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

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Virgili G, Curran K, Lucenteforte E, Peto T, Parravano M.
Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis.
Cochrane Database of Systematic Reviews 2023, Issue 6. Art. No.: CD007419.
DOI: 10.1002/14651858.CD007419.pub7.

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[Intervention Review]

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

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Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2023.

Citation: Virgili G, Curran K, Lucenteforte E, Peto T, Parravano M. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2023, Issue 6. Art. No.: CD007419. DOI: 10.1002/14651858.CD007419.pub7.

ABSTRACT

Background

Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) can reduce oedema, improve vision, and prevent further visual loss. These drugs have replaced laser photocoagulation as the standard of care for people with DMO. In the previous update of this review, we found moderate-quality evidence that, at 12 months, aflibercept was slightly more effective than ranibizumab and bevacizumab for improving vision in people with DMO, although the difference may have been clinically insignificant (less than 0.1 logarithm of the minimum angle of resolution (logMAR), or five Early Treatment Diabetic Retinopathy Study (ETDRS) letters, or one ETDRS line).

Objectives

The objective of this updated review was to compare the effectiveness and safety of the different anti-VEGF drugs in RCTs at longer follow-up (24 months).

Search methods

We searched various electronic databases on 8 July 2022.

Selection criteria

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

Data collection and analysis

We used standard Cochrane methods for pairwise meta-analysis and we augmented this evidence using network meta-analysis (NMA) methods. We used the Stata 'network' meta-analysis package for all analyses. We used the CINeMA (Confidence in Network Meta-Analysis) web application to grade the certainty of the evidence.

Main results

We included 23 studies (13 with industry funding) that enrolled 3513 people with DMO (median central retinal thickness (CRT) 460 microns, interquartile range (IQR) 424 to 482) and moderate vision loss (median best-corrected visual acuity (BCVA) 0.48 logMAR, IQR 0.42 to 0.55).

One study that investigated ranibizumab versus sham and one study that mainly enrolled people with subclinical DMO and normal BCVA were not suitable for inclusion in the efficacy NMA.

Consistent with the previous update of this review, we used ranibizumab as the reference drug for efficacy, and control (including laser, observation, and sham) as the reference for systemic safety.

Eight trials provided data on the primary outcome (change in BCVA at 24 months, in logMAR: lower is better). We found no evidence of a difference between the following interventions and ranibizumab alone: aflibercept (mean difference (MD) −0.05 logMAR, 95% confidence interval (CI) −0.12 to 0.02; moderate certainty); bevacizumab (MD -0.01 logMAR, 95% CI −0.13 to 0.10; low certainty), brolucizumab (MD 0.00 logMAR, 95% CI −0.08 to 0.07; low certainty), ranibizumab plus deferred laser (MD 0.00 logMAR, 95% CI −0.11 to 0.10; low certainty), and ranibizumab plus prompt laser (MD 0.03 logMAR, 95% CI −0.04 to 0.09; very low certainty).

We also analysed BCVA change at 12 months, finding moderate-certainty evidence of increased efficacy with brolucizumab (MD −0.07 logMAR, 95%CI −0.10 to −0.03 logMAR), faricimab (MD −0.08 logMAR, 95% CI −0.12 to −0.05), and aflibercept (MD −0.07 logMAR, 95 % CI −0.10 to −0.04) compared to ranibizumab alone, but the difference could be clinically insignificant.

Compared to ranibizumab alone, NMA of six trials showed no evidence of a difference with aflibercept (moderate certainty), bevacizumab (low certainty), or ranibizumab with prompt (very low certainty) or deferred laser (low certainty) regarding improvement by three or more ETDRS lines at 24 months.

There was moderate-certainty evidence of greater CRT reduction at 24 months with brolucizumab (MD −23 microns, 95% CI −65 to −1 9) and aflibercept (MD −26 microns, 95% CI −53 to 0.9) compared to ranibizumab. There was moderate-certainty evidence of lesser CRT reduction with bevacizumab (MD 28 microns, 95% CI 0 to 56), ranibizumab plus deferred laser (MD 63 microns, 95% CI 18 to 109), and ranibizumab plus prompt laser (MD 72 microns, 95% CI 25 to 119) compared with ranibizumab alone.

Regarding all-cause mortality at the longest available follow-up (20 trials), we found no evidence of increased risk of death for any drug compared to control, although effects were in the direction of an increase, and clinically relevant increases could not be ruled out. The certainty of this evidence was low for bevacizumab (risk ratio (RR) 2.10, 95% CI 0.75 to 5.88), brolucizumab (RR 2.92, 95% CI 0.68 to 12.58), faricimab (RR 1.91, 95% CI 0.45 to 8.00), ranibizumab (RR 1.26, 95% CI 0.68 to 2.34), and very low for conbercept (RR 0.33, 95% CI 0.01 to 8.81) and aflibercept (RR 1.48, 95% CI 0.79 to 2.77). Estimates for Antiplatelet Trialists Collaboration arterial thromboembolic events at 24 months did not suggest an increase with any drug compared to control, but the NMA was overall incoherent and the evidence was of low or very low certainty.

Ocular adverse events were rare and poorly reported and could not be assessed in NMAs.

Authors' conclusions

There is limited evidence of the comparative efficacy and safety of anti-VEGF drugs beyond one year of follow-up. We found no clinically important differences in visual outcomes at 24 months in people with DMO, although there were differences in CRT change. We found no evidence that any drug increases all-cause mortality compared to control, but estimates were very imprecise. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often under-treated, and the individuals exposed to these drugs may be less healthy than trial participants.

PLAIN LANGUAGE SUMMARY

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

What is the aim of this review?
The aim of this Cochrane Review was to find out which is the best type of anti-vascular endothelial growth factor (anti-VEGF) medicine for diabetic macular oedema (DMO) two years after treatment initiation.

Key messages
There may be no clinically important differences in visual outcomes among anti-VEGF medicines at two years in people with DMO, although we did find differences in the effect of medicines on retinal thickness. There is no evidence that any medicine increases the risk of death or major cardiovascular events compared to control.

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

How is diabetic macular oedema treated?
One type of treatment for DMO is anti-VEGF. This type of medicine is given by means of an injection into the eye. It can reduce the swelling at the back of the eye and prevent visual loss. These medicines might have unwanted effects, particularly related to the blood vessels in the rest of the body.

What did we want to find out?
The previous version of this review found minor differences in effects between anti-VEGF medicines at one year, which were unlikely to be clinically significant. In this update, we investigated if any differences in efficacy and safety exist after two years.

What did we do?
We included all studies comparing anti-VEGF medicines with each other or with control and summarised data at two years.

What did we find?
We found 23 relevant studies. Thirteen were industry-sponsored studies from the USA, Europe, or Asia. Ten studies received no industry funding and were from the USA, Europe, the Middle East, and South America.

There were results at two years for the medicines ranibizumab, bevacizumab, aflibercept, and brolucizumab. One study investigated conbercept, but this medicine is approved only in China. Results were available only at one year for the newest medicine faricimab. These anti-VEGF medicines were compared with no treatment, sham treatment, laser treatment, or each other. People participating in the studies received the medicines every month for the first three to six months, then less frequently. Decisions about long-term treatment were based on visual acuity or by looking at the back of the eye.

We found that all anti-VEGF medicines prevent visual loss and can improve vision in people with DMO, with no important differences in vision at two years between aflibercept, bevacizumab, brolucizumab, and ranibizumab, although aflibercept and brolucizumab yield a better control of retinal swelling than other medicines.

There was no evidence that these medicines increase the risk of death or cardiovascular events, but the quality of this evidence was poor.

What are the limitations of the evidence?
Few studies provided data comparing anti-VEGF medicines at two years, and estimates were often imprecise.

How up to date is this review?
We searched for studies that had been published up to 6 October 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: mean change in best-corrected visual acuity from baseline to 24 months

Patient or population: people with diabetic macular oedema

Settings: clinical

Intervention: intravitreal antiangiogenic drugs alone (aflibercept, bevacizumab, brolucizumab), ranibizumab plus deterred or prompt laser, and laser alone

Comparison: ranibizumab alone

Outcome: mean change in BCVA at 24 months, measured in logMAR (lower is better)

Equivalence criterion: 0.1 logMAR (equivalent to 5 ETDRS letters, or 1 ETDRS line)

Intervention (vs ranibizumab alone)	No. of studies (participants)	MD (95% CI)[a]	Certainty of evidence	SUCRA[g]
Aflibercept	3 (641)	**−0.05logMAR** (−0.12 to 0.02)	**Moderate**[b]	89.5
Bevacizumab	3 (261)	**−0.01 logMAR** (−0.13 to 0.10)	**Low**[b,c]	55.2
Brolucizumab	1 (154)	**0.00logMAR** (−0.08 to 0.07)	**Low**[d]	62.2
Ranibizumab deferred laser	1 (139)	**0.00logMAR** (−0.11 to 0.10)	**Low**[b]	56.9
Ranibizumab prompt laser	3 (287)	**0.03logMAR** (−0.04 to 0.09)	**Very low**[e,f]	32.7
Laser	5 (598)	**0.13 logMAR** (0.6 to 0.20)	**Low**[b,f]	0.3

BCVA: best-corrected visual acuity; **CI:** confidence interval; **ETDRS**: Early Treatment Diabetic Retinopathy Study; **logMAR:** logarithm of the minimum angle of resolution; **MD:** mean difference; **SUCRA**: Surface Under the Cumulative RAnking curve.

[a] Relative to mean BCVA change from baseline with ranibizumab alone (−0.19 logMAR in 3 trials, 341 participants).
[b] Downgraded for imprecision: 95% CI exceeding level of clinical significance (0.1 logMAR) on one side (−1 level) or both sides (−2 levels).
[c] Downgraded for incoherence: direct and indirect evidence 95% prediction intervals differ, and their interpretation supports different conclusions favouring one treatment (−1 level) or either treatment (−2 levels).
[d] Downgraded (−2 levels) for publication bias, since two-year data were only available for one of two substudies (KESTREL) on ClinicalTrials.gov and as an ARVO abstract.
[e] Downgraded for heterogeneity: 95% predictive interval, but not meta-analytic estimate, exceeding the clinical significance threshold (0.1 logMAR) on one side (−1 level) or both sides (−2 levels).
[f] Downgraded for within-study risk of bias.

[g] SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017). The value for ranibizumab was 53.3.

Summary of findings 2. Summary of findings: mean change in best-corrected visual acuity from baseline to 12 months

Patient or population: people with diabetic macular oedema

Settings: clinical

Intervention: intravitreal antiangiogenic drugs alone (aflibercept, bevacizumab, conbercept, faricimab), ranibizumab plus deterred or prompt laser, and laser alone

Comparison: ranibizumab alone (11 studies, 1140 participants)

Outcome: mean change in BCVA at 12 months (lower is better)

Equivalence criterion: 0.1 logMAR (equivalent to 5 ETDRS letters, or 1 ETDRS line)

Intervention (vs ranibizumab alone)	No. of studies (participants)	MD (95% CI)[a]	Certainty of evidence	SUCRA[e]
Faricimab (PTI)	1 (632)	**−0.08logMAR** (−0.12 to −0.05)	**Moderate**[b]	94.4
Aflibercept	5 (1592)	**−0.07logMAR** (−0.10 to −0.04)	**Moderate**[b]	80.0
Brolucizumab	1(368)	**−0.07logMAR** (−0.10 to −0.03)	**Moderate**[b]	78.8
Conbercept	1 (125)	**−0.05logMAR** (−0.11 to 0.01)	**Low**[b,c]	69.6
Bevacizumab	5 (373)	**−0.01 logMAR** (−0.04 to 0.02)	**Moderate**[c]	41.1
Ranibizumab deferred laser	1 (188)	**0.01logMAR** (−0.04 to 0.05)	**High**	30.7
Ranibizumab prompt laser	7 (746)	**0.01logMAR** (−0.01 to 0.03)	**Moderate**[c]	20.4
Laser	13 (1296)	**0.12logMAR** (0.10 to 0.14)	**Moderate**[d]	0.0

BCVA: best-corrected visual acuity; **CI:** confidence interval; **ETDRS**: Early Treatment Diabetic Retinopathy Study; **logMAR:** logarithm of the minimum angle of resolution; **MD:** mean difference; **PTI:** personalised treatment interval; **SUCRA**: Surface Under the Cumulative RAnking curve.

[a] Relative to mean BCVA change from baseline with ranibizumab (−0.20 logMAR in 11 studies, 1140 participants).
[b] Downgraded for imprecision: 95% CI exceeding level of clinical significance (0.1 logMAR) on one side (−1 level).
[c] Downgraded for within-study risk of bias (-1 level).

[d] Downgraded for incoherence: direct and indirect evidence 95% prediction intervals differ, and their interpretation supports different conclusions favouring one treatment (−1 level).
[e] SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017). The value for ranibizumab was 34.8.

Summary of findings 3. Summary of findings: gain of three or more ETDRS lines from baseline to 24 months

Patient or population: people with diabetic macular oedema

Settings: clinical

Intervention: intravitreal antiangiogenic drugs alone (aflibercept, bevacizumab, brolucizumab), ranibizumab plus deterred or prompt laser, and laser alone

Comparison: ranibizumab alone (2 studies, 224 participants)

Outcome: gain of 3 or more ETDRS lines from baseline to 24 months

Equivalence criterion: RR 0.80 to 1.25

Intervention (vs ranibizumab alone)	No. of studies (participants)	Absolute risk (95% CI)[a]	Relative risk (95% CI)	Certainty of evidence	SUCRA[d]
Aflibercept	2 (487)	0.37 (0.30 to 0.48)	**1.10** (0.87 to 1.41)	**Moderate**[b]	90.2
Bevacizumab	1 (185)	0.33 (0.25 to 0.43)	**0.97** (0.74 to 1.26)	**Low**[b]	62.0
Ranibizumab prompt laser	2 (170)	0.27 (0.17 to 0.44)	**0.80** (0.49 to 1.28)	**Very low**[b,c]	41.3
Ranibizumab deferred laser	1 (139)	0.27 (0.16 to 0.44)	**0.76** (0.46 to 1.28)	**Low**[b]	37.0
Laser	4 (559)	0.16 (0.11 to 0.23)	**0.47** (0.32 to 0.68)	**High**	0.2

CI: confidence interval; **ETDRS**: Early Treatment Diabetic Retinopathy Study; **SUCRA**: Surface Under the Cumulative RAnking curve[c].

[a] Relative risk with intervention multiplied by absolute risk with ranibizumab alone (0.34 in 2 trials, 224 participants).
[b] Downgraded for imprecision: 95% CI exceeding level of clinical significance (RR 0.80 or 1.25) on one side (−1 level) or both sides (−2 levels).
[c] Downgraded for within-study risk of bias (-1 level).
[d] SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017). The value for ranibizumab was 69.4.

Summary of findings 4. Summary of findings: mean change in central retinal thickness from baseline to 24 months

Patient or population: people with diabetic macular oedema

Settings: clinical

Intervention: intravitreal antiangiogenic drugs alone (aflibercept, bevacizumab, brolucizumab), ranibizumab plus deterred or prompt laser, and laser alone

Comparison: ranibizumab alone (1 study, 191 participants)

Outcome: mean change in CRT at 24 months (microns, lower is better)

Equivalence criterion: 50 microns

Intervention (vs ranibizumab alone)	No. of studies (participants)	MD (95% CI)[a]	Certainty of evidence	SUCRA[c]
Aflibercept	3 (640)	**−26 microns** (−53 to 1)	**Moderate**[b]	92.8
Brolucizumab	1 (154)	**−23microns** (−65 to −19)	**Moderate**[b]	87.7
Bevacizumab	2 (261)	**28 microns** (0 to 56)	**Moderate**[b]	49.3
Ranibizumab deferred laser	1 (136)	**63microns** (18 to 109)	**Moderate**[b]	25.2
Ranibizumab prompt laser	1 (136)	**72microns** (25 to 119)	**Moderate**[b]	15.0
Laser	4 (563)	**75microns** (42 to 109)	**Moderate**[b]	11.1

CI: confidence interval; **CRT:** central retinal thickness; **MD:** mean difference; **SUCRA**: Surface Under the Cumulative RAnking curve.

[a]Relative to median CRT change from baseline with ranibizumab (−135 microns in 1 trial, 191 participants).
[b] Downgraded for imprecision: 95% CI exceeding level of clinical significance (50 microns) on one side (−1 level) or both sides (−2 levels).
[c] SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017). The value for ranibizumab was 68.9.

Summary of findings 5. Summary of findings: all-cause mortality at longest available follow-up

Patient or population: people with diabetic macular oedema

Settings: clinical

Intervention: intravitreal antiangiogenic drugs (aflibercept, bevacizumab, brolucizumab, conbercept, faricimab, ranibizumab)

Comparison: control (15 studies, 2126 participants), including laser, observation, sham

Outcome: all-cause mortality at longest available follow-up

Equivalence criterion: RR 0.80 to 1.25

Drug (vs. control)	No. studies (no. participants)	Absolute risk[a] (95%CI)	Relative risk (95% CI)	Certainty of evidence	SUCRA[e]
Aflibercept	10 (2644)	0.027 (0.014 to 0.050)	**1.48** (0.79 to 2.77)	**Very low**[b,c]	48.1
Bevacizumab	4 (305)	0.038 (0.014 to 0.106)	**2.10** (0.75 to 5.88)	**Low**[b]	29.6
Brolucizumab	1 (368)	0.053 (0.012 to 0.227)	**2.92** (0.68 to 12.6)	**Low**[b]	20.2
Conbercept	1 (125)	0.006 (0.0 to 0.159)	**0.33** (0.01 to 8.81)	**Very low**[b,d]	81.7
Faricimab	2 (1262)	0.034 (0.008 to 1.44)	**1.91** (0.45 to 8.00)	**Low**[b]	35.2
Ranibizumab	11 (2065)	0.023 (0.012 to 0.042)	**1.26** (0.68 to 2.34)	**Low**[b]	59.4

CI: confidence interval; **SUCRA**: Surface Under the Cumulative RAnking curve.

[a] Relative risk for drug vs. control multiplied by absolute risk with control (0.018 in 15 trials, 2126 participants).
[b] Downgraded for imprecision: 95% CI exceeding level of clinical significance (RR= 0.80 or 1.25) on one side (−1 level) or both sides (−2 levels).
[c] Downgraded for incoherence: direct and indirect evidence 95% prediction intervals differ, and their interpretation supports different conclusions favouring one treatment (−1 level) or either treatment (−2 levels).
[d] Downgraded for within-study risk of bias (-1 level).
[e] SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017). The control value was 75.8 (higher number means safer).

Summary of findings 6. Summary of findings: Antiplatelet Trialists Collaboration arterial thromboembolic events at longest available follow-up

Patient or population: people with diabetic macular oedema

Settings: clinical

Intervention: intravitreal antiangiogenic drugs (aflibercept, bevacizumab, brolucizumab, conbercept, faricimab, ranibizumab)

Comparison: control (13 studies, 1619 participants), including laser, observation, sham (risk = 0.044)

Outcome: Antiplatelet Trialists Collaboration arterial thromboembolic events at longest available follow-up

Equivalence criterion: RR 0.80 to 1.25

Drug	No. of studies (participants)	Absolute risk (95% CI)[a]	Relative risk (95% CI)	Certainty of evidence	SUCRAf
Aflibercept	10 (2701)	0.048 (0.028 to 0.081)	**1.08** (0.63 to 1.85)	**Very low**[b,c]	37.1
Bevacizumab	3 (310)	0.043 (0.017 to 0.106)	**0.97** (0.39 to 2.41)	**Low**[b]	46.8
Brolucizumab	1 (369)	0.021 (0.007 to 0.068)	**0.48** (0.15 to 1.54)	**Low**[b,d]	84.8
Conbercept	1 (125)	0.044 (0.009 to 0.194)	**0.99** (0.20 to 4.42)	**Very low**[b,d,e]	45.1
Faricimab	2 (1262)	0.040 (0.014 to 0.114)	**0.91** (0.32 to 2.59)	**Low**[b,d]	50.6
Ranibizumab	11 (1501)	0.047 (0.027 to 0.081)	**1.06** (0.63 to 1.85)	**Very low**[b,c]	39.5

CI: confidence interval; **SUCRA**: Surface Under the Cumulative RAnking curve.

[a] Relative risk for drug vs. control multiplied by absolute risk for control (0.044 in 13 trials, 1619 participants).
[b] Downgraded for imprecision: 95% CI exceeding level of clinical significance (RR < 0.80 or > 1.25) on one side (−1 level) or both sides (−2 levels).
[c] Downgraded one level for incoherence: direct and indirect evidence points to opposite direction and has poor overlap.
[d] Only indirect evidence: not downgraded further as large imprecision already means uncertain effect, including clinically significant increase.
[e] Downgraded for within-study bias (-1 level).
[f] SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017). The control value was 46.1.

BACKGROUND

Description of the condition

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

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

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

Since the 1980s, the clinical gold standard to detect macular oedema has been fundus examination with contact lens, but non-contact lenses can also be used for this purpose with good sensitivity. Optical coherence tomography (OCT) is increasingly used as an objective and reproducible tool to measure retinal thickness, and some experts suggest it could constitute the new gold standard for diagnosing DMO (Olson 2013; Ontario HTA 2009). The most severe form of DMO is clinically significant macular oedema (CSMO), which the Early Treatment Diabetic Retinopathy Study (ETDRS) defines as a condition that meets any of the following criteria (ETDRS 1985).

- Retinal oedema within 500 µm of the centre of the fovea
- Hard exudates within 500 µm of the centre of the fovea, if associated with adjacent retinal thickening (which may be outside the 500 µm limit)
- One disc area of retinal oedema (1500 µm) or larger, any part of which is within one disc diameter of the centre of the fovea

Since the introduction of OCT, research has demonstrated good agreement between this technique and the clinical gold standard (slit-lamp examination with a contact lens) for detecting the presence of macular oedema; moreover, OCT may be more sensitive in cases of mild foveal thickening (Brown 2004). A simple OCT-based classification defines DMO as centre-involving or non-centre-involving (Browning 2008).

Description of the intervention

Antiangiogenic therapy has largely replaced laser photocoagulation and become a standard of care for the treatment of DMO (Jampol 2014, Virgili 2014). The UK National Institute for Clinical Excellence (NICE) technology appraisal guidance recommends anti-vascular endothelial growth factor (VEGF) agents only for people with DMO of at least 400 microns, as anti-VEGFs are not cost-effective below this thresholdhttps://www.nice.org.uk/guidance/ta346(TA274 2013; TA346 2015; TA799 2022). The previous version of this review found minor differences between anti-VEGF drugs at one year; these differences were likely to be clinically unimportant (Virgili 2018). Anti-VEGF treatments inhibit VEGF angiogenic activity, binding to VEGF protein and thus preventing its receptor activation or interaction. Researchers originally hypothesised that these drugs could be an alternative adjunctive treatment for DMO (Cunningham 2005), following evidence that VEGF-A plays a key role in the occurrence of increased vascular permeability in ocular diseases such as DMO (Aiello 2005).

