ClinicalEvidence

Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema

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ABSTRACT

INTRODUCTION: Diabetic retinopathy is the most common microvascular complication of diabetes. It is also the most common cause of blindness in working-age adults in industrialised nations. Older people and those with worse diabetes control, hypertension, and hyperlipidaemia are most at risk. Diabetic macular oedema, which can occur at any stage of diabetic retinopathy, is related to increased vascular permeability and breakdown of the blood retinal barrier, in part related to increased vascular endothelial growth factor (VEGF) levels. About 1% to 3% of people with diabetes suffer vision loss because of diabetic macular oedema. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical questions: What are the effects of intravitreal VEGF inhibitors versus each other for diabetic macular oedema? What are the effects of intravitreal VEGF inhibitors plus laser therapy versus intravitreal VEGF inhibitors alone for diabetic macular oedema? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 240 studies. After deduplication and removal of conference abstracts, 149 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 90 studies and the further review of 59 full publications. Of the 59 full articles evaluated, eight systematic reviews and four RCTs were added at this update. We performed a GRADE evaluation for four PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for six comparisons based on information about the effectiveness and safety of intravitreal VEGF inhibitors aflibercept, bevacizumab, and ranibizumab, and each of these intravitreal VEGF inhibitors plus laser therapy.

QUESTIONS

INTERVENTIONS

INTRAVITREAL VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS (VEGF) VERSUS EACH OTHER

Beneficial

INTRAVITREAL VEGF INHIBITORS PLUS LASER THERAPY V INTRAVITREAL VEGF INHIBITORS ALONE

Unknown effectiveness

Unlikely to be beneficial

Covered elsewhere in Clinical Evidence

Age-related macular degeneration

Footnote

*Based on consensus and RCT evidence published after the search date of this overview

Key points

- Diabetic retinopathy is the most common microvascular complication of diabetes. It is also the most common cause of blindness in working-age adults in industrialised nations. Older people and those with worse diabetes control, hypertension, and hyperlipidaemia are most at risk.

  Diabetic retinopathy can cause microaneurysms, haemorrhages, exudates, changes to blood vessels, and retinal thickening.

  Diabetic macular oedema, which can occur at any stage of diabetic retinopathy, is related to increased vascular permeability and breakdown of the blood retinal barrier, in part related to increased vascular endothelial growth factor (VEGF) levels.

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In addition to increased vascular permeability, it is characterised by central retinal thickening and the deposition of hard exudates.

Involvement of macular oedema in the central subfield, as identified on optical coherence tomography, is associated with a reduction in visual acuity.

Diabetic macular oedema is now the principal cause of vision loss in people with type 2 diabetes and affects 21 million people worldwide.

- The previous version of this overview examined treatments for diabetic retinopathy. However, for this updated overview we have focused on selected interventions for diabetic macular oedema.
- We searched for evidence from RCTs and systematic reviews of RCTs on the effects of ranibizumab, bevacizumab, pegaptanib, and aflibercept for our comparisons of interest. We found no evidence for pegaptanib. As it is not licensed for the treatment of diabetic macular oedema and not in general clinical use, this drug was not included in the overview for this update.
- Several anti-VEGF agents are also currently used for the treatment of wet age-related macular degeneration (see the *BMJ Clinical Evidence* overview on Age-related macular degeneration: anti-vascular endothelial growth factor treatment) and retinal vein occlusion. However, because the pathophysiology, response to treatment, and prognosis vary among the different indications, it is not sufficient to assume that if a treatment is more effective in one condition, this will be applicable to all. Therefore, head-to-head data are required for all conditions.
- Considering only the evidence from RCTs and systematic reviews meeting our inclusion criteria for this overview, we don't know whether intravitreal ranibizumab, bevacizumab, or aflibercept differ in effectiveness at improving visual acuity or central macular thickness in people with diabetic macular oedema.

  Published after the search date of this overview, the DRCRN 2015 study is a large, multicentre RCT that directly compared intravitreal ranibizumab, aflibercept, and bevacizumab in people with centre-involved diabetic macular oedema. We have included this study in the Comment section of the overview.

  This RCT found that: for patients with poor baseline visual acuity or significant central macular thickening, treatment with intravitreal aflibercept may be more effective than with other anti-VEGF agents. While in patients with good baseline visual acuities and lesser central retinal thickening there may be little difference in efficacy between intravitreal bevacizumab, ranibizumab, or aflibercept.

  Further studies directly comparing these anti-VEGF agents are needed to validate the findings from this RCT.
- In clinical practice, other factors such as cost, local availability, and individual response to treatment may play a role in deciding optimal treatment.
- Anti-VEGF agents given intra-ocularly can enter the systemic circulation and may result in a small increase in the absolute risk of arteriothromboembolic events.
- No significant differences appear to exist between ranibizumab, aflibercept, and bevacizumab in ocular or systemic adverse events, but studies were not powered to detect small changes and excluded patients with previous arteriothromboembolic events.
- We found no RCT evidence on the effectiveness of intravitreal aflibercept plus laser therapy compared with intravitreal aflibercept alone in people with diabetic macular oedema.

  We found no evidence of additional benefit in terms of visual outcomes in eyes with centre-involving diabetic macular oedema by combining macular laser therapy with either intravitreal ranibizumab or bevacizumab compared with intravitreal ranibizumab or bevacizumab alone.
- Laser treatment close to fixation has potential to vision loss and paracentral scotomas. If required, can be deferred in order to maintain visual gains.

Clinical context

GENERAL BACKGROUND

Diabetic macular oedema (DMO) is a sight-threatening condition, treated until recently with focal or grid macular laser treatment. However, conventional laser treatment can cause scarring with a prolonged onset of response over a period of months. The aim of treatment is visual stability rather than gain. Anti-vascular endothelial growth factor (anti-VEGF) agents provide a rapid improvement in reduction of oedema and resultant improvement in the visual acuity without retinal scarring. However, the treatment is not sustained, and repeat treatments are required in order to maintain visual gain. Several anti-VEGF agents are in current use for the treatment of wet age-related macular degeneration (see the *BMJ Clinical Evidence* overview on Age-related macular degeneration: anti-vascular endothelial growth factor treatment) and retinal vein occlusion. As such, there are several head-to-head trials looking at the comparative effectiveness among these treatments for the different pathologies. The pathophysiology, response to treatment and prognosis vary among these indications, and it is not sufficient to assume that if a treatment is more effective in one condition, this will be applicable to all. Therefore, head-to-head data are required for all conditions.

FOCUS OF THE REVIEW

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This overview focuses on the comparison of the three anti-VEGF treatments in use in current clinical practice. Knowledge of which agent is the most effective in eyes with diabetic macular oedema is of benefit in providing a tailored treatment to patients. There is increasing pressure and focus on cost effectiveness, which has led to the widespread use of unlicensed intra-ocular bevacizumab. Thus, we have also focused on the comparative efficacy and safety of bevacizumab compared to the licensed anti-VEGF agents. Comparison with aflibercept, which has a slightly different mode of action to ranibizumab and bevacizumab, is important to provide evidence of any improved efficacy. The gold standard of treatment was previously laser treatment and, therefore, this modality should be included in an overview of treatment for diabetic macular oedema. There are several intra-ocular corticosteroid treatments licensed for use in diabetic macular oedema (dexamethasone intravitreal implant and fucinolone acetonide intravitreal implant). These may have a particular role in chronic diabetic macular oedema unresponsive to anti-VEGF treatment, and so are not covered in this overview.

COMMENTS ON EVIDENCE

Although outside the scope of this overview, most studies and analyses that we found on individual VEGF inhibitors were comparing VEGF inhibitors to inactive control or laser. However, head-to-head RCTs between different VEGF inhibitors are now being reported. Much of the published data used eyes, rather than people, as the unit of analysis. We found many analyses that compared VEGF inhibitors plus laser with laser alone, rather than the comparison of VEGF inhibitors plus laser with VEGF inhibitor alone, which is the subject of this overview. For our pre-specified comparisons of interest, we found most evidence on ranibizumab and bevacizumab, and no evidence on the effects of pegaptanib. As pegaptinib is not routinely used for the treatment of diabetic macular oedema, it is not included any further in this overview.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, June 2010, to September 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 240 studies. After deduplication and removal of conference abstracts, 149 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 90 studies and the further review of 59 full publications. Of the 59 full articles evaluated, eight systematic reviews and four RCTs were added at this update.

