macular edema - results of two phase III randomized trials [abstract]. *71st Scientific Sessions June 24 - 28, 2011, San Diego Convention Center - San Diego, California* 2011;Abstract No, 133-LBOR.

141. Soheilian M, Ramezani A, Yaseri M, et al. Initial macular thickness and response to treatment in diabetic macular edema. *Retina* 2011;31:1564-73.

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Appendix 1: Methods of the literature search

Searches for clinical trials

Ovid MEDLINE 1948-July week 2, 2012 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012

1. Diabetic Retinopathy/dt [Drug Therapy]
2. Macular Edema/dt [Drug Therapy]
3. (diabet* adj2 macular adj (edema or oedema)).tw.
4. (diabet* adj2 maculopathy).tw.
5. (diabet* adj2 retinopathy).tw.
6. 1 or 2 or 3 or 4 or 5
7. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).tw.
8. exp Vascular Endothelial Growth Factor A/
9. exp Fluocinolone Acetonide/
10. exp Triamcinolone/
11. 7 or 8 or 9 or 10
12. 6 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. (masked or sham or placebo or control group or random*).tw.
16. 13 or 14 or 15
17. 12 and 16
18. (case reports or editorial or letter or review).pt.
19. 17 not 18
20. limit 19 to humans

Embase 1947 to 2012 Week 27

1. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).m_titl.
2. (diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy).m_titl.
3. 1 and 2
4. random*.tw.
5. 3 and 4

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ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor* in Record Title and diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy in Record Title

Web of Science® – with Conference Proceedings (updated 2012-07-12)

Title=(ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*) AND Title=(diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy) AND Title=(random*)

Searches for systematic reviews

Ovid MEDLINE(R) Daily Update July 11, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012

1. Diabetic Retinopathy/dt [Drug Therapy]
2. Macular Edema/dt [Drug Therapy]
3. (diabet* adj2 macular adj (edema or oedema)).tw.
4. (diabet* adj2 maculopathy).tw.
5. (diabet* adj2 retinopathy).tw.
6. 1 or 2 or 3 or 4 or 5
7. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).tw.
8. exp Vascular Endothelial Growth Factor A/
9. exp Fluocinolone Acetonide/
10. exp Triamcinolone/
11. 7 or 8 or 9 or 10
12. 6 and 11
13. (systematic review or meta-analysis or pubmed or medline).tw.
14. meta-analysis.pt.
15. cochrane.af.
16. 13 or 14 or 15
17. 12 and 16

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Cochrane Database of Systematic Reviews and Technology Assessments Database, Cochrane Library July Issue, 2012

"ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor* in Record Title and diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy in Record Title

Searches for safety and adverse events

Ovid MEDLINE(R) Daily Update July 11, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2012 ; Embase 1980to 2012 week 27

1. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or aflibercept or vegf trap-eye or macugen or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).m_titl.
2. (diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy).m_titl.
3. 1 and 2
4. (risk or safety or adverse or harm or pharmacovigilance).tw.
5. (side-effect* or precaution* or warning* or contraindication$ or contra-indication* or tolerability or toxic*).tw.
6. 4 or 5
7. 3 and 6

Searches of the annual meeting abstracts (for trials, reviews and safety studies)

- ARVO (Association for Research in Vision and Ophthalmology) (2002 to 2012)
- ADA (American Diabetes Association) (2002-2012)
- EASD (European Association for the Study of Diabetes) (2002-2012)

Other searches

Web sites of the following

- Drugs@FDA: FDA Approved Drug Products
- European Medicines Association
- ClinicalTrials.gov
- EU Clinical Trials Register

National Institute for Health and Clinical Excellence

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Appendix 2: Ongoing Trials in ClinicalTrials.gov

- Schmidt-Erfurth and colleagues are comparing ranibizumab and bevacizumab in DME (NCT00545870)
- TRIASTIN study is comparing ranibizumab, triamcinolone and sham injection (NCT00682539)
- Maturi and colleagues are comparing bevacizumab plus dexamethasone with bevacizumab alone (NCT01309451)
- IBeTA study (Jorge and colleagues) is comparing bevacizumab (1.5mg) plus laser, triamcinolone (4mg) plus laser with laser alone (NCT00997191)
- Chaudhry and colleagues are evaluating ranibizumab in patients who have failed with 3-6 injections of bevacizumab (NCT01253694)
- MIDME study (Pfizer) is comparing pegaptanib 0.3mg with sham injection. NCT01175070
- Figueira and colleagues are comparing pegaptanib plus laser with laser alone (NCT01281098)
- RESPOND (Novartis) is comparing ranibizumab (0.5mg) alone with ranibizumab plus laser or laser alone (NCT01135914)
- RETAIN (Novartis) study is comparing two different ranibizumab algorithms; "treat and extend" versus as needed (NCT01171976)
- RED-ES (Novartis) is comparing ranibizumab with laser in patients with visual impairment due to DME (NCT00901186)
- READ 3 study (Do and colleagues) are comparing two doses of ranibizumab 0.5 mg and 2 mg (NCT01077401)
- VIVID-DME and VISTA DME studies (Bayer) are comparing aflibercept with laser. (NCT01331681 and NCT01363440)
- Gillies and colleagues are comparing bevacizumab with dexamethasone (NCT01298076)
- Soheilian and colleagues are performing a phase I study looking at the use of diclofenac compared with bevacizumab in DME (NCT00999791)
- López-Miranda and colleagues are comparing the use of bevacizumab before and after laser therapy (NCT00804206)
- NEVANAC study is comparing triamcinolone alone with triamcinolone plus nepafenac (NSAID) (NCT00780780)
- Elman and colleagues are comparing laser alone, laser combined with an intravitreal injection of triamcinolone, laser combined with an intravitreal injection of ranibizumab, or intravitreal injection of ranibizumab alone (NCT00444600)
- BRDME (Schlingemann and collagues) study is comparing the use of bevacizumab and ranibizumab in the treatment of patients with DME (OCT central area thickness > 275 µm) (NCT01635790)
- Wiley and colleagues are comparing bevacizumab and ranibizumab in patients with DME in at least one eye(NCT01610557)
- Protocol T study (Wells and colleagues) is comparing effectiveness of a aflibercept, bevacizumab, and ranibizumab for DME (NCT01627249)
- Allergan funded study comparing safety and efficacy of 700 µg dexamethasone implant against 0.5 mg ranibizumab in patients with DME (NCT01492400)
- Pfizer funded study comparing effectiveness of 0.3 mg pegaptanib against sham injection (NCT01100307)

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- Allergan funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 µg and 350 µg) against sham in patients with DME (NCT00168389)
- Allergan funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 µg and 350 µg) against sham in patients with DME (NCT00168337)

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Figure 1 - PRISMA

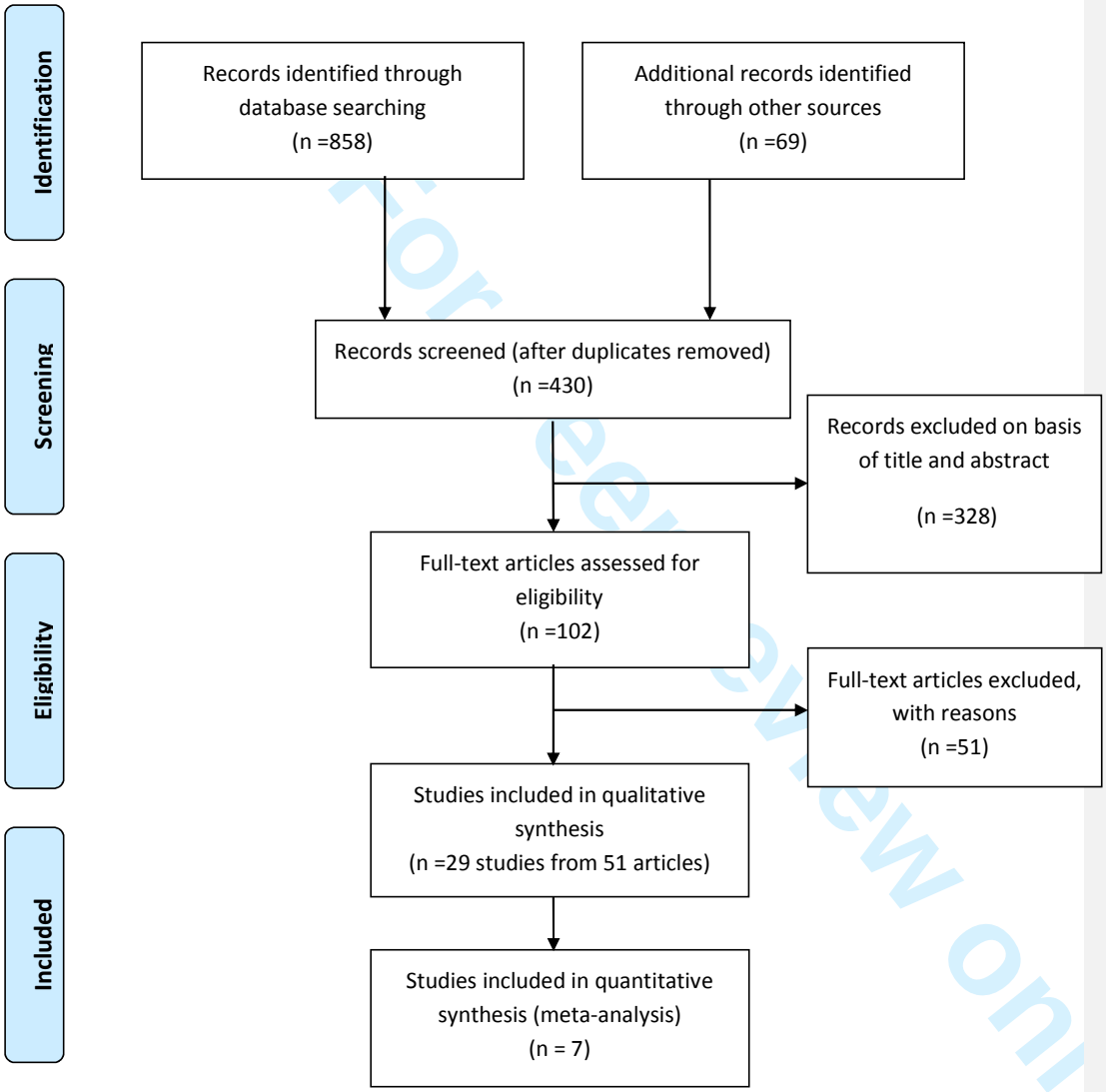

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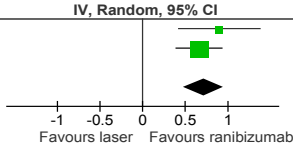
Figure 2 Ranibizumab 0.5mg alone versus laser alone

2.1 Mean change in BCVA

Study or Subgroup	Rani 0.5 mg Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	0.14	0.17	37	-0.01	0.16	38	24.1%	0.90 [0.42, 1.38]
RESTORE 2011	0.12	0.13	115	0.02	0.17	110	75.9%	0.66 [0.39, 0.93]
Total (95% CI)			**152**			**148**	**100.0%**	**0.72 [0.48, 0.95]**

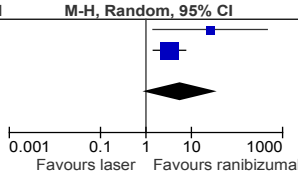
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 6.02 (P < 0.00001)



2.2 Proportion with >15 letter gain

Study or Subgroup	Rani 0.5 mg Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
READ-2 2009	9	37	0	38	28.0%	25.67 [1.43, 459.42]
RESTORE 2011	26	115	9	110	72.0%	3.28 [1.46, 7.37]
Total (95% CI)		**152**		**148**	**100.0%**	**5.83 [0.90, 37.86]**
Total events	35		9			

Heterogeneity: Tau² = 1.09; Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 1.85 (P = 0.06)



2.3 CMT

Study or Subgroup	Rani 0.5 mg Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	-103.73	126.76	37	-144.76	109.22	38	47.2%	0.34 [-0.11, 0.80]
RESTORE 2011	-118.7	115.07	115	-61.3	132.29	110	52.8%	-0.46 [-0.73, -0.20]
Total (95% CI)			**152**			**148**	**100.0%**	**-0.08 [-0.87, 0.71]**

Heterogeneity: Tau² = 0.29; Chi² = 8.96, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.20 (P = 0.84)

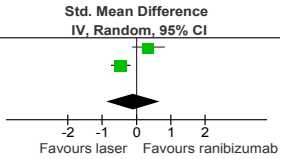
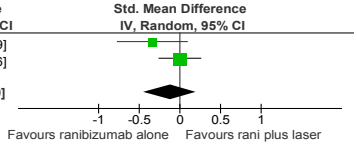


Figure 3 Ranibizumab 0.5mg plus laser versus ranibizumab 0.5mg alone

3.1 Mean change in BCVA

Study or Subgroup	Rani 0.5 plus laser Mean	SD	Total	Rani 0.5mg alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
READ-2 2009	0.08	0.18	42	0.14	0.17	42	36.5%	-0.34 [-0.77, 0.09]
RESTORE 2011	0.12	0.16	118	0.12	0.13	116	63.5%	0.00 [-0.26, 0.26]
Total (95% CI)			**160**			**158**	**100.0%**	**-0.12 [-0.44, 0.20]**

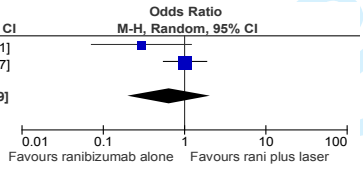
Heterogeneity: Tau² = 0.02; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 0.76 (P = 0.45)



3.2 Proportion with >15 letter gain

Study or Subgroup	Rani 0.5 plus laser Events	Total	Rani 0.5mg alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
READ-2 2009	3	40	8	37	36.3%	0.29 [0.07, 1.21]
RESTORE 2011	27	118	26	115	63.7%	1.02 [0.55, 1.87]
Total (95% CI)		**158**		**152**	**100.0%**	**0.65 [0.20, 2.09]**
Total events	30		34			

Heterogeneity: Tau² = 0.46; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.73 (P = 0.47)



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3.3 CMT

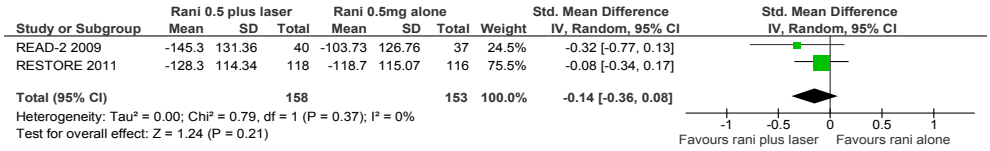
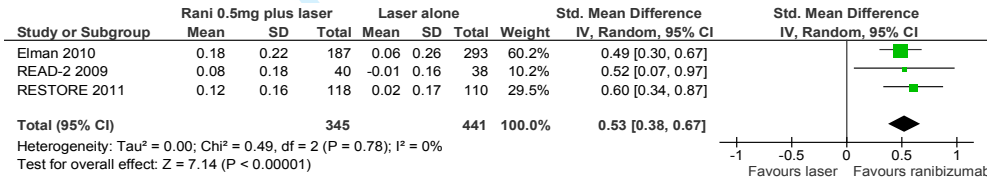
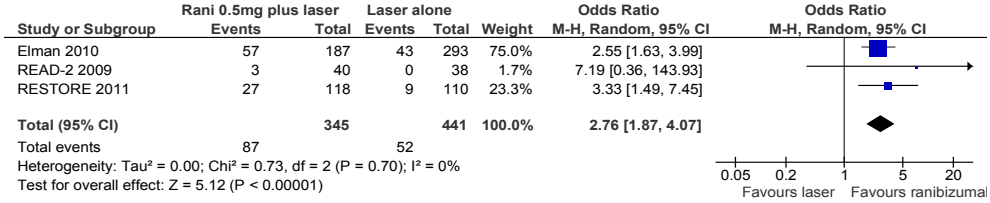


Figure 4 Ranibizumab 0.5mg plus laser versus laser alone

4.1 Mean change in BCVA



4.2 Proportion with >15 letter gain



4.3 CMT

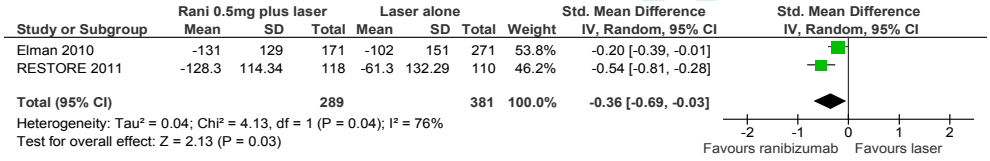


Figure 5 Pegaptanib 0.3mg versus sham injection

5.1 Proportion with >15 letter gain

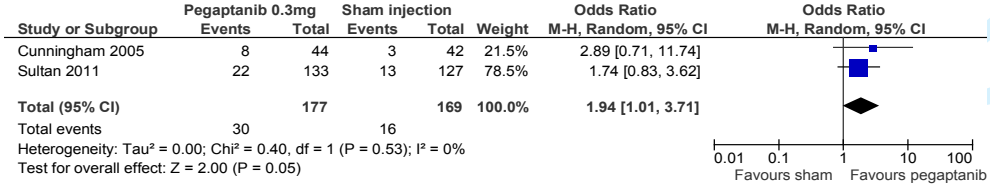


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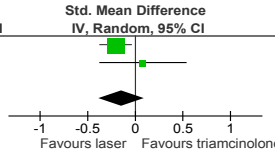
Figure 6 Triamcinolone 4mg versus laser alone