Grid or focal laser photocoagulation is not suitable for all people with DMO; therefore, initial studies on the efficacy of antiangiogenic drugs for DMO used either laser or sham procedures as current practice comparators (Macugen 2005; RESOLVE 2010; RESTORE 2011; Soheilian 2007), and no directly comparative randomised controlled trials (RCTs) were published until 2015 (DRCRnet 2015). One 2022 study showed subthreshold macular laser to be as effective as standard laser in people with centre-involved DMO and retinal thickness below 400 microns (Lois 2022), for whom anti-VEGF is generally not recommended (Baker 2019).

Intravitreal antiangiogenic therapy has acceptable safety; endophthalmitis, the major adverse event (fewer than 1/1000 injections) is related to the surgical injection procedure, rather than the drug itself.

Steroids represent another therapeutic option for DMO. They are administered as intravitreal injections or sustained release implants to obtain high local concentrations, maximising their anti-inflammatory, angiostatic, and anti-permeability effects while minimising systemic toxicity (Ciulla 2004; Haller 2010; Kuppermann 2010). However, intravitreal steroids may cause cataract and ocular hypertension, and the visual outcome is dependent on the lens status or the need for cataract surgery after about one year (Campochiaro 2010; Haller 2010). Some investigators consider that intravitreal steroids are preferable in people with anti-VEGF-resistant and chronic DMO, as an alternative to switching between anti-VEGF drugs (Hussain 2015). This is consistent with the EU label of the only approved dexamethasone intravitreal implant in Europe: "Ozurdex is indicated for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy" (EMA 2022a).

For ranibizumab, the EU label prescribes a 0.5 mg dosage, and indicates that "treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD [age-related macular degeneration], DME, PDR [proliferative diabetic retinopathy] and RVO [retinal vein occlusion], initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters" (EMA 2022b). In the USA, ranibizumab "0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days)" (FDA 2014).

Aflibercept is approved for use in the USA, and "the recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal

injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)" (FDA 2011). The EU label is similar (EMA 2023a).

Bevacizumab is widely used off-label; its use has been questioned based on regulatory and safety issues (Banfi 2013), but is still key for treating chorioretinal vascular disease in low- and middle-income countries thanks to its low cost (Stewart 2016).

More recently, anti-VEGF drugs with longer duration of effects have been made available with the goal of extending treatment intervals and reducing the number of injections. These include brolucizumab (EMA 2023b; FDA 2019; KITE and KESTREL 2022) and faricimab (FDA 2022: YOSEMITE and RHINE 2022).

Conbercept is another anti-VEGF drug for intravitreal use; it has been approved to treat AMD and DMO in China only (Liu 2022).

How the intervention might work

VEGF plays a key role in the occurrence of increased vascular permeability in ocular diseases such as DMO (Aiello 2005). Anti-VEGF agents inhibit VEGF angiogenic activity, binding to VEGF protein and thus preventing its receptor activation and interaction, with various degree of affinity (Parravano 2021). The targets differ between drugs, and newer drugs also bind other cytokines, such as angiopoietin 2 (Ang-2) inhibitor (YOSEMITE and RHINE 2022).

Why it is important to do this review

DMO results in a significant burden of low vision and blindness, hence the importance of assessing and updating the evidence base for the effectiveness and safety of these agents. There is a continuing clinical need to establish evidence-based recommendations regarding anti-VEGF agents. The previous version of this review provided estimates of the relative safety and efficacy of different antiangiogenic drugs to treat DMO at 12 months. There is evidence that about two-thirds of people with DMO need treatment up to five years, although the number of injections may be low after year 2, and only 8% of participants received 20 or more injections in years 3 to 5 (Glassman 2020).

OBJECTIVES

The objective of this updated review was to compare the effectiveness and safety of the different anti-VEGF drugs in RCTs at longer follow-up (24 months).

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs.

Types of participants

People with DMO and an indication for anti-VEGF treatment (in most settings this means OCT evidence of central retinal thickness (CRT) above 400 microns). We expected to include most of the studies included in Virgili 2018, except those with follow-up shorter than nine months.

Types of interventions

We included studies that evaluated any antiangiogenic drug with anti-VEGF modalities versus another antiangiogenic drug with anti-VEGF modalities, laser treatment, sham, or no treatment. The Description of the intervention section presents the reasons for selecting both direct and indirect treatments. As explained in Description of the intervention, steroids may be comparable to anti-VEGF drugs, but they require a different approach, specifically regarding patient subgroups and timing. Consequently, including studies that evaluate steroids could lead to violation of similarity in a review aiming to compare different anti-VEGF drugs, and so we decided to exclude steroids.

Regarding drug dose and monitoring/retreatment regimen, in efficacy analyses we included schemes that were either on-label or commonly used in clinical practice, such as the treatment as needed (PRN) regimen, as presented in the Description of the intervention section. For ranibizumab, both 0.3 mg and 0.5 mg doses were eligible. We merged these two ranibizumab doses into one group in our network meta-analysis (NMA), as studies have found no difference between them when used monthly (Heier 2016). Regarding aflibercept, we selected the eight-weekly retreatment regimen, as this is the approved label in the first year. We used all available data regardless of dose and regimen for safety analyses, in accordance with Moja 2014 and the previous version of this review.

Types of outcome measures

Primary outcomes

We considered that mean continuous best-corrected visual acuity (BCVA) was the preferred outcome measure in trials on DMO at the time of this update. We also recognised a need for longer-term results, as people with DMO are followed for several years and tend to stabilise during the second year of treatment.

Therefore, the primary outcome for this update was change in BCVA (logarithm of the minimum angle of resolution (logMAR: lower is better)), measured using ETDRS charts, between baseline and 24 months.

Secondary outcomes

- Mean change in BCVA from baseline to 12 months, measured using ETDRS charts
- Proportion of participants with at least 15 ETDRS letters (three ETDRS lines or 0.3 logMAR) of improvement in BCVA from baseline to 24 months
- Mean change in CRT from baseline to 24 months, measured using OCT
- Mean change in quality of life from baseline to 24 months, measured using a validated instrument
- Need for rescue laser within 24 months' follow-up

We pooled measurements at varying lengths of follow-up in annual intervals, plus or minus six months, the primary analysis being that at 24 months. Where multiple time points were available, we chose the time point closest to 24 months, or the latest time point in the window frame in the case of symmetry.

Adverse events

Most large studies reported a large number of adverse events, often grouped by ocular anatomic district, or, if systemic, by MedDRA (Medical Dictionary for Regulatory Activities) system organ class. Based on our experience with the previous version of this review, we decided to report adverse events for which we believe further evidence should be collected (Khanani 2022; Reibaldi 2022).

We considered the following adverse events.

- All-cause mortality
- Antiplatelet Trialists Collaboration (ATC) arterial thromboembolic events (ATC 1994)
- Ocular serious adverse events, as defined by the investigators, and including at least endophthalmitis, severe retinal vascular occlusion, and retinal detachment. We planned to present the frequency of each event in tabular form.

We analysed adverse events at the longest available follow-up time (Moja 2014), as in the previous version of this review (Virgili 2018).

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases and registries for RCTs and controlled clinical trials, applying no language or publication year restrictions. The date of the search was 8 July 2022.

- Cochrane Central Register of Controlled Trials (CENTRAL, which contains the Cochrane Eyes and Vision Trials Register; 2021, Issue 10) in the Cochrane Library (searched 8 July 2022; Appendix 1)
- MEDLINE Ovid (1946 to 8 July 2022; Appendix 2)
- Embase Ovid (1980 to 8 July 2022; Appendix 3)
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to 8 July 2022; Appendix 4)
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 6 October 2021; Appendix 5)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 8 July 2022; Appendix 6)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int; searched 8 July 2022; Appendix 7).

Searching other resources

We handsearched the reference lists of the included trials for other possible trials. We accessed the Novartis Clinical Trials database (www.novartis.com/clinicaltrials) on 28 May 2014 and checked all trials indexed under the headings "ophthalmic disorders" and "ranibizumab".

Data collection and analysis

Selection of studies

Two review authors independently selected the studies for inclusion (KC, MP, IG). First, we examined the titles and abstracts of all reports identified by the electronic searches and handsearching, classifying them as definitely eligible, potentially eligible, and definitely ineligible. We obtained and assessed full-text copies of all eligible and potential records, and classified studies as included, awaiting assessment, and excluded. The review authors were unmasked to the study authors, institutions, and trial results during this assessment. We resolved any disagreements by involving a third review author (GV).

Data extraction and management

Two review authors independently extracted the data for the primary and secondary outcomes into Excel forms developed by Cochrane Eyes and Vision (KC, MP). We piloted this form on a few studies. We resolved any discrepancies by discussion. One review author entered all data into Review Manager Web (RevMan Web 2022), and a second review author checked the entered data. If standard deviations (SDs) were not reported in the publication and could not be obtained from the study authors, we imputed them from SDs of other studies with the same comparison.

Assessment of risk of bias in included studies

Two review authors (KC, MP) independently assessed the included trials for risk of bias according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We assessed the following parameters.

- Random sequence generation and allocation concealment
- Blinding of participants, personnel, and outcome assessors
- Incomplete outcome data
- Selective reporting
- Other potential sources of bias

We judged each study at low, high, or unclear risk of bias, for each parameter.

If the information available in the published trial reports was inadequate to assess methodological quality, we contacted the trial authors for clarification. In our protocol, we specified that if the trial authors did not respond within six months, we would assess the trial based on the available information (Parravano 2008). However, for this update of the review, we waited only one month.

Measures of treatment effect

Data analysis followed the guidelines set out in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017). For dichotomous outcomes, we calculated a summary risk ratio (RR) with its 95% confidence interval (CI). For continuous outcomes, we calculated the mean difference (MD) and 95% CI. If studies had used different scales to measure the same continuous outcome, we would have calculated standardised mean differences (SMDs).

We did not use ranking measures in this review, as we were mainly interested in only three drugs: aflibercept, bevacizumab, and ranibizumab.

Unit of analysis issues

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

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

Dealing with missing data

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

Assessment of heterogeneity

In standard pairwise meta-analyses, we estimated heterogeneity variances for each direct comparison. We assessed the presence of statistical heterogeneity within each pairwise comparison using the I^2 statistic (Higgins 2017). The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter (Tau^2) estimated from the NMA models.

Assessment of reporting biases

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

Data synthesis

Methods for direct treatment comparisons

If there was no substantial statistical heterogeneity and no clinical heterogeneity between trials, we combined the results in a meta-analysis using a random-effects model. We used a fixed-effect model if the number of trials was three or less. In the case of substantial statistical heterogeneity (i.e. I^2 value above 50%) or clinical heterogeneity, we combined the results in a meta-analysis using a random-effects model if the individual trial results had a consistent direction of effect (i.e. RR or MD and CIs largely fell on one side of the null line); when the individual trial results had an inconsistent direction of effect, we did not combine study results but presented a narrative or tabulated summary of each study.

Methods for indirect and mixed comparisons

We performed NMA using the multivariate meta-analysis model, considering different treatment comparisons as different outcomes (Salanti 2012). For this analysis, we used the 'network' suite of commands available in Stata (Stata 2021; White 2015).

We presented mixed effects as RRs for dichotomous outcomes and MDs for continuous outcomes, each with their 95% CIs. We prepared league tables presenting mixed comparisons in the lower left corner and direct comparisons in the upper right corner, to enable inspection of both types of evidence.

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency

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

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network, we used the 'design-by-treatment' model through the 'network' command in Stata (Stata 2021; White 2015). This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results, as well as any disagreement between direct and indirect evidence. Using this approach, we judged the presence of inconsistency from any source in the entire network based on a Chi^2 test.

Subgroup analysis and investigation of heterogeneity

We identified too few studies to conduct subgroup analyses of efficacy at 24 months.

In most studies with 24-month data, participants had baseline BCVA between 0.35 and 0.8 logMAR and CRT between 400 and 500 microns, except for Baker 2019 (excluded) and READ2 2009 (CRT below 300 microns).

Sensitivity analysis

In the previous update of this review, we conducted post-hoc sensitivity analyses excluding studies at high risk of bias, which did not change our conclusions (Virgili 2018). In this update, there were too few trials with data at 24 months to conduct such analyses.

Summary of findings and assessment of the certainty of the evidence

We prepared one summary of findings table for each of the following outcomes.

- Mean BCVA change from baseline to 24 months
- Mean BCVA change from baseline to 12 months
- Gain of three or more ETDRS lines from baseline to 24 months
- Mean change in CRT from baseline to 24 months
- All-cause death at longest available follow-up
- ATC arterial thrombotic events at longest available follow-up

Because most of the available evidence is still on ranibizumab, we reported on the comparison of each intervention versus ranibizumab alone for efficacy outcomes. We used control (including laser, observation, and sham) as a comparator for safety outcomes.

We graded the certainty of the evidence for mixed estimates using the CINeMA platform (Nikolakopoulou 2020). We estimated the absolute risk in the control group from the data in the included studies as the raw proportion with event for dichotomous outcomes and the median value for continuous outcomes. We took into account the recommendations provided in Chapters 11 and 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Chaimani 2022; Schunemann 2022), as well as guidance provided by Yepes-Nuñez 2019. The CINeMA platform and methodological

framework evaluates the confidence in the results from NMAs in the following six domains.

- Within-study bias (referring to the impact of risk of bias in the included studies)
- Reporting bias (referring to publication and other reporting bias)
- Indirectness
- Imprecision
- Heterogeneity
- Incoherence

In the CINeMA framework, heterogeneity and incoherence are two dimensions of inconsistency that describe the extent to which the prediction interval overlaps with the CI, and the significance testing of the difference between direct and indirect evidence when both are available for a comparison.

Decisions regarding imprecision, heterogeneity and incoherence require the specification of a range of equivalence for relative effects (RR) based on absolute effects. For mean change in visual acuity, we considered one ETDRS line (0.1 logMAR) to be the minimal clinically important difference that was used for non-inferiority in trials on DMO (OZDRY 2015, PLACID 2013) and AMD (CATT 2011). We selected a range of equivalence between RR 0.80 and RR 1.25 for dichotomous outcomes. We made this choice post hoc after discussing its implications on relative and absolute effects for each outcome. The GRADE Working Group recommends the use of thresholds for clinically important effects of different sizes to rate imprecision in NMAs (Brignardello-Petersen 2019).

In the summary of findings tables, we also presented SUCRA (Surface Under the Cumulative RAnking curve) values. SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017).

We assessed transitivity, or similarity of the characteristics of the studies. We expected the transitivity assumption would hold as long as treatment comparisons were not related to the following factors.

- Acute versus chronic DMO, defined using the cut-off of three or more years of duration
- Average severity of DMO using OCT CRT of 400 micrometres as a cut-off
- Treatment regimen, such as monthly versus less than monthly and number of injections in the first year
- Drug dose for ranibizumab, since this is commercially available in two doses (0.3 mg in the USA, 0.5 mg elsewhere)
- Whether the trial was industry sponsored

Study data and Stata.do command files used to run all analyses are available at osf.io/ps87h/?view_only=e619a5c5ff07410eadb73035acbe688a.

RESULTS

Description of studies

See the Characteristics of included studies table, Characteristics of excluded studies table, and Characteristics of ongoing studies table.

Results of the search

Searches run in July 2022 yielded 2788 records. After 882 duplicates were removed, the Cochrane Information Specialist screened the remaining 1906 records and excluded 1661 references that were irrelevant to the scope of the review. We screened the titles and abstracts of the remaining 245 references and obtained 18 full-text reports for further assessment. Some industry-sponsored trials included twin studies, which we have combined in a single record (KITE and KESTREL 2022; RISE and RIDE 2013; VIVID and VISTA 2015; YOSEMITE and RHINE 2022). We included eight new trials for this update (Baker 2019; KITE and KESTREL 2022; Chatzirallis 2020; Li 2019 (REFINE); Liu 2022; RETAIN 2016; VIVID and VISTA 2015; YOSEMITE and RHINE 2022). The previous version of this review had 24 included studies; however, for this update, we reclassified eight studies as excluded (Ahmadieh 2008; Azad 2012; Ishibashi 2014; Lopez-Galvez 2014; Macugen 2005; Macugen 2011; Turkoglu 2015; Wiley 2016). In addition, Korobelnik 2014, which was included in the previous version, provided 12-month data from the VIVID and VISTA trials, so we included it under our new reverence VIVID and VISTA 2015. Therefore, the number of included studies is now 23.

We assessed and excluded a further 10 studies in this update (Afridi 2016 (READ-3); BOULEVARD 2019; BRDME 2020; Cornish 2018 (BEVORDEX); Ding 2015; Eichenbaum 2018; Fang 2016; Lafuente 2017; Li 2015; Payne 2021).

In the 2018 version of this review, there were eight ongoing studies and eight studies awaiting classification. These studies have been completed or excluded in this update. Following the new search, three new ongoing studies have been identified (Characteristics of ongoing studies).

See Figure 1.

Figure 1. PRISMA diagram showing the study selection process.

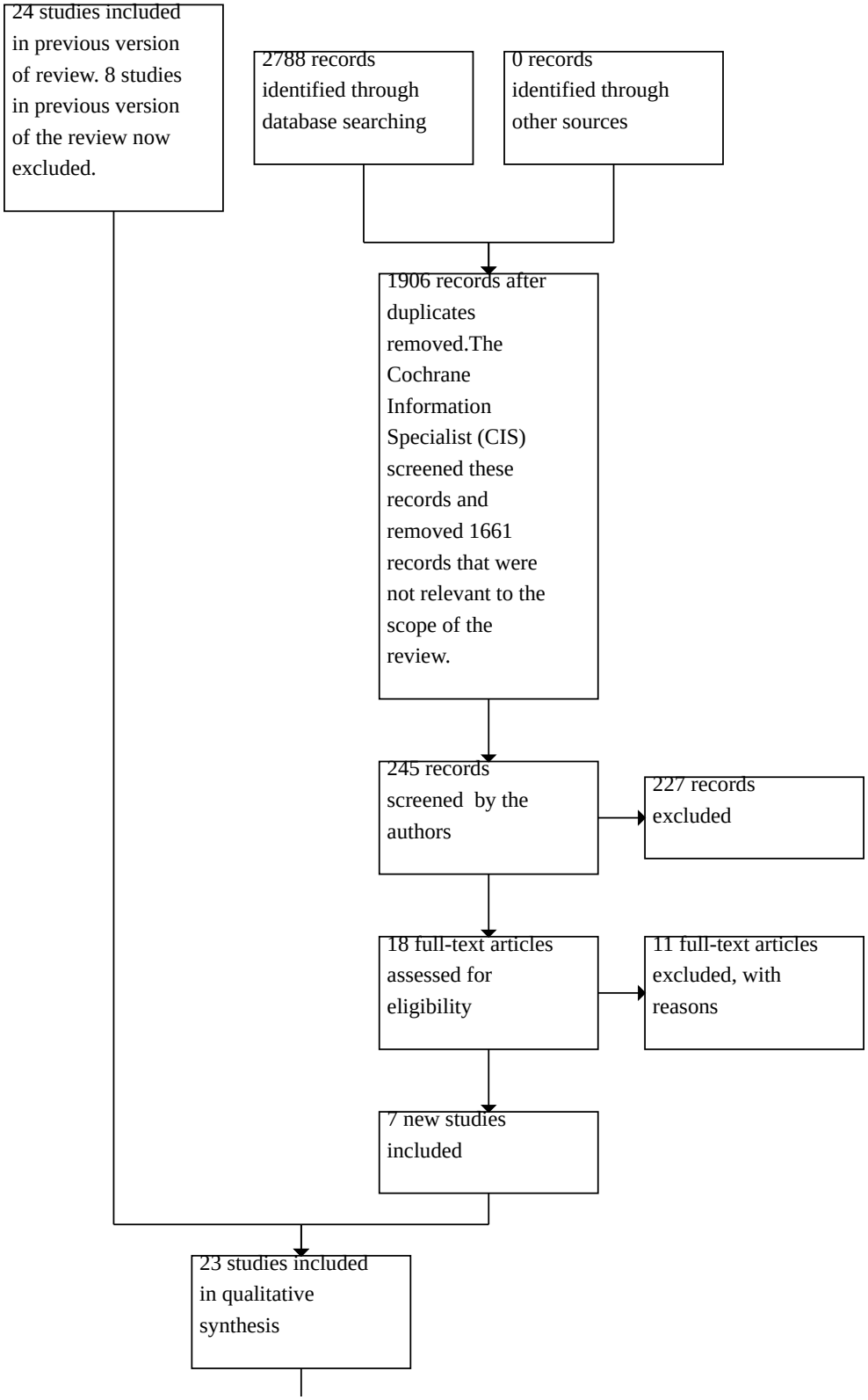
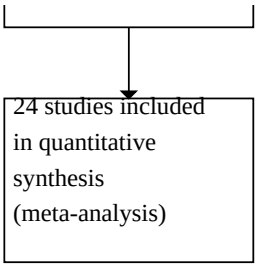


Figure 1. (Continued)



Included studies

We included 23 studies in this updated systematic review and NMA. Eight studies were industry-sponsored, multicentre RCTs conducted in the USA or Europe (DA VINCI 2011; READ2 2009; RELATION 2012; RESOLVE 2010; RESPOND 2013; RESTORE 2011; RISE and RIDE 2013; VIVID and VISTA 2015), whereas REVEAL 2015 was industry-sponsored but conducted in Asia.

Seven studies were independent RCTs conducted in the USA, Canada, UK, Athens, Turkey, and China (Baker 2019; BOLT 2010; Chatzirallis 2020; Ekinci 2014; Li 2019 (REFINE); LUCIDATE 2014; Nepomuceno 2013). DRCRnet 2010 and DRCRnet 2015 received public sponsorship, mainly from the US National Eye Institute, and were conducted in the USA. DRCRnet 2015 was the only large parallel-arm study to compare the commercially available drugs (aflibercept, bevacizumab, ranibizumab). It was a publicly-funded trial with monthly monitoring and treatment as needed.

Only nine trials maintained the randomisation scheme at two years' follow-up (BOLT 2010; DRCRnet 2010; DRCRnet 2015; KITE and KESTREL 2022; READ2 2009; RETAIN 2016; RISE and RIDE 2013; Soheilian 2007; VIVID and VISTA 2015).

YOSEMITE and RHINE 2022 were the first global, double-masked RCTs to evaluate a personalised treatment interval (PTI) regimen for DMO, based on the concept of treat and extend (YOSEMITE and RHINE 2022).