DEFINITION

Diabetes mellitus is a major health problem estimated to affect 387 million people [1] or 9% of the world's population as of 2014 [2] and 3.3 million people or about 6% of the population in the UK. [3] [4] [5] [6] [7] This is expected to rise to 592 million people worldwide by 2035. [1] Diabetic retinopathy is the most common microvascular complication of diabetes. [8] It is also the most common cause of blindness in working-age adults in industrialised nations. [9] [10] Almost half of those with diabetes will have some degree of retinopathy at any given time. Diabetic retinopathy can be classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The earliest visible signs in NPDR are micro-aneurysms and retinal haemorrhages. With increasing ischaemia, cotton wool spots, venous beading, and intraretinal microvascular abnormalities develop (moderate/severe NPDR). Vision loss is primarily from the development of abnormal new retinal vessels (PDR), which can lead to haemorrhage, fibrosis, traction, and retinal detachment. Diabetic macular oedema (DMO) is a sight-threatening condition that can occur at any stage of diabetic retinopathy. It is characterised by increased vascular permeability, central retinal thickening, and the deposition of hard exudates. Increased levels of vascular endothelial growth factor (VEGF) causes increased vascular permeability; increased levels are found in the vitreous of patients with diabetic macular oedema. When this is present close to or at the central macula, it is termed 'clinically significant macular oedema'. **Anti-VEGF treatment for DMO** For this overview, we have focused on the effects of the three most widely used intravitreal VEGF inhibitors compared with each other, and also the effects of intravitreal drugs alone compared with combination treatment with macular laser for treatment of DMO. Laser treatment has been shown to reduce risks of moderate vision loss from clinically significant macular oedema, but treatment can lead to retinal scarring with resultant reduced vision, especially in eyes with central involvement. Intravitreal treatment with anti-VEGF agents results in reduced central retinal thickness with associated improvements in the vision over and above treatment with laser. Re-classification of clinically significant macular oedema, which was based on biomicroscopic examination of centre-involving DMO defined by optical coherence tomography classification, identifies those who would most benefit from treatment with anti-VEGF agents. Unlike laser treatment, use of anti-VEGF agents results in a more rapid but less sustained effect, requiring repeated treatments to maintain effects.

INCIDENCE/ PREVALENCE

Diabetic eye disease is responsible for 14% of registrable blindness in the UK [11] and for 2% of blindness worldwide. [12] [13] Diabetic retinopathy affects 93 million people worldwide. [8] DMO is now the principal cause of vision loss in people with type 2 diabetes [9] and affects 21 million people worldwide. [8] Of people living with diabetes, about 1% to 3% suffer vision loss because of DMO. [14] [15]

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AETIOLOGY/ RISK FACTORS

Duration of diabetes is the strongest factor influencing the development of retinopathy, with more than 60% of those with type 2 diabetes having some form of diabetic retinopathy after 20 years. There are several modifiable systemic risk factors strongly associated with retinopathy, including glycaemic control, blood pressure, and dyslipidaemia. Evidence from several well-conducted RCTs and observational studies show that tight glycaemic control reduces the incidence and progression of retinopathy. [16] For type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) showed that each 1% decrease in HbA1c (e.g., 75 mmol/mol to 64 mmol/mol [9% to 8%]) reduces the risk of retinopathy by 39%, [17] and this beneficial effect persisted long after the period of intensive control. [18] In type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) showed that each 10% decrease in HbA1c reduces the risk of microvascular events, including retinopathy, by 25%. [19] A Cochrane review in 2015 demonstrated that there is good evidence that more intensive blood pressure control intervention protects patients with both diabetes and hypertension against developing new diabetic retinopathy. [20] There is also some evidence that intensive BP control is protective against progression of diabetic retinopathy. However, the review did not find that tight BP control reduced the risk of progression of vision loss from diabetic retinopathy. There is good evidence that treatment of dyslipidaemia with fenofibrate protects patients with diabetes against progression of diabetic retinopathy. [21] The ACCORD Eye Study showed that combination lipid therapy with fenofibrate and simvastatin reduced the progression of retinopathy by about one third, from 10.2% to 6.5%, over 4 years, compared with simvastatin treatment alone. [22] Other risk factors include pregnancy, [23] renal impairment, [24] race, [25] inflammation, [26] and genetic influences. [27]

PROGNOSIS

Natural history studies from the 1960s found that at least half of people with proliferative diabetic retinopathy progressed to Snellen visual acuity of less than 6/60 (20/200) within 3 to 5 years. [28] [29] [30] After 4 years' follow-up, the rate of progression to less than 6/60 (20/200) visual acuity in the better eye was 1.5% in people with type 1 diabetes, 2.7% in people with non-insulin-dependent type 2 diabetes, and 3.2% in people with insulin-dependent type 2 diabetes. [31]

AIMS OF INTERVENTION

To prevent visual disability, partial sight, and blindness; to improve quality of life, with minimum adverse effects.

OUTCOMES

Visual acuity (measured using an ETDRS chart, unless otherwise stated); incidence of visual disability (visual acuity 6/24 [20/80] or worse in the better eye), partial sight registration (visual acuity 6/60 [20/200] or worse in the better eye), and registrable blindness (visual acuity 3/60 [10/200] or worse in the better eye); **adverse effects**. Clinically important loss of vision is often defined as loss of 15 ETDRS letters (2 or more Snellen lines) of acuity, roughly equivalent to doubling of the visual angle (visual angle is the angle subtended at the eye of the smallest letter visible by that eye) — a measure used extensively in research. Also, we have reported on central macular thickness, which is the retinal thickness within the area defined by the Early Treatment of Diabetic Retinopathy Study 9-sector layout. [32] The central macular thickness is used as a criterion for treatment eligibility by the National Institute for Health and Care Excellence. [33]

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date September 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to September 2014, Embase 1980 to September 2014, The Cochrane Database of Systematic Reviews issue 9, 2014 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing more than 20 individuals (or at least 10 per intervention if multiple-intervention studies), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We also included network meta-analyses from systematic reviews where these were reported. Where we have reported such analyses, we have clearly indicated that they are network, and may not include RCTs with direct head-to-head comparisons for our pre-specified comparisons of interest. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the

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harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of laser treatments in people with diabetic retinopathy? What are the effects of drug treatments for diabetic retinopathy? What are the effects of treatments for vitreous haemorrhage? We have added two new questions at this update: What are the effects of intravitreal vascular endothelial growth factor (VEGF) inhibitors versus each other for diabetic macular oedema? What are the effects of intravitreal vascular endothelial growth factor (VEGF) inhibitors plus laser therapy versus intravitreal VEGF inhibitors alone for diabetic macular oedema? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 25). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of intravitreal vascular endothelial growth factor (VEGF) inhibitors versus each other for diabetic macular oedema?**

OPTION **RANIBIZUMAB (INTRAVITREAL) VERSUS OTHER INTRAVITREAL VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS (BEVACIZUMAB, AFLIBERCEPT)** New

- For GRADE evaluation of interventions for Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema, see table, p 25 .
- Considering only the evidence from RCTs and systematic reviews meeting our inclusion criteria for this overview, we don't know whether intravitreal ranibizumab and intravitreal bevacizumab differ in effectiveness at improving visual acuity or central macular thickness at 6 to 12 months in people with diabetic macular oedema.
- No significant differences appear to exist between bevacizumab, aflibercept, and ranibizumab in ocular or systemic adverse events, but studies were not powered to detect small changes and excluded patients with previous arteriothrombolic events.
- Published after the search date of this overview, the DRCRN 2015 study is a large, multicentre RCT that directly compared intravitreal ranibizumab, aflibercept, and bevacizumab in people with centre-involved diabetic macular oedema. We have added this study to the Comment, p 5 section.
- The DRCRN study found that in eyes with good baseline visual acuities (>69 ETDRS letters) and lesser central retinal thickening, there was little statistical difference in efficacy in terms of visual outcomes at 1 year between bevacizumab and ranibizumab or aflibercept. In eyes with poorer baseline vision (<69 ETDRS letters), ranibizumab may result in poorer visual outcomes at 1 year in comparison with aflibercept.
- Further studies directly comparing these anti-VEGF agents are needed to validate the findings from the DRCRN study.

Benefits and harms

Intravitreal ranibizumab versus other intravitreal VEGF inhibitors:

We found eight systematic reviews (search dates 2008; [34] 2011; [35] [36] [37] [38] 2012; [39] [40] and 2014 [41]). The reviews had differing inclusion and exclusion criteria and reported different analyses. One review identified an

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abstract of an RCT comparing ranibizumab with bevacizumab. [40] This RCT has subsequently been published, and we have reported the RCT directly from the original report. [42] Two reviews reported a network analysis involving ranibizumab, [37] [41] and one review reported an exploratory indirect analysis. [39] We found one further subsequent RCT. [43] We have reported any RCTs or direct or network meta-analyses in the reviews we found below.

Intravitreal ranibizumab versus intravitreal bevacizumab:

We found one review (search date 2011) that reported a network meta-analysis. [37] In addition, we found another review (search date 2012) that reported an exploratory indirect comparison (see Further information on studies). [39] We found two subsequent RCTs that directly compared ranibizumab with bevacizumab. [42] [43] However, evidence was weak (see Further information on studies).