6.1 Mean change in BCVA

Study or Subgroup	Triamcinalone 4mg alone Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ip 2008	-0.06	0.44	254	0.02	0.34	330	78.2%	-0.21 [-0.37, -0.04]
Lam 2007	-0.7	10.7	38	-1.6	11.5	37	21.8%	0.08 [-0.37, 0.53]
Total (95% CI)			**292**			**367**	**100.0%**	**-0.14 [-0.38, 0.09]**

Heterogeneity: Tau² = 0.01; Chi² = 1.36, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.22 (P = 0.22)



6.2 Proportion with >15 letter gain

Study or Subgroup	Triamcinalone 4mg alone Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ip 2008	43	254	59	330	95.6%	0.94 [0.61, 1.44]
Lam 2007	2	38	2	37	4.4%	0.97 [0.13, 7.29]
Total (95% CI)		**292**		**367**	**100.0%**	**0.94 [0.61, 1.43]**
Total events	45		61			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)

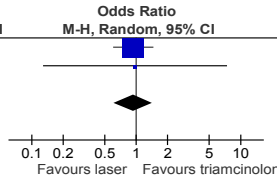
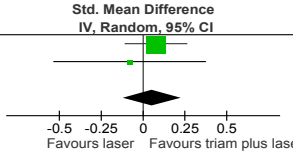


Figure 7 Triamcinolone 4mg plus laser versus laser alone

7.1 Mean change in BCVA

Study or Subgroup	Triam 4mg plus laser Mean	SD	Total	Laser alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Elman 2010	0.08	0.26	186	0.06	0.26	293	85.9%	0.08 [-0.11, 0.26]
Lam 2007	0.7	10.7	38	1.6	11.5	37	14.1%	-0.08 [-0.53, 0.37]
Total (95% CI)			**224**			**330**	**100.0%**	**0.05 [-0.12, 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)



7.2 Proportion with >15 letter gain

Study or Subgroup	Triam 4mg plus laser Events	Total	Laser alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Elman 2010	39	186	43	293	94.7%	1.54 [0.96, 2.49]
Lam 2007	2	38	2	37	5.3%	0.97 [0.13, 7.29]
Total (95% CI)		**224**		**330**	**100.0%**	**1.50 [0.94, 2.40]**
Total events	41		45			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)

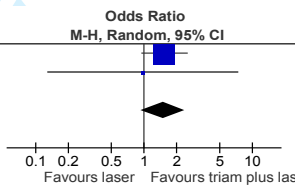


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Table 1: List of excluded studies

Study	Reason
Active comparator trials	
Cho 2010[87]	Single dose
DRCRN 2010 (Googe 2010)[88]	<6 mths f/u
Faghihi 2008[89]	Single dose
Figueroa 2008[90]	Single dose
Isaac 2012[91]	Single dose
Paccola 2008[92]	Single dose
Prager 2011[93]	<25 pts per arm
Ozturk 2011[94]	Non-RCT
Marey 2011[95]	<6 mths
Shahin 2010[96]	Single dose
Pegaptanib	
Loftus 2011[97]	Quality of life data.
Ranibizumab	
Ferrone 2011[98]	<25 pts per arm
Bevacizumab	
Solaiman 2010[99]	Single dose
DRCRN –Scott 2007[100]	<25 pts per arm
Lee 2011[101]	Non-RCT
Isaac 2012[91]	Single dose
Trimacinolone	
Audren 2006a[102]	Single dose (dosing study)
Audren 2006b[103]	Single dose
Avitabile 2005[104]	Mixed RVO and DMO
Bandello 2004[105]	Case report + PDR
Bonini 2005[106]	Single dose injection technique
Cellini 2008[107]	Single injection PSTI
Cardillo 2005[108]	Single injection PSTI
Chung 2008[109]	Single injection PSTI
Dehghan 2008[110]	Single dose
DRCRN -Chew 2007[111]	<25 pts per arm
Gil 2011[112]	<25 pts per arm
Entezari 2005[113]	<6 months
Hauser 2008[114]	Single dose
Jonas 2006[115]	Single dose
Joussen 2007[116]	Study protocol
Avci 2006[117]	Anaesthetic technique
Kang 2006[118]	Single dose
Kim 2008[119]	Single injection and CME
Lam 2007b[120]	Single injection
Lee 2009[121]	Single injection
Maia 2009[122]	Single dose
Massin 2004[123]	Single dose
Mohamed 2009[124]	Post-hoc analysis
Nakamura 2004[125]	Single dose
Spandau 2005[126]	Single dose
Tunc 2005[127]	<6 months

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Verma 2004[128]	Single dose
Wickremasinghe 2008[129]	Single dose
Yalcinbayir 2011[130]	Single dose
Dexamethasone	
Haller 2010[131]	<6 months
Haller 2009[132]	<25pts per arm
Kuppermann 2007 [133]	Mixture of macular oedema causes
Boyer 2011[134]	Non-randomised
Fluocinolone	
Campochiaro 2010[135]	<25pts per arm
Diclofenac	
Elbendary 2011 [71]	<35pts per arm

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Table 2~~16~~: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Anti-VEGFs							
Ranibizumab							
READ-2 Study [28,47]	Unclear	Unclear	Unclear	Yes (91.3% completion)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Juvenile Diabetes Research Foundation, Genentech Inc.
RESOLVE Study (Massin 2010)[36]	Yes	Yes	Yes (patients and outcome assessors)	Yes (82% completion in sham arm, 90.2% with ranibizumab)	Yes	Comparison groups similar at baseline; power analysis unclear	Novartis Pharma, Switzerland
RESTORE Study (Mitchell 2011)[24]	Yes	Unclear	Yes (patients, outcome assessors)	Yes (87.3 to 88.3% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Novartis Pharma, Switzerland
RISE and RIDE (Nguyen 2012)[38]	Yes	Yes	Yes (patients, treating physician masked to assigned dose of ranibizumab)	Yes (2 year study completed by 83.3% of patients in RISE and by 84.6% in RIDE)	Yes	Comparison groups similar at baseline; ITT analysis; power analysis carried out (power adequate for primary endpoint)	Genentech Inc.
Bevacizumab							
BOLT Study (Michaelides 2010)[23,52]	Yes	Unclear	Partial (outcome assessors, not patients)	Yes (97.5% completion)	Yes	Comparison groups similar at baseline (except laser group had longer duration of clinically significant DMO); power analysis carried out (power adequate for VA changes)	Moorfields Special Trustees, National Institute for Health Research
Faghihi 2010[53]	Yes	Unclear	Yes (patient	Yes (100% completion)	Yes	Comparable groups at baseline	Not specified

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Lam 2009[35]	Yes	Yes	Yes (patients and technicians assessing BCVA, OCT and IOP)	Yes (92.3% follow-up at 6 months)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	supported in part by the Action for Vision Eye Foundation Hong Kong (charity)
Pegaptanib							
Cunningham 2005 / Adamis 2006[39,57]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (95% completion)	Yes	Comparison groups similar at baseline; acknowledge lack of power to detect differences between doses of pegaptanib	Eyetech Pharmaceuticals Inc., New York, and Pfizer Inc., New York
Sultan 2011[40]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (69.9 to 73.8% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Pfizer Inc., New York
Aflibercept							
Da Vinci 2010 [30,58]	Unclear (predetermined randomization scheme)	Unclear	Yes (patients)	Yes (85% completion)	Yes	Comparison groups similar at baseline, power calculation completed	Regeneron Pharmaceuticals, Inc., New York
Steroids							
Dexamethasone							
Haller 2010[59]	Yes	Unclear	Yes (patients to dexamethasone dose, outcome assessors)	Yes (92% completion)	Yes	Comparison groups similar at baseline; power analysis carried out, but study not powered to detect differences in subgroups	Oculex Pharmaceuticals Inc.
Fluocinolone							
FAME Study (Campochiaro 2011)[29,60]	Unclear	Unclear	Partial (patients, masking of outcome assessment not mentioned)	Yes (drop-out rate 19.0 to 22.7%)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Alimera Sciences Inc., Atlanta, Georgia; Psivida Inc., Watertown, Massachusetts

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Pearson 2011[43]	Yes	Unclear	Third party masked design (patient and investigator not masked)	No losses to follow-up	Yes	Demographic characteristics were similar between implant and SOC groups; power calculation done, study adequately powered.	Bausch & Lomb Inc, Rochester, New York
Triamcinolone							
DRCR Network 2008 [22,61,63,64]	Yes	Unclear	Partial (patients to triamcinolone dose, outcome assessors not formally masked but generally not aware of participant's study group)	Yes (81 to 86% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services
Gillies 2006 / 2007 / 2009 / Sutter 2004[32,136-138]	Yes	Yes	Yes (patients, outcome assessors)	Yes (91% completion intervention, 83% control)	Yes	Comparison groups similar at baseline (but limited demographic data); power analysis carried out (power adequate for VA changes)	Sydney Eye Hospital Foundation and Juvenile Diabetes Research Foundation, New York
Gillies 2011[33]	Yes	Yes	Yes (patients, outcome assessors)	Yes (84.5% completion)	Yes	power analysis carried out (power adequate for VA changes)	National Health and Medical Research Council, Canberra, Australia, and the Sydney Eye Hospital Foundation, Sydney, Australia
Lam 2007[34]	Yes	Yes	Partial (outcome assessors)	No losses to follow-up	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	Action for Vision Foundation, Hong Kong
Ockrim 2008/Sviprasad 2008[42,62]	Yes	Unclear	Unclear	Yes (94% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Special Trustees of Moorfields Eye Hospital
Active comparator trials							

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Ahmadieh 2008[31]	Yes	Yes	Yes (patients and outcome assessors)	Unclear	Yes	CMT lower in control group at baseline ($p<0.05$), other baseline values similar; power analysis carried out (power adequate for CMT changes)	Not reported
DRCR Network [21,46]	Yes	Unclear	Yes (patients, except deferred laser group: outcome assessors); masking discontinued after the first year	Yes (1 year completion for 91-95% of eyes)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and Human Services; Ranibizumab provided by Genentech, triamcinolone provided by Allergan Inc.; companies also provided funds to defray the study's clinical site costs
Lim 2012[55]	Yes	Unclear	Yes (investigators only)	Yes (7.5% drop out after enrollment)	Yes	Groups similar at baseline. The bevacizumab group received more injections.	Not reported
Soheilian [37,41]	Yes	Yes	Yes (patients and outcome assessors)	Unclear (36 week completion for 76 to 88%)	Yes	CMT significantly lower and VA significantly better in MPC group at baseline, other baseline values similar; power analysis carried out (power adequate for VA changes)	Ophthalmic Research Centre, Labbafinejad Medical Center, Tehran

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Table 23: Ranibizumab trials

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
READ-2 Study (Nguyen 2009 / Nguyen 2010)[28,47] **USA** Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months, 2 year extension [no relevant outcomes as IVR received by all groups by that time, no safety outcomes for 2 year data]	**N:** 126 eyes of 126 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO, BCVA 20/40 to 20/320, CMT ≥250 µm, HbA1c ≥6% within 12 months before randomization; expectation that scatter laser photocoagulation not required for 6 months **Exclusion criteria:** contributing causes to reduced BCVA other than DMO, focal/grid laser within 3 months, intraocular steroid within 3 months, intraocular VEGF antagonist within 2 months **Age:** 62 years **Sex:** 52 to 69% female **Diabetes type:** not reported **HbA1c:** 7.39 to 7.77% **Baseline VA:** ETDRS letter score 24.85 to 28.35 **Baseline CMT:** excess foveal thickness 198.75 to 262.52 µm **Comorbidities:** not reported	**Group 1 (IVR, n=42 eyes):** IV injections of 0.5 mg ranibizumab at baseline, 1, 3, and 5 months **Group 2 (L, n=42 eyes):** focal/grid laser at baseline and 3 months if CMT ≥250 µm **Group 3 (IVRL, n=42 eyes):** IV injections of 0.5 mg ranibizumab at baseline and 3 months, followed by focal/grid laser treatment 1 week later **Regimen for all groups:** after 6 months, patients could receive IV injections of ranibizumab no more than every 2 months or focal/grid laser no more than every 3 months if CMT ≥250 µm **Laser** Modified ETDRS protocol was used	**At 6 months** **BCVA (ETDRS):** **BCVA (letters)** / **p** ***IVR*** +7.24 / 0.0003 vs L ***L*** -0.43 ***IVRL*** +3.80 / NS vs IVR or L **plus ≥3 lines** ***IVR*** 22% / <0.05 vs L ***L*** 0 ***IVRL*** 8% **CMT (OCT):** **CMT (µm)** / **p** ***IVR*** -106.3 / all <0.01 vs baseline, NS for elimination of ≥50% excess foveal thickness between groups ***L*** -82.8 ***IVRL*** -117.2
READ-3 Study (Do 2012) USA[50] **Design:** phase 2, 2-arm RCT **Follow-up:** 6 months	**N:** 152 eyes **Inclusion criteria:** NR **Exclusion criteria:** NR **Age:** NR **Sex:** NR **Diabetes type:** NR **HbA1c:** NR **Baseline VA:** Mean BCVA Snellen equivalent 20/63 in the 2.0 mg group and 20/80 in the 0.5 mg group **Baseline CST (central subfield thickness):** 432 µm in the 2.0 mg group and 441 µm in the 0.5 mg group **Comorbidities:** NR	**Group 1 (IVR2.0, n=NR):** monthly injections **Group 2 (IVR0.5, n=NR):** monthly injections After month 6, eyes evaluated and additional ranibizumab injections given on an as needed basis if DMO still present on OCT.	**At 6 months:** **BCVA** **Mean BCVA letters gain** / **p** ***IVR2.0*** +7.46 / NR ***IVR0.5*** +8.69 / NR **CST** **CST reduction** ***IVR2.0*** -163.86 µm / NR ***IVR0.5*** -169.27 µm / NR