We did not extract data on comparisons of antiangiogenic therapy with triamcinolone and other intravitreal steroids because this comparison is the subject of another Cochrane Review (Grover 2008). We imputed SDs of change in CRT for six studies (Chatzirallis 2020; Ekinci 2014; KITE and KESTREL 2022; Nepomuceno 2013; REVEAL 2015; YOSEMITE and RHINE 2022). We contacted study authors when CRT data were missing from publications.

Finally, we included Baker 2019 in analyses of safety outcomes but not efficacy outcomes, as the population was very different from those of other studies and included people with normal or near-normal visual acuity and milder DMO detected with OCT (below 400 microns in most participants), with a ceiling effect in visual acuity change. We provided a brief narrative description of this study's efficacy findings in the Discussion section.

Types of participants

Trials included participants with a clinical diagnosis of DMO, and often these trials used OCT for confirming macular centre involvement. Baseline visual acuity of participants was generally between 20/200 and 20/40. Specifically, median BCVA across study arms was 0.48 logMAR (interquartile range (IQR) 0.42 to 0.55), and median CRT was 460 microns (IQR 424 to 482).

Most trials required a three- to six-month interval from previous central or peripheral laser, and a few small studies excluded people with previous antiangiogenic treatment.

Types of interventions

Thirteen studies assessed ranibizumab (Chatzirallis 2020; DRCRnet 2015; Ekinci 2014; Li 2019 (REFINE); LUCIDATE 2014; Nepomuceno 2013; READ2 2009; RESOLVE 2010; RESPOND 2013; RESTORE 2011; RETAIN 2016; REVEAL 2015; RISE and RIDE 2013); five studies investigated bevacizumab (BOLT 2010; DRCRnet 2015; Ekinci 2014; Nepomuceno 2013; Soheilian 2007) and six studies assessed aflibercept (Chatzirallis 2020; DA VINCI 2011; DRCRnet 2015; KITE and KESTREL 2022; VIVID and VISTA 2015; YOSEMITE and RHINE 2022). KITE and KESTREL 2022 was the only study to investigate brolucizumab, and YOSEMITE and RHINE 2022 was the only study to assess the efficacy and safety of faricimab. A single study investigated conbercept (Liu 2022). The drug dose was the same in most studies (0.5 mg ranibizumab, 1.25 mg bevacizumab, 2 mg aflibercept, 6 mg brolucizumab, 0.5 mg conbercept, and 6.0 mg faricimab). We did not include drugs that were not commercially available such as 3 mg brolucizumab.

One study on aflibercept evaluated laser photocoagulation for 24 months versus monthly injections of aflibercept for 24 months (2q4) versus a regimen of five initial monthly injections of aflibercept followed by eight-weekly injections (2q8) to 12 months followed by a 'treat-and-extend' (T&E) regimen in year two (VIVID and VISTA 2015). In RETAIN 2016, participants were randomised to receive either a ranibizumab T&E regimen with or without laser or a ranibizumab PRN regimen.

YOSEMITE and RHINE 2022 was the only study to have a PTI dosing regimen. Participants in the faricimab PTI group received injections every four weeks to week 14 (four injections), then adjustable dosing up to every 16 weeks. The other two arms (aflibercept and faricimab) received injections every four weeks to week 20, then fixed dosing every eight weeks until week 96.

PRN retreatment criteria were based on OCT and visual acuity in 12 studies (Baker 2019; Chatzirallis 2020; DA VINCI 2011; DRCRnet 2010; DRCRnet 2015; Ekinci 2014; KITE and KESTREL 2022; Liu 2022; LUCIDATE 2014; RESOLVE 2010; RETAIN 2016; VIVID and VISTA 2015), on visual acuity alone in three studies (Li 2019 (REFINE); Nepomuceno 2013; Soheilian 2007), and on OCT alone

in another three studies (BOLT 2010; READ2 2009; RISE and RIDE 2013). RELATION 2012 and RESPOND 2013 did not clearly describe PRN retreatment criteria.

Types of outcomes

Only eight studies reached 24 months' follow-up and reported the primary outcome, mean change in BCVA (BOLT 2010; DRCRnet 2010; DRCRnet 2015; KITE and KESTREL 2022; READ2 2009; RETAIN 2016; Soheilian 2007; VIVID and VISTA 2015).

Excluded studies

There are currently 46 excluded studies in the review. See the Characteristics of excluded studies table for the list of exclusions with reasons.

Risk of bias in included studies

We made very few high risk of bias judgments (Figure 2). This was likely due to the exclusion of trials with short-term follow-up and lower quality.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

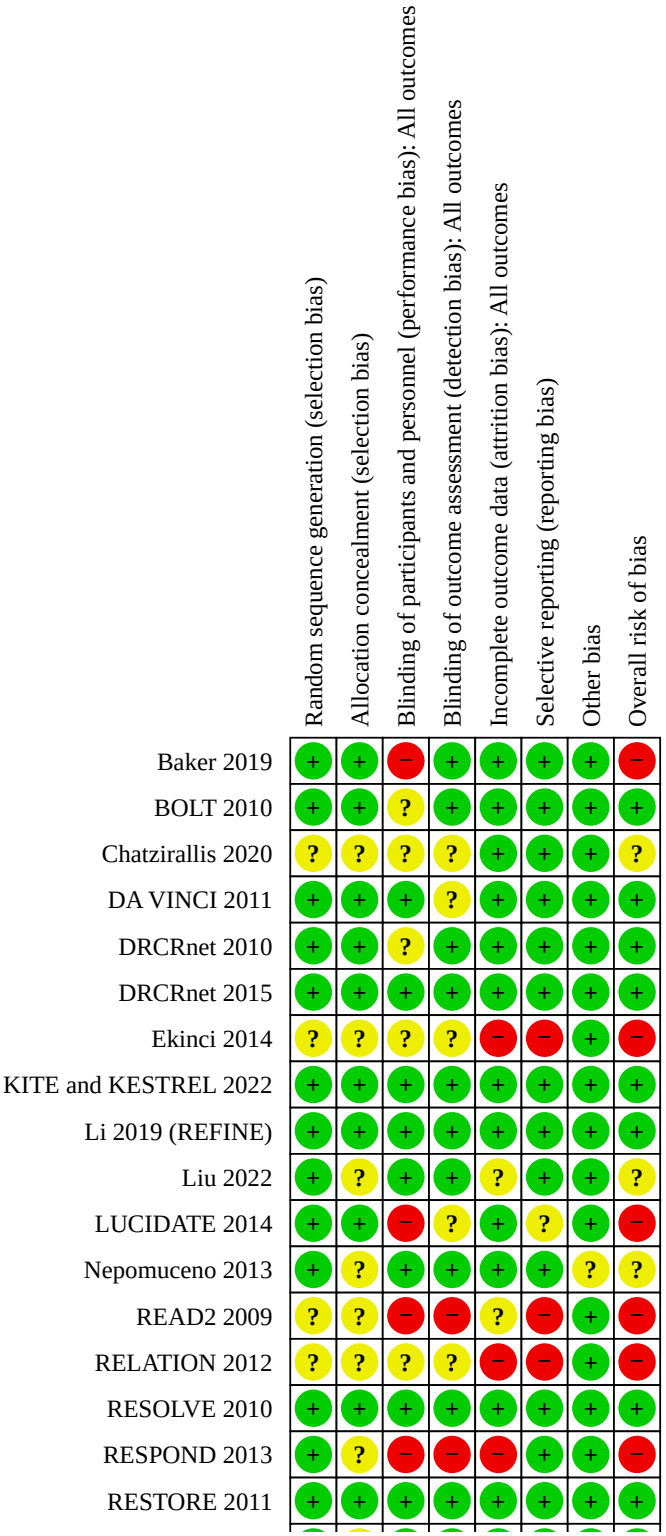
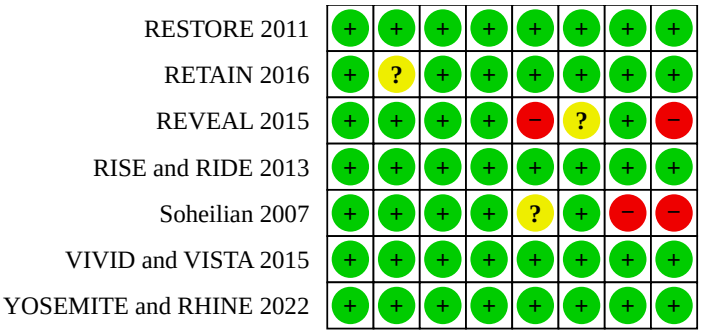


Figure 2. (Continued)



Allocation

We considered 18 studies at low risk of bias related to random sequence generation (Baker 2019; BOLT 2010; DA VINCI 2011; DRCRnet 2010; DRCRnet 2015; KITE and KESTREL 2022; Li 2019 (REFINE); LUCIDATE 2014; Nepomuceno 2013; RESOLVE 2010; RESPOND 2013; RESTORE 2011; RETAIN 2016; REVEAL 2015; RISE and RIDE 2013; Soheilian 2007; VIVID and VISTA 2015; YOSEMITE and RHINE 2022) and five studies at unclear risk (Chatzirallis 2020; Ekinci 2014; Liu 2022 READ2 2009; RELATION 2012). We judged 15 studies at low risk of bias related to allocation concealment (Baker 2019; BOLT 2010; DA VINCI 2011; DRCRnet 2010; DRCRnet 2015; KITE and KESTREL 2022; Li 2019 (REFINE); LUCIDATE 2014; RESOLVE 2010; RESTORE 2011; REVEAL 2015; RISE and RIDE 2013; Soheilian 2007; VIVID and VISTA 2015; YOSEMITE and RHINE 2022) and eight at unclear risk (Chatzirallis 2020; Ekinci 2014; Liu 2022; Nepomuceno 2013; READ2 2009; RELATION 2012; RESPOND 2013; RETAIN 2016). No studies received a high risk judgement for selection bias.

Blinding

Masking of participants and personnel was low risk in 14 studies (KITE and KESTREL 2022; DA VINCI 2011; DRCRnet 2015; Li 2019 (REFINE); Liu 2022; Nepomuceno 2013; RESOLVE 2010; RESTORE 2011; RETAIN 2016; REVEAL 2015; RISE and RIDE 2013; Soheilian 2007; VIVID and VISTA 2015; YOSEMITE and RHINE 2022) , unclear in five studies (BOLT 2010; Chatzirallis 2020; DRCRnet 2010; Ekinci 2014; RELATION 2012), and high risk in four studies (Baker 2019; LUCIDATE 2014; READ2 2009; RESPOND 2013).

Blinding of outcome assessment was low risk in 14 studies (Baker 2019; BOLT 2010; DRCRnet 2010; DRCRnet 2015; KITE and KESTREL 2022; Li 2019 (REFINE); Liu 2022; Nepomuceno 2013; RESTORE 2011; RETAIN 2016; REVEAL 2015; RISE and RIDE 2013; Soheilian 2007; YOSEMITE and RHINE 2022), unclear risk in seven studies (Chatzirallis 2020; DA VINCI 2011; Ekinci 2014; LUCIDATE 2014; RELATION 2012; RESOLVE 2010; VIVID and VISTA 2015), and high risk in two studies (READ2 2009; RESPOND 2013).

Incomplete outcome data

We considered 15 trials at low risk of attrition bias (Baker 2019; BOLT 2010; Chatzirallis 2020; DA VINCI 2011; DRCRnet 2010; DRCRnet 2015; KITE and KESTREL 2022; Li 2019 (REFINE); LUCIDATE 2014;Nepomuceno 2013 RESOLVE 2010; RESTORE 2011; RETAIN 2016; VIVID and VISTA 2015; YOSEMITE and RHINE 2022), four at unclear risk (Liu 2022; READ2 2009; RISE and RIDE 2013; Soheilian 2007), and four at high risk (Ekinci 2014; RELATION 2012; RESPOND 2013; REVEAL 2015). Ekinci 2014 excluded 15 participants after randomisation due to ocular and systemic complications, and three studies lost many more participants in the laser arm than in the ranibizumab arms (RELATION 2012; RESPOND 2013; REVEAL 2015).

Selective reporting

We judged 18 studies at low risk for reporting bias (Baker 2019; BOLT 2010;Chatzirallis 2020; DA VINCI 2011; DRCRnet 2010; DRCRnet 2015; KITE and KESTREL 2022; Li 2019 (REFINE); Liu 2022; Nepomuceno 2013; RESOLVE 2010; RESPOND 2013; RESTORE 2011; RETAIN 2016; RISE and RIDE 2013; Soheilian 2007; VIVID and VISTA 2015; YOSEMITE and RHINE 2022), two at unclear risk (LUCIDATE 2014; REVEAL 2015), and three at high risk (Ekinci 2014; READ2 2009; RELATION 2012).

Reporting was complete for mean BCVA change at one or two years in all 24 trials. Mean CRT was missing for one trial (READ2 2009), and we had to impute the SD for mean CRT in six trials (Chatzirallis 2020; Ekinci 2014; KITE and KESTREL 2022; Nepomuceno 2013; REVEAL 2015; YOSEMITE and RHINE 2022). Finally, two-year data on brolucizumab were only available for the KESTREL substudy of KITE and KESTREL 2022, as reported on clinicaltrials.gov/ct2/show/NCT03481634?term=brolucizumab&cond=dme&draw=2&rank=3 (accessed on May 1st, 2023) and as an abstract on iovs.arvojournals.org/article.aspx?articleid=2781369.

Other potential sources of bias

Baseline visual acuity was not balanced across study arms in Soheilian 2007: it was around 20/100 in the bevacizumab and bevacizumab-triamcinolone arms versus 20/70 in the laser arm, suggesting that participants in the laser arm had milder CSMO. The trial investigators adjusted for baseline values in the analyses, which also took into account the within-participant correlation (150 eyes of 129 participants, 16% of participants with both eyes in the analyses). However, we could not take within-participant correlation into account when analysing dichotomous visual acuity. One study included both eyes of some participants (15/48) in analyses (Nepomuceno 2013).

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

Effects of interventions

See: **Summary of findings 1** Summary of findings: mean change in best-corrected visual acuity from baseline to 24 months; **Summary of findings 2** Summary of findings: mean change in best-corrected visual acuity from baseline to 12 months; **Summary of findings 3** Summary of findings: gain of three or more ETDRS lines from baseline to 24 months; **Summary of findings 4** Summary of findings: mean change in central retinal thickness from baseline to 24 months; **Summary of findings 5** Summary of findings: all-cause mortality at longest available follow-up; **Summary of findings 6** Summary of findings: Antiplatelet Trialists Collaboration arterial thromboembolic events at longest available follow-up

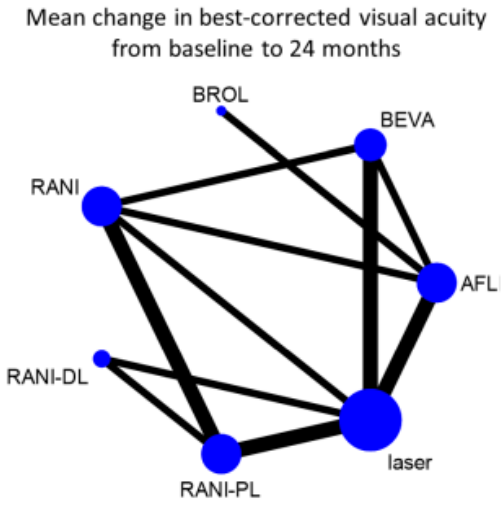
As in the previous version of this review, we adopted ranibizumab as a reference for efficacy outcomes, and control (including laser, observation, and sham) for systemic safety outcomes. We provided a narrative description of ocular safety outcomes.

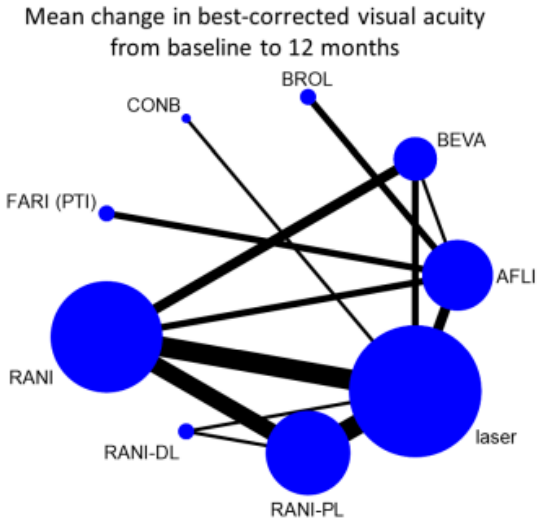
We made a post-hoc decision to exclude RISE and RIDE 2013 from efficacy analyses, as the comparison it evaluated (monthly ranibizumab versus sham) is not of current interest and would only add imprecision to our estimate of relative effects between anti-VEGF drugs. We conducted a sensitivity analysis including this study and reported on the impact of its inclusion. We included RISE and RIDE 2013 in safety analyses, pooling sham treatment with laser for systemic safety.

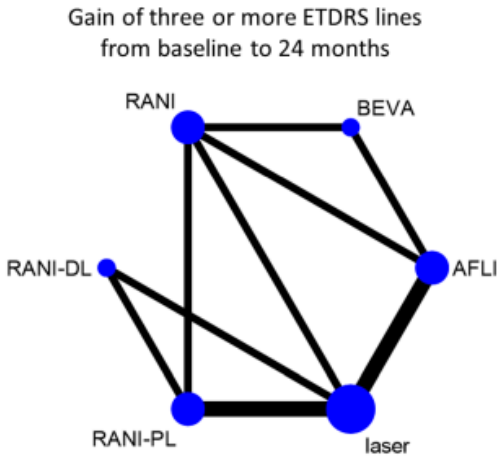
We also excluded Baker 2019 from efficacy analyses, as the population differed from those of other studies, with limited chances of vision improvement and a more favourable functional prognosis (visual acuity of 20/25 or better, and CRT below 400 microns in most participants; see transitivity assessment in Assessment of risk of bias in included studies).

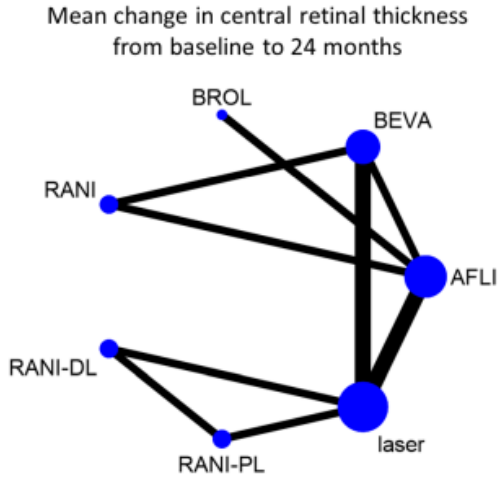
Figure 3 presents all network maps. The main results are presented in Summary of findings 1, Summary of findings 2, Summary of findings 3, Summary of findings 4, Summary of findings 5, and Summary of findings 6, and graphically in Figure 4. For the results of direct meta-analyses and a comparison of pooled results from NMA with pairwise meta-analyses, see Figure 5, Figure 6, Figure 7, Figure 8, Figure 9, and Figure 10). Mixed estimates and pairwise estimates of effect are presented in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6.

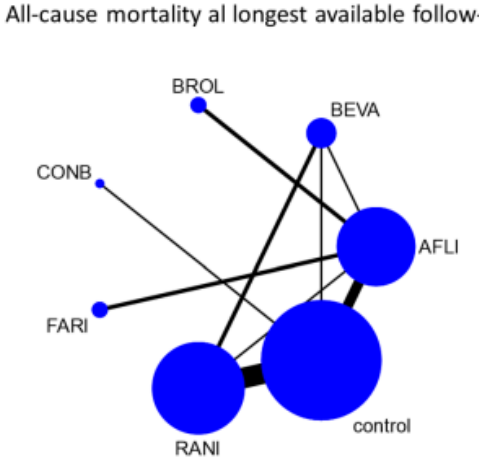
Figure 3. Network maps for all outcomes. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.











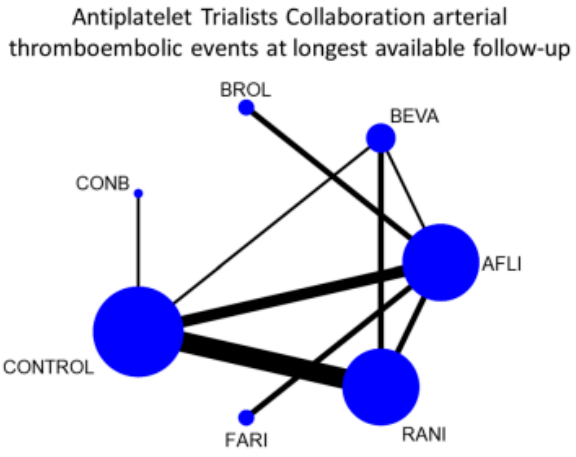


Figure 4. Forest plots for the main comparison, all outcomes. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.

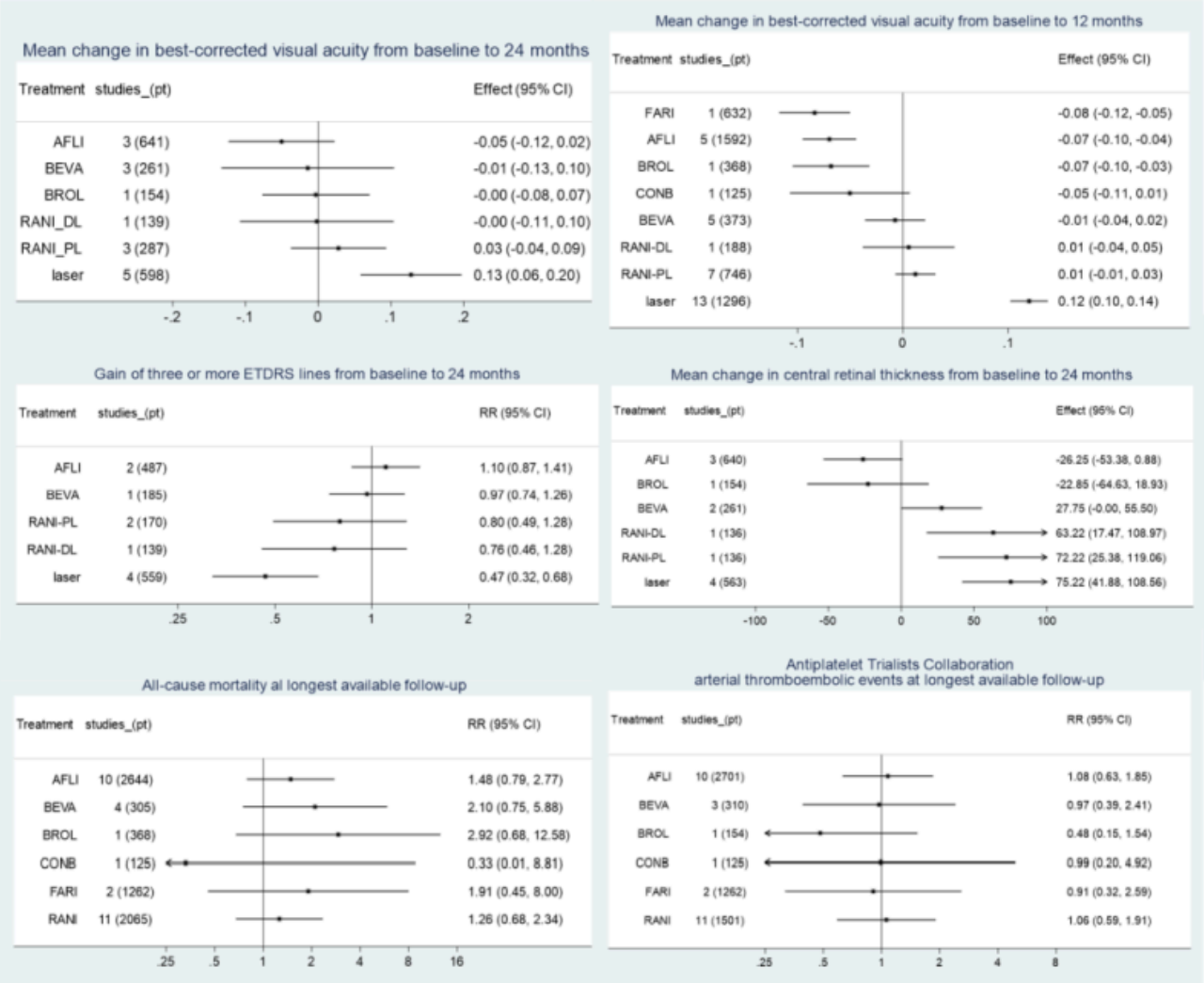


Figure 5. Pairwise meta-analysis and mixed estimates for the mean change in visual acuity at 24 months. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.