Visual acuity

Intravitreal ranibizumab compared with intravitreal bevacizumab We don't know whether intravitreal ranibizumab and intravitreal bevacizumab differ in effectiveness at improving visual acuity or central macular thickness at 6 to 12 months in people with diabetic macular oedema (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Visual acuity					
[42] RCT	48 people, centre-involved diabetic macular oedema (DMO), mean age 64 years, mean duration of diabetes 16 years, mean HbA1c 8.6, 50% with retinopathy treated with panretinal photocoagulation	**Mean best corrected visual acuity (BCVA) , 48 weeks** 0.36 logMAR with intravitreal bevacizumab 0.34 logMAR with intravitreal ranibizumab 60 eyes (45 people) included in this analysis	P = 0.1886 The RCT reported that at week 48, there was a mean BCVA improvement of about 11 letters in the bevacizumab group and about 13 letters in the ranibizumab group compared with baseline	⟷	Not significant
[42] RCT	48 people, centre-involved DMO, mean age 64 years, mean duration of diabetes 16 years, mean HbA1c 8.6, 50% with retinopathy treated with panretinal photocoagulation	**Proportion of eyes gaining 10 or more ETDRS letters , 48 weeks** 61% of eyes with intravitreal bevacizumab 68% of eyes with intravitreal ranibizumab Absolute results reported graphically 60 eyes (45 people) included in this analysis	P >0.05	⟷	Not significant
[42] RCT	48 people, centre-involved DMO, mean age 64 years, mean duration of diabetes 16 years, mean HbA1c 8.6, 50% with retinopathy treated with panretinal photocoagulation	**Proportion of eyes gaining 15 or more ETDRS letters , 48 weeks** 39% of eyes with intravitreal bevacizumab 48% of eyes with intravitreal ranibizumab Absolute results reported graphically 60 eyes (45 people) included in this analysis	P >0.05	⟷	Not significant
[42] RCT	48 people, centre-involved DMO, mean age 64 years, mean duration of diabetes 16 years, mean HbA1c 8.6, 50% with retinopathy	**Mean central subfield thickness (micrometres) , 48 weeks** 329.7 with intravitreal bevacizumab 280.9 with intravitreal ranibizumab	P = 0.4865 The RCT reported that at week 48, there was a mean reduction of about 120 micrometres compared with baseline in both groups	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	treated with panretinal photocoagulation	60 eyes (45 people) included in this analysis			
[43] RCT	About 100 eyes of 100 people, average age age 65–68 years, average diabetes duration 16 years, mean HbA1c 7.2–7.4	**Mean BCVA , baseline to 12 months** 0.22 to 0.38 with intravitreal bevacizumab 0.24 to 0.39 with intravitreal ranibizumab Number in analysis not clear (see Further information on studies)	Reported as no significant difference between groups P value not reported The RCT reported that both groups improved significantly from baseline See Further information on studies	⟷	Not significant
[43] RCT	About 100 eyes of 100 people, average age age 65–68 years, average diabetes duration 16 years, mean HbA1c 7.2–7.4	**Mean central macular thickness (micrometres) , baseline to 12 months** 438.8 to 342.3 with intravitreal bevacizumab 489.8 to 339.3 with intravitreal ranibizumab Number in analysis not clear (see Further information on studies)	Reported as no significant difference between groups P value not reported The RCT reported that both groups improved significantly from baseline See Further information on studies	⟷	Not significant
[37] Systematic review	People with DMO 5 RCTs in this analysis Network analysis	**Improvement of >2 lines on ETDRS scale , 6–12 months** 21/77 (27%) with intravitreal bevacizumab 60/152 (39%) with intravitreal ranibizumab 5 treatments included in this network analysis	OR 0.95 95% credible interval 0.23 to 4.32 Note: this is an indirect analysis and should be interpreted with caution; no RCT included in the network directly compared bevacizumab with ranibizumab (see Further information on studies)	⟷	Not significant
[37] Systematic review	People with DMO 5 RCTs in this analysis Network analysis	**Mean changes in BCVA , 6–12 months** with intravitreal bevacizumab with intravitreal ranibizumab Absolute results not reported 5 treatments included in this network analysis	Treatment effect –0.08 logMAR 95% credible interval –0.19 logMAR to +0.04 logMAR Note: this is an indirect analysis and should be interpreted with caution; no RCT included in the network directly compared bevacizumab with ranibizumab (see Further information on studies)	⟷	Not significant
[37] Systematic review	People with DMO 5 RCTs in this analysis Network analysis	**Mean changes in central macular thickness (micrometres) , 6–12 months** with intravitreal bevacizumab with intravitreal ranibizumab Absolute results not reported 5 treatments included in this network analysis	Treatment effect –6.9 micrometres 95% credible interval –88.5 micrometres to +65.4 micrometres Note: this is an indirect analysis and should be interpreted with caution; no RCT included in the network directly compared bevacizumab with ranibizumab (see Further information on studies)	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[42] RCT	48 people, centre-involved DMO,	**Adverse effects** with bevacizumab	Not reported		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	mean age 64 years, mean duration of diabetes 16 years, mean HbA1c 8.6, 50% with retinopathy treated with panretinal photocoagulation	with ranibizumab Absolute results not reported 2 people developed endophthalmitis and 1 person developed increased blood pressure in the ranibizumab group 1 person who had both interventions developed worsening of renal function (serum creatinine from 2.0 mg/dL to 2.9 mg/dL), which resolved No MIs, CVAs, or gastrointestinal bleeding were reported There was no significant change from baseline in mean intraocular pressure in either group			
[43] RCT	About 100 eyes of 100 people, average age age 65–68 years, average diabetes duration 16 years, mean HbA1c 7.2–7.4	**Adverse effects** with bevacizumab with ranibizumab The RCT reported that no complications such as intraocular pressure or arterial hypertension were observed as a result of intravitreal injections However, in another section it noted that there were 3 cases of endophthalmitis as well as other events that led to exclusion from the study (see Further information on studies)	Not reported		

No data from the following reference on this outcome. [37]

Intravitreal ranibizumab versus intravitreal aflibercept:

We found one review, which reported a network meta-analysis (see option on Aflibercept (intravitreal) v other intravitreal VEGF inhibitors (ranibizumab, bevacizumab), p 12).

Further information on studies

[42] *Participants and regimens* The RCT included people with centre-involved diabetic macular oedema (defined as central subfield thickness >300 micrometres), despite at least one macular laser photocoagulation session, and best corrected visual acuity (BCVA) between 0.3 logMAR and 1.6 logMAR (Snellen equivalent 20/40 to 20/800). Mean baseline BCVA was 0.60 logMar in the intravitreal bevacizumab group versus 0.63 logMAR in the intravitreal ranibizumab group (Snellen 20/80 *v* 20/85, P = 0.680). If both eyes were eligible, after the first eye was randomised, the contralateral eye received the other treatment. Re-treatment was performed monthly if central subfield thickness was greater than 275 micrometres. In total, 48 people (number of eyes not reported) were randomised and 45 people (60 eyes; 15 people with both eyes, 30 people with single eye) were included in the final analysis. Of the three people not included in the final analysis: one person in the ranibizumab group developed *Staphylococcus aureus* endophthamitis; one person with bevacizumab developed advanced posterior subcapsular cataract; and one person missed three follow-up visits. The mean number of injections was 9.84 with bevacizumab versus 7.67 with ranibizumab (P = 0.005). Rescue therapy was laser photocoagulation or to continue on medication for an additional three consecutive visits. In total, nine eyes with intravitreal bevacizumab met rescue therapy criteria, versus four eyes with intravitreal ranibizumab (P = 0.042).

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[42] *Methods* The RCT reported the method of randomisation and the masking of examiners, but allocation concealment was not described. [42] People were randomised; however, the results were analysed by eyes. There may also have possibly been a crossover effect in the 15 people who had bilateral (different) anti-VEGF treatments. [42]

[43] *Participants and regimens* The RCT included people with clinically significant macular oedema (>300 micrometres). Exclusion criteria included intravitreal treatment at another centre or laser within the last 6 months. Participants were given the study injections at an interval of 1 month for the first three doses, and an additional three injections were applied if the central macular thickness was greater than 275 micrometres or if there was an increase in at least three ETDRS letters in BCVA compared with baseline. Further injections could be given after the sixth injection if the central macular thickness was greater than 275 micrometres or if there was an increase in at least two letters. The average number of injections was 5.1 with intravitreal bevacizumab versus 6.5 with intravitreal ranibizumab (P <0.05).

[43] *Methods* The RCT reported that "about 100 eyes of 100 participants" were included, and that participants with endophthalmitis (3 people), CVA / MI (2), uncontrolled hypertension (4), pregnancy (1), renal failure (1), and cataract formation during follow-up (4) were excluded from the study. The RCT did not report in which groups these events occurred. The number of participants included in the final analysis was unclear. The method of randomisation, allocation concealment, and blinding was not described.

[37] *Intravitreal ranibizumab versus intravitreal bevacizumab: network comparison* Indirect comparisons may be subject to bias and should be interpreted with caution. The analysis did not include either of the subsequent RCTs that directly compared the two interventions. [42] [43] The common comparator used in the network was multiple laser therapy. In total, five RCTs were included in the network. The review noted that the number of included studies was small and the wide credible intervals could not rule out that one drug was superior to another. [37] There were differences between the included trials: some included people already treated with laser therapy, while others people were laser naive; some studies included both eyes, while others included only the worse eye. The review concluded that sufficiently powered, direct head-to-head trials were needed. [37] The review noted that all the RCTs included in the analysis were of good methodological quality. [37]

[39] The review extracted data from included RCTs for a gain of two or more lines or three or more lines using random effects logistic regression, and indirectly compared ranibizumab with bevacizumab and ranibizumab with pegaptanib. However, these analyses were exploratory only, not part of a formal network meta-analysis, and we have therefore not reported them further.

Comment:

Adverse effects

We found little information on the relative adverse effects of different vascular endothelial growth factor (VEGF) inhibitors compared with each other from direct comparisons. We found one systematic review (search date 2013), which included a meta-analysis on six RCTs (READ-2; DRCR 2010; RESTORE 2010; RESOLVE 2010; RISE & RIDE 2012; REVEAL) and compared ranibizumab with no ranibizumab (sham), and examined adverse events including cerebrovascular accidents (CVAs), myocardial infarctions (MIs), vascular death, and overall mortality. [44] All trials had exclusion criteria for systemic vascular conditions at enrolment. However, the control groups varied between the RCTs (laser, sham, triamcinolone), and the analysis did not directly compare adverse effects of different VEGF inhibitors, so we have not reported these data further. We found one further systematic review (search date 2012), which included five studies (READ-2; DRCR 2010 [plus expanded 2-year follow-up of this trial]; RESOLVE 2010; RESTORE 2010: RISE & RIDE 2012) and included a meta-analysis on thromboembolic events. [45] However, the control groups varied between the RCTs (laser, sham, triamcinolone), and the analysis did not compare different VEGFs, so we have not reported these data analyses further.