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
RESOLVE Study (Massin 2010)[36] Multicenter international **Design:** 3-arm placebo-controlled RCT **Follow-up:** 12 months	**N:** 151 eyes of 151 patients **Inclusion criteria:** >18 years, type 1 or 2 DM, clinically significant DMO, BCVA 20/40 to 20/160, HbA1c <12%, decreased vision attributed to foveal thickening from DMO, laser photocoagulation could be safely withheld in the study eye for at least 3 months after randomization **Exclusion criteria:** unstable medical status, panretinal laser photocoagulation performed within 6 months before study entry, previous grid/laser photocoagulation except patients with only mild laser burns at least 1000 µm from the centre of the fovea performed >6 months previously **Age:** 63 to 65 (range 32 to 85) years **Sex:** 43.1 to 49.0% female **Diabetes type:** 96.1 to 98.0% type 2 DM **HbA1c:** 7.3 to 7.6 (range 5.3 to 11.1) % **Baseline VA:** ETDRS letter score 59.2 to 61.2 SD9.0 to 10.2 **Baseline CMT:** 448.9 to 459.5 SD102.8 to 120.1 µm **Comorbidities:** not reported	**Group 1 (IVR0.3, n=51 eyes):** 0.3 mg (0.05 ml) IV ranibizumab, 3 monthly injections (dose up to 0.6 mg, see below) **Group 2 (IVR0.5, n=51 eyes):** 0.5 mg IV (0.05 ml) ranibizumab, 3 monthly injections (dose up to 1.0 mg, see below) **Group 3 (C, n=49 eyes):** sham treatment, 3 monthly injections **Regimen for all groups:** after month 1, the injection dose could be doubled if CMT remained >300 µm or was >225 µm and reduction in retinal oedema from previous assessment was <50 µm; once injection volume was 0.1 ml it remained that for subsequent injections; if treatment had been withheld for >45 days, subsequent injections restarted at 0.05 ml; 68.6% of dose doubling with ranibizumab, 91.8% with sham; 34.7% of rescue laser photocoagulation in sham group, 4.9% in ranibizumab group	**At 12 months** **BCVA (ETDRS):** **BCVA (letters) p** ***IVR0.3*** +11.8 SD6.6 <0.0001 vs C ***IVR0.5*** +8.8 SD11.0 <0.0001 vs C ***C*** -1.4 SD14.2 **change ≥10 letters** ***IVR0.3*** gain 72.5% loss 0 <0.0001 vs C ***IVR0.5*** gain 49.0% loss 9.8% 0.001 vs C ***C*** gain 18.4% loss 24.5% **CMT (OCT):** **CMT (µm) p** ***IVR0.3*** -200.7 SD122.2 <0.0001 vs C ***IVR0.5*** -187.6 SD147.8 <0.0001 vs C ***C*** -48.4 SD153.4
RESTORE Study (Mitchell 2011/ Mitchell 2012)[24,49] Multicenter international **Design:** 3-arm RCT **Follow-up:** 12 months	**N:** 345 eyes of 345 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, HbA1c ≤10%, visual impairment due to DMO (eligible for laser treatment), stable medication for management of diabetes, BCVA ETDRS letter score 39 to 78 **Exclusion criteria:** concomitant eye conditions that could affect VA, active intraocular inflammation or infection, uncontrolled glaucoma in either eye, panretinal laser photocoagulation within 6 months or focal/grid laser photocoagulation within 3 months prior to study entry, history of stroke, hypertension. **Age:** 62.9 to 64.0 SD8.15 to 9.29 years **Sex:** 37.1 to 47.7% female **Diabetes type:** 86.4 to 88.8% type 2 DM **HbA1c:** not reported	**Group 1 (IVR, n=116 eyes):** 0.5 mg IV ranibizumab plus sham laser (median injections 7 (range 1 to 12), median sham laser treatments 2 (range 1 to 5)) **Group 2 (IVRL, n=118 eyes):** 0.5 mg IV ranibizumab plus active laser (median injections 7 (range 2 to 12), median laser treatments 1 (range 1 to 5)) **Group 3 (L, n=111 eyes):** laser treatment plus sham injections (median sham injections 7 (range 1 to 12), median laser treatments 2 (range 1 to 4)) **Regimen for all groups:** 3 initial monthly injections, followed by retreatment schedule; 1 injection per month if stable VA not reached;	**At 12 months** **BCVA (ETDRS):** **BCVA (letters) p** ***IVR*** +6.1 SD6.43 <0.0001 vs L ***IVRL*** +5.9 SD7.92 <0.0001 vs L ***L*** +0.8 SD8.56 **BCVA change categories** ***IVR*** plus ≥10: 37.4% loss ≥10: 3.5% <0.0001 vs L ***IVRL*** plus ≥10: 43.2% loss ≥10: 4.2% <0.0001 vs L ***L*** plus ≥10: 15.5% loss ≥10: 12.7% **CMT (OCT):**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	Baseline VA: ETDRS letter score 62.4 to 64.8 SD9.99 to 11.11 **Baseline CMT:** 412.4 to 426.6 SD118.01 to 123.95 **Comorbidities:** not reported	**Laser** retreatments in accordance with ETDRS guidelines at intervals no shorter than 3 months from previous treatment	**CMT (µm) / p** ***IVR*** -118.7 SD115.07 — 0.0002 vs L ***IVRL*** -128.3 SD114.34 — <0.0001 vs L ***L*** -61.3 SD132.29
REVEAL Study (Ohji 2012) Japan Multicenter[48] **Design:** phase III double-masked RCT **Follow-up:** 12 months	**N:** 396 patients **Inclusion criteria:** NR **Exclusion criteria:** NR **Age:** 61.1 years **Sex:** NR **Diabetes type:** 98.7% with type 2 diabetes **HbA1c:** 7.5% **Baseline VA:** 58.6 letters **Baseline CMT:** 421.9 µm **Comorbidities:** NR	**Group 1 (IVR 0.5 + sham laser, n=133):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA **Group 2 (IVR 0.5+ active laser, n=132):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA **Group 3 (sham injection + active laser, n=131):** Day 1, month 1, 2 and pro-re-nata thereafter based on BCVA Active/sham laser photocoagulation performed according to ETDRS guidelines at ≥3 month intervals.	**At 12 months BCVA:** **Mean average change from baseline to month 1 to 12 / p** ***IVR + sham laser*** +5.9 — vs laser <0.0001 ***IVR + laser*** +5.7 — vs laser <0.0001 ***Laser + sham*** +1.4 **Mean change from baseline to month12 in BCVA and CRT** ***IVR + sham laser*** +6.6; -148.0 µm — vs C <0.0001 ***IVR + laser*** +6.4; -163.8 µm — vs C <0.0001 ***Laser + sham*** +1.8; -57.1 µm
RISE Study (Brown 2011/Nguyen 2012)[38,139] USA Multicenter **Design:** 3-arm double-blind sham-controlled RCT **Follow-up:** 24 months	**N:** 377 eyes of 377 patients **Inclusion criteria:** ≥18 years, type 1 or 2 diabetes, BCVA 20/40 to 20/320, DMO CMT ≥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 or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction **Age:** 61.7 to 62.8 SD8.9 to 10.0 (range 21 to 87) years **Sex:** 41.6 to 48% female	**Group 1 (IVR0.3, n=125 eyes):** 0.3 mg IV ranibizumab **Group 2 (IVR0.5, n=125 eyes):** 0.5 mg IV ranibizumab **Group 3 (C, n=127 eyes):** sham injection **Regimen for all groups:** monthly injections; need for macular rescue laser assessed monthly starting at month 3	**At 24 months BCVA:** **plus ≥15 letters / p** ***IVR0.3*** 44.8% — <0.0001 vs C ***IVR0.5*** 39.2% — =0.0002 vs C ***C*** 18.1% **Loss of <15 letters** ***IVR0.3*** 97.6% — =0.0086 vs C ***IVR0.5*** 97.6% — =0.0126 vs C ***C*** 89.8%

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	Diabetes type: type 1 or 2 **HbA1c:** 7.7% SD 1.4 to 1.5; ≤8% (65 to 68.3%); >8% (31.7% to 35%) **Baseline VA:** Mean ETDRS letter score 54.7 to 57.2; ≤20/200 (7.9 to 13.6%); >20/200 but <20/40 (72.4 to 72.8%); ≥20/40 (13.6 to 19.7%) **Baseline CMT:** 463.8 to 474.5 µm **Comorbidities:** History of smoking 46.4 to 51.2%		**Snellen equivalent of 20/40 or better** ***IVR0.3*** 60.0% <0.0001 vs C ***IVR0.5*** 63.2% <0.0001 vs C ***C*** 37.8% **Mean BCVA gain (letters)** ***IVR0.3*** +12.5 SD14.1 <0.0001 vs C ***IVR0.5*** +11.9 SD12.1 <0.0001 vs C ***C*** +2.6 SD13.9 **CFT:** **Mean change from baseline** **p** ***IVR0.3*** -250.6 SD212.2 <0.0001 vs C ***IVR0.5*** -253.1 SD183.7 <0.0001 vs C ***C*** -133.4 SD209.0
RIDE study (Boyer 2011/Nguyen 2012)[38,140] USA Multicentre **Design:** 3-arm double-blind sham-controlled RCT **Follow-up:** 24 months	**N:** 382 eyes **Inclusion criteria:** ≥18 years, type 1 or 2 diabetes, BCVA 20/40-20/320 and DMO CMT ≥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 or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction **Age:** 61.8 to 63.5 (range 22 to 91) years **Sex:** 37 to 49.1% female **Diabetes type:** type 1 or 2 **HbA1c:** 7.6 SD1.3 to 1.5; ≤8% (65.8 to 67.5%); >8% (32.5 to 34.2%) **Baseline VA:** Mean ETDRS letter score 56.9 to 57.5	**Group 1 (IVR0.3, n=125 eyes):** 0.3 mg IV ranibizumab **Group 2 (IVR0.5, n=127 eyes):** 0.5 mg IV ranibizumab **Group 3 (C, n=130 eyes):** sham injection **Regimen for all groups:** Patients were eligible for rescue macular laser starting at Month 3	**At 24 months** **BCVA:** **More than 15 letters** **p** ***IVR0.3*** 33.6% <0.0001 vs. C ***IVR0.5*** 45.7% <0.0001 vs. C ***C*** 12.3% **Less than 15 letters** ***IVR0.3*** 1.6% >0.05 vs C ***IVR0.5*** 3.9% <0.05 vs. C ***C*** 8.5% **Snellen equivalent of 20/40 or better** ***IVR0.3*** 54.4% =0.0002 vs C

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)		
	Baseline CMT: 447.4 to 482.6 µm **Comorbidities:** history of smoking 33.6 to 51.6%		***IVR0.5***	62.2%	<0.0001 vs C
			C	34.6%	
				Mean BCVA gain (letters)	
			IVR0.3	+10.9 SD10.4	<0.0001vs C
			IVR0.5	+12.0 SD14.9	<0.0001 vs. C
			C	+2.3 SD14.2	
			CMT:		
				Mean change from baseline	**p**
			IVR0.3	-259.8 SD169.3	<0.0001 vs C
			IVR0.5	-270.7 SD201.6	<0.0001 vs C
			C	-125.8 SD198.3	

Abbreviations: BCVA – best corrected visual acuity, CMT – central macular thickness, DM – diabetes mellitus, DMO – diabetic macular oedema, DP – diastolic pressure, DR – diabetic retinopathy, HR QoL – health-related quality of life, IOP – intraocular pressure, IQR – interquartile range, IV – intravitreal, NEI VFQ-25 – National Eye Institute Visual Function Questionnaire-25, NPDR – nonproliferative diabetic retinopathy, NR – not reported, OCT – optical coherence tomography, PDR – proliferative diabetic retinopathy, PRP – panretinal photocoagulation, RCT – randomized controlled trial, SD – standard deviation, SP – systolic pressure, VA – visual acuity, VEGF – vascular endothelia growth factor, vs – versus, CSME – clinically significant macular oedema, MLT/MPC – macular laser therapy/macular photocoagulation, IVR – intravitreal ranibizumab, IVB – intravitreal bevacizumab, IVP – intravitreal pegaptanib, IVVTE – intravitreal VEGF Trap Eye, C - control, DIL - dexamethasone followed by laser, DDS - dexamethasone, SRFA – fluocinolone, SOC – standard of care, IVT - intravitreal triamcinolone, L – laser, IVTL intravitreal triamcinolone plus laser **Notes:** injections are intravitreal unless otherwise noted

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Table ~~34~~ 34: Bevacizumab studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
BOLT Study (Michaelides 2010/ Rajendram 2012)) [23,52,85] **UK** **Design:** 2-arm RCT **Follow-up:** 12 months	**N:** 80 eyes of 80 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, BCVA in the study eye 35 to 69 ETDRS letters at 4 m (≥6/60 or ≤6/12), center-involving clinically significant DMO with CMT ≥270 µm; media clarity, papillary dilation and cooperation sufficient for adequate fundus imaging; a least 1 prior macular laser therapy; IOP <30 mmHg; fellow eye BCVA ≥3/60; fellow eye received no anti-VEGF in past 3 months and no expectation of such therapy **Exclusion criteria:** (ocular for study eye) macular ischemia, macular oedema due to causes other than DMO, coexistent ocular disease affecting VA or DMO, any treatment for DMO in prior 3 months, PRP within 3 months prior to randomization or anticipated, PDR, HbA1c >11.0%, medical history of chronic renal failure; any thromboembolic event within 6 months prior to randomization, unstable angina, evidence of active ischemia on ECG; major surgery within 28 days of randomization or planned; participation in an investigational drug trial; systemic anti-VEGF or pro-VEGF treatment within 3 months of enrollment; pregnancy, lactation; intraocular surgery within 3 months of randomization; aphakia; uncontrolled glaucoma; significant external ocular disease **Age:** 64.2 SD8.8 years **Sex:** 31% female **Diabetes type:** 90% type 2 DM, 10% type 1 DM **HbA1c:** 7.5 to 7.6 SD1.2 to 1.4% **Baseline VA:** ETDRS letter score 54.6 to 55.7 SD8.6 to 9.7 **Baseline CMT:** 481 to 507 SD121 to 145 µm **Comorbidities:** 19% mild NPDR (level 35), 46% moderate NPDR (level 43), 19% moderately severe NPDR (level 47), 13% severe NPDR (level 53), 3% moderate PDR (level 65), 79 to 88% phakic	**Group 1 (MLT, n=38 eyes):** modified ETDRS macular laser therapy; reviewed every 4 months up to 52 weeks; retreatment performed if clinically indicated by ETDRS guidelines (median 4 laser treatments) **Group 2 (IVB, n=42 eyes):** 1.25 mg (0.05 ml) IV bevacizumab at baseline, 6 and 12 weeks; subsequent IVB injections (up to 52 weeks) guided by an OCT-based retreatment protocol (median 13 injections) **Laser** Modified ETDRS protocol, retreatment by ETDRS guidelines	**At 24 months** **BCVA (ETDRS):** **BCVA.mean (SD) p** ***MLT*** -0.5 (10.6) ***IVB*** +8.6 (9.1) 0.005 vs MLT **BCVA gain categories (letters)** ***MLT*** gaining ≥10: 7%; losing >15: 4% ***IVB*** gaining ≥10: 49% 0.001 vs MLT; losing >15: 32% 0.004 vs MLT **CMT (OCT):** **CMT (µm, quartiles) p** ***MLT*** -118 SD171 ***IVB*** -146 SD122 0.62 vs MLT •

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr>
<td>Lam 2009[35]
Hong Kong

Design: 2-arm RCT
Follow-up: 6 months</td>
<td>N: 52 eyes of 52 patients
Inclusion criteria: ≥18 years, type 1 or 2 DM, clinically significant DMO (slit-lamp biomicroscopy, ETDRS criteria; leakage confirmed by fluorescein angiography, CMT ≥250 µm on OCT), BCVA ≥1.3 ETDRS logMAR units; only patients with diffuse DMO recruited
Exclusion criteria: macular oedema due to reasons other than diabetes, significant media opacities, macular ischemia of ≥1 disk area, vitreomacular traction, PDR, aphakia, glaucoma or ocular hypertension, previous anti-VEGF treatment, intraocular surgery except uncomplicated cataract extraction (but > 6 months prior), focal DMO, any laser procedure within previous 4 months, subtenon or intravitreal triamcinolone injection within 6 months, pregnancy.
Age: 65.3 SD8.9 years
Sex: 46.2% female
Diabetes type: not reported
HbA1c: 7.5 SD1.0%
Baseline VA: 0.61 SD0.29 logMAR
Baseline CMT: 466 SD127 µm
Comorbidities: not reported</td>
<td>Group 1 (IVB1.25, n=26 eyes): 1.25 mg bevacizumab (0.05 ml)
Group 2 (IVB2.5, n=26 eyes): 2.5 mg bevacizumab (0.1 ml)
Regimen for all groups: 3 monthly IV injections, topical 0.5% levofloxacin 4x/day for up to 2 weeks after each injection</td>
<td>At 6 months
BCVA (ETDRS chart):
<table><tr><th></th><th>BCVA (logMAR)</th><th>p</th></tr><tr><td>IVB1.25</td><td>0.11 SD0.31 [+5.5 letters]</td><td>0.018 vs baseline, NS vs IVB2.5</td></tr><tr><td>IVB2.5</td><td>0.13 SD0.26 [+6.5 letters]</td><td>0.003 vs baseline</td></tr></table>CMT (OCT):
<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVB1.25</td><td>96</td><td>0.002 vs baseline, NS vs IVB2.5</td></tr><tr><td>IVB2.5</td><td>74</td><td>0.013 vs baseline</td></tr></table>Subgroups:
For patients with previous DMO treatment (mainly laser): no significant reduction in CMT at 6 months (452 µm at baseline to 416 µm at 6 months, p=0.22); no significant improvement in BCVA (0.66 logMAR at baseline to 0.56 logMAR at 6 months [+5 letters], p=0.074)</td>
</tr>
<tr>
<td>Faghihi 2010[53]
Iran

Design: 2-arm RCT
Follow-up: 6 months</td>
<td>N: 80 eyes of 40 patients
Inclusion criteria: Bilateral non-tractional CSME, 10/10> V.A≥ 1/10, Controlled blood pressure.
Exclusion criteria: Advanced or advanced active PDR, Significant cataract, Glaucoma, History of recent vascular accident (e.g, MI, CVA), Previous treatment of CSME or PDR, or pharmacotherapy for CSME, macular ischemia and uncontrolled hypertension.
Age: 57.7±8 years.
Sex: 27.5% females
Diabetes type: NR
HbA1c: 8.42±1.82 g/dl
Baseline VA: 0.326 to 0.409 (SD 0.279 to 0.332)
Baseline CMT: 277 um to 287 um (SD 78 to 98)
Comorbidities: not reported</td>
<td>Group 1 (IVB, n= 40 eyes): 1.25mg bevacizumab
Group 2 (IVB+MPC, n= 40 eyes): 1.25mg bevacizumab
Regimen for all groups: Eyes examined every two months and if evidence of CSME IVB was injected. mean of the number of IVB injections in IVB group and IVB+MPC group were 2.23±1.24 and 2.49±1.09 respectively.</td>
<td>At 6 months
Mean change in BCVA (ETDRS chart):
<table><tr><th></th><th>BCVA (logMAR)</th><th>p</th></tr><tr><td>IVB</td><td>0.138</td><td><0.05 vs baseline</td></tr><tr><td>IVB+MPC</td><td>0.179</td><td><0.05 vs baseline</td></tr></table>
no statistically significant difference between the two groups
CMT (OCT):
<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVB</td><td>-39</td><td><0.05 vs baseline</td></tr><tr><td>IVB+MPC</td><td>-39</td><td><0.05 vs baseline</td></tr></table>
no statistically significant difference between the two groups</td>
</tr>
</table>