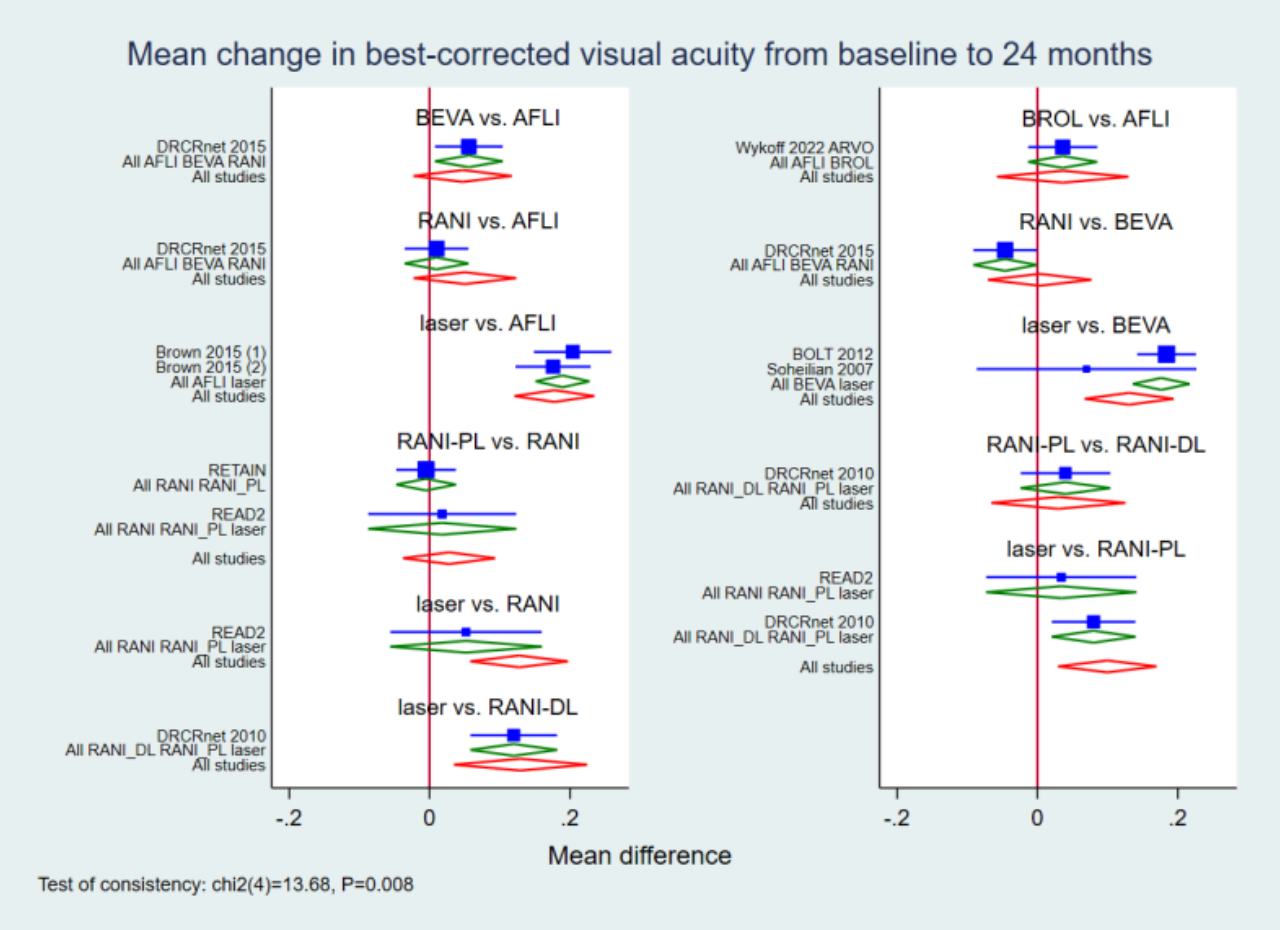


Figure 6. Pairwise meta-analysis and mixed estimates for the mean change in visual acuity at 12 months. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.

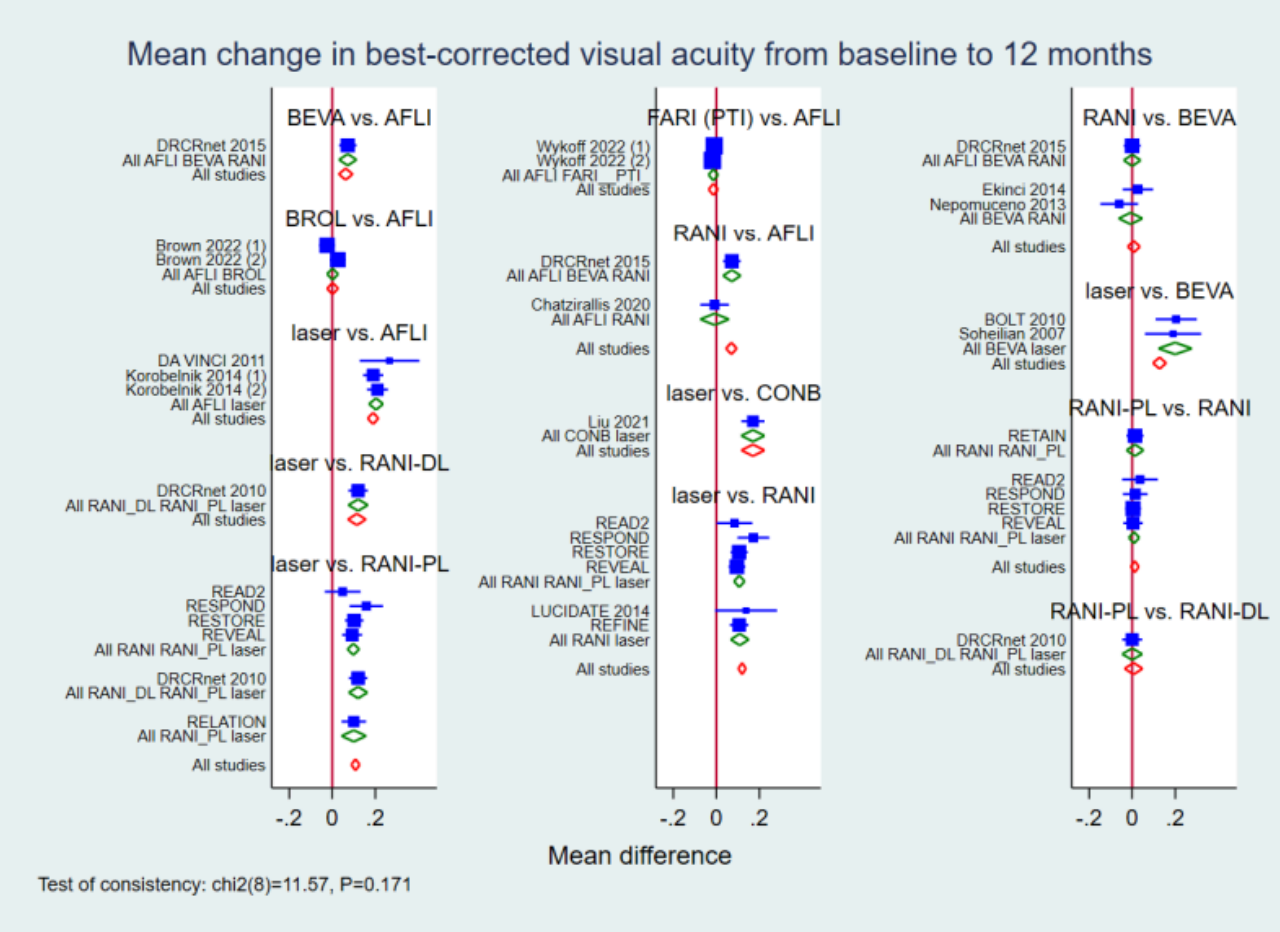


Figure 7. Pairwise meta-analysis and mixed estimates for the gain of three or more lines of visual acuity at 24 months.

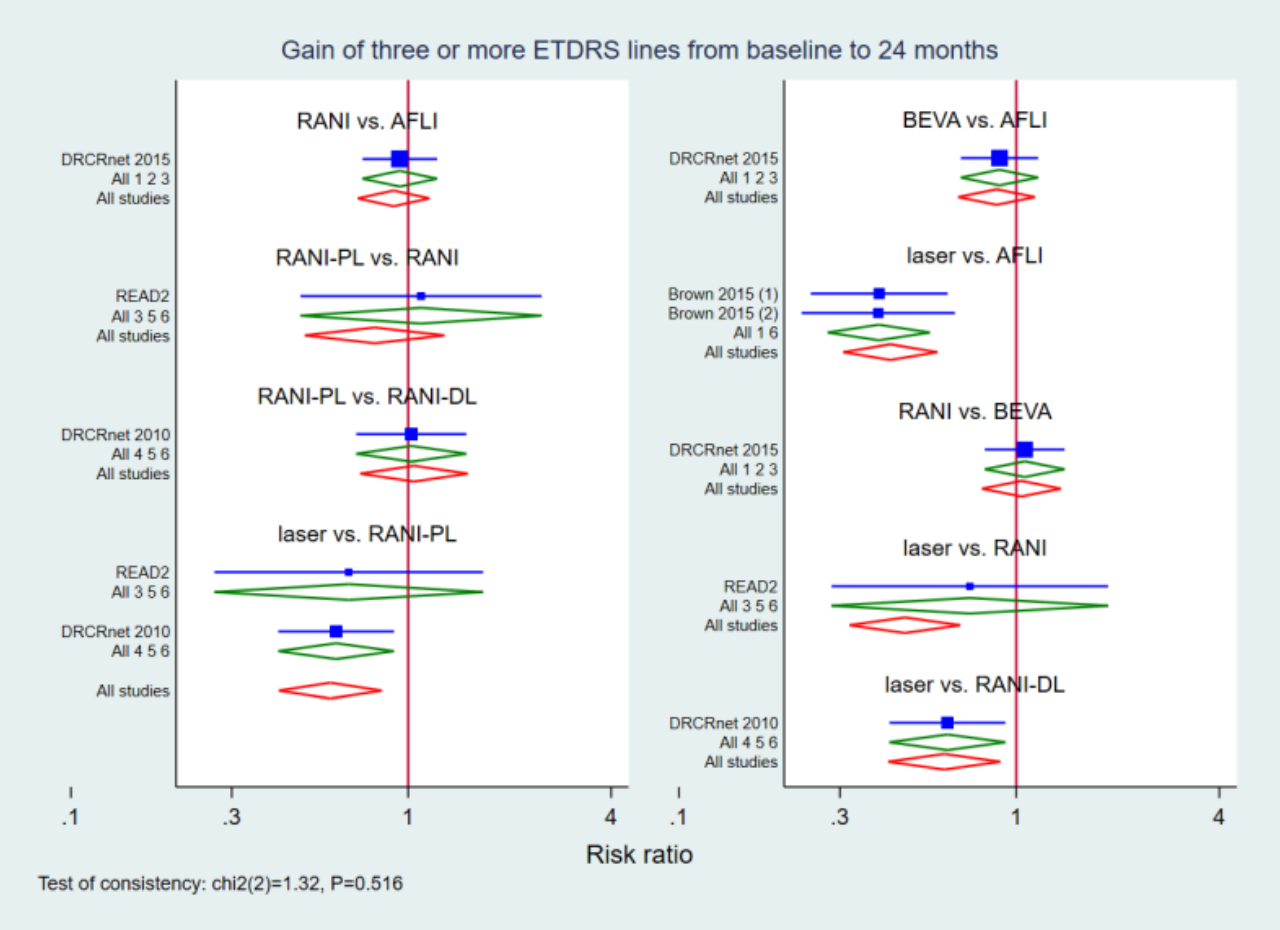


Figure 8. Pairwise meta-analysis and mixed estimates for the mean change in central retinal thickness at 24 months. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.

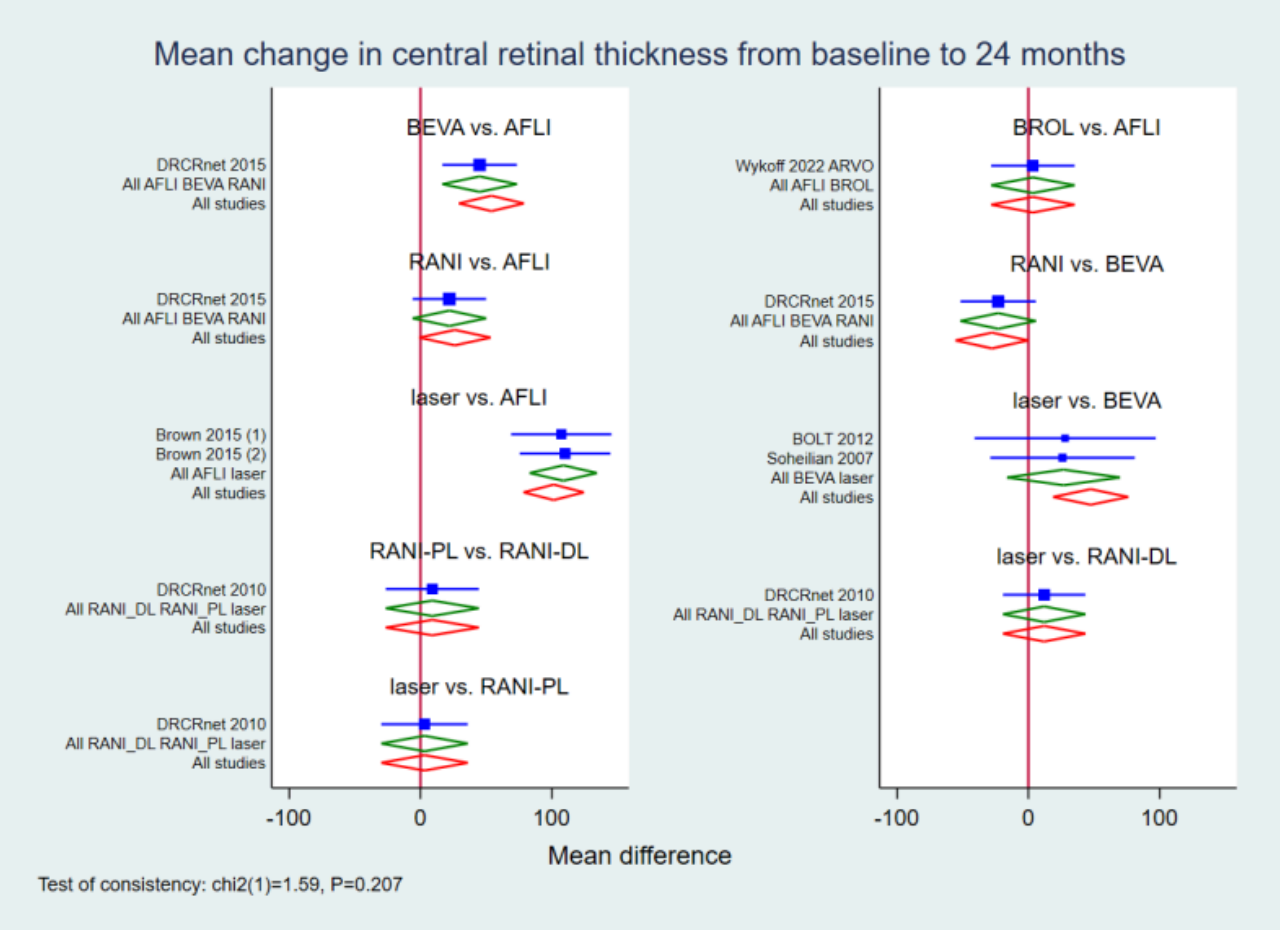


Figure 9. Pairwise meta-analysis and mixed estimates for all-cause mortality at longest available follow-up. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.

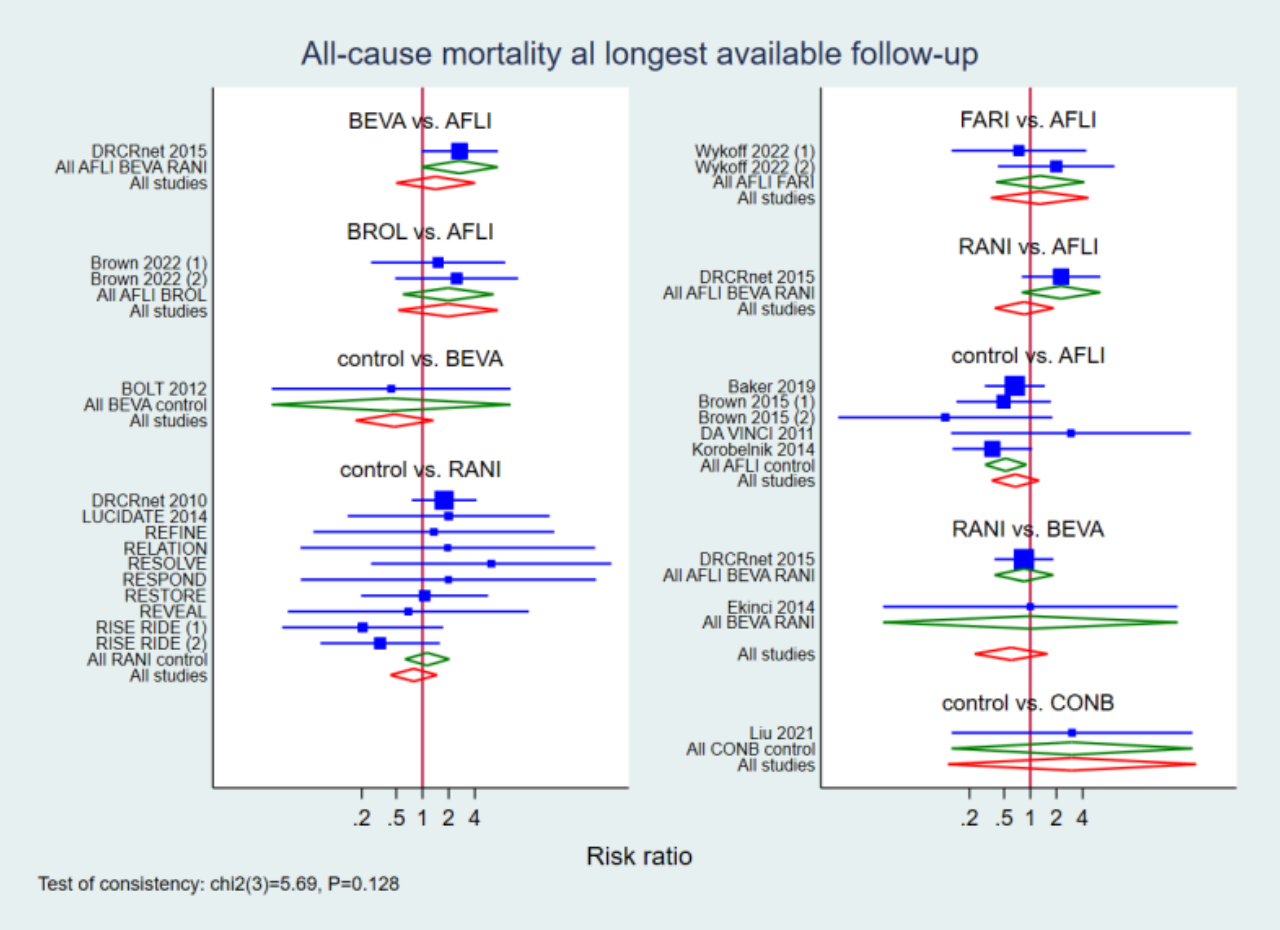
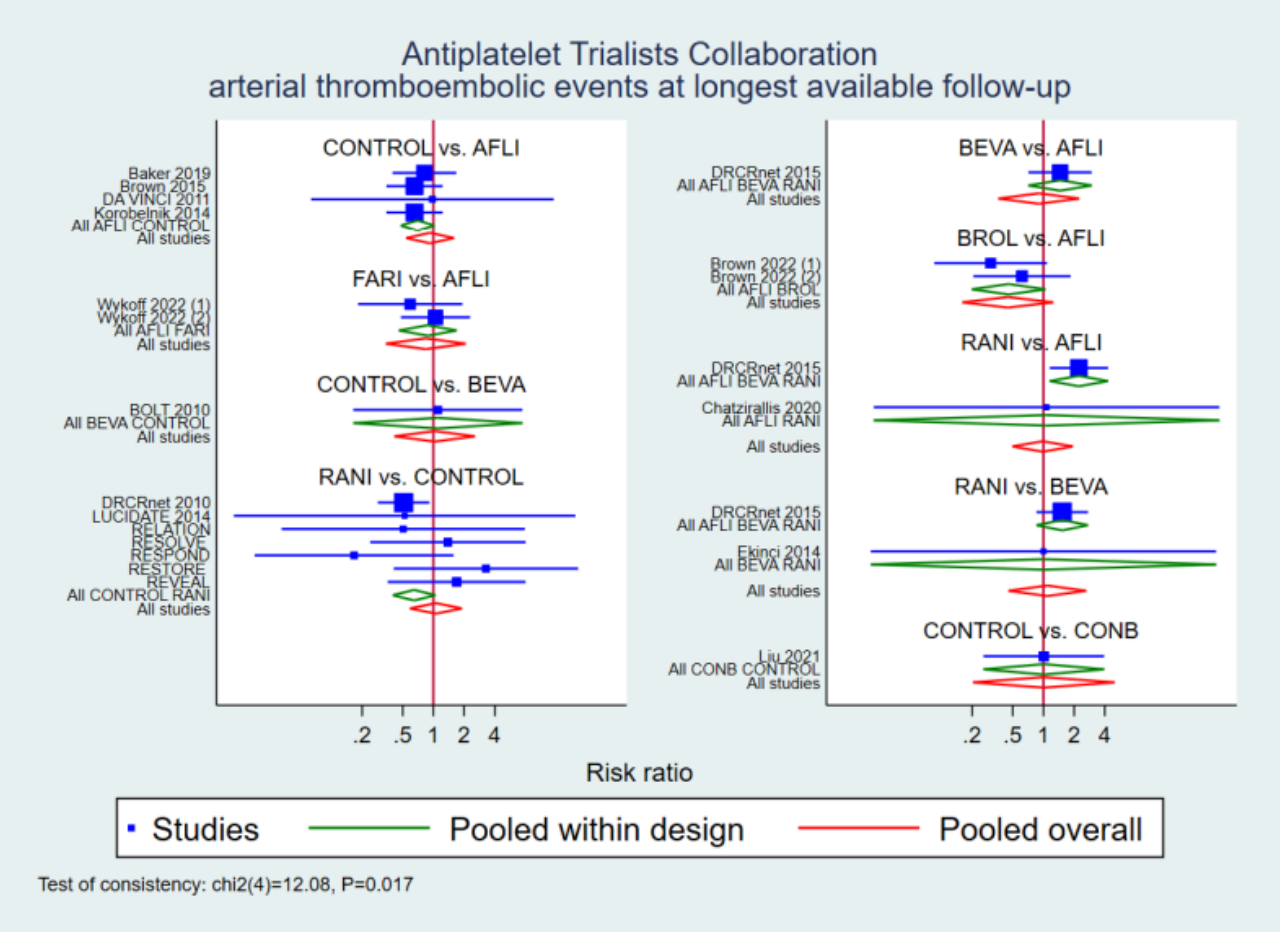


Figure 10. Pairwise meta-analysis and mixed estimates for arterial thromboembolic events at longest available follow-up. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.