Pooled data for the treatment for wet age-related macular oedema using ranibizumab, with regard to the risk of a cerebrovascular accident (CVA), found both increased risk of CVA in comparison to control and increased risk with 0.5 mg versus 0.3 mg ranibizumab, although this was not statistically significant. [46] As a result, the diabetic trials looked at the efficacy and safety profile of treatments using 0.3 mg versus 0.5 mg ranibizumab for the treatment of diabetic macular oedema. The RESOLVE and the RIDE & RISE trials both had dual dosing of ranibizumab. These papers showed there to be no difference in the efficacy between the 0.3 mg and 0.5 mg doses; however, there was a perceived reduced systemic risk and, therefore, the FDA advisory committee in the US have approved the 0.3 mg dose for the treatment of DMO. Subsequent trials conducted in the US have always used the 0.3 mg dose. However, in Europe the 0.5 mg dose is approved for use.

Further RCTs

Since the search date of this overview, the DRCRN 2015 study (660 adults, 89 sites), a large, US-based multicentre RCT was published, which directly compared ranibizumab, aflibercept, and be-

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vacizumab in adults with diabetic macular oedema involving the macular centre and causing vision impairment. [47] The primary outcome was mean change in visual acuity at 1 year. One eye (the study eye) of each participant was randomly allocated to one of the three interventions according to a 1:1:1 ratio via a pre-defined standardised re-treatment protocol (intravitreal aflibercept [n = 224], intravitreal bevacizumab [n = 218], intravitreal ranibizumab [n = 218]). If the other eye (the non-study eye) required anti-VEGR treatment, the same agent as had been administered in the study eye was used. Interventions were administered at baseline and regularly every 4 weeks, unless the visual acuity was 20/20 or better, with a central subfield thickness below a defined eligibility threshold, and there was no improvement or worsening subsequent to the previous two injections. Participants also received laser therapy at or after 24 weeks if there was persistent diabetic macular oedema (protocol-defined criteria). Follow-up visits every 4 weeks assessed best corrected visual acuity (BCVA) and performed dilated ocular examination and spectral or time-domain optical coherence tomography.

Analysis of mean change in visual acuity from baseline to 1 year showed greater improvement with aflibercept compared with ranibizumab, and with bevacizumab; however, this only becomes statistically significant if baseline visual acuity is taken into account. In eyes with good baseline visual acuity (>69 ETDRS letters) and lesser central retinal thickening, there was little statistical difference in efficacy in terms of visual outcomes at 1 year between intravitreal aflibercept and bevacizumab or ranibizumab. However, in eyes with poorer baseline vision (<69 ETDRS letters), intravitreal aflibercept was associated with statistically better visual outcomes at 1 year in comparison with intravitreal ranibizumab (difference in mean improvement in letter score from baseline: 4.7 letters, 95% CI 1.4 to 8.0 letters, P = 0.003), and with intravitreal bevacizumab (difference in mean improvement in letter score from baseline: 6.5 letters, 95% CI 2.9 to 10.1 letters, P <0.001). The chance of three lines of vision improvement in patients with visual acuity of 69 ETDRS letters or less at baseline was 63% greater with aflibercept compared with bevacizumab, and 34% greater with aflibercept compared with ranibizumab.

The greater efficacy of aflibercept started to become apparent as early as 4 weeks after the initiation of treatment. The effect of aflibercept on visual acuity outcomes was greater when pre-treatment central subfield thickness was greater. In eyes with poorer baseline vision, there was a trend for better visual outcomes with ranibizumab at 1 year in comparison with bevacizumab (difference in mean improvement of letter score from baseline: 1.8 letters, 95% CI –1.1 to +4.8 letters, P = 0.21); this was not significant.

Both ranibizumab and aflibercept showed greater reductions in central retinal subfield thickness at 1 year compared with bevacizumab. No significant differences were found among the study groups in serious adverse events, hospitalisation, death, or major cardiovascular events.

Further studies directly comparing these anti-VEGF agents are needed to validate the findings from the DRCRN 2015 study. We also identified two further ongoing RCTs that will directly compare different VEGF inhibitors (IBERA-DME; CADME). [39]

General comments on all VEGF inhibitors

All intravitreal injections have a potential risk of endophthalmitis. [39] The reported rate of endophthalmitis for intravitreal injections (both intravitreal triamcinolone and intravitreal VEGF inhibitors), per injection, varies from 0.05% to 1.60%. [48] [49]

The longer-term local and systemic adverse effects of continual use of VEGF inhibitors (in particular, bevacizumab) remain unknown in people with diabetes. Repeat injections of all the intravitreal VEGF inhibitor agents are needed to maintain effects.

VEGF has important roles in the development of new blood vessels, vascular remodelling after injury, and development of collateral circulation to bypass obstructed vessels, and VEGF proteins can influence survival and health of several types of cells including neurons in the brain, retinal neurons, and the retinal pigment epithelium. This has led to concerns about potential ocular and systemic adverse effects from long-term VEGF inhibition. [50] [51]

Meta-analyses of RCTs using systemic anti-VEGF therapy in cancer reported potentially life-threatening adverse events: in particular, hypertensive emergencies, arteriothromboembolic events (ATE), including myocardial infarction, and cerebrovascular and peripheral vascular events. [52] Intra-ocular treatment uses significantly smaller doses and shows low reported levels of ATE. Serum concentrations of ranibizumab after intravitreal injections are very low, with maximum levels lower than that necessary to inhibit the biological activity of VEGF by 50%. The systemic exposure following intravitreal injections of ranibizumab, bevacizumab, and aflibercept do vary, and studies evaluating intraocular use of anti-VEGF therapy have generally excluded patients with previous vascular events and have not been powered to detect small changes in systemic safety. [53] Further

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studies are needed to evaluate the risks and benefits of the various agents, the optimum treatment regimen, and combinations of treatment. Recent results from RCTs are promising, and the prognosis for people with vision-threatening diabetic retinopathy is improved with emerging treatments, which will add to our armamentarium when combating diabetic macular oedema.

Clinical guide

Based on the data from clinical studies, ranibizumab was granted approval by the European Medicines Agency (EMA) for use in eyes with visual impairment from diabetic macular oedema in January 2011.

NICE published guidance in February 2013 recommending treatment with ranibizumab for visual impairment from DMO, provided that the treated eye has central retinal thickness (CRT) greater than 400 micrometres measured on optical coherence tomography (OCT) at the start of treatment. [33] The recommendation to restrict treatment only to eyes with more than 400 micrometres thickening was based on additional cost-analysis of subgroup data that showed greater effectiveness in terms of visual acuity improvements in eyes with more than 400 micrometres thickening at baseline. The decision to limit treatment to this group was criticised by many who felt that NICE had not focused on the more important outcome of maintenance of good vision and the added value of earlier treatment, and that differences in algorithms used to measure CRT by different OCT machines (reported variance of >50 micrometres) could lead to inequality and variation in access to treatment in the real world.

Results from the DRCRN 2015 study reported, on average, better outcomes for the subgroup of eyes with central thickening more than 400 micrometres with aflibercept in terms of vision improvement, compared to ranibizumab. [47] However, there were large variations in responses for individual eyes.

In clinical practice, other factors may also play a role in deciding the optimal treatment for an individual patient, including previous good response to ranibizumab or bevacizumab in the fellow eye, funding constraints, and equality of access to the medications. Alternative treatments such as intravitreal corticosteroids may also have a role, especially in chronic cases unresponsive to previous anti-VEGF treatment or where a strong inflammatory basis is suspected.

OPTION BEVACIZUMAB (INTRAVITREAL) VERSUS OTHER INTRAVITREAL VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS (RANIBIZUMAB, AFLIBERCEPT) New

- For GRADE evaluation of interventions for Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema, see table, p 25 .
- Considering only the evidence from RCTs and systematic reviews meeting our inclusion criteria for this overview, we don't know whether intravitreal bevacizumab and intravitreal ranibizumab differ in effectiveness at improving visual acuity or central macular thickness at 6 to 12 months in people with diabetic macular oedema.
- We found no RCTs that directly compared intravitreal bevacizumab with aflibercept or any indirect analyses of these comparisons in people with diabetic macular oedema.
- No significant differences appear to exist between intravitreal bevacizumab, aflibercept, and ranibizumab in ocular or systemic adverse events, but studies were not powered to detect small changes and excluded patients with previous arteriothrombolic events.
- Published after the search date of this overview, the DRCRN 2015 study, is a large, multi-centre RCT that directly compared intravitreal ranibizumab, aflibercept, and bevacizumab in people with centre-involved diabetic macular oedema. We have added this study to the Comment in the option on Ranibizumab, p 5 .
- The DRCRN study found that in eyes with good baseline visual acuities (>69 ETDRS letters) and lesser central retinal thickening, there was little statistical difference in efficacy in terms of visual outcomes at 1 year between bevacizumab and ranibizumab or aflibercept. In eyes with poorer baseline vision (<69 ETDRS letters), there was a trend for poorer visual outcomes with bevacizumab in comparison with ranibizumab, but this was not significant.
- Further studies directly comparing these anti-VEGF agents are needed to validate the findings from the DRCRN study.