Abbreviations: See table 2

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Table 45: Pegaptanib and aflibercept studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Pegaptanib			
Cunningham 2005 / Adamis 2006 [39,57] **USA** **Design:** 4-arm phase II RCT **Follow-up:** 36 weeks	**N:** 172 eyes of 172 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO involving the center of the macula with corresponding leakage from microaneurysms, retinal telangiectasis, or both; clear ocular media, BCVA letter scores between 68 and 25 in the study eye and at least 35 in the fellow eye; IOP ≤23 mmHg, focal photocoagulation could be safely deferred for 16 weeks; no ECG abnormalities, no major serological abnormalities **Exclusion criteria:** history of panretinal or focal photocoagulation; neodymium:yttrium–aluminum–garnet laser or peripheral retinal cryoablation in previous 6 months; any ocular abnormality interfering with VA assessment or fundus photography; vitreoretinal traction; vitreous incarceration; retinal vein occlusion involving the macula; atrophy/scarring/fibrosis or hard exudates involving the center of the macula; history of intraocular surgery within previous 12 months, myopia of ≥8 diopters, axial length of ≥25mm, likelihood of requiring panretinal photocoagulation within following 9 months; cataract surgery within 12 months; active ocular or periocular infection; previous therapeutic radiation to the eye, head, or neck;; known serious allergies to fluorescein dye; HbA1c ≥13%, pregnancy **Age:** 61.3 to 64.0 SD9.3 to 10.1 years **Sex:** 45 to 55% female **Diabetes type:** 5 to 10% IDDM **HbA1c:** 7.1 to 7.7 SD1.2 to 1.6 **Baseline VA:** letter score 55.0 to 57.1 SD9.1 to 11.5 **Baseline CMT:** 423.2 to 476.0 µm **Comorbidities:** not reported	**Group 1 (IVP0.3, n=44 eyes):** 0.3 mg IV pegaptanib (90 µl) (median 5 injections (range 1 to 6)) **Group 2 (IVP1, n=44 eyes):** 1 mg IV pegaptanib (90 µl) (median 6 injections (range 3 to 6)) **Group 3 (IVP3, n=42 eyes):** 3 mg IV pegaptanib (90 µl) (median 6 injections (range 1 to 6)) **Group 4 (C, n=42 eyes):** sham injection (median 5 injections (range 1 to 6)) **Regimen for all groups:** injections at baseline, week 6 and week 12; thereafter, additional injections administered every 6 weeks at the discretion of the investigators if judged indicated (maximum of 6 injections up to week 30); laser photocoagulation allowed after week 13 if judged indicated by the study-masked ophthalmologist (25% for IVP0.3, 30% for IVP1, 40% for IVP3, 48% for C)	**At 36 weeks** **BCVA:** **BCVA (letters) / p** ***IVP0.3*** +4.7 / 0.04 vs C ***IVP1*** +4.7 / 0.05 vs C ***IVP3*** +1.1 / NS vs C ***C*** -0.4 **plus ≥10 letters** ***IVP0.3*** 34% / 0.003 vs C ***IVP1*** 30% ***IVP3*** 14% ***C*** 10% **CMT (OCT):** **CMT (µm, 95% CI) / p** ***IVP0.3*** -68.0 (-118.9 to -9.88) / 0.02 vs C ***IVP1*** -22.7 (-76.9 to +33.8) / NS vs C ***IVP3*** -5.3 (-63.0 to +49.5) / NS vs C ***C*** +3.7 Subgroups: • of 16 participants with retinal neovascularization at baseline, 8 of 13 (62%) in the pegaptanib groups and 0 of 3 in the sham group had regression of neovascularization at 36 weeks
Sultan 2011[40] Multicenter international **Design:** 2-arm placebo-controlled RCT	**N:** 260 eyes of 260 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO involving the center of the macula not associated with ischemia, CMT ≥250 µm, BCVA letter score 65 to 35, IOP ≤21 mmHg, clear ocular media **Exclusion criteria:** any abnormality other than DMO affecting VA assessment, vitreomacular traction; yttrium-aluminium-garnet laser, peripheral retinal cryoablation, laser retinopexy for retinal tears, focal or	**Group 1 (IVP, n=133 eyes):** 0.3 mg IV pegaptanib sodium (mean number of injections 12.7 SD4.6) **Group 2 (C, n=127 eyes):** sham injection (mean number of injections 12.9 SD4.4)	**At 1 year** **BCVA (ETDRS):** **BCVA (letters) / p** ***IVP*** +5.2 / <0.05 vs C ***C*** +1.2 **plus ≥10**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Follow-up: 2 years (primary efficacy endpoint at 1 year)	grid photocoagulation within prior 16 weeks; panretinal photocoagulation <6 months before baseline or likely to be needed within 9 months; significant media opacities; intraocular surgery in prior 6 months; pathologic high myopia; prior radiation in region of study eye; history of severe cardiac or peripheral vascular disease, stroke in prior 12 months, major surgery in prior 1 month, treatment in prior 90 days with any investigational agent or with bevacizumab for any nonocular condition, HbA1c ≥10% or signs of uncontrolled diabetes, hypertension, known relevant allergies; pregnant or lactating **Age:** 62.3 to 62.5 SD9.3 to 10.2 years **Sex:** 39 to 46% female **Diabetes type:** 6.3 to 7.5% type 1 DM, 92.5 to 93.7% type 2 DM **HbA1c:** 42.5 to 45.9% <7.6%, 54.1 to 57.5% >7.6% **Baseline VA:** letter score 57.0 to 57.5 SD8.1 to 8.9 **Baseline CMT:** 441.6 to 464.6 SD135.5 to 148.5 µm **Comorbidities:** not reported	**Regimen for all groups:** injections every 6 weeks up to week 48 (9 injections); at investigator determination (ETDRS criteria), laser photocoagulation could be performed at week 18, with possible repeat treatment at a minimum of 17 weeks later (maximum 3 treatments per year) (laser treatments in 25.2% of IVP group and 45% of C group); in year 2, injections as judged necessary	**letters** ***IVP*** 36.8% 0.0047 vs C ***C*** 19.7% **Retinopathy:** **increase in degree by ≥2 steps** ***IVP*** 4.1% 0.047 vs C ***C*** 12.4% **decrease in degree by ≥2 steps** ***IVP*** 10.2% NS vs C ***C*** 3.1% **CMT (OCT):** **decrease in CMT** ***IVP*** ≥25%: 31.7% NS s C ≥50%: 14.6% ***C*** ≥25%: 23.7% ≥50%: 11.9% **At 2 years** **BCVA (ETDRS):** **BCVA (letters) p** ***IVP*** +6.1 <0.01 vs C ***C*** +1.3 **plus ≥10 letters** ***IVP*** 38.3% NS vs C ***C*** 30.0% **Retinopathy:** **increase in degree by ≥2 steps** ***IVP*** 6.3% NS vs C ***C*** 13.8% **decrease in degree by ≥2 steps** ***IVP*** 16.3% 0.03 vs C ***C*** 3.8% **CMT (OCT):** **decrease in CMT** ***IVP*** ≥25%: 40.4% NS vs C ≥50%: 19.2%

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
			C ≥25%: 44.6% ≥50%: 26.1% **QoL:** • NEI VFQ-25: between group differences not significant at 54 weeks; at 102 weeks, significantly greater improvement in composite score and subscales distance vision activities, social functioning and mental health with pegaptanib • EQ-5D: no significant differences between groups in EQ-5D scores at weeks 54 or 102

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td>Aflibercept</td><td></td><td></td><td></td></tr>
<tr><td>DA VINCI 2010 (Do 2011)
Multicenter[30,58]

Design: 5-arm phase II RCT
Follow-up: 24 weeks</td><td>N: 221 eyes of 221 patients
Inclusion criteria: aged >18 years and diagnosed with type 1 or 2 diabetes mellitus, with DMO involving the central macula defined as CRT (>250 um in the central subfield. Participants were required to have BCVA letter score at 4 m of 73 to 24. 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: history of vitreoretinal surgery; panretinal 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; proliferative diabetic retinopathy (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 visual acuity or require medical or surgical intervention during the study period: active iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT; history of idiopathicor autoimmune uveitis; structural damage to the center of the macula that is likely to preclude improvement in visual acuity after the resolution of macular oedema; uncontrolled glaucoma or previous filtration surgery; infectious blepharitis, keratitis, scleritis, or conjunctivitis; or current treatment for serious systemic infection: 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 (even if the eye met all other entry criteria); or an ocular condition in the fellow eye with a poorer prognosis than the study eye
Age: 60.7 to 64.0 years (SD 8.1 to 11.5)
Sex: % female 35.6% to 47.6%
Diabetes type: % type 2, 88.6% to 97.7%
HbA1c: 7.85 to 8.10 (SD 1.71 to 1.94)
Baseline VA: 57.6 to 59.9 (SD 10.1 to 12.5)
Baseline CMT: 426.1 um to 456.6 um (SD 111.8 to 152.4)
Co morbidities: history of any cardiac disease was twice as common in the VEGF Trap-Eye groups compared with the laser group.</td><td>Trial of VEGF Trap-Eye (VTE), randomized on a 1:1:1:1:1 basis
Group 1 (IVVTE1, n=44 eyes): IV VTE, 0.5 mg every 4 weeks
Group 2 (IVVTE2, n=44 eyes): IV VTE, 2 mg every 4 weeks
Group 3 (IVVTE3, n=42 eyes): IV VTE, 2 mg for 3 initial months then every 8 weeks
Group 4 (IVVTE4, n=45 eyes): IV VTE, 2 mg for 3 initial months then as needed
Group 5 (L, n=44 eyes): laser photocoagulation
Laser Modified ETDRS protocol</td><td>At 6 months
<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>IVVTE1</td><td>+8.6</td><td>0.005 vs L</td></tr><tr><td>IVVTE2</td><td>+11.4</td><td><0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>+8.5</td><td>0.008 vs L</td></tr><tr><td>IVVTE3</td><td>+10.3</td><td>0.0004 vs L</td></tr><tr><td>L</td><td>+2.5</td><td></td></tr><tr><td></td><td>plus ≥10 letters</td><td></td></tr><tr><td>IVVTE1</td><td>50%</td><td>NR</td></tr><tr><td>IVVTE2</td><td>64%</td><td>NR</td></tr><tr><td>IVVTE3</td><td>43%</td><td>NR</td></tr><tr><td>IVVTE3</td><td>58%</td><td>NR</td></tr><tr><td>L</td><td>32%</td><td>NR</td></tr></table><table><tr><th></th><th>CMT(um)</th><th></th></tr><tr><td>IVVTE1</td><td>-144.6</td><td>0.0002 vs L</td></tr><tr><td>IVVTE2</td><td>-194.5</td><td><0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>-127.3</td><td>0.007 vs L</td></tr><tr><td>IVVTE3</td><td>-153.3</td><td><0.0001 vs L</td></tr><tr><td>L</td><td>-67.9</td><td></td></tr></table>At 12 months<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>IVVTE1</td><td>+11.0</td><td>≤0.0001 vs L</td></tr><tr><td>IVVTE2</td><td>+13.1</td><td>≤0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>+9.7</td><td>≤0.0001 vs L</td></tr><tr><td>IVVTE3</td><td>+12.0</td><td>≤0.0001 vs L</td></tr><tr><td>L</td><td>-1.3</td><td></td></tr><tr><td></td><td>plus ≥15 letters</td><td></td></tr><tr><td>IVVTE1</td><td>40.9%</td><td>0.0031 vs L</td></tr><tr><td>IVVTE2</td><td>45.5%</td><td>0.0007 vs L</td></tr><tr><td>IVVTE3</td><td>23.8%</td><td>0.1608 vs L</td></tr><tr><td>IVVTE3</td><td>42.2%</td><td>0.0016 vs L</td></tr><tr><td>L</td><td>11.4%</td><td></td></tr></table></td></tr>
</table>

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)		
				plus ≥10 letters	
			IVVTE1	57%	0.0031 vs L
			IVVTE2	71%	0.0007 vs L
			IVVTE3	45%	0.1608 vs L
			IVVTE3	62%	0.0016 vs L
			L		
				CMT(µm)	
			IVVTE1	-165.4	< 0.0001 vs L
			IVVTE2	-227.4	< 0.0001 vs L
			IVVTE3	-187.8	< 0.0001 vs L
			IVVTE3	-180.3	< 0.0001 vs L
			L	-58.4	

Abbreviations: See table 2

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Table ~~5~~6: Dexamethasone and fluocinolone studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Dexamethasone			
Callanan 2011USA[44] **Design:** 2-arm RCT **Follow-up:** 12 months	**N:** 253 eyes of 253 patients **Inclusion criteria:** diffuse DMO, CMT ≥275 µm, BCVA ≥34 and ≤70 letters **Exclusion criteria:** not reported **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (DIL, n=126 eyes):** dexamethasone IV implant followed by laser photocoagulation after 1 month (mean 1.6 implants; 78.6% completion) **Group 2 (L, n=127 eyes):** laser alone (79.5% completion) **Regimen for all groups:** if needed, patients were retreated with the dexamethasone implant at months 6 or 9, and with laser at months 4, 7, and 10; mean 2.2 laser treatments per patient **Laser protocol** not reported	**At 12 months** **BCVA:** **plus ≥10 l tters** **p** ***DIL*** 28% NS vs L ***L*** 24% • patients in DIL group had significantly greater increases in BCVA from baseline than patients in the laser group (p<0.05) at months 1 to 9 only **CMT (OCT):** • patients in DIL group had significantly greater mean reductions from baseline in CMT at months 1 and 6 only (p<0.001)
Haller 2010[59] **USA** Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months (180 days), primary outcome 3 months (90 days)	**N:** 171 eyes of 171 patients **Inclusion criteria:** ≥12 years, DMO persisting for ≥90 days after laser treatment or medical therapy, BCVA by ETDRS between 20/40 (67 letters) and 20/200 (35 letters) due to clinically detectable DMO; analysis includes only eyes with DMO associated with DR **Exclusion criteria:** history of vitrectomy in the study eye; use of systemic, periocular, or intraocular steroids within 30 days of enrollment; moderate or severe glaucoma in the study eye; poorly controlled hypertension (SP >160 mmHg or DP >90 mmHg); poorly controlled diabetes (HbA1c >13%) **Age:** 62.9 to 63.8 years SD10.2 to 12.0 **Sex:** 45.6 to 49.1% female **Diabetes type:** not reported **HbA1c:** 7.3 to 7.6% **Baseline VA:** letter score 54.4 to 54.7 SD9.96 to 11.88 **Baseline CMT:** 417.5 to 446.5 µm SD123.7 to 155.9 **Comorbidities:** 19 to 21% prior cataract extraction	**Group 1 (DDS350, n=57 eyes):** 350 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity **Group 2 (DDS700, n=57 eyes):** 700 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity **Group 3 (C, n=57 eyes):** no treatment **Regimen for all groups:** eyes demonstrating a VA loss of ≥5 letters could be treated with any other therapy (including laser photocoagulation and IV triamcinolone) (n=4 with photocoagulation or IV triamcinolone in the C group, n=2 in the DDS350 group, none in the DDS700 group)	**At 90 days** **BCVA (ETDRS):** **plus ≥10 letters** **p** ***DDS350*** 21% [graph] NS vs C ***DDS700*** 33% 0.007 vs C ***C*** 12% **CMT (OCT):** **CMT (µm)** **p** ***DDS350*** -42.57 SD95.96 NS (p=0.07) vs C ***DDS700*** -132.27 SD160.86 <0.001 vs C ***C*** +30.21 SD82.12 **At 180 days** **BCVA (ETDRS):** **plus ≥10 letters** **p** ***DDS350*** 20% [graph] NS vs C ***DDS700*** 33% [graph] NS vs C ***C*** 23% [graph]
Fluocinolone			

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr>
<td>FAME Study (Campochiaro 2011/ Campochiaro 2012) [29,60]