Primary outcome: change in best-corrected visual acuity from baseline to 24 months

This analysis included eight studies (10 datasets) with the following arms: aflibercept (3 trials, 641 participants), bevacizumab (3 trials, 261 participants), brolucizumab (1 trial, 154 participants), ranibizumab (3 trials, 341 participants), ranibizumab with deferred laser (1 trial, 139 participants), ranibizumab with prompt laser (3 trials, 287 participants), and laser alone (5 trials, 598 participants).

The NMA showed overall inconsistency (P = 0.008). We detected significant loop-specific inconsistency for the comparison between ranibizumab and bevacizumab, with direct evidence favouring bevacizumab (MD −0.047 logMAR, 95% CI −0.92 to 0.02) and indirect evidence favouring ranibizumab (MD 0.103 logMAR, 95% CI 0.32 to 1.74; P = 0.001). We accepted the consistency model as primary analysis and downgraded the certainty of this evidence for this comparison. We found no evidence of a difference between anti-VEGF drugs and ranibizumab, which yielded a median value of change in BCVA across trials of −0.19 logMAR (Figure 4). The certainty of the evidence for the comparison with ranibizumab was moderate for aflibercept, very low for ranibizumab with prompt laser, and low for other comparisons, for reasons presented in Summary of findings 1. The SUCRA values for individual interventions were, in descending order: aflibercept 89.5, brolucizumab 62.2, bevacizumab 55.2, ranibizumab 53.8, and laser 0.3.

The sensitivity analysis including RISE and RIDE 2013 did not change the interpretation of the pooled estimates of effects.

Change in best-corrected visual acuity from baseline to 12 months

The NMA included 20 trials (26 datasets) with the following arms: aflibercept (5 trials, 1592 participants), bevacizumab (5 trials, 373 participants), brolucizumab (1 trial, 368 participants), conbercept (1 trial, 125 participants), faricimab (1 trial, 632 participants), ranibizumab (11 trials, 1140 participants), ranibizumab with deferred laser (1 trial, 188 participants), ranibizumab with prompt laser (7 trials, 746 participants), and laser alone (13 trials, 1296 participants).

There was no overall inconsistency (P = 0.171), although there was modest inconsistency for the comparison of both bevacizumab and ranibizumab compared with laser (respectively: P = 0.045; P = 0.034), but direct and indirect estimates of effect were in the same direction.

We found evidence of improved efficacy with faricimab (MD −0.08 logMAR, 95% CI −0.12 to −0.05), aflibercept (−0.07 logMAR, 95% CI −0.10 to −0.04) and brolucizumab (−0.07, 95% CI −0.10 to −0.03) compared with ranibizumab (median BCVA change of all study arms was −0.20 logMAR), but it was unclear whether the difference was clinically significant due to imprecision (Figure 4). The certainty of the evidence versus ranibizumab was moderate for aflibercept, brolucizumab, faricimab, and low for conbercept, and was moderate for bevacizumab and ranibizumab plus prompt, and high for ranibizumab plus deferred laser (Summary of findings 2).

The SUCRA values were, in descending order: faricimab 94.4, aflibercept 80.0, brolucizumab 78.8, conbercept 69.6, bevacizumab 41.1, ranibizumab 34.8, and laser 0.0.

Gain of three or more ETDRS lines from baseline to 24 months

With the exclusion of RISE and RIDE 2013, the NMA included five trials (six datasets) with the following arms: aflibercept (2 trials, 487 participants), bevacizumab (1 trial, 185 participants), ranibizumab (2 trials, 224 participants), ranibizumab with deferred laser (1 trial, 139 participants), ranibizumab with prompt laser (2 trials, 170 participants), and laser alone (4 trials, 559 participants).

There was no overall inconsistency (P = 0.516) and no loop-specific inconsistency. The raw proportion of three or more lines gain with ranibizumab was 34%. We found no evidence that any drug differed from ranibizumab, as 95% CIs included both beneficial and harmful effects (Figure 4). The certainty of the evidence was moderate for aflibercept, and low or very low for other comparisons, except for laser (high). See Figure 4

SUCRA values were, in descending order: aflibercept 90.2, ranibizumab 69.4, bevacizumab 62.0, ranibizumab with deferred laser 37.0, ranibizumab with prompt laser 41.3, and laser 0.2.

Change in central retinal thickness from baseline to 24 months

The NMA included six trials (7 datasets) with the following arms: aflibercept (3 trials, 640 participants), bevacizumab (2 trials, 261 participants), brolucizumab (1 trial, 154 participants), ranibizumab (1 trial, 191 participants), ranibizumab with deferred laser (1 trial, 136 participants), ranibizumab with prompt laser (1 trial, 136 participants), and laser alone (4 trials, 563 participants).

There was no overall inconsistency (P = 0.207) and no loop-specific inconsistency. The median value of CRT reduction across ranibizumab arms was −135 microns. Aflibercept (MD −26 microns, 95% CI −53 to 0.9) and brolucizumab (MD −23 microns, 95% CI −65 to -19) led to a greater CRT reduction than ranibizumab, but 95% CIs included no difference. Compared with ranibizumab alone, participants had a smaller CRT reduction with bevacizumab (MD 28 microns, 95% CI 0 to 56), ranibizumab plus deferred laser (MD 63 microns, 95% CI 18 to 109), and ranibizumab plus prompt laser (MD 72 microns, 95% CI 25 to 119). See Figure 4. The certainty of the evidence was moderate for all comparisons with ranibizumab. See Summary of findings 4.

The SUCRA values were, in descending order: aflibercept 92.8, brolucizumab 87.7, ranibizumab 68.9, bevacizumab 49.3, ranibizumab with deferred laser 25.2, ranibizumab with prompt laser 15.0, and laser 11.1.

All-cause mortality at longest available follow-up

With Baker 2019, the NMA included 20 trials (24 datasets) with the following arms: aflibercept (10 trials, 2644 participants), bevacizumab (4 trials, 305 participants), brolucizumab (1 trial, 368 participants), conbercept (1 trial, 125 participants), faricimab (2 trials, 1262 participants), ranibizumab (11 trials, 2065 participants), and control (15 trials, 2126 participants).

There was no overall inconsistency (P = 0.128), although we found that the comparison of aflibercept with control showed inconsistency of direct and indirect evidence (RR 0.52, 95% CI 0.30 to 0.90 vs RR 2.45, 95% CI 0.76 to 7.93; P = 0.019). Controls had a death rate of 1.8%. There was no evidence of increased risk of death for any drug compared to control, although all effects (except for conbercept, which was very imprecise) were in the direction of an increase, and we could not rule out clinically relevant increase (Figure 4). The certainty of this evidence was low for bevacizumab, brolucizumab, faricimab, ranibizumab, and very low for conbercept and aflibercept.

The SUCRA values were, in descending order of safety: conbercept 81.7, control 75.8, ranibizumab 59.4, aflibercept 48.1, faricimab 35.2, bevacizumab 29.6, and brolucizumab 20.2.

See Summary of findings 5.

Antiplatelet Trialists Collaboration arterial thromboembolic events at longest available follow-up

With Baker 2019, the NMA included 20 trials (23 datasets) with the following arms: aflibercept (10 trials, 2701 participants), bevacizumab (3 trials, 310 participants), brolucizumab (1 trial, 369 participants), conbercept (1 trial, 125 participants), faricimab (2 trial, 1262 participants), ranibizumab (11 trials, 1501 participants), and control (13 trials, 1619 participants).

There was overall inconsistency (P = 0.017) and loop-specific inconsistency for two loops, as follows.

Aflibercept versus control

- Direct evidence: RR 0.70 (95% CI 0.48 to 1.02); indirect evidence: RR 3.16 (95% CI 1.43 to 6.94); P = 0.001

Ranibizumab versus control

- Direct evidence: RR 1.55 (0.95 to 2.50); indirect evidence: RR 0.35 (95% CI 0.17 to 0.72); P = 0.001

Aflibercept versus ranibizumab

- Direct evidence: RR 2.18 (95% CI 1.14 to 4.16); indirect evidence: RR 0.45 (95% CI 0.25 to 0.84); P = 0.001

We still used NMA estimates from a consistency model and considered the certainty of evidence to be low or very low due to both imprecision and incoherence for the comparisons of interest. We took this conservative approach because direct evidence pointed in different directions; we did not attempt to implement the suggestion provided in Brignardello-Petersen 2019, which states that these domains should not be downgraded independently unless there is evidence of an impact on the decisions made on thresholds for clinical significance (RR below 0.80 or above 1.25).

The comparison of bevacizumab and control was coherent, with an NMA estimate of RR 0.97 (95% CI 0.39 to 2.41; low-certainty evidence). The comparison was only indirect between control and brolucizumab (RR 0.48, 95% CI 0.15 to 1.54) or faricimab (0.91, 0.32 to 2.59), and conbercept and control (0.99, 0.20 to 4.42; low-certainty evidence).

We found no evidence that any drug increased arterial thrombotic events compared to control. Controls had a crude event rate of 0.044 (Summary of findings 6).

Ocular adverse events at the longest available follow-up

Ocular adverse events were rare. Endophthalmitis is related to the procedure rather than the drug, and occurred in 0.24% to 0.80% of participants during the studies. Vascular disorders, retinal vein occlusion and retinal artery occlusion rarely occurred (0 to 6 participants (0% to 0.54%) across drug types).

The lowest figure for intraocular inflammation was recorded for ranibizumab (3/2566 participants, 0.12%) and the highest for aflibercept (23/578 cases, 3.98% on a per-injection basis in VIVID and VISTA 2015), and for brolucizumab (10/368 participants, 2.72%), However, ocular inflammation was recorded in 12/2126 cases (0.56%) for aflibercept on a per-participant basis in other studies, which highlights the need for standardising definitions.

Intervention	No. of participants	Endophthalmitis	Retinal detachment	Vascular disorders	Retinal vein occlusion	Retinal artery occlusion/embolism	Intraocular inflammation
Bevacizumab	376	1 (0.27)	2 (0.53)	0 (0)	1 (0.27)	2 (0.53)	2 (0.53)[a]
Ranibizumab	2566	14 (0.54)	5 (0.19)	6 (0.23)	1 (0.04)	3 (0.12)	3 (0.12)
		5 (0.24)	7 (0.33)	0 (0)	1 (0.05)	4 (0.19)	12 (0.56)
		0 (0)	2 (0.35)	0 (0)	NR[c]	2 (0.35)	23 (3.98)
Conbercept	125	1 (0.80)	NR[c]	NR[c]	NR[c]	NR[c]	1 (0.80)
Brolucizumab	368	1 (0.27)	0 (0)	NR[c]	2 (0.54)	1 (0.27)	10 (2.72)[a]
Faricimab	1264	4 (0.32)	1 (0.08)	NR[c]	3 (0.24)	0 (0)	6 (0.47)[a]
Laser	1806	2 (0.11)	2 (0.11)	3 (0.17)	1 (0.06)	1 (0.06)	4 (0.22)

Footnotes:

[a] One retinal vasculitis reported with brolucizumab, one choroiditis reported with bevacizumab, and one choroiditis with faricimab. All other intraocular inflammation related to anterior inflammation.

[b] VIVID and VISTA; recorded number of events based on number of injections.

[c] NR refers to no reported data. We assume no data reported means no adverse events.

Other outcomes

Durability

In KITE and KESTREL 2022, 104 (55.1%) and 90 (50.3%) of brolucizumab 6 mg subjects were maintained on a q12w interval (every 12 weeks) to week 52. Under the condition that a brolucizumab-treated eye successfully completed the first q12w interval with no observed disease activity, the probabilities for remaining on q12w dosing up to week 52 increased to 87.6% for brolucizumab 6 mg in KESTREL and 95.1% for brolucizumab 6 mg in KITE. At the week 52 visit, 60 (21%) participants in YOSEMITE and 62 (20%) participants in RHINE achieved faricimab dosing q12w; and 151 (53%) participants in YOSEMITE and 157 (51%) participants in RHINE achieved dosing q16w. Approximately two-thirds of participants reached q12w or q16w dosing at week 52 without an interval reduction below every 12 weeks during year 1 (n = 194 (68%) in YOSEMITE and n = 198 (64%) in RHINE; YOSEMITE and RHINE 2022).

Quality of life and use of rescue laser during follow-up

There were insufficient data to conduct NMAs at 24 months for quality of life and use of rescue laser during follow-up. Only RISE and RIDE 2013 and VIVID and VISTA 2015 reported mean change in quality of life from baseline to 24 months using a validated instrument (National Eye Institute Visual Function Questionnaire-25). Liu 2022, RESPOND 2013, and RESTORE 2011 reported on the mean change in quality of life from baseline to 12 months. Only VIVID and VISTA 2015 (aflibercept arms) and RISE and RIDE 2013 provided rescue laser up to 24 months.

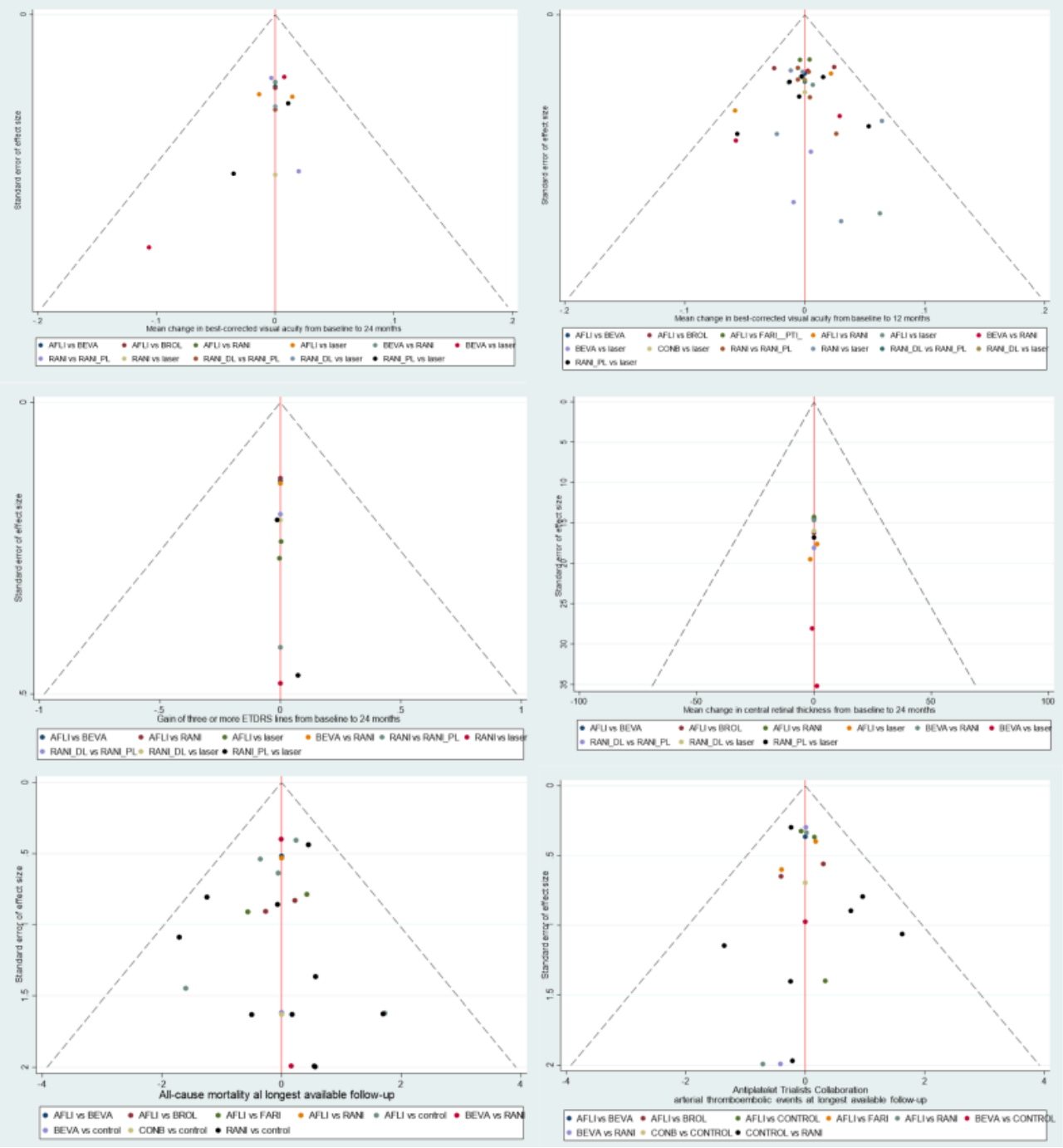
Similarities between studies

Table 7 shows baseline characteristics (BCVA, CRT) and the number of injections across study and treatment arms. Overall, most studies included participants with mean BCVA of around 20/60 and CRT between 400 and 500 microns, which we consider sufficiently homogeneous, with the exception of Baker 2019, which included people with normal vision and borderline DMO, and which we excluded from the efficacy meta-analyses. The number of injections was high compared with current practice (7 to 10 in year 1), except in a few small studies that delivered a low number of injections. We suspected no heterogeneity between studies using 0.3 mg versus 0.5 mg ranibizumab. In the safety analyses, we included two studies with monthly injections (one arm of VIVID and VISTA 2015 in year 1 for aflibercept and RISE and RIDE 2013 for ranibizumab) and there was no apparent heterogeneity from lower intensity regimens in other studies. Regarding sponsorship, there were fewer industry-sponsored studies on bevacizumab, but these studies were also smaller than other studies, and we were unable to assess the impact of such differences. Finally, we did not consider the OCT model used in each study as a source of heterogeneity in CRT change, as this variable was balanced between the arms of each study.

Selective reporting

Comparison-adjusted funnel plots showed no definite asymmetry for any outcome (Figure 11).

Figure 11. Contour-enhanced funnel plots for all outcomes. AFLI: aflibercept; BEVA: bevacizumab; BROL: brolucizumab; CONB: conbercept; ETDRS: Early Treatment Diabetic Retinopathy Study; FARI: faricimab; RANI: ranibizumab; RANI-DL: ranibizumab with deferred laser; RANI-PL: ranibizumab with prompt laser.



Sensitivity analyses on studies at low risk of bias

There were too few studies with 24 months' follow-up to conduct this sensitivity analysis, which we had conducted post hoc in the previous update of this review.

DISCUSSION

Summary of main results

This updated review and NMA found limited evidence of the relative efficacy of anti-VEGF drugs at 24 months. Most trials abandoned randomisation in the second follow-up year. We found no evidence of a clinically significant difference in our primary outcome (BCVA change from baseline to 24 months) between anti-VEGF drugs.

With ranibizumab as the reference drug, the certainty of evidence for the primary outcome was moderate for aflibercept, low for bevacizumab, brolucizumab and ranibizumab plus deferred laser, and very low for ranibizumab plus prompt laser. For the outcome gain of three or more lines of vision, we found moderate-certainty evidence of no difference for the comparisons ranibizumab alone versus aflibercept, low-certainty evidence versus bevacizumab, ranibizumab plus deferred laser, and very low-certainty evidence for ranibizumab plus prompt laser.

This substantial equivalence in functional outcomes is not mirrored in anatomic outcomes: we found moderate-certainty evidence that aflibercept and brolucizumab were more effective than ranibizumab for reducing CRT; and that bevacizumab, ranibizumab plus prompt laser, and ranibizumab plus deferred laser were less effective than ranibizumab alone.

Among the outcomes included in the previous version of this review, we collected the mean change in BCVA at 12 months. Compared to ranibizumab alone, we found high-certainty evidence that ranibizumab plus deferred laser yielded similar improvement, and moderate-certainty evidence that aflibercept, bevacizumab, brolucizumab and faricimab resulted in greater improvement in BCVA compared to ranibizumab alone, but this difference was unlikely to be clinically significant. In fact, this difference was mostly below the threshold of one ETDRS line (five letters or 0.1 logMAR), which has been used for non-inferiority trials on DMO (OZDRY 2015, PLACID 2013) and AMD (CATT 2011).

We also added data on the durability of brolucizumab and faricimab. More than half of participants treated with brolucizumab 6 mg were maintained on a 12-week interval at one year. Two-thirds of participants treated with faricimab reached 12-week or 16-week intervals at one year.

This updated review with more long-term and sparse data found no evidence that any anti-VEGF drug increases all-cause mortality or ATC arterial thromboembolic events compared to control, but estimates were imprecise and the certainty of evidence was low or very low for death. The NMA on ATC arterial thromboembolic events was affected by overall and loop-specific incoherence, and we also considered this evidence as low or very-low certainty.