Benefits and harms

Intravitreal bevacizumab versus other intravitreal VEGF inhibitors:

We found six systematic reviews (search dates 2008; [34] 2011; [35] [37] [38] and 2012 [39] [40]). The reviews had differing inclusion and exclusion criteria, and reported different analyses. One review identified an abstract of an RCT comparing bevacizumab with ranibizumab. [40] This RCT has subsequently been published, and we have reported the RCT directly from the original report. [42] One review reported a network analysis involving bevacizumab,

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[37] and one review reported an exploratory indirect analysis. [39] We found one further subsequent RCT. [43] We have reported any RCTs or direct or network meta-analyses in the reviews we found below.

Intravitreal bevacizumab versus intravitreal ranibizumab:

We found one network meta-analysis, one indirect exploratory comparison, and two subsequent RCTs (see option on Ranibizumab (intravitreal) versus other intravitreal VEGF inhibitors (bevacizumab, aflibercept), p 5).

Intravitreal bevacizumab versus intravitreal aflibercept:

We found no RCTs that directly compared the two treatments. We found no network meta-analyses.

Comment:

See Comment for option on Ranibizumab (intravitreal) versus other intravitreal VEGF inhibitors (bevacizumab, aflibercept), p 5 .

Clinicians should be aware that bevacizumab is not currently licensed for use in eyes. Bevacizumab is licensed for use in cancer, and its systemic use is known to be associated with an increased risk of thromboembolic events, including stroke. It is unknown if the significantly smaller dose used intravitreally has any significant systemic toxicity. The longer-term local and systemic adverse effects of continual use of vascular endothelial growth factor (VEGF) inhibitors (in particular, bevacizumab) remain unknown in people with diabetes. Repeat injections of all the intravitreal VEGF inhibitor agents are needed to maintain effects.

Previous systematic reviews, network meta-analyses, and small RCTs reported no significant difference between bevacizumab and ranibizumab in terms of efficacy or safety.

The DRCRN 2015 study, a large, multicentre RCT that compared bevacizumab directly with ranibizumab and aflibercept, was published after the search date for this overview. For further details please see Comment section in the Ranibizumab, p 5 option. [47]

There is an important concern with regard to the preparation of bevacizumab. The bevacizumab used in the DRCRN study was repackaged at a central pharmacy into single-use glass vials. These vials underwent independent testing for sterility, purity, and potency prior to use. In worldwide clinical practice, variability in potency of repackaged bevacizumab has been reported along with higher rates of endophthalmitis directly linked to poor compounding. [54] [55]

Clinical guide

Clinicians need to balance the evidence suggesting that both aflibercept and ranibizumab may be more effective, especially in eyes with poorer vision, with ability for the patient to access the ongoing timely treatment needed. Bevacizumab is very effective at improving vision and retinal thickening in eyes with diabetic macular oedema (DMO), and would be preferable to no treatment in cases of inability to access licensed anti-VEGF agents due to cost constraints or due to national guidelines. [33]

OPTION AFLIBERCEPT (INTRAVITREAL) VERSUS OTHER INTRAVITREAL VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS (RANIBIZUMAB, BEVACIZUMAB) New

- For GRADE evaluation of interventions for Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema, see table, p 25 .
- Considering only the evidence from RCTs and systematic reviews meeting our inclusion criteria for this overview, we don't know whether intravitreal aflibercept and intravitreal ranibizumab differ in effectiveness at improving visual acuity or central macular thickness at 6 to 12 months in people with diabetic macular oedema.
- We found no RCTs that directly compared intravitreal aflibercept with bevacizumab, or any indirect analyses of these comparisons in people with diabetic macular oedema.

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- No significant differences appear to exist between intravitreal bevacizumab, aflibercept, and ranibizumab in ocular or systemic adverse events, but studies were not powered to detect small changes and excluded patients with previous arteriothrombolic events.
- Published after the search date of this overview, the DRCRN 2015 study is a large, multicentre RCT that directly compared intravitreal ranibizumab, aflibercept, and bevacizumab in people with centre-involved diabetic macular oedema. We have added this study to the Comment in option on Ranibizumab, p 5 .
- The DRCRN study found that in eyes with good baseline visual acuities (>69 ETDRS letters) and lesser central retinal thickening, there was little difference in efficacy in terms of visual outcomes at 1 year between intravitreal aflibercept and bevacizumab or ranibizumab. In eyes with poorer baseline vision (<69 ETDRS letters), the study found that intravitreal aflibercept may result in better visual outcomes at 1 year in comparison with intravitreal ranibizumab and compared with intravitreal bevacizumab.
- Further studies directly comparing these anti-VEGF agents are needed to validate the findings from the DRCRN study.

Benefits and harms

Intravitreal aflibercept versus other intravitreal VEGF inhibitors:

We found six systematic reviews (search dates 2008; [34] 2011; [35] [38] 2012; [39] [40] and 2014 [41]). The reviews had differing inclusion and exclusion criteria and reported different analyses. We have not reported any RCTs or direct or network meta-analyses in the reviews we found below.

Intravitreal aflibercept versus intravitreal ranibizumab:

We found one review (search date 2014), which reported a network meta-analysis (see Further information on studies). [41] We found no RCTs that directly compared aflibercept with ranibizumab.

Visual acuity

Intravitreal aflibercept compared with intravitreal ranibizumab We don't know whether intravitreal aflibercept and intravitreal ranibizumab differ in effectiveness at improving visual acuity (by at least 10 letters [2 lines] on the ETDRS scale) in people with diabetic macular oedema at 6 to 12 months, as we found insufficient evidence from a network meta-analysis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Visual acuity					
[41] Systematic review Network analysis	People with diabetic macular oedema (DMO) 8 RCTs in this analysis	**Treatment effect (defined as percentage of people improving best corrected visual acuity [BCVA] of at least 10 letters [2 lines] on ETDRS scale) , 6–12 months** with intravitreal ranibizumab PRN with intravitreal aflibercept bimonthly Absolute results not reported 5 treatments included in this analysis	OR 1.59 95% credible interval 0.61 to 5.37 (random effects model) A fixed effects analysis was also not significant (OR 1.49, 95% CI 0.80 to 2.78) Note: this is an indirect analysis and should be interpreted with caution; no RCT included in the network directly compared ranibizumab with aflibercept This analysis also included data from three RCTs not yet fully published in peer-reviewed journals (see Further information on studies)	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [41]

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Intravitreal aflibercept versus intravitreal bevacizumab:

We found no RCTs that directly compared the two treatments. We found no network meta-analyses.

Further information on studies

[41] *Network comparison* Indirect comparisons may be subject to bias and should be interpreted with caution. None of the included RCTs directly compared aflibercept with ranibizumab. The review included eight RCTs in the network. The review noted that three of the eight RCTs included were not yet published in full (1 RCT data on file; congress presentation for 2 RCTs). It noted that, overall, the studies were of good quality, although in one RCT masking was not clearly reported and randomisation and blinding was also unclear. The review noted that higher proportions of people responded to laser therapy in the aflibercept RCTs than in the ranibizumab RCTs, which may have reflected different baseline characteristics between trials. Four of the five listed authors were employees of the pharmaceutical company that produces ranibizumab.

Comment:

See Comment sections for option on Ranibizumab (intravitreal) versus other intravitreal VEGF inhibitors (bevacizumab, aflibercept), p 5 .

Aflibercept has been approved for use in centre-involving diabetic macular oedema (DMO) by the FDA in July 2014, with the European Medicines Agency (EMA) approvals in August 2014.

NICE published guidance in July 2015 recommending treatment with aflibercept for visual impairment from DMO, provided that the treated eye has central retinal thickness (CRT) greater than 400 micrometres measured on optical coherence tomography (OCT) at the start of treatment (similar guidelines to ranibizumab). [33] [56]

Published after the search date of this overview, the DRCRN 2015 study is a large, multicentre RCT that directly compared intravitreal ranibizumab, aflibercept, and bevacizumab in people with centre-involved diabetic macular oedema. For further details, please see Comment in option on Ranibizumab, p 5

Based on the DRCRN study, aflibercept would be the preferred anti-VEGF treatment in eyes with poorer baseline vision and worse central macular oedema. [47] Further studies directly comparing these anti-VEGF agents are needed to validate the findings from the DRCRN Study.

Clinical guide

Treatment with anti-VEGF agents has shifted the emphasis on examination and definition of what is considered clinically significant macular oedema. ETDRS defined clinically significant macular oedema via biomicroscopic examination; however, OCT-guided definition has leant towards centre-involving macular oedema. Treatment has shown a significant effect within 1 month of treatment, but ongoing treatment is required, with initial frequent treatments required in year 1 in order to maintain stability, and with reducing frequency in subsequent follow-up years. [47] [57] [58]

QUESTION **What are the effects of intravitreal vascular endothelial growth factor (VEGF) inhibitors plus laser therapy versus intravitreal VEGF inhibitors alone for diabetic macular oedema?**

OPTION **INTRAVITREAL RANIBIZUMAB PLUS LASER THERAPY VERSUS INTRAVITREAL RANIBIZUMAB ALONE** New

- For GRADE evaluation of interventions for Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema, see table, p 25 .
- Published after the search date of this overview, the DRCRN 2015 study, a large, multicentre RCT that directly compared intravitreal ranibizumab, aflibercept, and bevacizumab in people with centre-involved diabetic macular oedema (see Comment, p 5). In eyes with centre-involving diabetic macular oedema (DMO), combination treatment of ranibizumab and macular laser showed no additional benefit in terms of visual outcomes compared with ranibizumab treatment alone.