Multicenter international

Design: 3-arm placebo-controlled RCT
Follow-up: 24 months; abstract with 36 month outcomes</td>
<td>N: 956 eyes of 956 patients
Inclusion criteria: DMO, CMT ≥250 µm despite at least 1 prior focal/grid macular laser photocoagulation treatment, BCVA ETDRS letter score between 19 and 68 (20/50 to 20/400)
Exclusion criteria: glaucoma, ocular hypertension, IOP >21 mmHg, taking IOP lowering drops; laser treatment for DMO within 12 weeks of screening, any ocular surgery in the study eye within 12 weeks of screening; ocular or systemic steroid therapy; active ocular infection; pregnancy
Age: 62.5 SD9.4 years
Sex: 40.6%
Diabetes type: 6.6% type 1 DM, 92% type 2 DM, 1.4% uncertain
HbA1c: 7.8 SD1.59 %
Baseline VA: ETDRS letter score 53.4 SD12.23
Baseline CMT: 469.0 SD164.78 µm
Comorbidities: 47.1% cataract at baseline, 62.7 to 67.4% phakic</td>
<td>Group 1 (SRFA0.2, n=375 eyes): intravitreal insert releasing 0.2 µg/day fluocinolone acetonide (FA) (2, 3, or 4 treatments received by 21.3, 1.9 and 0.3%)
Group 2 (SRFA0.5, n=393 eyes): intravitreal insert releasing 0.5 µg/day fluocinolone acetonide (2, 3, or 4 treatments received by 22.6, 2.5 and 0.3%)
Group 3 (C, n=185 eyes): sham injection (2, 3, or 4 treatments received by 19.5, 2.7 and 1.6%)
Regimen for all groups: patients could receive rescue focal/grid laser therapy any time after the first 6 weeks for persistent oedema (35.2 to 36.7% in FA groups, 58.9% control group, p<0.001); treatments were allowed every 3 months for persistent or recurrent oedema; patients eligible for another FA insert at 1 year if ≥5 letter reduction in BCVA or >50 µm CMT increase from best status</td>
<td>At 24 months
BCVA (ETDRS):
<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>SRFA0.2</td><td>+4.4</td><td>0.02 vs C</td></tr><tr><td>SRFA0.5</td><td>+5.4</td><td>0.017 vs C</td></tr><tr><td>C</td><td>+1.7</td><td></td></tr><tr><td></td><td>plus ≥15 letters</td><td></td></tr><tr><td>SRFA0.2</td><td>29%</td><td>0.002 SRFA vs C</td></tr><tr><td>SRFA0.5</td><td>29%</td><td></td></tr><tr><td>C</td><td>16%</td><td></td></tr></table>Subgroups:
• BCVA benefits only in pseudophakic eyes (cataract surgery before or during the study), in phakic eyes, BCVA letter score was reduced by 5 (high dose) and 9 (low dose) from baseline at 24 months

CMT (optical coherence tomography):<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>SRFA0.2</td><td>-167.8</td><td>0.005 vs C</td></tr><tr><td>SRFA0.5</td><td>-177.1</td><td><0.001 vs C</td></tr><tr><td>C</td><td>-111.3</td><td></td></tr></table>• effect maintained at 36 months

At 36 months<table><tr><td></td><td>plus ≥15 letters</td><td></td></tr><tr><td>SRFA0.2/ 0.5</td><td>28.7%</td><td>0.018 SRFA vs C</td></tr><tr><td>C</td><td>18.9%</td><td></td></tr></table></td>
</tr>
<tr>
<td>Pearson 2011[43]
USA
Multicenter

Design: 2-arm RCT
Follow-up: 36 months</td>
<td>N: 196 patients
Inclusion criteria: persistent or recurrent unilateral or bilateral DMO with retinal thickening involving fixation of ≥1 disc area in size, ETDRS visual acuity of ≥20 letters (20/400) to ≤68 letters (20/50) and ≥1 macular laser treatment in the study eye more than 12 weeks prior to enrollment
Exclusion criteria: Ocular surgery within 3 months prior to enrolment, uncontrolled IOP within the past 12 months while on ≥1 antiglaucoma medication, IOP of ≥22 mmHg at screening while on ≥1 antiglaucoma medication, peripheral retinal detachment in the area of implantation or media</td>
<td>Group 1 (SRFA, n= 127): 0.5 mg sustained release fluocinolone acetonide intravitreal implant
Group 2 (SOC, n= 69): standard of care – either repeat laser or observation
Laser ETDRS protocol</td>
<td>At 3 years

BCVA:<table><tr><td></td><td>gain ≥15 letters</td><td>p</td></tr><tr><td>SRFA</td><td>31%</td><td>NS</td></tr><tr><td>SOC</td><td>20%</td><td></td></tr><tr><td></td><td>loss ≥15 letters</td><td></td></tr><tr><td>SRFA</td><td>17%</td><td>NS</td></tr><tr><td>SOC</td><td>14%</td><td></td></tr></table>CMT:</td>
</tr>
</table>

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
	opacity precluding diagnosis of status in the study eye **Age:** 61.4-62.7 years **Sex:** 41.7-42% female **Diabetes type:** 62.3-70% on insulin **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported		**Mean change in baseline CMT** / **p** ***SRFA*** -86 / **NS** ***SOC*** -110

Abbreviations: See table 2

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Table 67: Triamcinolone studies

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
DRCR Network 2008 (Ip 2008a / 2008b / Beck 2009 / Bressler 2009)[22,61,63,64] **USA** Multicenter **Design:** 3-arm RCT **Follow-up:** 2 years, additional 3 year follow-up	**N:** 840 eyes of 693 patients **Inclusion criteria:** >18 years, type 1 or 2 DM, study eye: (1) BCVA (E-ETDRS) between 24 and 73 (20/320 and 20/40), (2) retinal thickening due to DMO involving the center of the macula main cause for visual loss, (3) CMT ≥250 µm, (4) no expectation of scatter photocoagulation within 4 months **Exclusion criteria:** any prior treatment with IV corticosteroids, peribulbar steroid injection within prior 6 months, photocoagulation for DMO within prior 15 weeks, panretinal scatter photocoagulation within prior 4 months, pars plana vitrectomy, history of open-angle glaucoma or steroid-induced IOP elevation requiring IOP-lowering treatment, and IOP ≥25 mmHg **Age:** 63 SD9 years **Sex:** 49% female **Diabetes type:** 95% type 2 DM, 5% type 1 DM **HbA1c:** 7.9 SD1.8% **Baseline VA:** ETDRS letter score 59 SD11 (~20/63) **Baseline CMT:** 24 SD130 µm **Comorbidities:** 21% pseudophakic, 2% ocular hypertension, 7% mild NPDR, 13% moderate NPDR, 40% moderately severe NPDR, 11% severe NPDR, 23.5% mild to moderate, 3% high risk PDR	**Group 1 (IVT1, n=256 eyes):** 1 mg IV triamcinolone (3.5 treatments) **Group 2 (IVT4, n=254 eyes):** 4 mg IV triamcinolone (3.1 treatments) **Group 3 (L, n=330 eyes):** focal/grid photocoagulation (2.9 treatments) **Regimen for all groups:** retreatment protocol: where indicated, retreatment was performed within 4 weeks after the follow-up visit and no sooner than 3.5 months from the time of last treatment; eyes were generally retreated unless: (1) little or no oedema involving the center of the macula present and CMT ≤225 µm, (2) VA letter score ≥79 (20/25 or better), (3) substantial improvement in macular oedema since last treatment (e.g., ≥ 50% decrease in CMT), (4) clinically significant adverse effect from prior treatment, (5) additional treatment deemed futile (<5 letter improvement in VA letter score or lack of CMT reduction), and (6) for laser group, complete focal/grid photocoagulation already given, with no areas identified for which additional treatment was indicated **Laser** Modified ETDRS protocol as used in prior DRCR.net protocols	**At 2 years** **BCVA (E-ETDRS):** ***IVT1*** BCVA (letters): -2 SD18; p: 0.02 vs L, NS vs IVT4 ***IVT4*** BCVA (letters): -3 SD22; p: 0.002 vs L ***L*** BCVA (letters): +1 SD17 **BCVA gain categories** ***IVT1*** +10 or more: 25%, +9 to -9: 50%, -10 or more: 26%; 0.03 vs L, NS vs IVT4 ***IVT4*** +10 or more: 28%, +9 to -9: 44%, -10 or more: 28%; 0.01 vs L ***L*** +10 or more: 31%, +9 to -9: 50%, -10 or more: 19% Subgroups: • similar results when considering only pseudophakic eyes or eyes with minimal cataract • no substantially different results based on baseline VA, baseline CMT, history of focal/grid photocoagulation for DMO • 3 year results consistent with 2 year results for BCVA and CMT **CMT (OCT):** ***IVT1*** CMT (µm): -86 SD167; p: <0.001 vs L, NS vs IVT4 ***IVT4*** CMT (µm): -77 SD160; p: <0.001 vs L ***L*** CMT (µm): -139 SD148 **Progression of retinopathy:** ***IVT1*** 2 yrs: 29%; 3 yrs: 35% ***IVT4*** 2 yrs: 21%; 3 yrs: 30%; p: <0.05 vs L

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			L 31% 37%
Gillies 2006 / 2007 / 2009 / Sutter 2004 [32,136-138] **Australia** **Design:** 2-arm placebo-controlled RCT **Follow-up:** 2 years, additional 3-year follow-up	**N:** 69 eyes of 43 patients **Inclusion criteria:** patients with persistent (≥3 months after adequate laser treatment) DMO involving the central fovea, BCVA in the affected eye ≤6/9 **Exclusion criteria:** uncontrolled glaucoma, loss of vision due to other causes, systemic treatment with >5 mg prednisolone (or equivalent) daily, intercurrent severe systemic disease, any condition affecting follow-up or documentation **Age:** 62.4 to 69.6 SD9.2 to 12.5 years **Sex:** 52% female **Diabetes type:** not reported **HbA1c:** 7.63 to 8.28 SD1.12 to 1.41 **Baseline VA:** ETDRS letter score 60.5 to 61.3 SD11.9 to 13.2 **Baseline CMT:** 439 to 444 SD101 to 125 µm **Comorbidities:** 25% pseudophakic	**Group 1 (IVT, n=34 eyes):** 4 mg (0.1 ml) IV triamcinolone acetonide (mean 2.6 injections over 2 years) **Group 2 (C, n=35 eyes):** placebo injection (subconjunctival saline injection) (mean 1.8 injections over 2 years) **Regimen for all groups:** retreatment considered at each visit as long as treatments were at least 6 months apart (retreatment if VA decreased ≥5 letters from previous peak value and persistent CMT >250 µm), if no improvement after 4 weeks, further laser treatment was applied (n=1 laser treatment in intervention group, n=16 in placebo group, p=0.0001) **Laser** ETDRS protocol	**At 2 years** **BCVA (ETDRS):** ***IVT*** +3.1 (0.01 vs C) ***C*** -2.9 **CVA gain categories** ***IVT*** +10 or more: 21%; +9 to -9: 70%; -10 or more: 9% (0.013 vs C) ***C*** +10 or more: 12%; +9 to -9: 62%; -10 or more: 25% **CMT (OCT):** ***IVT*** -125 (0.009 vs C, difference between groups 59 µm (95% CI 15, 104)) ***C*** -75
Gillies 2011[33] **Australia** **Design:** 2-arm RCT **Follow-up:** 24 months	**N:** 84 eyes of 54 patients **Inclusion criteria:** DMO involving the central fovea, CMT ≥250 µm, BCVA 17 to 70 letters (~20/40 to 20/400), laser treatment could be safely delayed for 6 weeks without significant adverse effects **Exclusion criteria:** uncontrolled glaucoma, controlled glaucoma but with a glaucomatous visual field defect, loss of vision resulting from other causes, systemic treatment with >5 mg prednisolone (or equivalent) daily, retinal laser treatment within 4 months, intraocular surgery within 6 months, concurrent severe systemic disease, any condition affecting follow-up or documentation **Age:** 65.4 to 66.9 SD8.9 to 9.5 years **Sex:** 38.1 to 47.6% female **Diabetes type:** not reported **HbA1c:** 7.81 to 8.02 SD1.44 to 1.63 % **Baseline VA:** letter score 55.2 to 55.5 SD11.3 to 12.5 **Baseline CMT:** 482.1 to 477.4 SD122.7 to 155.5 µm **Comorbidities:** not reported	**Group 1 (IVTL, n=42 eyes):** 4 mg (0.1 ml) IV triamcinolone acetonide followed by laser treatment (at least 1 retreatment in 2nd year in 69%) **Group 2 (L, n=42 eyes):** sham injection followed by laser treatment (at least 1 retreatment in 2nd year in 45%) **Regimen for all groups:** retreatment with injection followed by laser at discretion of chief investigator, with at least 6 weeks between treatments; no retreatment if: (1) investigator considered the macula nearly flat and CMT <300 µm; (2) VA was ≥79 letters (20/25) or VA had improved by ≥5 letters compared with the best VA after treatment or baseline acuity; (3) laser	**At 24 months** **BCVA (ETDRS):** ***IVTL*** +0.76 (NS vs L) ***L*** -1.49 **BCVA gain categories** ***IVTL*** +10 or more: 36%; +9 to -9: 31%; -10 or more: 33% (0.049 vs L) ***L*** +10 or more: 17%; +9 to -9: 59%; -10 or more: 24% Subgroups: • BCVA outcome not significantly affected by cataract surgery **CMT (OCT):**

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		treatment was considered by the investigator as inappropriate or had no potential for improvement	***IVTL*** -137.1 NS vs L ***L*** -109.6
Kim 2010[45] **Korea** **Design:** 2-arm RCT **Follow-up:** 3 years	**N:** 86 eyes of 75 patients **Inclusion criteria:** diffuse DMO **Exclusion criteria:** not reported **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (IVT, n=38 eyes):** 4 mg IV triamcinolone (1.88 additional treatments, completion 68.1%) **Group 2 (IVTL, n=48 eyes):** macular laser photocoagulation 4 weeks after 4 mg IV triamcinolone (0.92 additional treatments, completion 77.1%) **Regimen for all groups:** additional treatment possible, criteria not mentioned **Laser protocol** not reported	**At 3 years** **BCVA:** not reported **Outcomes related to DMO:** **no DMO recurrence** **p** ***IVT*** 3.9% ***IVTL*** 24.3% 0.028 vs IVT **time DMO not present** ***IVT*** 10.33 months ***IVTL*** 19.88 months 0.027 vs IVT
Lam 2007[34] **Hong Kong** **Design:** 3-arm RCT **Follow-up:** 6 months (2 years planned)	**N:** 111 eyes of 111 patients **Inclusion criteria:** >18 years, type 1 or 2 DM, clinically significant DMO (ETDRS), CMT ≥250 µm **Exclusion criteria:** macular oedema due to causes other than diabetic maculopathy, signs of vitreomacular traction, proliferative diabetic retinopathy, aphakia, history of glaucoma or ocular hypertension, macular ischemia, any laser procedure within 3 months, ocular surgery within 6 months, significant media opacities **Age:** 64.7 to 67.2 SD8.2 to 10.3 years **Sex:** 42 to 59% female **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** ETDRS logMAR 0.64 to 0.72 SD0.34 to 0.36 **Baseline CMT:** 385 to 424 SD91 to 108 µm **Comorbidities:** 66 to 84% phakic eyes	**Group 1 (IVT, n=38 eyes):** 4 mg IV triamcinolone (no retreatments) **Group 2 (IVTL, n=36 eyes):** 4 mg IV triamcinolone followed by grid laser photocoagulation (ETDRS) (laser treatment once the macular oedema had reduced to <250 µm at the foveal center or at 1 to 2 months after injection, whichever was earlier) **Group 3 (L, n=37 eyes):** grid laser photocoagulation (n=3 retreatments) (no retreatments) **Regimen for all groups:** in case of recurrence or persistence of macular oedema, retreatment offered according to study group, at intervals no less than 4 months **Laser** ETDRS protocol	**At 6 months** **BCVA (ETDRS):** **BCVA improvement** **p** ***IVT*** -0.7 SD 10.7 log MAR plus ≥15 letters: 5% NS between groups ***IVTL*** -1.1 SD 10.8 log MAR plus ≥15 letters: 3% ***L*** -1.6 SD 11.5 log MAR plus ≥15 letters: 5% **CMT (OCT):** **CMT (µm)** **p** ***IVT*** 342 SD124 [-54] NS between groups, <0.01 vs baseline ***IVTL*** 307 SD181 [-116] <0.01 vs baseline ***L*** 350 SD169 [-35]

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<table>
<tr>
<td>Ockrim 2008 / Sivaprasad 2008
[42,62]
UK