Of interest, almost all point estimates of all-cause mortality were in the direction of increased risk compared with control, though with large imprecision. Our scope was to compare drugs; however, this observation is consistent with the findings of Reibaldi 2022, which showed a trend towards an increased risk of death with an increasing number of anti-VEGF injections. We believe this evidence is inconclusive and highlights the need for further studies, such as observational studies based on large electronic databases with a specific focus on high-risk patient subgroups (e.g. with previous stroke or major cardiovascular events).

We collected limited data on intraocular inflammation, especially acute inflammatory retinal vascular occlusion, an event that studies have ascribed to brolucizumab (Baumal 2020; Baumal 2021). Future reviews of this newly recognised and potentially severe complication of commercially available anti-VEGF drugs could include observational studies (Khanani 2022).

Overall completeness and applicability of evidence

The evidence used to build the NMA was much sparser at 24 months compared to 12 months, because most trials became open-label after one year. In real practice, high treatment and monitoring standards can be achieved in highly regulated health systems (Jiang 2015; Patrao 2016). However, in some clinical settings, many people with DMO are under-treated or have a high rate of discontinuation, and visual benefit is lower than in trials, with treatment needed for several years (Peto 2022; Sugimoto 2022; Zirpel 2021). A pragmatic RCT is needed to assess the real-world effectiveness of anti-VEGF treatment for DMO, which could be dependent on the adequacy of monitoring treatment response (which, in turn, is sensitive to resource constraints, as found for AMD; Pagliarini 2014). Moreover, our review did not include evidence on safety from non-randomised, real-world data. Real-world studies suggest that people with DMO may differ from those in RCTs (Ziemssen 2017).

We did not consider the differences in regimens, which may impact both clinical practice in terms of diagnostic workload, and cost-effectiveness, depending on the balance between cost and number of injections. One systematic review comparing treat-and-extend versus PRN regimens in people with DMO found little difference at 12 and 24 months (Sarhoia 2022), unlike in people with AMD (Li 2020). Moreover, most studies included in this review update delivered between seven and 12 injections in the first year, and could be considered treatment-intensive regimens compared to real world settings. This may limit the applicability of our results to standard clinical practice, especially in settings where under-treatment is common.

Finally, we were able to extract data regarding the number of participants who required rescue laser for only eight trials, giving us the following results for different anti-VEGF drugs: aflibercept 65/1116 (5.8%), bevacizumab 9/32 (28.1%), conbercept 5/125 (4.0%), and ranibizumab (78/382 (20.4%). We believe this information is unreliable due to small sample size and differences in design and duration of the eight trials.

Quality of the evidence

For risk of bias judgements and reasons for downgrading, see Summary of findings 1, Summary of findings 2, Summary of findings 3, Summary of findings 4, Summary of findings 5, and Summary of findings 6. Within-study bias was not a concern, but imprecision and heterogeneity affected the certainty of evidence in NMAs of systemic safety. Inconsistency was an issue for the primary outcome and in the NMA on ATC arterial thromboembolic events, which contained few trials for drugs other than aflibercept and ranibizumab; we took inconsistency into account by downgrading the certainty of evidence when direct and indirect evidence significantly differed.

We had no concerns regarding transitivity and generalisability, or indirectness according to GRADE (Schünemann 2011), as the studies included a broad range of people with DMO similar to those in clinical practice.

Though we found robust evidence for aflibercept and ranibizumab at 24 months, only a few trials reported 24-month data for bevacizumab, and only indirect comparisons were possible for

brolucizumab; this made data interpretation more difficult. Data on faricimab are currently available only at 12 months.

Finally, 13 trials were industry-sponsored, which may have influenced their reporting.

Potential biases in the review process

The study selection process for this review was comprehensive and included hand-searching eligible studies and similar reviews. The small number of studies at 24 months may have reduced the reliability of estimates of effect and increased incoherence, inconsistency, and the influence of specific treatment choices on the results. We adopted a conservative approach to grading the certainty of the evidence (e.g. we downgraded for both imprecision and incoherence for ATC arterial thromboembolic events).

Agreements and disagreements with other studies or reviews

Although we did not systematically search for other reviews on anti-VEGF treatments for DMO, we found other NMAs comparing anti-VEGF drugs for DMO.

Wang 2022 included studies that compared aflibercept, ranibizumab, or conbercept with other monotherapies. They found that aflibercept improved BCVA compared to ranibizumab and bevacizumab at 12 months, but that there was insufficient evidence to identify which anti-VEGF had superior efficacy or safety at 24 months. Estimates were substantially comparable to those in our review.

Muston 2018 analysed data only at 12 months and found that aflibercept at 8-week intervals was superior to ranibizumab PRN for mean BCVA change, with effects similar to those reported in this review. Zhang 2021 analysed data only at six months, so their results are not comparable with ours.

AUTHORS' CONCLUSIONS

Implications for practice

In people with centre-involved diabetic macular oedema (DMO), aflibercept, bevacizumab, brolucizumab, and ranibizumab improved vision at 24 months. The differences among drugs are unlikely to be clinically significant, but the certainty of the evidence is variable, and the number of studies is small. Aflibercept and brolucizumab may reduce retinal thickening more than other drugs, with uncertain clinical significance. Only 12-month data were available for faricimab, which, together with aflibercept, may be more effective than ranibizumab and bevacizumab for improving vision at this shorter follow-up.

We found no differences in safety measures between antiangiogenic drugs that are currently available to treat DMO; however, our estimates were imprecise, inconsistent, or both imprecise and inconsistent for Antiplatelet Trialists Collaboration arterial thromboembolic events and all-cause mortality.

Implications for research

The evidence used to build the NMA was much sparser at 24 months compared to 12 months, because most trials became open-label after one year. There is a need to generate more evidence on the long-term (two years or longer) comparative effects of these anti-vascular endothelial growth factor (anti-VEGF) agents, including the switch between different drugs. Observational studies based on large electronic databases or registries should investigate systemic and ocular safety, particularly in people with diabetes or high cardiovascular risk.

ACKNOWLEDGEMENTS

For the 2023 update, Cochrane Eyes and Vision (CEV) created and executed the search strategies.

We would like to thank the following people.

- Winfried Amoaku (University of Nottingham and Nottingham University Hospitals NHS Trust) for content peer review
- Riaz Qureshi (University of Colorado Anschutz Medical Campus) for methods peer review
- Dr Catrarina Santos for providing data on KITE and KESTREL 2022
- Anupa Shah (Managing Editor for CEV) for assistance throughout the review process

Jennifer Evans (Co-ordinating Editor for CEV) and Professor Noemi Lois (Editor for CEV) signed off the update for publication.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Baker 2019

Study characteristics	
Methods	Multicentre RCT Only 1 eye per participant was included.
Participants	Countries: USA and Canada Number of people randomised: 702 (702 eyes) Mean age: 59 (SD 10) years Sex: 38% females Inclusion criteria: • Age ≥ 18 years • Diagnosis of diabetes mellitus (type 1 or type 2) Exclusion criteria: • History of chronic renal failure requiring dialysis or kidney transplant • A condition that, in the opinion of the investigator, would preclude participation in the study (e.g. unstable medical status, including bp, cardiovascular disease, and glycaemic control) • Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior to randomisation or plans to do so in the next 4 months • Participation in an investigational trial within 30 days of randomisation that involved treatment with any drug that has not received regulatory approval for the indication being studied • Known allergy to any component of the study drug • Systolic bp > 180 mmHg or diastolic bp > 110 mmHg • Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomisation • For women of childbearing potential: pregnancy, lactation, or intention to become pregnant within the next 24 months

Baker 2019 *(Continued)*

- Plan to move away from the area of the clinical centre to an area not covered by another clinical centre during the 24 months of the study

Interventions	Intervention 1: aflibercept 2 mg every 4 weeks (n = 236) Intervention 2: laser photocoagulation (n = 240) Comparator: observation (n = 236; excluded from review)
Outcomes	Primary outcome: • Decrease from baseline of ≥ 5 letters of visual acuity (≥ 1 line on an eye chart) at 2 years Secondary outcomes: • Mean change in visual acuity from baseline • Visual acuity of ≥ 84 letters (Snellen equivalent of 20/20) • Loss of ≥ 10 and ≥ 15 letters of visual acuity • Gain of ≥ 5 letters of visual acuity • Mean change in CST from baseline • Proportion of eyes with ≥ 10% CST change from baseline (considered a clinically important change) • Proportion of eyes with ≥ 10% decrease in CST from baseline with CST below thresholds for DMO defined by CST according to OCT machine and sex (Heidelberg Spectralis ≥ 305 µm in women and ≥ 320 µm in men; Zeiss Cirrus ≥ 290 µm in women and ≥ 305 µm in men) • 1 and 2 log-step worsening and improvement in CST • Mean change in OCT retinal volume from baseline. Exploratory outcomes: • Change in visual acuity over 2 years (area under the curve analysis of common visits at 8, 52, and 104 weeks) • ≥ 2-step worsening and improvement in diabetic retinopathy severity level on colour fundus photographs graded by a central reading centre • Change in low-contrast visual acuity • Proportion of eyes with leakage on fluorescein angiography • Development of vitreous haemorrhage Follow-up: 2 4 months
Notes	Dates participants enrolled: November 2013–September 2016 Funding: "Research supported by the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases (award numbers UG1EY014231 and UG1EY023207). Regeneron provided the study drug (aflibercept) and funds to the DRCR Retina Network to cover clinical site costs". Conflicts of interest: reported on page 1890 Trial registration: NCT01909791

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed on the study website using a permuted block design (random block sizes of 3 and 6) stratified by site and recent or planned CI-DME treatment in the nonstudy eye using computer-generated random numbers. Study eyes were randomly assigned 1:1:1 to 2.0 mg of aflibercept, focal/grid laser photocoagulation, or observation. In the laser photocoagulation

Baker 2019 *(Continued)*

		and observation groups, aflibercept injections were initiated during follow-up if visual acuity met prespecified worsening criteria."
Allocation concealment (selection bias)	Low risk	"Randomization was performed on the study website using a permuted block design (random block sizes of 3 and 6) stratified by site and recent or planned CI-DME treatment in the nonstudy eye using computer-generated random numbers. Study eyes were randomly assigned 1:1:1 to 2.0 mg of aflibercept, focal/grid laser photocoagulation, or observation. In the laser photocoagulation and observation groups, aflibercept injections were initiated during follow-up if visual acuity met prespecified worsening criteria."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Technicians were masked to treatment assignment at annual visits. Investigators and participants were not masked."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Technicians were masked to treatment assignment at annual visits. Investigators and participants were not masked."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Excluding deaths, the 2-year completion rate was 92% (625/681)."; "For eyes not completing the 2-year visit, multiple imputation was used to impute missing data in the primary analysis. There were 77 eyes that had values imputed: 21 in the aflibercept group; 28 in the laser photocoagulation group; and 28 in the observation group."
Selective reporting (reporting bias)	Low risk	Primary outcomes reported and consistent with our review.
Other bias	Low risk	No other bias identified. DCRNet trial.
Overall risk of bias	High risk	High risk of performance bias.

BOLT 2010

Study characteristics	
Methods	Parallel-group RCT 1 eye per person; if both eyes were eligible, eye with worse VA was selected
Participants	Country: UK Number of people randomised: 80 (80 eyes) Mean age: 64 (SD 8.8) years Sex: 31% females Inclusion criteria: • Age ≥ 18 years • Diabetes mellitus • BCVA in the study eye between 35 and 69 ETDRS letters at 4 m (Snellen equivalent 6/60 or 6/12) • Centre-involving CSMO with CRT on OCT of ≥ 270 µm • Media clarity, pupillary dilation, and subject co-operation sufficient for adequate fundus imaging • ≥ 1 prior macular laser therapy

BOLT 2010 *(Continued)*

- IOP < 30 mmHg
- Ability to return for regular study visits
- Fellow eye ≥ BCVA 3/60
- No anti-VEGF treatment in fellow eye within the past 3 months and no expectation of such treatment during the study

Exclusion criteria (for study eye):

- Macular ischaemia (FAZ ≥ 1000 µm GLD or severe perifoveal intercapillary loss on FFA)
- Macular oedema due to a cause other than DMO
- Pre-existing ocular condition that was likely to preclude VA improvement despite resolution of macular oedema
- Ocular condition that may affect macular oedema or alter VA during the course of the study, any treatment for DMO in the preceding 3 months
- PRP within 3 months of enrolment or anticipated 6 months thereafter
- PDR except for tufts of new vessels elsewhere < 1 disc in area with no vitreous haemorrhage
- HbA1c > 11.0%
- Medical history of chronic renal failure requiring dialysis or kidney transplantation
- BP > 170/100 mmHg
- Any thromboembolic event within 6 months
- Unstable angina, or evidence of active ischaemia on electrocardiogram at time of screening
- Major surgery within 28 days of randomisation or planned during the subsequent 12 months
- Participation in an investigational drug trial within 30 days of randomisation (or any time during the study)
- Systemic anti-VEGF or pro-VEGF treatment within 3 months of enrolment
- Pregnancy, breast feeding, or intention to become pregnant within the study period
- Intraocular surgery within 3 months of randomisation
- Aphakia
- Uncontrolled glaucoma
- Significant external ocular disease

Interventions	Intervention: bevacizumab 1.25 mg (6- and 12-week time points; 42 eyes) Comparator: macular laser therapy (38 eyes)
Outcomes	Primary outcome: • Mean change in BCVA (EDTRS letters measured at 4 m) Secondary outcomes: • Mean CRT and mean change in CRT • Gain and loss of 15 and 10 letters of ETDRS • Loss of 30 ETDRS letters • Retinopathy severity (ETDRS grading) • Safety • GLD of the FAZ • Area of the FAZ • Retinal nerve fibre layer thickness • Other ocular side effects • Systemic side effects, including thromboembolic events, BP, and ECG findings Follow-up: 12 and 24 months
Notes	Dates participants enrolled: May 2007–August 2009

BOLT 2010 *(Continued)*

	Funding: "Supported by grants from Moorfields Special Trustees and the National Institute for Health Research UK to the Biomedical Research Center for Ophthalmology based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology."
	Conflict of interest: none, see page 1086
	Trial registration: eudract.ema.europa.eu (Identifier: 2007-000847-89)

Risk of bias

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

Chatzirallis 2020

Study characteristics

Methods	Parallel group RCT 1 eye per person. In bilateral cases, 1 eye was randomly chosen
Participants	Country: Greece Number of people randomised: 112 (112 eyes) Mean age: 64.6 (SD 8.9) years

Chatzirallis 2020 *(Continued)*

	Sex: 45.5% females Inclusion criteria: • Type 2 diabetes mellitus • Central involved DMO • CRT ≥320 µm Exclusion criteria: • AMD • Retinal vein occlusion • Vitreomacular traction • Intraocular inflammation • Cornea disorders • Media opacities • Uncontrolled glaucoma • High myopia > 6D • Previous trauma • Intraocular surgery within the last 6 months • Ischaemic heart diseases or prior stroke • Reliable evaluation of EZ could not be performed due to poor image quality
Interventions	Intervention: ranibizumab 0.5 mg PRN (54 eyes) Comparator: aflibercept 2 mg PRN (58 eyes)
Outcomes	Primary outcome: • Change in BCVA and CRT at month 12 and 18 compared to baseline in each group, as well as the comparison between the 2 groups Secondary outcomes: • Prognostic factors for visual outcome Follow-up: 1, 2, 3, 6, 12 and 18 months
Notes	Dates participants enrolled: July 2016–June 2018 Funding: not reported Conflict of interest: none, see page 321 Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Eligible patients were randomized at baseline into two groups, using stratified randomization: i) Group I (n=54), patients receiving 0.5mg ranibizumab and ii) Group II (n=58), patients receiving aflibercept 2 mg."
Allocation concealment (selection bias)	Unclear risk	No data available.
Blinding of participants and personnel (performance bias)	Unclear risk	No data available.

Chatzirallis 2020 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported (no loss to follow-up).
Selective reporting (reporting bias)	Low risk	No protocol available but primary outcomes stated in the methods.
Other bias	Low risk	No other bias identified.
Overall risk of bias	Unclear risk	Most items are unclear or low risk.

DA VINCI 2011

Study characteristics	
Methods	Parallel group RCT 1 eye per person, unclear how eye selected
Participants	Countries: USA, Canada, Austria Number of people randomised: 221 (221 eyes) Mean age: 62 (SD 9.9) years Sex: 31% females Inclusion criteria: • Age ≥ 18 years • Diabetes mellitus • DMO involving the central macula, defined as CRT ≥ 250 µm in the central subfield based on Stratus OCT • BCVA letter score at 4 m of 73-24 (Snellen equivalent: 20/40–20/320) measured by the ETDRS protocol • For women of childbearing potential: use of reliable form of birth control during the study period Exclusion criteria (for study eye): • History of vitreoretinal surgery • PRP or macular laser photocoagulation or use of intraocular or periocular corticosteroids or anti-angiogenic drugs within 3 months of screening • Vision decrease due to causes other than DMO • PDR (unless regressed and currently inactive) • Ocular inflammation • Cataract or other intraocular surgery within 3 months of screening • Laser capsulotomy within 2 months of screening • Aphakia • Spherical equivalent of > −8 dioptres or any concurrent disease that would compromise VA or require medical or surgical intervention during the study period Exclusion criteria (for either eye):

DA VINCI 2011 *(Continued)*

- Active iris neovascularisation
- Vitreous haemorrhage
- Traction retinal detachment
- Preretinal fibrosis involving the macula
- Visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT
- History of idiopathic or autoimmune uveitis
- Structural damage to the centre of the macula that is likely to preclude improvement in VA after the resolution of macular oedema
- Uncontrolled glaucoma or previous filtration surgery
- Infectious blepharitis, keratitis, scleritis, or conjunctivitis
- Current treatment for serious systemic infection

Exclusion criteria (systemic):

- Uncontrolled diabetes mellitus
- Uncontrolled hypertension
- History of cerebral vascular accident or myocardial infarction within 6 months
- Renal failure requiring dialysis or renal transplant
- Pregnancy or lactation
- History of allergy to fluorescein or povidone iodine
- Only 1 functional eye
- Ocular condition in the fellow eye with a poorer prognosis than the study eye

Interventions	Intervention 1: VEGF Trap-Eye 0.5 mg every 4 weeks (44 eyes; excluded from this review) Intervention 2: VEGF Trap-Eye 2 mg every 4 weeks (44 eyes) Intervention 3: VEGF Trap-Eye 2 mg for 3 initial monthly doses and then every 8 weeks (42 eyes) Intervention 4: VEGF Trap-Eye 2 mg 3 initial monthly doses and then PRN (45 eyes) Comparator: laser photocoagulation (44 eyes)
Outcomes	Primary outcome: • Change in BCVA from baseline to week 24 (ETDRS chart at 4 m) Secondary outcomes: • Retinal thickness assessed by OCT • Safety and tolerability • Change in BCVA from baseline at week 52 • Proportion of eyes that gained at least 15 ETDRS letters in BCVA compared with baseline at weeks 24 and 52 • Change in CRT (central subfield on OCT) from baseline to weeks 24 and 52 • Number of focal laser treatments given Follow-up: 24 and 52 weeks
Notes	Dates participants enrolled: December 2008–June 2009 Funding: "Sponsored by Regeneron Pharmaceuticals, Inc., Tarrytown, New York." Conflicts of interest: see page 1826 Trial registration: NCT00789477

DA VINCI 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was handled by an IVRS vendor. The study statistician at REGENERON provided the randomization plan and reviewed and approved the dummy rand table. Study Data Management at REGENERON tested the randomization function extensively along with the Clinical team."
Allocation concealment (selection bias)	Low risk	"Sites called into IVRS to randomize patients and received the randomization number and drug kit assignment at the completion of the call. The site also received a confirmation email. Neither of these contained the actual randomization assignment. The randomization assignments were kept by the IVRS vendor in a secure, access-controlled database and were delivered to REGENERON by the IVRS vendor at the primary endpoint database lock."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To maintain participant masking, sham injections were performed on visits when an active dose was not given, and a sham laser was given to the VEGF Trap-Eye groups at week 1. Study drug and sham injections and laser and sham laser treatments were performed by an unmasked physician who had no other role in the study except to assess adverse events (AEs) immediately posttreatment. Sham injections followed the active treatment protocol with the exception that no needle was attached to the syringe, and the syringe hub was gently applied to the sclera to mimic an injection. Sham laser consisted of placing a contact lens on the study eye and positioning the patient in front of the laser machine for the approximate duration of a laser treatment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"A separate masked physician was assigned to assess adverse events (AEs) and retreatment and rescue criteria and to supervise the masked assessment of efficacy. Every effort was made to ensure that all other study site personnel remained masked to treatment assignment to facilitate an unbiased assessment of efficacy and safety."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Two randomised patients did not receive treatment and 19 patients discontinued the study after receiving at least 1 treatment for the following reasons: lost to follow-up (6 patients), withdrew consent (6 patients), death (3 patients), treatment failures (2 patients), AE (1 patient), and protocol deviation (1 patient). Discontinuations were evenly distributed among the 5 treatment groups." Comment: LOCF used.
Selective reporting (reporting bias)	Low risk	Primary outcome declared and consistent with our review.
Other bias	Low risk	No other bias identified.
Overall risk of bias	Low risk	Low risk of bias for most items.

DRCRnet 2010

Study characteristics	
Methods	Parallel group and within-person RCT

DRCRnet 2010 *(Continued)*

	1 or 2 study eyes per person. If both eyes eligible, right eye randomised first and then left eye assigned to "sham plus prompt laser group". If right eye already assigned to this group, then left eye assigned randomly to 1 of the other 3 groups.
Participants	Country: USA Number of people randomised: 691 (854 eyes) Mean age: 63 (SD 10) years Sex: 44% females Inclusion criteria (general): • Age ≥ 18 years • Diabetes Inclusion criteria (in study eye): • Best-corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS Visual Acuity Test) VA letter score 78-24 (20/32–20/320) • Definite retinal thickening due to DMO on clinical examination involving the centre of the macula assessed to be the main cause of visual loss • Retinal thickness measured on TD-OCT ≥ 250 microns in the central subfield Exclusion criteria: • Treatment for DMO within previous 4 months • PRP within the previous 4 months or anticipated need for PRP within the next 6 months • Major ocular surgery within the previous 4 months • History of open-angle glaucoma or steroid-induced IOP elevation that required IOP-lowering treatment • IOP ≥ 25 mmHg Exclusion criteria (participant): • Systolic BP 180 mmHg or diastolic BP 110 mmHg, myocardial infarction, other cardiac event requiring hospitalisation, cerebrovascular accident, transient ischaemic attack, or treatment for acute congestive heart failure within 4 months before randomisation
Interventions	Intervention 1: ranibizumab (0.5 mg) at baseline and 4 weeks. Laser photocoagulation performed 3 to 7 days after the injection (187 eyes) Intervention 2: ranibizumab (0.5 mg) and deferred laser at 24 weeks (188 eyes) Intervention 3: triamcinolone acetonide 4 mg at baseline and sham injection at 4 weeks. Laser photocoagulation performed 3 to 7 days after the injection (186 eyes; excluded from this review) Comparator: laser photocoagulation performed 3 to 7 days after the injection (186 eyes)
Outcomes	Primary outcome: • BCVA and safety at 12 months Secondary outcomes: • CRT Follow-up: every 4 weeks for 12 months. After 12 months, the trial was unmasked and follow-up continued to 3 years
Notes	Dates participants enrolled: March 2007–December 2008

DRCRnet 2010 *(Continued)*

Funding: "Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, and EY018817. The funding organization (National Institutes of Health) participated in oversight of the conduct of the study and review of the manuscript but not directly in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation of the manuscript. Genentech provided the ranibizumab for the study, and Allergan, Inc., provided the triamcinolone for the study. In addition, Genentech and Allergan, Inc., provided funds to the DRCR.net to defray the study's clinical site costs. As described in the DRCR.net Industry Collaboration Guidelines (available at www.drcr.net), the DRCR.net had complete control over the design of the protocol, the ownership of the data, and all editorial content of presentations and publications related to the protocol."