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- Complications of macular laser treatment include paracentral scotomas, lateral spread of laser scars with potential future foveal involvement, colour vision impairment, subfoveal fibrosis, increased central exudate, secondary choroidal neovascularisation, and inadvertent treatment to the fovea.
- Use of macular laser close to the foveal avascular zone is not recommended as first-line treatment in eyes with centre-involving DMO.
- In eyes with focal areas of macular oedema away from the foveal centre that still meet the original ETDRS classification of 'clinically significant', laser may have a role in reducing the risk of future vision loss.

Benefits and harms

Intravitreal ranibizumab plus laser therapy versus intravitreal ranibizumab alone:

We found eight systematic reviews (search date 2008; [34] 2011; [35] [36] [37] [38] 2012; [39] [40] and 2014 [41]). We found no subsequent RCTs. We found one review (search date 2012) that pooled data from two RCTs (READ 2 [59] and RESTORE; [60] see Further information on studies). [40] The review also included one further RCT (REVEAL), which was reported as a meeting abstract, and one further RCT, [61] both of which were outside the inclusion criteria for this *BMJ Clinical Evidence* overview (see Comment, p 14).

Visual acuity

Intravitreal ranibizumab plus laser therapy compared with intravitreal ranibizumab alone We don't know whether the addition of laser therapy to intravitreal ranibizumab is more effective than intravitreal ranibizumab alone at improving visual acuity or central macular thickness in people with diabetic macular oedema at 6 to 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Visual acuity					
[40] Systematic review	People with diabetic macular oedema (DMO) 2 RCTs in this analysis	**Mean change in best corrected visual acuity (BCVA) (units not specified) , 6–12 months** with intravitreal ranibizumab plus laser photocoagulation with intravitreal ranibizumab alone or plus sham laser Absolute results not reported 318 eyes in this analysis	Mean difference –0.12 95% CI –0.44 to +0.20 P = 0.45	⟷	Not significant
[40] Systematic review	People with DMO 2 RCTs in this analysis	**Proportion of eyes with >15 ETDRS letter gain , 6–12 months** 30/158 (19%) with intravitreal ranibizumab plus laser photocoagulation 34/152 (22%) with intravitreal ranibizumab alone or plus sham laser	OR 0.65 95% CI 0.20 to 2.09 P = 0.47	⟷	Not significant
[40] Systematic review	People with DMO 2 RCTs in this analysis	**Central macular thickness , 6–12 months** with intravitreal ranibizumab plus laser photocoagulation with intravitreal ranibizumab alone or plus sham laser Absolute results not reported 311 eyes in this analysis	Mean difference –0.14 95% CI –0.36 to +0.08 P = 0.37	⟷	Not significant

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[40] Systematic review	People with DMO 2 RCTs in this analysis	**Adverse effects** with intravitreal ranibizumab plus laser photocoagulation with intravitreal ranibizumab alone or plus sham laser The review reported that one RCT (RESTORE; 234 eyes in two arms) found eye pain (13 events with ranibizumab *v* 10 events with ranibizumab plus laser), conjunctival haemorrhage (8 *v* 10), IOP increase (1 *v* 1), arterial thromboembolic events (6 *v* 1), hypertension (9 *v* 6), and deaths (2 *v* 2), while the other RCT (READ-2; 84 eyes in two arms) found vitreous haemorrhage (1 *v* 3), stroke (0 *v* 1; not related to study drug), and deaths (0 *v* 1; related to CVA).	Not reported		

Further information on studies

[40] *Pooled analysis: participants and regimens* The review pooled data from two RCTs. The first included RCT (READ-2; multi-centre) was a three-armed RCT. One group (ranibizumab alone; 42 eyes) received intravitreal ranibizumab at baseline, 1, 3, and 5 months, while the other group (ranibizumab plus laser; 42 eyes) received intravitreal injections at baseline and 3 months, with focal/grid laser 1 week later. The RCT included adults (inclusion criteria included 18 years or older, type 1 or 2 diabetes, best corrected visual acuity [BCVA] 20/40–20/320, central macular thickness [CMT] 250 micrometres or more, HbA1c 6% or greater; excluded if laser within 3 months) with the expectation that scatter laser photocoagulation would not be required for 6 months. It reported on baseline data (HbA1c 7.39%–7.77%, baseline ETDRS letter score 24.85–28.35, baseline CMT excess foveal thickness 198–262 micrometres). The review reported outcomes at 6 months, the primary end point of the study. After 6 months, people in the combined group could receive further ranibizumab plus laser or ranibizumab alone. The second included RCT (RESTORE) was also a three-armed RCT. One group (116 eyes) received intravitreal ranibizumab plus sham laser (3 initial monthly injections, followed by 1 injection per month if stable visual acuity not reached; median injections 7, range 1–12; median sham laser 1, range 1–5), while the other group (118 eyes) received intravitreal ranibizumab injections (same protocol as other group; median injections 7, range 2–12) plus active laser (median treatments 1, range 1–5; re-treatments in accordance with ETDRS guidelines at times no shorter than 3 months from previous treatments). The RCT included adults (inclusion criteria included 18 years or older, type 1 or 2 diabetes, BCVA ETDRS letters score 39–78, HbA1c 10% or less) in people with diabetic macular oedema suitable for laser treatment. It reported on baseline data (HbA1c not reported, baseline ETDRS letter score 62.4–64.8, baseline CMT 412.4–426.6 micrometres). The review reported outcomes at 1 year.

[40] *Methods* The review reported that the first RCT (READ-2) had unclear allocation sequence generation, unclear allocation concealment, and unclear masking. The comparison groups were similar at baseline, and there was 91.3% completion. The second RCT (RESTORE) had unclear allocation concealment, with an 88% completion rate.

Comment: The review included two further RCTs. [40] The first RCT was reported only as a conference abstract (REVEAL). The study was a three-armed RCT (396 people). One group (ranibizumab plus sham laser; 133 people) received intravitreal ranibizumab at day 1, month 1, month 2, and after based on best corrected visual acuity (BCVA), while the other group (ranibizumab plus active laser; 132 people) received similar injections. The third arm was sham injection plus active laser. It did not report the laser administration details. Inclusion and exclusion criteria were not reported. The review reported outcomes at 1 year (changes from baseline to 12 months: BCVA [units not further specified]: +6.4 with intravitreal ranibizumab plus laser *v* +6.6 with intravitreal ranibizumab plus sham laser;

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central macular thickness: –163.8 micrometres with intravitreal ranibizumab plus laser *v* –148.0 micrometres with intravitreal ranibizumab plus sham laser; number in analysis not reported; between-group analysis not reported). [40] The REVEAL report was published after the search date of this *BMJ Clinical Evidence* overview. [62]

The review [40] included one further RCT (DRCRN 2010), [61] which reported outcomes at 1 year. It compared sham injection plus prompt laser; ranibizumab plus prompt laser; ranibizumab plus deferred laser (24 weeks or above); and triamcinolone plus prompt laser. Although its main analysis was at 1 year, it also reported some data at the 16-week study visit on "success criteria" for eyes (defined as visual acuity letter score 84 or above or optical coherence tomography [OCT] central subfield <240 micrometres). It found that 47/187 (25%) of eyes in the ranibizumab plus prompt laser group achieved success compared with 41/188 eyes (22%) in the ranibizumab plus deferred laser at 24 weeks or above (statistical analysis between groups not reported). [61]

We found further follow-up reports of one RCT (READ) included in the meta-analysis at 2 years [63] and 3 years. [64] However, data were based on 64/84 (76%) and 52/84 (62%) of people randomised at 2 and 3 years, respectively, which is below the inclusion criteria for this *BMJ Clinical Evidence* overview. We found one further report of the other RCT (RESTORE) included in the meta-analysis, which looked at patient-reported visual function outcomes at 12 months (NEI VFQ-25 composite scores) and a subgroup analysis by the treated eye (better seeing eye/worse seeing eye). [65] However, there were no longer-term results reported.

The DRCRN 2010 (protocol I) both 1- and 2-year data compared treatment with intravitreal ranibizumab with either deferred or prompt laser with prompt laser alone. [61] [66] Although this comparison is outside of the question posed in this *BMJ Clinical Evidence* overview, it does look at the timing of the laser treatment with respect to the intravitreal treatment. This showed that there was significantly better visual outcomes for the group with combined laser and ranibizumab in comparison to laser alone; however, the timing of the laser showed greater efficacy in the deferred-laser group.

Clinical guide

As there is a more rapid response for macular oedema with anti-vascular endothelial growth factor (anti-VEGF) treatments, and the effect of laser can sometimes not be apparent before 3 months, any studies that have less than 6 months' follow-up data should be interpreted with caution due to the slower response time of laser. In addition, the laser treatment may have a more lasting effect that does not require the frequent re-treatment schedule of anti-VEGF treatment. As such there is still a place for laser in certain conditions.

For the group of patients that have definite central subfield involvement in macular oedema, treatment with anti-VEGF has been shown to be more effective in improving and maintaining the vision than laser treatment. However, people with focal areas of macular oedema away from the foveal centre that still meet the original ETDRS classification of 'clinically significant' may still benefit from laser treatment.