Design: 2-arm RCT
Follow-up: 1 year</td>
<td>N: 88 eyes of 88 patients
Inclusion criteria: clinically significant DMO persisting ≥4 months, ≥1 previous laser treatment, BCVA 6/12 to 3/60, VA in fellow eye ≥3/60, duration visual loss <24 months
Exclusion criteria: significant macular ischemia, baseline IO >23 mmHg, glaucoma, coexistent renal disease, loss of VA due to other causes, previous vitrectomy, intraocular surgery within 3 months of study entry, previous inclusion in other DR trials, inability to return to follow-up, inability to give informed consent
Age: 62.3 to 64.8 SD7.5 to 10.1 years
Sex: 28.9 to 34.9% female
Diabetes type: 97.8 to 100% type 2 DM
HbA1c: 7 to 7.8 IQR6.5 to 8.7%
Baseline VA: ETDRS letter score 53.0 to 54.6 SD13.3 to 14.2
Baseline CMT: 410.4 to 413.4 SD127.8 to 134.1 µm
Comorbidities: 17.8 to 19.5% PDR, 13.3 to 18.6% pseudophakia, 15 to 17.8% posterior vitreous detachment</td>
<td>Group 1 (IVT, n=43 eyes): 4 mg IV triamcinolone (mean number of IVT injections 1.8 (range 1 to 3))
Group 2 (L, n=45 eyes): ETDRS laser photocoagulation (mean number of grid laser sessions 2.1 (range 1 to 3))
Regimen for all groups: patients retreated at 4 and 8 months if they had persistent macular oedema
Laser ETDRS protocol</td>
<td>At 12 months

BCVA (ETDRS):
<table><tr><th></th><th>BCVA (letters)</th><th>p</th></tr><tr><td>IVT</td><td>-0.2</td><td>NS vs L</td></tr><tr><td>L</td><td>+1.7</td><td></td></tr><tr><th></th><th>plus ≥15 letters</th><th></th></tr><tr><td>IVT</td><td>4.8%</td><td>NS vs L</td></tr><tr><td>L</td><td>12.2%</td><td></td></tr></table>
CMT (optical coherence tomography):
<table><tr><th></th><th>CMT (µm)</th><th>p</th></tr><tr><td>IVT</td><td>-91.3</td><td>NS vs L</td></tr><tr><td>L</td><td>-63.7</td><td></td></tr></table></td>
</tr>
</table>

Abbreviations: See table 2

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Table 87: Trials assessing more than one drug

Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Ahmadieh 2008[31] **Iran** **Design:** 3-arm placebo-controlled RCT **Follow-up:** 24 weeks	**N:** 115 eyes of 101 patients **Inclusion criteria:** eyes with clinically significant DMO unresponsive to previous macular laser photocoagulation (last session >3 months prior) **Exclusion criteria:** visual acuity ≥20/40; history of cataract surgery within past 6 months; prior intraocular injection or vitrectomy, glaucoma or ocular hypertension; PDR with high-risk characteristics; vitreous hemorrhage; significant media opacity; presence of traction on the macula; pregnancy; serum creatinine ≥3 mg/100 ml; monocular patients **Age:** 59.7 SD8.3 years (range 39 to 74) **Sex:** 50.5% female **Diabetes type:** not reported, 27.6% to 33.3% on insulin **HbA1c:** 9.35% to 10.06% **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** (percentage of eyes) 13.9% history of cataract surgery, 81.7% NPDR, 4.3% early PDR, 13.9% regressed PDR; no iris neovascularization	**Group 1 (IVB, n=41 eyes):** bevacizumab 1.25 mg (0.05 ml) **Group 2 (IVB/IVT, n=37 eyes):** combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone **Group 3 (C, n=37 eyes):** sham injection **Regimen for all groups:** 3 consecutive IV injections at 6-week intervals	**At 24 weeks** **BCVA (Snellen chart):** ***IVB*** -0.18 (-0.29, -0.08) [+9 letters (4, 14.5)] — 0.01 vs C, NS vs IVB/IVT ***IVB/ IVT*** -0.21 (-0.30, -0.12) [+10.5 letters (6, 15)] — 0.006 vs C ***C*** -0.03 (-0.08, 0.14) [+1.5 letters (-7, 4)] **CMT (OCT):** ***IVB*** -95.7 (-172.2, -19.3) — 0.012 vs C, NS vs IVB/IVT ***IVB/ IVT*** -92.1 (-154.4, -29.7) — 0.022 vs C ***C*** 34.9 (7.9, 61.9)
ATEMD 2011 (Oliveira Neto 2010 / 2011) [56] Multicenter **Design:** 3-arm RCT **Follow-up:** 6 months **Note:** only 48.3% completion	**N:** 120 eyes of 120 patients **Inclusion criteria:** DMO, BCVA 20/40 to 20/400, CMT ≥275 µm **Exclusion criteria:** PDR, laser photocoagulation in previous 3 months, no IV corticosteroid or anti-VEGF in previous 3 months **Age:** not reported **Sex:** not reported **Diabetes type:** not reported **HbA1c:** not reported **Baseline VA:** not reported **Baseline CMT:** not reported **Comorbidities:** not reported	**Group 1 (IVB, n=NR eyes):** 1.25 mg (0.05 ml) of IV bevacizumab **Group 2 (IVT, n=NR eyes):** 4 mg (0.1 ml) of IV triamcinolone acetonide **Group 3 (IVB/IVT, n=NR eyes):** 1.25 mg (0.05 ml) of IV bevacizumab plus 4 mg (0.1 ml) of IV triamcinolone acetonide **Regimen for all groups:** monthly injections	**At 6 months** **BCVA:** • no significant difference between groups (between 1.7 and 2.3 lines gained in the different groups in 2010 report (n=18)) **CMT (OCT):** • CMT reduced in all 3 groups (between 17 and 33% reduction in the different groups in 2010 report (n=18)); no significant difference between groups
DRCR Network 2010 (Elman 2010, Elman 2011)[21,46] **USA** Multicenter	**N:** 854 eyes of 691 patients **Inclusion criteria:** ≥18 years, type 1 or 2 DM; study eye: (1) BCVA letter score 78 to 24 (20/32 to 20/320), (2) definite retinal thickening due to DMO assessed to be main cause of visual loss, (3) retinal thickness measured on time domain OCT ≥250 µm in central	**Group 1 (CPL, n=293 eyes):** sham injection plus prompt (within 3-10 days after injection) focal/grid photocoagulation **Group 2 (RPL, n=187 eyes):** 0.5 mg IV ranibizumab plus prompt focal/grid	**At 1 year** **BCVA (E-ETDRS Visual Acuity Test):** ***CPL*** +3 SD13 ***RPL*** +9 SD11 — <0.001 vs CPL

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
Design: 4-arm placebo-controlled RCT **Follow-up:** 1-2 years; 2 years extension (Elman 2011) for consenting patients	subfield (2 study eyes per patient could be included if both were eligible at study entry) **Exclusion criteria:** (1) treatment for DMO within the prior 3 months, (2) panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, (3) major ocular surgery within the prior 4 months, (4) history of open-angle glaucoma or steroid-induced IOP elevation, requiring IOP-lowering treatment, (5) IOP ≥25 mmHg; systolic pressure >180 mmHg, diastolic pressure >110 mmHg; myocardial infarction, other cardiac event requiring hospitalization, cerebrovascular accident, transient ischemic attack, treatment for acute congestive heart failure within 4 months before randomization **Age:** median 62 to 64 years (25th, 75th centile 55 to 58, 69 to 70) **Sex:** 41 to 46% female **Diabetes type:** 6 to 9% type 1 DM, 89 to 92% type 2 DM, 2 to 3% uncertain **HbA1c:** median 7.3 to 7.5% (25th, 75th centile 6.5 to 6.7, 8.3 to 8.6) **Baseline VA:** letter score 63 SD12 (~20/63 SD2.4 lines) **Baseline CMT:** 405 SD134 µm **Comorbidities:** 60 to 67% prior treatment for DMO; 61 to 68% with NPDR, 26 to 36% with PDR or PDR scars	photocoagulation **Group 3 (RDL, n=188 eyes):** 0.5 mg IV ranibizumab plus deferred (≥24 weeks) focal/grid photocoagulation **Group 4 (TPL, n=186 eyes):** 4 mg IV triamcinolone plus prompt focal/grid photocoagulation **Regimen for all groups:** Baseline treatment 0.5 mg IV ranibizumab and 4 mg preservative free triamcinolone; study treatment every 4 weeks up to 12 weeks, then retreatment algorithm: 16 to 20 weeks, monthly retreatment unless 'success' criteria were met (visual acuity letter score ≥84 (20/20) or OCT central subfield thickness <250 µm); 24 to 48 weeks, patients subdivided (according to predefined criteria) into 'success', 'improvement', 'no improvement' or 'failure'; 'improvement' group continued treatment, other groups treated at investigator discretion; alternative treatment permitted if eye met criteria for 'failure' or 'futility'. In the case of retreatment, ranibizumab could be given as often as every 4 weeks, and triamcinolone every 16 weeks (with sham injections as often as every 4 weeks). Retreatment for focal/grid laser (after ≥13 weeks from previous treatment) if there was oedema involving or threatening the center of the macula and if complete laser had not been given; retreatment algorithms facilitated by web-based real-time data entry system. Median number of drug injections before 1 year visit was 8-9 for ranibizumab, 3 for triamcinolone, and 5 sham injections. Retreatment between 1 and 2 years	***RDL*** +9 SD12 <0.001 vs CPL ***TPL*** +4 SD13 NS vs CPL **BCVA gain categories (letters)** ***CPL*** +10 or more: 28%; +9 to -9: 59%; -10 or more: 13% ***RPL*** +10 or more: 50%; +9 to -9: 45%; -10 or more: 4% <0.001 vs CPL ***RDL*** +10 or more: 47%; +9 to -9: 51%; -10 or more: 3% <0.001 vs CPL ***TPL*** +10 or more: 33%; +9 to -9: 52%; -10 or more: 14% NS vs CPL Subgroups: • BCVA results in TPL group substantially better for pseudophakic eyes than for phakic eyes (comparable to results for RPL and RDL groups) (p not reported) • no difference in results according to prior treatment for DMO, baseline VA, baseline CMT, baseline level of retinopathy, focal or diffuse oedema **CMT (OCT):** **CMT (µm) p** ***CPL*** -102 SD151 ***RPL*** -131 SD129 <0.001 vs CPL ***RDL*** -137 SD136 <0.001 vs CPL ***TPL*** -127 SD140 <0.001 vs CPL Subgroups: • pattern of CMT decrease similar for groups with CMT <400 µm and ≥400 µm at baseline • Significantly more patients with severe NPDR or worse improved by 2 levels or more in the ranibizumab groups (28%, no significant change in the other groups) **At 2 years (expanded results, Elman 2011)** **BCVA (E-ETDRS Visual Acuity Test):**

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
		(Elman 2011): median injections 2 in RPL group, 3 in RDL group; in TPL group 68% of eyes received at least 1 injection; at least one focal/grid laser sessions between 1 and 2 years: 51% CPL, 40% RPL, 29% RDL, 52% TPL **Laser** Modified ETDRS protocol as used in prior DRCR.net protocols	**BCVA (letters)** / **p** ***CPL (n=211)*** +3 SD15 ***RPL (n=136)*** +7 SD13 — 0.03 vs CPL ***RDL (n=139)*** +9 SD14 — <0.001 vs CPL ***TPL (n=142)*** +2 SD19 — NS vs CPL **BCVA gain categories (letters)** ***CPL*** +10 or more: 36%; +9 to -9: 52%; -10 or more: 13% ***RPL*** +10 or more: 44%; +9 to -9: 49%; -10 or more: 7% — NS vs CPL ***RDL*** +10 or more: 49%; +9 to -9: 48%; -10 or more: 3% — 0.01 vs CPL ***TPL*** +10 or more: 41%; +9 to -9: 40%; -10 or more: 19% — NS vs CPL **CMT (OCT):** **CMT (µm)** / **p** ***CPL*** -138 SD149 ***RPL*** -141 SD155 — 0.003 vs CPL ***RDL*** -150 SD143 — 0.01 vs CPL ***TPL*** -107 SD145 — NS vs CPL
Jorge 201 **Brazil**[51] **Design:** Prospective RCT **Follow-up:** 24 and 48 weeks [To date, 73% and 56% of patients completed 24 and 48 weeks respectively]	**N:** 63 eyes of 47 patients **Inclusion criteria:** Refractory cener-involving DMO **Exclusion criteria:** NR **Age:** NR **Sex:** NR **Diabetes type:** NR **HbA1c:** NR **Baseline VA:** NR **Baseline CMT:** NR **Comorbidities:** NR	**Group 1 (IVB 1.5 mg, n=NR):** injections at baseline and monthly if CSFT (central subfield thickness) measured by SDOCT (spectral domain OCT) >275 µm. **Group 2 (IVR 0.5 mg, n=NR) :** injections at baseline and monthly if CSFT >275 µm.	**At 48 weeks** **BCVA** **Mean BCVA reduction from baseline (logMAR)** / **p** ***IVB1.5*** -0.21 — vs baseline <0.05 at all-time points; vs IVR0.5: no significant difference at all time-points ***IVR0.5*** -0.21 — vs baseline <0.05 at all time-points

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Study	Participants and baseline values	Intervention	Outcome (change from baseline at study end)
			vs IVB1.5: no significant difference at all time-points **CSFT** **Mean CSFT reduction from baseline** / **p** ***IVB1.5*** -129.6 µm — vs baseline <0.05 at all-time points; vs IVR0.5 no significant different at all-time points ***IVR0.5*** -137.9 µm — vs baseline <0.05 at all-time points; vs IVB1.5 no significant different at all-time points
Lim 2012[55] **Korea** **Design:** 3-arm RCT **Follow-up:** 12 months	**N: 111 eyes of 105 patients** **Inclusion criteria:** eyes with clinically significant DMO based on ETDRS and DMO with central macular thickness of at least 300 µm by optical coherence tomography (OCT). **Exclusion criteria:** unstable medical status, including glycemic control and blood pressure; any previous treatment for DMO, including intravitreal, sub-Tenon injection or macular photocoagulation, history of vitreoretinal surgery, uncontrolled glaucoma; proliferative diabetic retinopathy with active neovascularization, previous panretinal photocoagulation, presence of vitreomacular traction, history of systemic corticosteroids within 6 months, contraindications for bevacizumab or triamcinolone acetonide. **Age:** 60.4 SD 7.4 (range 48 to 70) years **Sex:** 52% female	**Group 1 (IVB/IVT, n=36):** IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks and IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of addition injection 1.28 **Group 2 (IVB, n=38):** IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks. Mean number of injections 2.54. **Group 3 (IVT, n=37):** IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of injections 1.04 **Unclear if rescue laser was available** **IVB injections were repeated if CMT appeared >300 µm on OCT in at least 6-weeks in all three groups**	At 12 months **BCVA (logMAR)** / **p** ***IVB/IVT*** -0.15 ***IVB*** -0.16 ***IVT*** -0.16 0.088 (between groups) **CMT (µm)** / **p** ***IVB/IVT*** -199 ***IVB*** -179 ***IVT*** -200 0.132 (between groups)

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<table>
<tr><th>Study</th><th>Participants and baseline values</th><th>Intervention</th><th>Outcome (change from baseline at study end)</th></tr>
<tr><td></td><td>Diabetes type: NR
HbA1c: 7.2 SD 1.2 to 7.4 SD1.2
Baseline VA: 0.62 SD 0.23 to 0.65 SD 0.28 logMAR
Baseline CMT: 447 SD 110 to 458 SD 92 µm
Comorbidities: NR</td><td></td><td></td></tr>
<tr><td>Soheilian 2007 / Soheilian 2009/ Soheilian 2011/ Soheilian 2012
[37,41,54,141]
Iran

Design: 3-arm RCT
Follow-up: 36 weeks

[Soheilian 2007 reports 12 week results of the same trial, these were not considered here]</td><td>N: 150 eyes of 129 patients
Inclusion criteria: eyes with clinically significant DMO (ETDRS criteria)
Exclusion criteria: previous panretinal of focal laser photocoagulation, prior ocular surgery or injection, history of glaucoma or ocular hypertension, VA ≥20/40 or <20/300, iris neovascularization, high risk PDR, significant media opacity, monocularity, pregnancy, serum creatinine ≥3 mg/dL, uncontrolled DM
Age: 61.2 SD6.1 years
Sex: 47.3% female
Diabetes type: not reported
HbA1c: not reported
Baseline VA: 0.55 to 0.73 SD0.26 to 0.28 logMAR
Baseline CMT: 300 to 359 SD118 to 149 µm
Comorbidities: 94% NPDR, 6% early PDR</td><td>Group 1 (IVB, n=50 eyes): IV injection of bevacizumab 1.25 mg (0.05 ml) (retreatment IVB 14 eyes)
Group 2 (IVB/IVT, n=50 eyes): IV injection of combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone (retreatment IVB/IVT 10 eyes)
Group 3 (MPC, n=50 eyes): focal or modified grid laser (retreatment MPC 3 eyes)
Regimen for all groups:
Retreatments performed at 12 week intervals as required</td><td>At 36 weeks