Conflict of interest: "A complete list of all DRCR.net investigator financial disclosures can be found at www.drcr.net"

Trial registration: NCT00445003

Risk of bias

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

DRCRnet 2015

Study characteristics	
Methods	Parallel-group RCT 1 eye per person
Participants	Country: USA Number of people (eyes) randomised: 660 (660 eyes) Mean age: 61 (SD 10) years Sex: 47% females Inclusion criteria: • Age ≥ 18 years • Diabetes Inclusion criteria (in study eye): • Best-corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS Visual Acuity Test) VA letter score 78–24 (20/32–20/320) • Definite retinal thickening due to DMO on clinical examination involving the centre of the macula assessed to be the main cause of visual loss • Retinal thickness measured on TD-OCT ≥ 250 microns in the central subfield Exclusion criteria: • Treatment for DMO within previous 4 months • PRP within previous 4 months or anticipated need for PRP within the next 6 months • Major ocular surgery within previous 4 months • History of open-angle glaucoma or steroid-induced IOP elevation that required IOP-lowering treatment • IOP ≥ 25 mmHg Exclusion criteria (participant): • Systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg • Myocardial infarction, other cardiac event requiring hospitalisation, cerebrovascular accident, transient ischaemic attack, or treatment for acute congestive heart failure within 4 months before randomisation
Interventions	Intervention 1: aflibercept 2.0 mg every 4 weeks (224 eyes) Intervention 2: bevacizumab 1.25 mg every 4 weeks (218 eyes) Intervention 3: Ranibizumab 0.3 mg every 4 weeks (218 eyes) Retreatment algorithm: "In general, an eye will continue to receive an injection if the eye is improving or worsening on OCT or visual acuity. The first time an eye has not improved or worsened, the eye will receive an injection. If the eye has not improved or worsened for at least 2 consecutive 4-week injections and OCT central subfield thickness is <250µ and visual acuity is 20/20 or better, the injection will be deferred." "In general, focal/grid laser will be initiated at or after the 24 week visit if 1) the OCT central subfield thickness is ≥250µ or there is edema that is threatening the fovea and 2) the eye has not improved on OCT or visual acuity from the last two consecutive injections."
Outcomes	Primary outcome:

DRCRnet 2015 *(Continued)*

- BCVA and safety at 12 months

Secondary outcomes:

- CRT

Follow-up: after 12 months, the trial was unmasked and follow-up continued to 3 years

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was computer-generated by the DRCR.net co-ordinating centre. "Randomization was performed at the DRCR.net study website, in permuted blocks and with stratification according to study site and visual acuity in the study eye."
Allocation concealment (selection bias)	Low risk	Randomisation assignments were obtained through the DRCR.net study website, therefore no study personnel had access to the list or to the next assignment before it was assigned. "Randomization was performed at the DRCR.net study website, in permuted blocks and with stratification according to study site and visual acuity in the study eye."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study participants, reading-center graders, and the medical monitor who reviewed all adverse events were unaware of the treatment group assignments. Visual-acuity and OCT technicians were unaware of the treatment-group assignments at the 1-year visit. Investigators and study coordinators were aware of the treatment group assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Visual-acuity and OCT technicians were unaware of the treatment-group assignments at the 1-year visit."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The 2-year visit was completed by 90%, 85%, and 88% of the 660 randomised participants (91%, 90%, and 91% excluding deaths) in the aflibercept, bevacizumab, and ranibizumab groups, respectively (Fig S1, available at www.aaojournal.org). There were no substantial differences identified in the baseline

DRCRnet 2015 *(Continued)*

		characteristics of those who completed and those who did not complete the 2-year visit (Table S1, available at www.aaojournal.org)."
Selective reporting (reporting bias)	Low risk	Outcomes match those in the Study Protocol available at publicfiles.jaeb.org/AntiVEGFCompPrtclv5_03_18_14.pdf.
Other bias	Low risk	No other source of bias identified.
Overall risk of bias	Low risk	Low risk of bias for most items.

Ekinci 2014

Study characteristics	
Methods	Parallel group RCT 1 eye per person, unclear how eye selected
Participants	Country: Turkey Number of people randomised: unclear; 100 (100 eyes) Mean age: 67 (SD 11.5) years Sex: 68% females Inclusion criteria: • Clinically significant DMO (CRT > 300 mm), as found through FFA and OCT evaluations and dilate fundus examination, after 1-year follow-up period Exclusion criteria: • Intravitreal treatment at another centre • Additional diseases that might have an effect on sight (age-related macular degeneration, uveitis, occlusion on the vein root or branch, hereditary macular diseases) • PRP, grid or focal laser photocoagulation application or intraocular surgery within 6 months • Acute ocular infection, stroke, myocardial infarction, uncontrolled hypertension, pregnancy, renal failure, and cataract formation during the follow-up period were excluded from the study
Interventions	Intervention: bevacizumab 1.25 mg monthly (50 eyes) Comparator: ranibizumab 0.5 mg monthly (50 eyes) Retreatment criteria: “After the third dose of bevacizumab/ranibizumab for patients in Groups 1 and 2, an additional three consecutive bevacizumab/ranibizumab injections were applied if the central macular thickness was greater than 275 µm or if there was an increase in BCVA of at least three letters compared with baseline. After the sixth intravitreal injection, if the central macular thickness was greater than 275 mm or if there was an increase in BCVA of at least two letters, additional intravitreal injections were performed until stable visual acuity was obtained."
Outcomes	Outcomes (primary outcome not specified): • BCVA using the Snellen chart • CRT assessed with OCT • IOP assessed with applanation tonometer Follow-up: monthly intervals after treatment to 12 months

Ekinci 2014 *(Continued)*

Notes	Dates participants enrolled: 2011–2014 Funding: not reported Conflict of interest: see page 142 Trial registration: not reported

Risk of bias

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

KITE and KESTREL 2022

Study characteristics

Methods	Phase III, randomised, double-masked RCT One eye per person
Participants	Countries: KESTREL study was conducted across 118 sites in the USA, Europe, Latin America, Japan, Australia, and Israel. KITE was conducted at 79 sites in Europe and Asia. Number of people randomised: 926 Mean age: 63 (SD 10) years Sex: 36 % females

KITE and KESTREL 2022 *(Continued)*

	Inclusion criteria: • Age ≥ 18 years • Type 1 or 2 diabetes mellitus • Glycosylated haemoglobin (HbA1c) ≤ 10% • BCVA score between 78 and 23 letters inclusive, using ETDRS visual acuity testing charts at an initial testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening and baseline • Central-involved DME with CSFT of ≥320 µm on spectral domain optical coherence tomography (SD-OCT) at screening Exclusion criteria: • Active proliferative diabetic retinopathy in the study eye • Intraocular or periocular corticosteroids in the 6 months prior to baseline or prior anti-VEGF therapy at any time in the study
Interventions	**KESTREL:** Intervention 1: brolucizumab 3 mg, 5 loading doses every 6 weeks, followed by 12- or 8-week dosing intervals (190 eyes; excluded from review) Intervention 2: brolucizumab 6 mg, 5 loading doses every 6 weeks, followed by 12- or 8-week dosing intervals (189 eyes) Comparator: aflibercept 2 mg, 5 monthly loading doses followed by fixed 8-week dosing interval (187 eyes) **KITE:** Intervention 1: brolucizumab 6 mg, 5 loading doses every 6 weeks, followed by 12- or 8-week dosing intervals (179 eyes) Comparator: aflibercept 2 mg, 5 monthly loading doses followed by fixed 8-week dosing interval (181 eyes)
Outcomes	Primary outcome: • Mean BCVA change from baseline at Week 52 Secondary outcomes: • BCVA change from baseline averaged over the period of Week 40 through Week 52 (to account for differences in timing of treatment) • q12w treatment status at Week 52 (brolucizumab only) • q12w treatment status at Week 52 among eyes with no q8w need during the first q12w cycle (to evaluate the predictive value of the first q12w cycle; brolucizumab only) • Change from baseline in BCVA (including BCVA gain/loss ≥ 15 letters) • Change from baseline in CSFT • Status of subretinal fluid (SRF)/intraretinal fluid (IRF) • Percentage of subjects with CSFT < 280 µm at Week 52 • Change in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score from baseline • Incidence of ocular and non-ocular adverse events Follow-up: 52 weeks
Notes	Dates participants enrolled: July 2018–November 2020 Funding: "Financial support was provided by Novartis (Basel, Switzerland). The sponsor or funding organization participated in the design of the study; management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript."

KITE and KESTREL 2022 *(Continued)*

Conflicts of interest: see page 171

Trial registration: KESTREL NCT03481634, KITE NCT03481660

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eyes were randomized 1:1:1 to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg (KESTREL) or 1:1 to brolucizumab 6 mg or aflibercept 2 mg (KITE). "At baseline, all eligible patients were randomized via Interactive Response Technology (IRT) to one of the treatment arms. A patient randomization list was produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. The randomization scheme for patients was reviewed and approved by a member of the Randomization Group."
Allocation concealment (selection bias)	Low risk	"The randomization numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from patients and investigator staff."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The trials were double-masked. Subjects, investigators and site personnel were masked from treatment until the end of the study, except in the case of emergencies. The unmasked injecting investigator and site personnel did not perform BCVA, complete pre-injection ophthalmic examinations, DAAs or administer the Visual Function Questionnaire 25 (VFQ-25) assessment. To maintain masking, aflibercept-treated eyes underwent the same DAAs as brolucizumab-treated eyes and when study treatments were administered at different time points, sham injections were performed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An independent, masked review of fundus photography, fluorescein angiography and OCT images for patients enrolled in the study was performed at a CRC. DAA and disease stability assessment were performed for both treatment arms by the masked investigator at the protocol specified visits."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported in supplementary material with reasons for loss to follow-up. Discontinued the study prior to or at week 52: 18 (9.5%) in brolucizumab 6 mg, 15 (8-0%) in aflibercept 2 mg
Selective reporting (reporting bias)	Low risk	Study protocols available: clinicaltrials.gov/ct2/show/NCT03481634 and clinicaltrials.gov/ct2/show/NCT03481660.
Other bias	Low risk	No other bias identified.
Overall risk of bias	Low risk	All items low risk.

Li 2019 (REFINE)

Study characteristics

Methods	Phase III, 12-month, multicentre laser-controlled study The eye with the worse VA at screening or baseline visits was selected as the study eye

Li 2019 (REFINE) *(Continued)*

Participants	Country: China Number of people randomised: 384 Mean age: 58.7 (SD 8.7) years Sex: 53.6 females Inclusion criteria: • Written informed consent • Male or female Chinese patients aged ≥18 years • Type 1 or 2 diabetes mellitus (according to American Diabetes Association or WHO guidelines) and HbA1c ≤ 10.0% at Screening (Visit 1) • Any medication for the management of diabetes were required to be stable within 3 months prior to Visit 1, and expected to remain stable during the course of the study. Inclusion criteria for the study eye: • Visual impairment due to focal or diffuse DME in 1 or both eyes • BCVA score at both screening and baseline between 78 and 39 letters as measured by ETDRS-like charts at 4 meters, inclusively (approximately 20/32 to 20/160 Snellen equivalent) • If both eyes were eligible, the one with the worse VA at screening/baseline visits was selected as the study eye, unless the eye with the better VA was deemed to be more appropriate for study by the investigator based on medical reasons. Only the study eye was treated with intravitreal injection or laser, depending on treatment assignment. The other eye was defined as the fellow eye and only standard of care was allowed. Exclusion criteria: • Inability to comply with study or follow-up procedures • Pregnancy or lactation • Women of child-bearing potential not using effective methods of contraception during dosing of study treatment
Interventions	Intervention: ranibizumab 0.5 mg PRN (307 eyes) Comparator: laser photocoagulation as needed (77 eyes)
Outcomes	Primary outcome: • Mean average change in BCVA from Month 1 to Month 12 compared with baseline Secondary outcomes: • Mean change in BCVA from baseline to M12 • Mean change in CSFT from baseline to M1 • Proportion of patients with BCVA gain of ≥ 10 and ≥ 15 letters and loss of <10 and <15 letters from baseline at M12 • Proportion of patients with BCVA ≥ 73 letters (approximate20/40 Snellen chart equivalent) at Month 12 • Treatment exposure, number of retreatments, and retreatment patterns • Safety as assessed by ocular and non-ocular adverse events and serious adverse events over 12 months Follow-up: 12 months
Notes	Dates participants enrolled: November 2014–January 2017 Funding: no funding Conflict of interest: see page 540

Li 2019 (REFINE) *(Continued)*

Trial registration: NCT02259088

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomization list was produced by the interactive response technology (IRT) provider by using a validated system that automated the random assignment of patient numbers to randomization numbers.
Allocation concealment (selection bias)	Low risk	A randomisation list was produced by the interactive response technology (IRT) provider by using a validated system that automated the random assignment of patient numbers to randomisation numbers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, persons performing the assessments, Novartis clinical team and data analysts remained masked to the identity of the treatment assignment from the time of randomisation until database lock after study completion. Randomisation data were kept strictly confidential until the time of unmasking, and were not accessible by anyone else involved in the study with the exception of the treating investigator, the unmasked monitor and the unmasked data manager.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	VA assessor masked to the treatment assignment; evaluating investigator masked to the treatment assignment; treating investigator unmasked to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up numbers are low: RANI group 2/307, laser 0/77.
Selective reporting (reporting bias)	Low risk	Primary outcome declared and consistent with our review.
Other bias	Low risk	No other bias identified. Chinese study.
Overall risk of bias	Low risk	Low risk for all items.

Liu 2022

Study characteristics

Methods	Multicentre, randomised, double-masked, double-sham, parallel controlled, phase III trial (Sailing Study), followed by a 12-month open-label extension study. Only 1 eye was enrolled in the study.
Participants	Country: China Number of people randomised: 251 (251 eyes) Mean age: 58. 8 (SD 8.7) years Sex: 48.6% females Inclusion criteria: • Age >18 years • Type 1 or 2 diabetes mellitus

Liu 2022 *(Continued)*

- Haemoglobin A1c (HbA1c) < 10%
- DME involving the central fovea
- ETDRS BCVA between 73 and 24 letters (Snellen equivalent of 20/40–20/320)
- CRT >300 µm according to OCT imaging
- Clear ocular media and adequate pupil dilation for examination and imaging
- ETDRS BCVA of non-target eye ≥ 24 letters (equivalent to 20/320 of the Snellen vision)

Exclusion criteria:

- Active eye infection in either eye
- Any ophthalmic conditions leading to macular oedema or alterations in vision other than diabetic retinopathy
- Panretinal photocoagulation within 6 months prior to screening or local/grid retinal photocoagulation within 3 months prior to screening
- Treatment with anti-VEGF drugs (e.g. aflibercept, pegaptanib sodium, ranibizumab, bevacizumab) within 6 months prior to screening
- Any type of intraocular surgery (e.g. cataract surgery, yttrium aluminium garnet (YAG) posterior capsulotomy) within 3 months prior to screening
- Uncontrolled hypertension
- Stroke, transient ischaemic attack, myocardial infarction, or acute congestive heart failure within 6 months prior to screening.

Interventions	Intervention: sham laser and conbercept (0.5 mg, Chengdu Kanghong Biotech Co.) on day 0, followed by PRN conbercept treatments and sham laser treatments during the monthly follow-up per predefined criteria (126 eyes) Comparator: laser/sham injection group, received modified laser and then a sham intravitreal injection on day 0. Starting at month 3, the laser group received PRN sham injections and active laser treatments during the monthly follow-up per predefined criteria (125 eyes)
Outcomes	Primary outcome: • Mean change in BCVA from baseline to month 12 Secondary outcomes: • Change in CRT from baseline to month 12 and safety. Safety assessments included both ocular and non-ocular adverse events and serious adverse events. • Other endpoints included changes in CRT, total macular volume (TMV), fluorescein angiographic leakage area, BCVA, and the total score of 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) from baseline to month 12, as well as the proportion of ≤ 5, 10 and 15 letters vision gain or loss from baseline to months 6 and 12. Primary outcome of the extension study: • Mean change in BCVA from month 12 to 24 Secondary outcomes: • Long-term safety of conbercept • Change in BCVA from month 12 to 24 • Change in CRT from month 12 to 24 • Change in TMV from month 12 to 24 • Change in leakage area from month 12 to 24 and the number of injections in the extension study
Notes	Dates participants enrolled: August 2014–December 2015 Funding: "The study was supported by National Key R&D Program of China (2016YFC0904800 and 2019YFC0840607) and Chengdu Kanghong Biotechnology Inc. (number 36 ShuxiRoad, JinniuDistrict, Chengdu, China)."

Liu 2022 *(Continued)*

	Conflict of interest: see page 7
	Trial registration: NCT02194634

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	During the Sailing Study, the eligible patients were randomly assigned in a 1:1 ratio to receive either sham laser followed by conbercept (sham/conbercept group) or laser followed by a sham injection (laser/sham group) according to the interactive web response system.
Allocation concealment (selection bias)	Unclear risk	No data available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking was performed for the patients, masked investigators and statisticians. Treatments were performed by unmasked investigators who were not involved in any other study work.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking was performed for the participants, masked investigators and statisticians. Treatments were performed by unmasked investigators who were not involved in any other study work.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up: 3 in sham laser/conbercept group and 1 in laser/sham injection group Discontinued intervention: 9 in sham laser/conbercept group and 16 in laser/sham injection group
Selective reporting (reporting bias)	Low risk	Primary outcome declared and consistent with our review.
Other bias	Low risk	No additional bias.
Overall risk of bias	Unclear risk	Most of the items are low risk but two are unclear risk.

LUCIDATE 2014

Study characteristics

Methods	Parallel group RCT 1 eye per person, unclear how eye selected
Participants	Country: UK Number of people randomised: 33 (33 eyes) Median age: 66 (range 58.4 to 74.6) years Sex: 36% females Inclusion criteria: • Adult participants with type 1 or 2 diabetes

LUCIDATE 2014 *(Continued)*

- BCVA of 55–79 ETDRS letters (Snellen equivalent, 20/30-20/80) resulting from centre-involving DMO, with Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) central subfield thickness of 300 mm or more in the study eye

Exclusion criteria:

- Uncontrolled glaucoma
- Aphakia
- Cataract precluding fundus photography
- External ocular infections
- Previous anti-VEGF or laser treatment in the preceding 3 months in both eyes
- Angiographic evidence of macular ischaemia defined as FAZ GLD > 1000 mm or severe perifoveal capillary loss
- Other causes for macular oedema, for example after cataract surgery
- Other causes of visual loss in the study eye
- Other diseases that may affect the course of macular oedema in the study eye
- PDR, either active or treated within the previous 3 months
- HbA1c > 11.0%
- Past medical history of chronic renal failure requiring either dialysis or kidney transplantation
- BP > 170/100 mmHg
- Atherothrombotic event within 6 months before randomisation, including myocardial infarction, acute congestive heart failure, or other cardiac event
- Stroke or transient ischaemic attack
- Planned surgery
- Pregnancy or breastfeeding

Interventions	Intervention: • Ranibizumab (0.5 mg) every 4 weeks (22 eyes) Comparator: • Laser photocoagulation every 12 weeks (11 eyes)
Outcomes	Outcomes: • Change in ETDRS BCVA • Retinal sensitivity • Colour vision • Electrophysiologic parameters • Macular thickness and volume • Change in ETDRS severity grade of diabetic retinopathy from fundus photographs Follow-up: 48 weeks
Notes	Dates participants enrolled: November 2010–July 2011 Funding: Moorfields Eye Hospital NHS Foundation Trust Conflict of interest: see page 970 Trial registration: NCT01223612

Risk of bias

Bias	Authors' judgement	Support for judgement

LUCIDATE 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	"The randomization list was created using permuted blocks of varying sizes, held by the trial statistician and concealed from the researcher who enrolled, assessed, and allocated treatment to participants."
Allocation concealment (selection bias)	Low risk	"The randomization list was created using permuted blocks of varying sizes, held by the trial statistician and concealed from the researcher who enrolled, assessed, and allocated treatment to participants."
Blinding of participants and personnel (performance bias) All outcomes	High risk	No sham procedure.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The microperimetry and electrophysiologic assessors were masked to the patient treatment arm. Evaluation of OCT scans, fundus photographs and fluorescein angiograms was performed by masked Reading Centre graders. The protocol states that the visual acuity assessors were also masked to the patient treatment arm but due to a protocol deviation they had access to the source notes and were potentially unmasked."
Incomplete outcome data (attrition bias) All outcomes	Low risk	22/25 (88%) of anti-VEGF group compared to 11/12 (92%) laser group followed up.
Selective reporting (reporting bias)	Unclear risk	Unclear risk.
Other bias	Low risk	No other source of bias identified.
Overall risk of bias	High risk	High or unclear risk of bias for nearly half the items.