Clinicians should be aware that the laser protocols used in the studies may not match current clinical practice. Studies had pre-determined timing and criteria for using macular laser. Most studies utilised the laser treatment protocol specified in the ETDR studies, [67] which recommended laser to micro-aneurysms, intraretinal microvascular abnormalities, and even diffuse leakage from ischaemic vessels identified on fluorescein angiography in the area of clinically significant thickening, aiming for a definite light grey reaction. Treatment of lesions was allowed up to 500 micrometres from fixation, and if vision was reduced from persistent oedema, treatment up to 300 micrometres to the fovea was allowed.

Laser — in particular, visible treatment near fixation — can have delayed adverse effects, including paracentral scotomas and gradual spread or increase in laser scars with future vision loss. Vision deterioration can also be seen in eyes with diffuse oedema and extensive hard exudates from subretinal fibrosis and lipid migration centrally following laser treatment. [68] [69] [70] In current clinical practice these observations have led most clinicians to use 'modified' gentler and more targeted treatment, avoiding lesions less than 500 micrometres from fixation and avoiding ischaemic areas.

Further studies not included in this overview have looked at different formats of laser treatment, specifically with navigated laser systems (NAVILAS OD-OS GmbH, Teltow Germany) that require eye-tracking and, therefore, improved targeted treatment with image overlay of optical coherence tomography (OCT) and angiography. These have been investigated in conjunction with the use of anti-VEGF treatment and are thought to reduce the frequency of treatments required with anti-VEGF treatments alone. This option would thus enable the combination of the quick onset from

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the anti-VEGF treatment, with the sustained effect of laser. However, further trials are needed to look at the efficacy of this combination.

OPTION INTRAVITREAL BEVACIZUMAB PLUS LASER THERAPY VERSUS INTRAVITREAL BEVACIZUMAB ALONE New

- For GRADE evaluation of interventions for Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema, see table, p 25 .
- We don't know whether the addition of laser therapy to intravitreal bevacizumab is more effective than intravitreal bevacizumab alone at improving visual acuity in people with diabetic macular oedema (DMO) at 3 to 6 months. We found no longer-term results and evidence was weak.
- Complications of macular laser treatment include paracentral scotomas, lateral spread of laser scars with potential future foveal involvement, colour vision impairment, subfoveal fibrosis, increased central exudate, secondary choroidal neovascularisation, and inadvertent treatment to the fovea.
- Use of macular laser close to the foveal avascular zone is not recommended as first-line treatment in eyes with centre-involving DMO.
- In eyes with focal areas of macular oedema away from the foveal centre that still meet the original ETDRS classification of 'clinically significant', laser may have a role in reducing the risk of future vision loss.

Benefits and harms

Intravitreal bevacizumab plus laser therapy versus intravitreal bevacizumab alone:

We found five systematic reviews (search date 2008; [34] 2011; [35] [38] and 2012 [39] [40]). The reviews had different inclusion and exclusion criteria. One review (search date 2012) included one RCT (80 eyes in 40 people) that reported results at 6 months. [40] One review (search date 2008) [34] included one five-armed RCT (109 people; DRCRN 2007), [71] which we have reported directly from the original report, which reported outcomes at 3 months. One review (search date 2011) [38] included one three-armed RCT (62 eyes of 48 people) [72] that we have reported directly from the original report. In this RCT, one single intravitreal injection was given. We have, therefore, reported results at 3 months rather than longer term. Overall, the evidence from RCTs was weak and caution should be taken in interpreting these results (see Further information on studies).

Visual acuity

Intravitreal bevacizumab plus laser therapy compared with intravitreal bevacizumab alone We don't know whether the addition of laser therapy to intravitreal bevacizumab is more effective than intravitreal bevacizumab alone at improving visual acuity in people with diabetic macular oedema at 3 to 6 months. We found no longer-term results, and evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Visual acuity					
[40] Systematic review	People with diabetic macular oedema (DMO) Data from 1 RCT	**Mean change in best corrected visual acuity (BCVA) (ETDR chart) , 6 months** 0.138 logMAR with intravitreal bevacizumab 0.179 logMAR with intravitreal bevacizumab plus single macular photocoagulation 80 eyes of 40 people in this analysis	Reported as no statistically significant difference between groups P value not reported Both groups improved significantly from baseline (P <0.05)	⟷	Not significant
[40] Systematic review	People with DMO Data from 1 RCT	**Mean change in central macular thickness in micrometres (optical coherence tomography) , 6 months** –39 with intravitreal bevacizumab –39 with intravitreal bevacizumab plus single macular photocoagulation 80 eyes of 40 people in this analysis	Reported as no statistically significant difference between groups P value not reported Both groups improved significantly from baseline (P <0.05)	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[72] RCT **3-armed trial**	62 eyes of 48 people with DMO In review [38]	**Mean improvement in BCVA , 3 months** 15% with single intravitreal bevacizumab injection 23% with single intravitreal bevacizumab injection plus single laser photocoagulation Absolute numbers not reported Number of eyes in analysis not reported The remaining arm was macular laser photocoagulation only	Analysis between groups not reported The RCT reported that at 1 month, improvement was 38% with injection *v* 22% in the combined group (P value not reported) Caution should be taken in interpreting these results (see Further information on studies)		
[72] RCT **3-armed trial**	62 eyes of 48 people with DMO In review [38]	**Mean improvement in central macular thickness from baseline (micrometres) , 3 months** 88.83 with single intravitreal bevacizumab injection 160.29 with single intravitreal bevacizumab injection plus single laser photocoagulation Number of eyes in analysis not reported The remaining arm examined macular laser photocoagulation only	Analysis between groups not reported The RCT reported that at 1 month, improvement was 150.92 micrometres with injection *v* 110.30 micrometres in the combined group (P value not reported) Caution should be taken in interpreting these results (see Further information on studies)		
[71] RCT **5-armed trial**	121 people with DMO	**Visual acuity improvement (10 or more ETDRS letters) , 12 weeks** 7/22 (33%) with intravitreal bevacizumab at baseline and 6 weeks 4/22 (20%) with intravitreal bevacizumab at baseline and 6 weeks plus laser at 3 weeks See Further information on studies regarding remaining 3 arms	Analysis between groups not reported The RCT reported that there were no meaningful differences in visual acuity between groups at 12 weeks		
[71] RCT **5-armed trial**	121 people with DMO	**Visual acuity improvement (15 or more letters) , 12 weeks** 3/22 (14%) with intravitreal bevacizumab at baseline and 6 weeks 3/22 (14%) with intravitreal bevacizumab at baseline and 6 weeks plus laser at 3 weeks See Further information on studies regarding remaining 3 arms	Analysis between groups not reported The RCT reported that there were no meaningful differences in visual acuity between groups at 12 weeks		
[71] RCT **5-armed trial**	121 people with DMO	**Central subfield retinal thickness (micrometres) , median change from baseline to 12 weeks** –56 with intravitreal bevacizumab at baseline and 6 weeks –40 with intravitreal bevacizumab at baseline and 6 weeks plus laser at 3 weeks 42 people in this analysis See Further information on studies regarding remaining 3 arms	Analysis between groups not reported The RCT reported that there were no meaningful differences in central subfield thickness between groups at 12 weeks		

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Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[71] RCT **5-armed trial**	121 people with DMO	**Adverse effects** with intravitreal bevacizumab at baseline and 6 weeks with intravitreal bevacizumab at baseline and 6 weeks plus laser at 3 weeks The RCT reported 1 case of endophthalmitis following injection (group not specified) Among 107 subjects with bevacizumab injection, there were 2 reports of MI and 1 report of congestive cardiac failure; all had previous history of cardiac problems See Further information on studies regarding remaining 3 arms			

No data from the following reference on this outcome. [40] [72]

Further information on studies

[40] The RCT (80 eyes, 40 people) included people with bilateral non-tractional clinically significant macular oedema, and baseline values included mean HbA1c 8.42 g/dL, diabetes type not reported, baseline visual acuity 0.326 to 0.409 (units not specified), and baseline central macular thickness of 277 to 287 micrometres. Previous treatment of clinically significant macular oedema or proliferative diabetic retinopathy, or pharmacotherapy for clinically significant macular oedema, were excluded. The RCT compared bevacizumab with bevacizumab plus macular photocoagulation; the regimen for both groups included eyes being examined every 2 months, and if there was evidence of clinically significant macular oedema, the eye was injected. Mean number of injections was 2.23 in the intravitreal bevacizumab group versus 2.49 in the bevacizumab plus macular photocoagulation group (P value not reported). A single laser treatment was used. The review reported that allocation concealment was unclear, there was 100% completion, and groups were comparable at baseline.

[38] [72] The review noted that dropouts were not reported. The RCT (62 eyes of 42 people; single site) compared modified grid laser photocoagulation once at baseline (19 eyes), intravitreal bevacizumab once at baseline (21 eyes), and single intravitreal injection of bevacizumab followed by modified grid laser photocoagulation after 3 weeks (22 eyes). One surgeon performed the laser photocoagulation for all groups, and one reader interpreted all the angiographies and scans. Participants had to have diffuse DMO and a central macular thickness of at least 350 micrometres. The method of randomisation, allocation concealment, and blinding was not described. It was unclear whether the contralateral eye had the same or a different treatment.