BCVA (Snellen chart):
<table>
<tr><th></th><th>BCVA (logMAR), SD</th><th>p</th></tr>
<tr><td>IVB</td><td>-0.28 SD0.25
[+14 SD12.5 letters]</td><td>0.053 vs IVB/IVT or MPC</td></tr>
<tr><td>IVB/ IVT</td><td>-0.04 SD0.33
[+2 SD16.5 letters]</td><td>NS vs MPC</td></tr>
<tr><td>MPC</td><td>+0.01 SD0.27
[-0.5 SD13.5 letters]</td><td></td></tr>
<tr><td></td><td>Snellen line changes</td><td></td></tr>
<tr><td>IVB</td><td>+2 lines or more: 37.0%
stable within 2 lines: 59.3%
-2 lines or more: 3.7%</td><td>NS between groups</td></tr>
<tr><td>IVB/ IVT</td><td>+2 lines or more: 25.0%
stable within 2 lines: 54.2%
-2 lines or more: 20.8%</td><td></td></tr>
<tr><td>MPC</td><td>+2 lines or more: 14.8%
stable within 2 lines: 66.7%
-2 lines or more: 18.5%</td><td></td></tr>
</table>
CMT (OCT):
<table>
<tr><th></th><th>CMT (µm), SD</th><th>p</th></tr>
<tr><td>IVB</td><td>-56 SD140</td><td>0.044 vs baseline, NS between groups</td></tr>
<tr><td>IVB/ IVT</td><td>-5 SD113</td><td></td></tr>
<tr><td>MPC</td><td>-8 SD67</td><td></td></tr>
</table>
Subgroups:
• larger CMT reduction in subgroup with ≥400 µm at baseline (36 weeks: IVB -27.2 SD34.8%, IVB/IVT -8.8 SD35.9%, MPC -15.1 SD14.6%, p<0.001 versus baseline in IVB and MPC groups only)</td></tr>
</table>

Abbreviations: See table 2

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Table ~~8~~9: Ranibizumab safety data

	READ-2 study[28,47]	RESOLVE study[36]	RESTORE study[24]	RISE study[38]	RIDE study[38]
Number of patients	IVR: n=42; L: n=42; IVRL: n=42	IVR0.3: n=51; IVR0.5: n=51; C: n=49	IVR: n=116; IVRL: n=118; L: n=111	IVR0.3: 125; IVR0.5: 126; C: 123	IVR0.3: 125; IVR0.5: 124; C: 127
Ocular adverse events					
Eye pain	NR	IVR0.3: n=9 (18%); IVR0.5: n=9 (18%); C: n=10 (20%)	IVR: n=13 (11%); IVRL: n=10 (8%); L: n=12 (11%)	IVR0.3: 26%; IVR0.5: 21%; C: 19%	IVR0.3: 8%; IVR0.5: 12.9%; C: 7.1%
Conjunctival hyperaemia	NR	NR	IVR: n=9 (8%); IVRL: n=6 (5%); L: n=6 (5%)	NR	NR
Conjunctival haemorrhage	NR	IVR0.3: n=10 (20%); IVR0.5: n=13 (25%); C: n=7 (14%)	IVR: n=8 (7%); IVRL: n=10 (8%); L: n=0	IVR0.3: 54%; IVR0.5: 52%; C: 32%	IVR0.3: 40.8%; IVR0.5: 50.0%; C: 31.5%
IOP increase	NR	IVR0.3: n=6 (12%); IVR0.5: n=15 (29%); C: n=1 (2%)	IVR: n=1 (<1%); IVRL: n=1 (<1%);	IVR0.3: 20%; IVR0.5: 14%; C: 2%	IVR0.3:15.2%;IVR0.5: 18.5%; C: 11%
Vitreous haemorrhage	IVR: n=1 (2%); L: n=4 (10%); IVRL: n=3 (7%)	IVR0.3: n=1 (2%); IVR0.5: n=0; C: n=0	NR	IVR0.3: 3.2%; IVR0.5: 3.2%; C: 13%	IVR0.3: 0.8%; IVR0.5: 2.4%; C: 15%
Substantial worsening of DMO	L: n=1 (2%)		NR	NR	NR
Retinal ischaemia	NR	IVR0.3: n=0; IVR0.5: n=1 (2%); C: n=0	NR	NR	NR
Retinal artery occlusion	NR	IVR0.3: n=0; IVR0.5: n=1 (2%); C: n=0	NR	NR	NR
Endophthalmitis	NR	IVR0.3: n=1 (2%); IVR0.5: n=1 (2%); C: n=0	NR	IVR0.3: 0.8%; IVR0.5: 0; C: 0	IVR0.3 + IVR0.5: 1.2%; C: 0%
Retinal detachment	NR	IVR0.3: n=0; IVR0.5: n=0; C: n=1 (2%)	NR	IVR0.3: 0.8%; IVR0.5: 0; C: 0.8%	IVR0.3 + IVR0.5: 0.4%; C: 0%
Neovascularisation	NR	NR	NR	IVR0.3: 0; IVR0.5: 0; C: 0.8%	IVR0.3: 0.8%; IVR0.5: 0.8%; C: 5.5%
Traumatic cataract	NR	NR	NR	IVR0.3: 0.8%; IVR0.5: 0.8%; C: 0	IVR0.3 + IVR0.5: 0.4%; C: 0%
Uveitis	NR	NR	NR	NR	IVR0.3 + IVR0.5: 0.4%; C: 0%
Macular oedema	NR	NR	NR	IVR0.3: 16.8%; IVR0.5: 20.6%; C: 21.1%	IVR0.3: 19.2%; IVR0.5: 13.7%; C: 20.5%
Retinal exudates	NR	NR	NR	IVR0.3: 19.2%; IVR0.5: 17.5%; C: 20.3%	IVR0.3: 16.0%; IVR0.5: 15.3%; C: 11.0%
Retinal haemorrhage	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 12.7%; C: 20.3%	IVR0.3: 15.2%; IVR0.5: 22.6%; C: 18.9%

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Cataract	NR	NR	NR	IVR0.3: 16.8%; IVR0.5: 11.9%; C: 14.6%	IVR0.3: 20.0%; IVR0.5: 23.4%; C: 23.6%
Vitreous detachment	NR	NR	NR	IVR0.3: 13.6%; IVR0.5: 11.1%; C: 15.4%	IVR0.3: 8.8%; IVR0.5: 12.9%; C: 15.0%
Ocular hyperemia	NR	NR	NR	IVR0.3: 15.2%; IVR0.5: 11.1%; C: 10.6%	IVR0.3: 3.2%; IVR0.5: 3.2%; C: 7.9%
Vitreous floaters	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 14.3%; C: 5.7%	IVR0.3: 7.2%; IVR0.5: 8.1%; C: 3.1%
Eye irritation	NR	NR	NR	IVR0.3: 10.4%; IVR0.5: 9.5%; C: 6.5%	IVR0.3: 5.6%; IVR0.5: 5.6%; C: 3.1%
Foreign body sensation in eyes	NR	NR	NR	IVR0.3: 12.8%; IVR0.5: 7.1%; C: 4.1%	IVR0.3: 8.0%; IVR0.5: 2.4%; C: 5.5%
Systematic adverse events					
Arterial thromboembolic events	Stroke in 1 pt (2%) in IVRL group- not related to study drug	IVR0.3: n=0; IVR0.5: n=3 (6%); C: n=2 (4%)	IVR: n=6 (5%); IVRL: n=1 (<1%); L: n=1 (<1%)	IVR0.3: 3.2% (n=1 stroke); IVR0.5: 7.9% (n=5 strokes); C: 7.3% (n=2 strokes)	IVR0.3: 1.6% (stroke), 5.6% (heart attack); IVR0.5: 2.4% (stroke), 2.4% (heart attack); C: 1.6% (stroke), 5.6% (heart attack)
Hypertension	NR	IVR0.3: n=4 (8%); IVR0.5: n=5 ((10%); C: n=5 (10%)	IVR: n=9 (8%); IVRL: n=6 (5%); L: n=9 (8%)	Serious IVR0.3: 0.8%; IVR0.5: 3.2%; C: 0.8%	Serious IVR0.3: 1.6%; IVR0.5: 1.6%; C: 0%
Non-ocular haemorrhage	NR	IVR0.3: n=1 (2%); IVR0.5: n=1 (2%); C: n=0	IVR: n=1 (<1%); IVRL: n=0; L: n=1 (<1%)	NR	NR
Proteinuria	NR	NR	IVR: n=1 (<1%); IVRL: n=1 (<1%); L: n=0	NR	NR
Deaths	1 (2%) due to CVA in IVRL group	NR	IVR: n=2 (2%); IVRL: n=2 (2%); L: n=2 (2%)	IVR0.3: 2.4%; IVR0.5: 4.0%; C: 0.8%	IVR0.3: 3.2%; IVR0.5: 4.8%; C: 1.6%

NR – not reported, IVR – intra-vitreal ranibizumab, IVRL – intra-vitreal ranibizumab plus laser, C – control, L – laser, IOP –intra-ocular pressure, DMO – diabetic macular oedema,

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Table ~~9~~10: Bevacizumab safety

	BOLT study[23,52]	Lam 2009[35]	Faghihi 2010[53]
Number of patients	MLT: n=38; IVB: n=42	IVB1.25, n=26; IVB2.5, n=26	IVB 1.25 n= 40 IVB 1.25 plus MLT n=40
Ocular adverse events			**Not reported**
Loss of _15 or _30 ETDRS letters	MLT: n=1 transient, 3 at 24 month analysis; IVB: n=4 transient	No significant ocular events (IOP increase, retinal tear, retinal detachment, endophthalmitis); no significant difference in change in cataract scores between groups	
Vitreous haemorrhage	MLT: n=1; IVB: n=0		
Eye pain/irritation/watering during or after injection	MLT:n= 0; IVB: n=8		
Red eye after injection	MLT: n=0; IVB: n=8		
Endophthalmitis	NR		
Transient IOP increase	≥30 mm Hg - MLT: 0; IVB: n=4≥ 45 mm Hg – MLT: n=1; IVB: n=1		
Floaters after injection	MLT: n= 0; IVB: n=2		
Corneal epithelial defect	MLT:n=0; IVB:n=1		
Vitreomacular traction with macular oedema	MLT: n=1; IVB: n=0		
Systematic adverse events			
Anaemia	MLT: n=1; IVB: n=0	no systematic adverse effects (1 patient in 1.25 mg group with foot gangrene requiring amputation due to worsening diabetic neuropathy, considered unrelated to treatment)	
Vomiting after FFA	MLT: n=1; IVB: n=0		
Uncontrolled hypertension	MLT:n=0; IVB: n=1		
Polymyalgia rheumatica	MLT:n=0; IVB: n=1		
Intermittent claudication	MLT:n=0; IVB: n=1		
Gastroenteritis	MLT:n=0; IVB: n=1		
Fall	MLT:n=2; IVB: n=0		
Urinary tract infection	MLT:n=0; IVB: n=1		
Chest infection	MLT:n=0; IVB: n=1		
Headaches, dizziness, tiredness	MLT:n=1; IVB: n=0		
Bell palsy	MLT:n=1; IVB: n=0		
Admission for diabetic foot ulcer	MLT:n=1; IVB: n=1		
Admission for cholecystectomy	MLT:n=0; IVB: n=1		
Admission for fall/loss of consciousness	MLT:n=1; IVB: n=0		
Angina–hospital admission	MLT:n=1; IVB: n=0		
Cerebrovascular accident	MLT:n=1; IVB: n=0		
Myocardial infarction	MLT:n=0; IVB: n=2		
Coronary artery bypass graft	MLT:n=0; IVB: n=1		
Dyspnea, chest pain–admitted for hospital observation	MLT:n=0; IVB: n=1		

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DEATH	NR		

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Table 11:0 Pegaptanib safety

	Cunningham 2005/Adamis 2006[39,57]	Sultan 2011[40]
Number of patients	IVP0.3, n=44 eyes; IVP1, n=44 eyes; IVP3, n=42 eyes	IVP, n=133 eyes; C, n=127 eyes
Ocular adverse events		
Eye pain	Pegaptanib: 31%; C: 17%	IVP: 11.1%; C: 7.0%
Vitreous haemorrhage	Pegaptanib: 22%; C: 7%	IVP: 6.3%; C: 7.7%
Punctuate keratitis	Pegaptanib: 18%; C: 17%	IVP: 11.8%; C: 6.3%
Cataract	Pegaptanib: 13%; C: 10%	IVP: 8.3%; C: 9.2%
Eye discharge	Pegaptanib: 11%; C: 10%	NR
Conjunctival haemorrhage	Pegaptanib: 10%; C: 0%	IVP: 22.2%; C: 14.1%
Vitreous opacities	Pegaptanib: 9%; C: 5%	NR
Blurred vision	Pegaptanib: 7%; C: 5%	NR
Other vitreous disorder	Pegaptanib: 7%; C: 0%	NR
Other visual disturbance	Pegaptanib: 7%; C: 0%	NR
Culture-negative endophthalmitis	Pegaptanib: n=1	NR
IOP increase	NR	IVP: 17.4%; C: 6.3%
Retinal haemorrhage	NR	IVP: 6.3%; C: 10.6%
Retinal exudates	NR	IVP: 6.3%; C: 5.6%
Conjunctivitis	NR	IVP: 5.6%; C: 4.2%
Lacrimation increased	NR	IVP: 5.6%; C: 2.8%
Diabetic retinal oedema	NR	IVP: 11.1%; C: 17.6%
Macular oedema	NR	IVP: 9.7%; C: 11.6%
Systemic adverse events		
Non-ocular hypertension	NR	IVP: 13.9%; C: 9.9%
Cardiac disorders	NR	IVP: 6.9%; C: 5.6%
DEATHS	NR	IVP: n=4

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Table 121: aflibercept safety

	DA VINCI 2010[30,58]
Number of patients	IVVTE (all doses) n=175, laser n = 44
Ocular adverse events	
Conjunctival hemorrhage	At 6 months: Laser 18.2%, IVVTE 18.9% At 12 months: Laser 18.2%, IVVTE 26.9%
IOP increase	At 6 months: Laser 2.3%, IVVTE 9.7% At 12 months: Laser 2.3%, IVVTE 9.7%
Eye pain	At 6 months: Laser 4.5%, IVVTE 8.6% At 12 months: Laser 4.5%, IVVTE 13.7%
Ocular hyperaemia	At 6 months: Laser 4.5%, IVVTE 6.3% At 12 months: Laser 4.5%, IVVTE 7.4%
Vitreous floaters	At 6 months: Laser 4.5%, IVVTE 5.1% At 12 months: Laser 4.5%, IVVTE 6.9%
Endophthalmitis	At 6 months: Laser 0%, IVVTE 1.1% At 12 months: Laser 0%, IVVTE 1.1%
Uveitis	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: Laser 0%, IVVTE 0.6%
Diabetic retinal oedema	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 2.3%, IVVTE 4.6%
Visual acuity reduced	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 2.3%, IVVTE 0%
Vitreous hemorrhage	At 6 months: Laser 2.3%, IVVTE 0% At 12 months: Laser 6.8%, IVVTE 0%
Corneal abrasion	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: Laser 0%, IVVTE 4.6%
Retinal tear	At 6 months: Laser 0%, IVVTE 0.6% At 12 months: NR
Systematic events	
Hypertension	At 6 months: Laser 6.8%, IVVTE 9.7% At 12 months: Laser 0%, IVVTE 1.7%
Myocardial infarction	At 6 months: Laser 0%, IVVTE 1.1% At 12 months: Laser 0%, IVVTE 1.7%
Cerebrovascular event	At 6 months: Laser 0%, IVVTE1.1% At 12 months: Laser 2.3%, IVVTE 1.7%
Death	At 6 months: Laser 0%, IVVTE 1.7% At 12 months: Laser 2.3%, IVVTE 4.0%

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Table 123: Dexamethasone safety

	Callanan 2011[44]	Haller 2010[59]
Number of patients		
Ocular adverse events		
IOP elevation	DIL: 20% (p<0.001); 1% ≥10 mm Hg L: 1.6% ; 0% ≥10 mm Hg	
Cataract	NR	NR
Anterior chamber cells	NR	DDS350: 29.1%; DDS700: 26.4%; C: 1.8%
Anterior chamber flare	NR	DDS350: 27.3%; DDS700: 20.8%; C: 8.8%
Vitreous haemorrhage	NR	DDS350: 20.0%; DDS700: 22.6%; C: 5.3%
Eye pain	NR	DDS350: 18.2%; DDS700: 9.4%; C: 3.5%
Vitreous disorder	NR	DDS350: 20.0%; DDS700: 15.1%; C: 3.5%
Increased IOP	NR	DDS350: 14.5%; DDS700: 9.4%; C: 0%
Conjunctival haemorrhage	NR	DDS350: 14.5%; DDS700: 7.5%; C: 0%
Vitreous floaters	NR	DDS350: 7.3%; DDS700: 17.0%; C: 0%
		No significant differences in: reduced VA, eye irritation, abnormal sensation in eye, macular oedema, eye pruritus, retinal hemorrhage, DR, nonocular events

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Table 134: Fluocinolone safety