[34] [71] The review noted that method of allocation concealment was not reported, and overall visit completion rate was 93%. The five-armed trial compared: focal photocoagulation at baseline; 1.25 mg of intravitreal bevacizumab at baseline and sham injection at 6 weeks; 1.25 mg of intravitreal bevacizumab at baseline and further injection at 6 weeks; 2.5 mg of intravitreal bevacizumab at baseline and further injection at 6 weeks; 1.25 mg of intravitreal bevacizumab at baseline and further injection at 6 weeks plus photocoagulation at 3 weeks. We have reported the two arms with the same regimen of 1.25 mg of intravitreal bevacizumab at baseline and at 6 weeks, without and with laser. The RCT included people at least 18 years of age with visual acuity letter score 24 or above (E-ETDRS; 20/320 or better) and 78 or less (20/32 or worse), and central subfield thickness 275 micrometres and above. A subject could only have one study eye. At baseline (for all 5 groups), median visual acuity was 64, mainly type 2 diabetes (93%), HbA1c 6.9, 31% had no previous treatment, and 23% had mild proliferative diabetic retinopathy (PDR levels 60 and 61). The RCT reported outcomes at 12 weeks, after which additional treatment was at investigator discretion. One review noted that laser has a delayed action and many of the studies had short follow-up and may, therefore, not be powered to show a longer acting effect. Further

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studies are warranted on combination treatment with longer follow-up and comparisons with targeted and newer laser modalities such as micropulse.

Comment:

Clinical guide

Clinicians should be aware that bevacizumab is not currently licensed for use in eyes. Bevacizumab is licensed for use in cancer, and its systemic use is known to be associated with an increased risk of thromboembolic events, including stroke. It is unknown if the significantly smaller dose used intravitreally has any significant systemic toxicity. The longer-term local and systemic adverse effects of continual use of vascular endothelial growth factor (VEGF) inhibitors (in particular, bevacizumab) remain unknown in people with diabetes. Repeat injections of all the intravitreal VEGF inhibitor agents are needed to maintain effects.

As there is a more rapid response for macular oedema with anti-VEGF treatments, and the effect of laser can sometimes not be apparent before 3 months, any studies that have less than 6 months' follow-up data should be interpreted with caution due to the slower response time of laser. In addition, the laser treatment may have a more lasting effect that does not require the frequent re-treatment schedule of anti-VEGF treatment. As such, there is still a place for laser in certain conditions.

For the group of patients that have definite central subfield involvement in macular oedema, treatment with anti-VEGF has shown to be more effective in improving and maintaining the vision than laser treatment. However, people with focal areas of macular oedema away from the foveal centre that still meet the original ETDRS classification of 'clinically significant' may still benefit from laser treatment.

Clinicians should be aware that the laser protocols used in the studies may not match current clinical practice. Studies had pre-determined timing and criteria for using macular laser. Most studies utilised the laser treatment protocol specified in the ETDR studies, [67] which recommended laser to microaneurysms, intraretinal microvascular abnormalities, and even diffuse leakage from ischaemic vessels identified on fluorescein angiography in the area of clinically significant thickening, aiming for a definite light grey reaction. Treatment of lesions was allowed up to 500 micrometres from fixation, and if vision was reduced from persistent oedema, treatment up to 300 micrometres to the fovea was allowed.

Laser — in particular, visible treatment near fixation — can have delayed adverse effects, including paracentral scotomas and gradual spread or increase in laser scars with future vision loss. Vision deterioration can also be seen in eyes with diffuse oedema and extensive hard exudates from subretinal fibrosis and lipid migration centrally following laser treatment. [68] [69] [70] In current clinical practice these observations have led most clinicians to use 'modified' gentler and more targeted treatment avoiding lesions less than 500 micrometres from fixation, and avoiding ischaemic areas.

Further studies not included in this overview have looked at different formats of laser treatment, specifically with navigated laser systems (NAVILAS OD-OS GmbH, Teltow Germany) that require eye-tracking and, therefore, improved targeted treatment with image overlay of optical coherence tomography (OCT) and angiography. These have been investigated in conjunction with the use of anti-VEGF treatment and are thought to reduce the frequency of treatments required with anti-VEGF treatments alone. This option would thus enable the combination of the quick onset from the anti-VEGF treatment, with the sustained effect of laser. However, further trials are needed to look at the efficacy of this combination.

OPTION INTRAVITREAL AFLIBERCEPT PLUS LASER THERAPY VERSUS INTRAVITREAL AFLIBERCEPT ALONE New

- For GRADE evaluation of interventions for Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema, see table, p 25 .
- We found no RCT evidence on the effectiveness of intravitreal aflibercept plus laser therapy compared with intravitreal aflibercept alone in people with diabetic retinopathy.
- Complications of macular laser treatment include paracentral scotomas, lateral spread of laser scars with potential future foveal involvement, colour vision impairment, subfoveal fibrosis, increased central exudate, secondary choroidal neovascularisation, and inadvertent treatment to the fovea.

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- Use of macular laser close to the foveal avascular zone is not recommended as first-line treatment in eyes with centre-involving diabetic macular oedema (DMO).
- In eyes with focal areas of macular oedema away from the foveal centre that still meet the original ETDRS classification of 'clinically significant', laser may have a role in reducing the risk of future vision loss.

Benefits and harms

Intravitreal aflibercept plus laser therapy versus intravitreal aflibercept alone:

We found six systematic reviews (search date 2008; [34] 2011; [35] [38] 2012; [39] [40] and 2014 [41]) that examined the effects of vascular endothelial growth factor (VEGF) inhibitors for diabetic macular oedema. We found no RCTs or network meta-analyses for intravitreal aflibercept plus laser therapy versus intravitreal aflibercept alone.

Comment: See Comment sections for options on Intravitreal ranibizumab plus laser therapy versus intravitreal ranibizumab alone, p 14 and Intravitreal bevacizumab plus laser therapy versus intravitreal bevacizumab alone, p 18 .

GLOSSARY

Proliferative retinopathy Characterised by new vessels at the disc or elsewhere.

Best corrected visual acuity (BCVA) The best vision that can be achieved with correction (such as glasses), as measured on the standard eye chart.

ETDRS score A measure of visual acuity. The Early Treatment Diabetic Retinopathy Study (ETDRS) chart, [73] the gold standard tool for measuring visual acuity, [74] uses letters printed in lines of decreasing size, which are read from a fixed distance; usually 6 metres (20 feet) for distance acuity. The ETDRS visual acuity is written as a number – for example, 70 letters is equivalent to 6/24 Snellen. [75] ETDRS letter score is often represented as a Snellen equivalent for ease of comprehension.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Snellen visual acuity The Snellen chart usually includes letters, numbers, or pictures printed in lines of decreasing size, which are read or identified from a fixed distance; distance visual acuity is usually measured from a distance of 6 m (20 feet). The Snellen visual acuity is written as a fraction: 6/18 means that from 6 m away the best line that can be read is a line that could normally be read from a distance of 18 m away.

Very low-quality evidence Any estimate of effect is very uncertain.

Visual angle a measure used extensively in research, it describes the angle subtended at the eye of the smallest letter visible by that eye.

SUBSTANTIVE CHANGES

Ranibizumab (intravitreal) versus other intravitreal VEGF inhibitors (bevacizumab, aflibercept) New option. Eight systematic reviews [34] [35] [36] [37] [38] [39] [40] [41] and two RCTs [42] [43] added. Categorised as 'beneficial'.

Bevacizumab (intravitreal) versus other intravitreal VEGF inhibitors (ranibizumab, aflibercept) New option. Six systematic reviews [34] [35] [37] [38] [39] [40] and two subsequent RCTs [42] [43] added. Categorised as 'beneficial'.

Aflibercept (intravitreal) versus other intravitreal VEGF inhibitors (ranibizumab, bevacizumab) New option. Six systematic reviews added. [34] [35] [38] [39] [40] [41] Categorised as 'beneficial'.

Intravitreal ranibizumab plus laser therapy versus intravitreal ranibizumab alone New option. Eight systematic reviews added. [34] [35] [36] [37] [38] [39] [40] [41] Categorised as 'unlikely to be beneficial'.

Intravitreal bevacizumab plus laser therapy versus intravitreal bevacizumab alone New option. Five systematic reviews [34] [35] [38] [39] [40] and two RCTs [72] [71] added. Categorised as 'unlikely to be beneficial'.

Intravitreal aflibercept plus laser therapy versus intravitreal aflibercept alone New option. Six systematic reviews added. [34] [35] [38] [39] [40] [41] Categorised as 'unknown effectiveness'.

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GRADE **Evaluation of interventions for Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema.**

Important outcomes									Visual acuity
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of intravitreal vascular endothelial growth factor (VEGF) inhibitors versus each other for diabetic macular oedema?									
7 (at least 274) [37] [42] [43]	Visual acuity	Intravitreal ranibizumab versus intravitreal bevacizumab	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness point deducted for indirect comparison
8 (number unclear) [41]	Visual acuity	Intravitreal aflibercept versus intravitreal ranibizumab	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for indirect comparison
What are the effects of intravitreal vascular endothelial growth factor (VEGF) inhibitors plus laser therapy versus intravitreal VEGF inhibitors alone for diabetic macular oedema?									
2 (number unclear; at least 311 eyes) [40]	Visual acuity	Intravitreal ranibizumab plus laser therapy versus intravitreal ranibizumab alone	4	–2	0	0	0	Low	Quality points deducted for weak methods and incomplete reporting of results
3 (132) [40] [71] [72]	Visual acuity	Intravitreal bevacizumab plus laser therapy versus intravitreal bevacizumab alone	4	–3	0	–2	0	Very low	Quality points deducted for weak methods, sparse data, and incomplete reporting of results; directness points deducted for short follow-up, and for use of regimens not representative of clinical practice

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

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