	FAME study (Campochiaro 2011/2012)[29,60]	Pearson 2011[43]
Number of patients		
Ocular adverse events		
IOP at 12 months	NR	NR
Progression of cataract	NR	NR
Cataract	NR	SRFA: 55.9%; SOC: 21.7%
Transient vitreous floaters	NR	NR
Transient subconjunctival haemorrhage	NR	NR
Cataract surgery	SRFA0.2: 41.1% (74.9% of those without cataract surgery at baseline, 80.0% at 36 months); SRFA0.5: 50.9% (84.5% of those without cataract surgery at baseline, 87.2% at 36 months); C: 7% (23.1% of those without cataract surgery at baseline, 27.3% at 36 months)	NR
Glaucoma	SRFA0.2: 1.6%; SRFA0.5: 2.3%; C: 0.5%	NR
Increased IOP	SRFA0.2: 3.2%; SRFA0.5: 3.3%; C: 0%	SRFA: 69.3%; SOC: 11.6%
IOP >30 mmHg at any point during 36 months	SRFA0.2: 18.4%; SRFA0.5: 22.9%; C: 4.3%	NR
Trabeculectomy	SRFA0.2: 2.1%; SRFA0.5: 4.8%; C: 0%	NR
Other glaucoma surgery	SRFA0.2: 1.3%; SRFA0.5: 1.3%; C: 0.5%	NR
Trabeculoplasty	SRFA0.2: 0.8%; SRFA0.5: 2.3%; C: 0%	NR
Vitreous haemorrhage	NR	SRFA: 40.2%; SOC: 18.8%
Abnormal sensation in eye	NR	SRFA: 37%; SOC: 11.6%
Macular oedema	NR	SRFA: 34.6%
Eye pain	NR	SRFA: 26.8%; SOC: 15.9%
Eye irritation	NR	SRFA: 22%; SOC: 10.1%
Increased lacrimation	NR	SRFA: 22%; SOC: 8.7%
Photophobia	NR	SRFA: 21.3%; SOC: 21.7%
Blurred vision	NR	SRFA: 21.3%; SOC: 15.9%
Vitreous floaters	NR	SRFA: 21.3%; SOC: 8.7%
Systemic adverse events		
Serious cardiovascular events	SRFA0.2: 12.0%; SRFA0.5: 13.2%; C: 10.3%	
Pruritus	NR	SRFA: 38.6%; SOC: 21.7%
DEATHS	NR	NR

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Table 145: Triamcinolone safety

	DRCR Network 2008 (Ip 2008a / Ip 2008b / Beck 2009 / Bressler 2009) [22,61,63,64]	Gillies 2006 / 2007 / 2009 / Sutter 2004[32,136-138]	Gillies 2011[33]	Kim 2010[45]	Lam 2007[34]	Ockrim 2008 / Sivaprasad 2008[42,62]
Number of patients						
Ocular adverse events						
	At 2 years (or 3 years when indicated)	At 2 years	-	Not reported	-	At 12 months
IOP ≥30 mm Hg	IVT1: n=22; IVT4: n=53; L: n=3	NR	NR		NR	IVT: IOP significantly higher than in L group (18.2 mm Hg, range 12 to 26 mm Hg); no cases of glaucoma
IOP >22 mm Hg	NR	NR	NR		IVT: 37% (p=0.002 vs. L); IVTL: 36% (p=0.002 vs. L); L: 5%	NR
IOP ≥10 mm Hg from baseline	IVT1: n=41; IVT4: n=85; L: n=12	NR	NR		NR	NR
IOP ≥5 mm Hg	NR	IVT: 68% (p=0.007 vs. C); C: 10%	NR		NR	NR
IOP lowering medication used	IVT1: n=31; IVT4: n=76; L: n=25	IVT: 44% (p=0.0002 vs. C); C: 3%	IVTL: 64% (P<0.001); L: 24%		NR	NR
Cataract surgery	IVT1: 23% (of those phakic at baseline, 46% by 3 years (p<0.001 between all groups); IVT4: 51% (of those phakic at baseline, 83% by 3 years); L: 13% (of those phakic at baseline, 31% by 3 years)	IVT: 56% (of phakic eyes over 3 years, p<0.001 vs. C); C: 8% (of phakic eyes over 3 years)			NR	NR
Ptosis	NR	NR	NR		NR	NR
Retinal detachment	IVT1: n=2; IVT4: n=4; L: n=2	NR	NR		None	NR
Retinal vein occlusion	IVT1: n=1; IVT4: n=2; L: n=3	NR	NR		NR	NR
Retinal artery occlusion	IVT1: n=0; IVT4: n=0; L: n=1	NR	NR		NR	NR
Anterior ischemic optic neuropathy	IVT1: n=1; IVT4: n=0; L: n=0	NR	NR		NR	NR
Vitrectomy	IVT1: n=26; IVT4: n=19; L: n=31	NR	NR		NR	NR
Open angle glaucoma	IVT1: n=2; IVT4: n=7; L: n=2	NR	NR		NR	NR

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Glaucoma filtering surgery	IVT1: n=0; IVT4: n=2; L: n=0	NR	NR		NR	NR
Laser trabeculoplasty	IVT1: n=0; IVT4: n=1; L: n=0	IVT: n=2; C: n=0	IVTL: n=1		NR	NR
Ciliary body destruction	IVT1: n=0; IVT4: n=1; L: n=0	NR	NR		NR	NR
Endophthalmitis	IVT1: n=0; IVT4: n=;0 L: n=0	(Infectious) IVT: n=1; C: NR	(Culture-negative) IVTL: n=1		None	(sterile) IVT: n=1
pseudoendophthalmitis	IVT1: n=0; IVT4: n=;0 L: n=0	NR	NR		NR	NR
Chemosis	NR	NR	NR		NR	NR
% increase in cataract scores	NR	NR	NR		IVT: +1.0 SD1.1 (p=NS vs. L); IVTL: +1.3 SD1.9 (p=NS vs. L); L: +0.5 SD0.9	NR
Ocular hypertension (>21 mm Hg)	NR	NR	NR		NR	NR
Cataract progression	NR	NR	Phakic eyes, progression by ≥2 AREDS grade, IVTL: 64% (p<0.001); L: 11% (p<0.001)		NR	NR
Corneal decompensation	NR	IVT: NR; C: n=1	NR		NR	NR
Cataract surgery	NR	NR	IVTL: 61% (p<0.001); L: 0%		NR	IVT: n=2; L: n=1
Vitreous haemorrhage	NR	NR	NR		IVTL: n=1	
Lens opacity	NR	NR	NR		NR	Significantly greater change in lens opacity in IVT group than in L group (1.9)
DEATHS	N=33, unrelated to study treatment	IVT: n=1; C: n=2	IVTL: n=2; L: n=1		NR	NR

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Table 156: Safety data in trials assessing more than one drug

	Ahmadieh 2008[31]	ATEMD 2011 (Oliveira Neto 2011) [56]	DRCR Network 2010 (Elman 2010, Elman 2011)[21,46]	Lim 2012[55]	Soheilian 2007 / Soheilian 2009[37,41]
Number of patients					
	Ocular adverse events				
Mild anterior chamber reaction	IVB: 19.5% (n=8 eyes), resolved after one week of no treatment; IVB/IVT: 18.9% (n=7 eyes), resolved after one week of no treatment	NR	NR	NR	IVB: 20% (n=10 eyes), resolved after 1 week; IVB/IVT: 18% (n=9 eyes), resolved after 1 week
Marked anterior chamber reaction	IVB: n=1 (topical corticosteroid and cycloplegic drops)	NR	NR	NR	IVB: n=1 (topical corticosteroids and cycloplegic drops);
Progression of fibrous proliferation	IVB: n=1 with no sign of retinal traction	NR	NR	NR	IVB: n=1 with no sign of retinal traction;
Vitreous haemorrhage	IVB/IVT: n=1 after third injection (excluded from study)	NR	NR	NR	NR
IOP rise	IVB: 23, 22 and 28 mm Hg at 6, 12 and 18 weeks (anti-glaucoma drops)	NR	IOP elevation more frequent with triamcinolone + PL	IVB/IVT: 8.3% IVT: 10.8%	NR
IOP ≥10 mm Hg from baseline	NR	NR	CPL: n=16; RPL: n=10; RDL: n=5; TPL: n=70	NR	NR
IOP ≥30 mm Hg from baseline	NR	NR	CPL: n=3; RPL: n=2; RDL: n=4; TPL: n=46	NR	NR
Initiation of IOP lowering treatment at any visit	NR	NR	CPL: n=9; RPL: n=5; RDL: n=4; TPL: n=41	NR	NR
Iris neovascularization	None	NR	NR	NR	NR
Lens opactiy	None	NR	NR	NR	Severe lens opacity IVB/IVT: n=4 eyes; MPC: n=1 eye
Endophthalmitis	NR	NR	CPL: n=1; RPL: n=1; RDL: n=1; TPL: n=0	NR	None
Pseudoendophthalmitis	NR	NR	CPL: n=1; RPL: n=0; RDL: n=0; TPL: n=1	NR	NR
Ocular vascular event	NR	NR	CPL: n=1; RPL: n=1; RDL: n=0; TPL: n=2	NR	NR

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Retinal detachment	NR	NR	CPL: n=0; RPL: n=0; RDL: n=1; TPL: n=0	NR	None
Vitrectomy	NR	NR	CPL: n=7; RPL: n=0; RDL: n=3; TPL: n=0	NR	NR
Vitreous haemorrhage	NR	NR	CPL: n=15; RPL: n=3; RDL: n=4; TPL: n=2	NR	None
Cataract surgery	NR	NR	CPL: n=11 (of those phakic at baseline); RPL: n=6 (of those phakic at baseline); RDL: n=8 (of those phakic at baseline); TPL: n=19 (of those phakic at baseline)	NR	NR
Glaucoma surgery	NR	NR	NR	NR	NR
Retinal neovascularization	NR	NR	NR	NR	IVB: n=4 (all resolved); MPC: n=3 eyes (2 resolved)
Development of early PDR	NR	NR	NR	NR	IVB: n=1; IVB/IVT: n=4; MPC: n=3
Progression to high-risk PDR	NR	NR	NR	NR	IVB: n=4; IVB/IVT: n=3; MP: n=3
Ocular hypertension (≥23 mm HG)	NR	NR	NR	NR	IVB/IVT: 16% (n=8 of eyes), controlled medically in all except 1 that progressed to neovascular glaucoma
	Systemic adverse events				
Acute myocardial infarction		N=1, considered not to be related to the study drug	No specific systemic adverse events that could be attributed to chance		No significant blood pressure increase, no thromboembolic events
Deaths	C: n=1	N=1, considered not to be related to the study drug	CPL: n=8; RPL: n=5; RDL: n=3; TPL: n=2		IVB/IVT: n=2; MPC: n=2

NR – not reported, IVB – intra-vitreal bevacizumab, IVT- intravitreal triamcinolone, IVR – intra-vitreal ranibizumab, IVRL – intra-vitreal ranibizumab plus laser, C – control, L – laser, IOP –intra-ocular pressure, PDR – proliferative diabetic retinopathy, DMO – diabetic macular oedema,

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Table 16: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Anti-VEGFs							
Ranibizumab							
READ-2 Study [28,47]	Unclear	Unclear	Unclear	Yes (91.3% completion)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Juvenile Diabetes Research Foundation, Genentech Inc.
RESOLVE Study (Massin 2010)[36]	Yes	Yes	Yes (patients and outcome assessors)	Yes (82% completion in sham arm; 90.2% with ranibizumab)	Yes	Comparison groups similar at baseline; power analysis unclear	Novartis Pharma, Switzerland
RESTORE Study (Mitchell 2011)[24]	Yes	Unclear	Yes (patients, outcome assessors)	Yes (87.3 to 88.3% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Novartis Pharma, Switzerland
RISE and RIDE (Nguyen 2012)[38]	Yes	Yes	Yes (patients, treating physician masked to assigned dose of ranibizumab)	Yes (2 year study completed by 83.3% of patients in RISE and by 84.6% in RIDE)	Yes	Comparison groups similar at baseline; ITT analysis; power analysis carried out (power adequate for primary endpoint)	Genentech Inc.
Bevacizumab							
BOLT Study (Michaelides 2010)[23,52]	Yes	Unclear	Partial (outcome assessors, not patients)	Yes (97.5% completion)	Yes	Comparison groups similar at baseline (except laser group had longer duration of clinically significant DMO); power analysis carried out (power adequate for VA changes)	Moorfields Special Trustees, National Institute for Health Research
Faghihi 2010[53]	Yes	Unclear	Yes (patient	Yes (100% completion)	Yes	Comparable groups at baseline	Not specified

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Lam 2009[35]	Yes	Yes	Yes (patients and technicians assessing BCVA, OCT and IOP)	Yes (92.3% follow-up at 6 months)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	supported in part by the Action for Vision Eye Foundation Hong Kong (charity)
Pegaptanib							
Cunningham 2005 / Adamis 2006[39,57]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (95% completion)	Yes	Comparison groups similar at baseline; acknowledge lack of power to detect differences between doses of pegaptanib	Eyetech Pharmaceuticals Inc., New York, and Pfizer Inc., New York
Sultan 2011[40]	Yes	Unclear	Yes (patients and outcome assessors)	Yes (69.9 to 73.8% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Pfizer Inc., New York
Aflibercept							
Da Vinci 2010 [30,58]	Unclear (predetermined randomization scheme)	Unclear	Yes (patients)	Yes (85% completion)	Yes	Comparison groups similar at baseline; power calculation completed	Regeneron Pharmaceuticals, Inc., New York
Steroids							
Dexamethasone							
Haller 2010[59]	Yes	Unclear	Yes (patients to dexamethasone dose, outcome assessors)	Yes (92% completion)	Yes	Comparison groups similar at baseline; power analysis carried out, but study not powered to detect differences in subgroups	Oculex Pharmaceuticals Inc.
Fluocinolone							
FAME Study (Campochiaro 2011)[29,60]	Unclear	Unclear	Partial (patients, masking of outcome assessment not mentioned)	Yes (drop-out rate 19.0 to 22.7%)	Yes	Comparison groups similar at baseline; power analysis not mentioned	Alimera Sciences Inc., Atlanta, Georgia; Psivida Inc., Watertown, Massachusetts

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Pearson 2011[43]	Yes	Unclear	Third party masked design (patient and investigator not masked)	No losses to follow-up	Yes	Demographic characteristics were similar between implant and SOC groups; power calculation done, study adequately powered.	Bausch & Lomb Inc, Rochester, New York
Triamcinolone							
DRCR Network 2008 [22,61,63,64]	Yes	Unclear	Partial (patients to triamcinolone dose, outcome assessors not formally masked but generally not aware of participant's study group)	Yes (81 to 86% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services
Gillies 2006 / 2007 / 2009 / Sutter 2004[32,137-139]	Yes	Yes	Yes (patients, outcome assessors)	Yes (91% completion intervention, 83% control)	Yes	Comparison groups similar at baseline (but limited demographic data); power analysis carried out (power adequate for VA changes)	Sydney Eye Hospital Foundation and Juvenile Diabetes Research Foundation, New York
Gillies 2011[33]	Yes	Yes	Yes (patients, outcome assessors)	Yes (84.5% completion)	Yes	power analysis carried out (power adequate for VA changes)	National Health and Medical Research Council, Canberra, Australia, and the Sydney Eye Hospital Foundation, Sydney, Australia
Lam 2007[34]	Yes	Yes	Partial (outcome assessors)	No losses to follow-up	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes)	Action for Vision Foundation, Hong Kong
Ozkrim 2008/Sviprasad 2008[42,62]	Yes	Unclear	Unclear	Yes (94% completion)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Special Trustees of Moorfields Eye Hospital
Active comparator trials							

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Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
Ahmadieh 2008[31]	Yes	Yes	Yes (patients and outcome assessors)	Unclear	Yes	CMT lower in control group at baseline (p<0.05), other baseline values similar; power analysis carried out (power adequate for CMT changes)	Not reported
DRCR Network [21,46]	Yes	Unclear	Yes (patients, except deferred laser group; outcome assessors); masking discontinued after the first year	Yes (1 year completion for 91-95% of eyes)	Yes	Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes)	Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and Human Services; Ranibizumab provided by Genentech, triamcinolone provided by Allergan Inc.; companies also provided funds to defray the study's clinical site costs
Lim 2012[55]	Yes	Unclear	Yes (investigators only)	Yes (7.5% drop out after enrollment)	Yes	Groups similar at baseline. The bevacizumab group received more injections.	Not reported
Soheilian [37,41]	Yes	Yes	Yes (patients and outcome assessors)	Unclear (36 week completion for 76 to 88%)	Yes	CMT significantly lower and VA significantly better in MPC group at baseline, other baseline values similar; power analysis carried out (power adequate for VA changes)	Ophthalmic Research Centre, Labbafinejad Medical Center, Tehran

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figures 2-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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