Nepomuceno 2013

Study characteristics	
Methods	Parallel group RCT and within-person study People randomised to treatment but 2 eyes sometimes included. If 2 eyes included, fellow eye randomised to other treatment.
Participants	Country: Brazil Number of people randomised: 48 (63 eyes) Mean age: 64 (SD 8.9) years Sex: 55% females (based on eyes included in analyses) Inclusion criteria: • Centre-involved DMO defined as a central subfield thickness > 300 mm on Spectral Domain-OCT, despite ≥ 1 session of macular laser photocoagulation performed ≥ 3 months previously • BCVA ETDRS measurement between 0.3 logMAR (Snellen equivalent: 20/40) and 1.6 logMAR (Snellen equivalent: 20/800) Exclusion criteria: • Vitreomacular traction on SD-OCT

Nepomuceno 2013 *(Continued)*

- PDR needing PRP or anticipated to need PRP in the next 12 months
- Macular capillary dropout on fluorescein angiography
- History of glaucoma or ocular hypertension (defined as IOP > 22 mmHg)
- An ocular condition (other than diabetes) that, in the opinion of the investigator, might affect macular oedema or alter VA during the course of the study (e.g. retinal vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma)
- Systemic corticosteroid therapy
- Any condition that, in the opinion of the investigator, might preclude follow-up throughout the study period

Interventions	Intervention: bevacizumab (1.5 mg) monthly (32 eyes) Comparator: ranibizumab (0.5 mg) monthly (28 eyes) "Retreatment with the originally assigned treatment was performed monthly if central subfield thickness was greater than 275 mm." "If, after 3 consecutive injections, there was not a reduction in central subfield thickness of at least 10% or an increase in BCVA of at least 5 letters compared with baseline, the patient could, at the discretion of the treating ophthalmologist, receive focal/grid laser photocoagulation or continue to receive the same intravitreal medication for an additional 3 consecutive visits."
Outcomes	Outcomes reported in publication (primary outcome not specified): • BCVA (standardised ETDRS refraction protocol) • Retinal thickness (using OCT) Following outcomes listed on ClinicalTrials.gov: • Primary outcome measures: CSFT change (time frame: monthly from baseline to week 48; not designated as a safety issue); CSFT measured with SD-OCT • Secondary outcome measures: BCVA change (time frame: monthly from baseline to week 48; not designated as a safety issue); BCVA using ETDRS charts
Notes	Dates participants enrolled: July 2010–August 2011 Funding: "Fundacao de Amparo a` Pesquisa do Estado de Sao Paulo (FAPESP), grant number 2010/013368; and Fundacao Apoioao Ensino, Pesquisa e Assiste^ncia (FAEPA) do Hospital das Clınicas da Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paulo." Conflict of interest: see page 509 Trial registration: NCT01487629

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"... received the randomised treatment according to a computer-generated sequence."
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Examiners (E.T., F.P.P.A., R.P.) were masked regarding which treatment drug was used for each patient. Throughout the study, a single masked, certified examiner performed BCVA measurements prior to any other study procedure. Patients, OCT technicians, and fundus photographers were also masked to treatment group."

Nepomuceno 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Examiners (E.T., F.P.P.A., R.P.) were masked regarding which treatment drug was used for each patient. Throughout the study, a single masked, certified examiner performed BCVA measurements prior to any other study procedure. Patients, OCT technicians, and fundus photographers were also masked to treatment group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The 3 patients excluded from the outcomes analyses consisted of 1 patient in the IV ranibizumab group who developed Staphylococcus aureus endophthalmitis after the first injection (this patient chose to exit the study and he did not complete any further study visits); 1 patient in the IV bevacizumab group who developed advanced posterior subcapsular cataract, which precluded adequate SDOCT images, after the ninth follow-up visit; and 1 patient from the IV bevacizumab group who missed 3 consecutive follow-up visits."
Selective reporting (reporting bias)	Low risk	Both outcomes listed on trial registration reported.
Other bias	Unclear risk	15/48 participants with both eyes in analyses.
Overall risk of bias	Unclear risk	Low risk of bias for most items, but unclear for two items

READ2 2009

Study characteristics	
Methods	Parallel-group RCT 1 eye per person; if both eyes were eligible, the eye with the greater centre subfield thickness was entered.
Participants	Country: USA Number of people randomised: 126 (126 eyes) Mean age: 62 years Sex: 59% females Inclusion criteria: • Age ≥ 18 years • Diabetes • DMO • Reduction in VA between 20/40-20/320 • Centre subfield thickness measured by OCT ≥ 250 µm • HbA1c ≥ 6% within 12 months before randomisation • No potential contributing causes to reduced VA other than DMO • Reasonable expectation that scatter laser photocoagulation would not be required for the next 6 months Exclusion criteria: • Received focal/grid laser treatment within 3 months • Intraocular injection of steroid within 3 months • Intraocular injection of a VEGF antagonist within 2 months
Interventions	Intervention 1: ranibizumab 0.5 mg, at baseline and months 1, 3, and 5 (42 eyes)

READ2 2009 *(Continued)*

	Intervention 2: ranibizumab 0.5 mg plus laser photocoagulation, at baseline and month 3 (42 eyes) Comparator: laser photocoagulation at baseline and month 3 if needed (42 eyes) Starting at month 6, if retreatment criteria were met, all participants could be treated with ranibizumab.
Outcomes	Primary outcome: • Change in BCVA between baseline and follow-up Secondary outcomes: • Change in BCVA between baseline and month 24 • ≥ 3 lines' or ≥ 2 lines' improvement at month 24 • Change in foveal thickness between baseline and month 24 • Elimination of 90% or 50% excess foveal thickness Follow-up: 6 months and 24 months.
Notes	Dates participants enrolled: not reported Funding: "Sponsored by the Juvenile Diabetes Research Foundation and Genentech, Inc." Conflict of interest: see page 2181 Trial registration: NCT00407381

Risk of bias

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

RELATION 2012

Study characteristics	
Methods	Parallel-group RCT 1 eye per person, eye with worse VA selected
Participants	Country: Germany Number of people randomised: 128 (128 eyes) Mean age: 64 (SD 9.7) years Sex: 37% females Inclusion criteria: • Age ≥ 18 years • Diabetes • Visual impairment (BCVA between 78 and 39 letters, testing distance 4 m) due to focal or diffuse DMO in 1 or both eyes, eligible for laser treatment in the opinion of the investigator Exclusion criteria: • Other eye diseases and conditions that might affect VA • Other eye and systemic treatments • Pregnancy or the possibility of being pregnant • Inability to comply with follow-up
Interventions	Intervention 1: ranibizumab (0.5 mg) plus laser. "Laser treatment applied at baseline and reapplied if needed at intervals no shorter than 3 months from the last treatment. Ranibizumab intravitreal injection given at baseline, 30, 60 and 90 days and if needed, reapplied at intervals no shorter than 28 days from the last treatment" (85 eyes). Comparator: Laser plus sham injection. "Laser treatment applied at baseline and reapplied if needed at intervals no shorter than 3 months from the last treatment. Sham intravitreal injection given at baseline, at 30, 60 and 90 days and if needed, reapplied at intervals no shorter than 28 days from the last treatment" (43 eyes).
Outcomes	Primary outcome: • Mean change in BCVA from baseline to month 12 (ETDRS chart, 4 m) Secondary outcomes: • Adverse events
Notes	Dates participants enrolled: July 2010–May 2011, terminated early Funding: Novartis Conflict of interest: Novartis Trial registration: NCT01131585

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

RELATION 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as double-masked, but no details given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as double-masked, but no details given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: combined laser and ranibizumab: 7/85 (7%); laser 11/43 (26%).
Selective reporting (reporting bias)	High risk	Only mean change of VA and harms reported.
Other bias	Low risk	Study terminated early due to European Medicine Agency approval of ranibizumab for DMO, but this is independent of effect estimates.
Overall risk of bias	High risk	Unclear risk of bias for most items, but high for two items

RESOLVE 2010

Study characteristics	
Methods	Parallel group RCT 1 eye per person, eye with worse VA selected
Participants	Countries: unclear; investigators from Australia, Denmark, Austria, France, Germany, Italy, Korea, Portugal, Spain, Switzerland, UK Number of people randomised: 151 (151 eyes) Mean age: 64 (range 32 to 85) years Sex: 46% females Inclusion criteria: • Age ≥ 18 years • Diabetes mellitus • Stable HbA1c levels (≤ 12%) • DMO with centre involvement in 1 or both eyes • CRT ≥ 300 µm (Stratus Zeiss Meditec) • BCVA score between 73 and 39 letters inclusively, using ETDRS charts at a testing distance of 4 m (approximate Snellen equivalent of 20/40-20/160) • Decreased vision attributed to foveal thickening from DMO, that was not explained by any other causes in the opinion of the investigator

RESOLVE 2010 *(Continued)*

- Laser photocoagulation, additional or first treatment, could be withheld for at least 3 months after randomisation

Exclusion criteria:

- PRP (focal peripheral laser photocoagulation) performed within 6 months prior to study entry. Grid/central laser photocoagulation was excluded except for participants with only mild laser burns at least 1000 µm from the centre of the fovea performed more than 6 months before the trial commenced
- PDR in the study eye, with the exception of tufts of neovascularization < 1 disc area with no vitreous haemorrhage. As well as those with area of retinal ischaemia ≥ 500 µm and located ≤ 50 µm from the centre of the macula of the study eye as assessed by fluorescein angiography at visit 1 and confirmed by a central reading centre
- Unstable medical conditions such as poor glycaemic or BP control
- Hypertension with change in antihypertensive treatment within 2 months preceding start of trial (unless BP maintained <160/100 mmHg for ≥ 1 month prior to the first day of the trial by antihypertensive treatment)
- History of treatment with systemic corticosteroids within 4 months prior to randomisation; or topical, rectal or inhaled corticosteroids in current use more than 2 times per week
- Previous participation in a study on antiangiogenic drugs
- Ocular disorders and history of any condition that might confound the interpretation of study results or might render participant at high risk for treatment complications
- Ocular inflammation in either eye or history of cataract surgery in the study eye within 6 months before study initiation
- Pre-menopausal women not using adequate contraception and pregnant or nursing women

Interventions	Intervention: ranibizumab 0.3 mg or 0.5 mg, monthly. Rescue laser treatment permitted after 3 consecutive monthly injections (102 eyes) Comparator: sham injection, monthly. Rescue laser treatment permitted after 3 consecutive monthly injections (49 eyes)
Outcomes	Primary outcome • Mean change in BCVA from baseline at 1 month and 12 months Secondary outcomes • Mean change in BCVA and CRT from baseline at 12 months • Categorised BCVA outcome • Safety
Notes	Dates participants enrolled: not reported Funding: Novartis Conflict of interest: see page 2404 Trial registration: NCT00284050

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomised 1:1:1 to either ranibizumab (0.3 mg or 0.5 mg) or sham treatment according to a computer-generated randomised allocation schedule."
Allocation concealment (selection bias)	Low risk	"...allocation schedule (kept at a secure site and accessible only to the injecting physician"

RESOLVE 2010 *(Continued)*

		"Based on the patient strata the injecting physician would take the treatment allocation card and tear-off the cover and follow instructions to choose vial from the box as indicated (3 boxes, randomisation block size 3). The randomisation data were kept strictly confidential until database lock; not accessible to anyone involved in the study with the exception of injecting physician(s) and drug accountability monitor."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham injection for masking participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Masking was maintained through appointment of a minimum of 2 investigators at each study site; unmasked injecting physician and a masked evaluating physician (roles could not be switched)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants who completed the trial at 1 year: 92/102 ranibizumab and 40/49 sham. Reasons for dropouts were balanced. ITT analysis with LOCF.
Selective reporting (reporting bias)	Low risk	We could not find a protocol, but primary outcomes were stated in the methods and were those routinely used in the field.
Other bias	Low risk	No other source of bias identified.
Overall risk of bias	Low risk	Low risk of bias for most items.

RESPOND 2013

Study characteristics	
Methods	Parallel-group RCT 1 eye per person, unclear how eye selected
Participants	Country: Canada Number of people randomised: 239 (239 eyes) Mean age: 62 (SD 9.8) years Sex: 40% females Inclusion criteria: • Age ≥ 18 years • Stable type 1 or type 2 diabetes with HbA1c ≤ 10% • Visual impairment due to focal or diffuse DMO in 1 or both eyes, eligible for laser treatment in the opinion of the investigator Exclusion criteria: • Active conditions in study eye that could prevent improvement in VA • Active eye infection or inflammation • History of stroke, renal failure, or active hypertension

RESPOND 2013 *(Continued)*

Interventions	Intervention 1: ranibizumab 0.5 mg, administered as 3 monthly injections, then 10 months PRN injections given/withheld based on DME stability criteria (80 eyes). Intervention 2: ranibizumab (0.5 mg) plus laser. Ranibizumab administered as 3 monthly injections, then 10 months PRN injections given/withheld based on DME stability criteria. Laser administered on Day 1, and subsequent laser treatments could be administered if needed, according to ETDRS guidelines (78 eyes). Comparator: *l*aser, administered on Day 1, and subsequent laser treatments could be administered if needed, according to ETDRS guidelines (81 eyes).
Outcomes	Primary outcome: • Mean change from baseline in BCVA at 12 months Secondary outcomes: • Number of patients with visual acuity > 73 letters (time frame: 3, 6, 9, and 12 months) • Number of patients with improvement in BCVA (time frame: 3, 6, 9, and 12 months) • Time course of BCVA changes (time frame: 3, 6, 9, and 12 months) • Change in CRT and other anatomical changes (time frame: 3, 6, 9, and 12 months) • 15-letter (3-line) gain in BCVA (time frame: 3, 6, 9, and 12 months)
Notes	Dates participants enrolled: July 2010–March 2013 Funding: Novartis Conflict of interest: not reported (the study was obtained as a Novartis public report) Trial registration: NCT01135914

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was stratified by centre and followed a permutated block size of 6."
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked study (described as open-label).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked study (described as open-label).
Incomplete outcome data (attrition bias) All outcomes	High risk	More missing data in the laser arm (27%), mainly due to lack of efficacy, compared to the 2 ranibizumab arms (5% to 6%).
Selective reporting (reporting bias)	Low risk	VA, OCT data and harms adequately reported (only loss of vision not reported).
Other bias	Low risk	No other bias identified.

RESPOND 2013 *(Continued)*

Overall risk of bias	High risk	High risk of bias for most items.

RESTORE 2011

Study characteristics	
Methods	Parallel-group RCT 1 eye per person, eye with worse VA selected unless other eye more suitable for treatment
Participants	Countries: Europe, Australia, Canada, Turkey Number of people randomised: 345 (345 eyes) Mean age: 63 (SD 8.8) years Sex: 42% females Inclusion criteria: • Age ≥ 18 years • Diabetes mellitus (according to the American Diabetes Association or WHO guidelines) • HbA1c ≤ 10% • Visual impairment due to DMO • Stable medication for the management of diabetes within 3 months before randomisation and expected to remain stable during the study • Visual impairment due to focal or diffuse DMO in 1 or both eyes, eligible for laser treatment in the opinion of the investigator • BCVA letter score between 78 and 39, both inclusive, based on ETDRS-like VA testing charts administered at a starting distance of 4 m (approximate Snellen equivalent 20/32-20/160) • Decreased vision due to DMO and not other causes, in the investigator's opinion (at visit 1) Exclusion criteria: • Concomitant conditions in the study eye that could prevent the improvement in VA on the study treatment in the investigator's opinion • Active intraocular inflammation or infection in either eye • Uncontrolled glaucoma in either eye (e.g. IOP > 24 mmHg on medication, or according to the investigator's judgement) • Laser PRP (within 6 months) or focal/grid laser photocoagulation (within 3 months) before study entry • Treatment with antiangiogenic drugs in the study eye within 3 months before randomisation • History of stroke • Systolic BP > 160 mmHg or diastolic BP > 100 mmHg • Untreated hypertension • Change in antihypertensive treatment within 3 months preceding baseline
Interventions	Intervention 1: ranibizumab (0.5 mg) plus laser. Ranibizumab given monthly, laser treatment given on day 1 and intervals of 3 months as necessary (118 eyes) Intervention 2: ranibizumab (0.5 mg) and sham laser. Ranibizumab given monthly, laser treatment given on day 1 and intervals of 3 months as necessary (116 eyes) Comparator: laser treatment plus sham injections. Laser treatment given on day 1 and intervals of 3 months as necessary, monthly sham injections given for 3 consecutive months (111 eyes)
Outcomes	Primary outcome:

RESTORE 2011 *(Continued)*

- Mean average change in BCVA from baseline over 12 months

Secondary outcomes:

- VA improvement
- BCVA letter score 73 (20/40 Snellen equivalent) at month 12
- Mean change in BCVA letter score
- Mean change in central retinal (subfield) thickness
- Patient-reported outcomes
- Safety

Follow-up: 12 months

Notes	Dates participants enrolled: not reported Funding: Novartis Conflict of interest: study authors reported financial support of Novartis or were Novartis employees Trial registration: NCT00906464

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization list was produced by, or under the responsibility of, Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio."
Allocation concealment (selection bias)	Low risk	Central randomisation using an electronic Case Report Form after each participant was included by study investigators.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The masked BCVA assessor evaluated the visual acuity of the patient and provided the results to the evaluating investigator who also was masked to the treatment assignment. The evaluating investigator was responsible for all other aspects of the study, excluding the injection procedures. Based on all the performed clinical assessments and the visual acuity (VA) results received from the BCVA assessor, the evaluating investigator had to decide on the treatment requirements for the patient each month and communicated this decision to the treating investigator. The treating investigator was unmasked to the treatment assignment and performed all injections or laser treatment as well as the corresponding sham treatments. He/she was required not be involved in any other aspect of the study and not to divulge the patient's treatment assignment to anyone. Once the designated roles were determined, the roles could not be switched at any time during the conduct of the study. Every effort was made to limit the number of unmasked study personnel to ensure the integrity of this masked study. An independent review and standardized grading of fundus photography, fluorescein angiography, and optical coherence tomography (OCT) images for the patients screened and enrolled in the study was performed at a central reading center that did not have access to any other data of the patients."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The masked BCVA assessor evaluated the visual acuity of the patient and provided the results to the evaluating investigator who also was masked to the treatment assignment. The evaluating investigator was responsible for all other aspects of the study, excluding the injection procedures. Based on all the performed clinical assessments and the visual acuity (VA) results received from the BCVA assessor, the evaluating investigator had to decide on the treatment requirements for the patient each month and communicated this decision to

RESTORE 2011 *(Continued)*

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

RETAIN 2016

Study characteristics	
Methods	24-month single-masked study 1 eye was treated as the study eye. If both eyes were eligible, the eye with worse VA was selected as the study eye.
Participants	Countries: Europe Number of people randomised: 372 Mean age: 63.7 (SD 9.5) years Sex: 37.6% females Inclusion criteria: • Age > 18 years • Type 1 or 2 diabetes mellitus (defined per American Diabetes Association or WHO guidelines) with glycosylated haemoglobin (HbA1c) values ≤ 12% at screening • ETDRS BCVA letter score ranging from 78 to 39, inclusive (approximate Snellen equivalent of 20/32–20/160) • Visual impairment due to focal or diffuse DMO of any extent or thickness in 1 or both eyes, eligible for laser treatment in the opinion of the investigator Exclusion criteria: • Within 0.5 disc diameter of the centre of the macula in the study eye likely to preclude improvement in VA following the resolution of macular oedema • BCVA >73 letters and central subfield thickness (CSFT) < 300 µm in the study eye

RETAIN 2016 *(Continued)*

- Any intraocular surgery in the study eye within 3 months prior to randomisation; history of vitrectomy in study eye regardless of time prior to randomisation
- Panretinal and focal/grid laser photocoagulation in the study eye within 6 and 3 months prior to randomisation
- Treatment with antiangiogenic drugs in either eye (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, vascular endothelial growth factor (VEGF)-Trap) within 3 months prior to randomisation
- Active intraocular inflammation in either eye (grade trace or above); any active infection in either eye (conjunctivitis, keratitis, scleritis, uveitis or endophthalmitis); or uncontrolled glaucoma in either eye (IOP > 24 mm Hg on medications or per investigator's judgement).

Interventions	Intervention 1: ranibizumab 0.5 mg and laser. Ranibizumab given monthly, laser treatment given on day 1 and intervals of 3 months as necessary (121 eyes) Intervention 2: ranibizumab 0.5 mg only, given monthly (128 eyes) Comparator: ranibizumab 0.5 mg PRN (123 eyes)
Outcomes	Primary outcome: • Mean average change in BCVA from baseline to month 1 through month 12 Secondary outcomes: • Evaluation of the mean average change in BCVA from baseline to month 1 through month 24 • Mean change in BCVA and change in CSFT from baseline to months 12 and 24 • Mean number and pattern of treatments over 12 and 24 months • Visual Functioning Questionnaire (VFQ-25) change from baseline in total score at month 12 and month 24 • EuroQol (EQ-5D) Thermometer Score: change from baseline at month 12 and month 24 • Impact of laser on the number of re-treatments in the T&E group and incidence of ocular and non-ocular adverse events and serious adverse events Follow-up: 12 months and 24 months
Notes	Dates participants enrolled: September 2010–April 2013 Funding: Novartis Pharma AG, Switzerland Conflicts of interest: see page 794 Trial registration: NCT01171976

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from patients and masked investigator staff. Each patient was uniquely identified in the study by a combination of his/her centre number and patient number. The centre number was assigned by Novartis to the investigative site. At Visit 2, the treating investigator randomised patients who fulfilled the inclusion/exclusion criteria using the sealed treatment allocation cards supplied by Novartis.
Allocation concealment (selection bias)	Unclear risk	The investigator was required to maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Allocation concealment not described clearly.

RETAIN 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was single-masked: the treating investigator (not masked) would see the laser burns and patients with prior laser experience could distinguish true laser from sham laser treatments. VA assessor and patient were both masked to treatment assignment. The Evaluating investigator (masked to the treatment assignment) performed BCVA and other study efficacy assessments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluating investigator (masked to the treatment assignment) performed BCVA and other study efficacy assessments but did not perform postinjection IOP measurements and judged the presence or absence of BCVA stability and the presence or absence of DME disease activity/recurrence.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients did not complete study, 14 in T&E RANI group, 11 in T&E Rani group, 15 in PRN group. Lost to follow-up: 4 in T&E RANI group, 0 in T&E Rani group, 2 in PRN group.
Selective reporting (reporting bias)	Low risk	Primary outcomes reported and consistent with our review.
Other bias	Low risk	No other source of bias identified.
Overall risk of bias	Low risk	Low risk of bias for most items and 1 unclear risk, however allocation concealment was mandatory in industrial trials at that time.

REVEAL 2015

Study characteristics	
Methods	Parallel-group RCT 1 eye per person, eye with worse VA selected unless other eye more suitable for treatment
Participants	Countries: China, Hong Kong, Japan, South Korea, Singapore, Taiwan Number of people randomised: 396 (396 eyes) Mean age: 61 (SD 9.86) years Sex: 44% females Inclusion criteria: • Age ≥18 years • Diabetes mellitus (according to the American Diabetes Association or WHO guidelines) • HbA1c ≤ 10% • Visual impairment due to DMO • Stable medication for the management of diabetes within 3 months before randomisation and expected to remain stable during the study • Visual impairment due to focal or diffuse DMO in 1 or both eyes, eligible for laser treatment in the opinion of the investigator • BCVA letter score between 78 and 39, both inclusive, based on ETDRS-like VA testing charts administered at a starting distance of 4 m (approximate Snellen equivalent 20/32-20/160) • Decreased vision due to DMO and not other causes, in the investigator's opinion (at visit 1) Exclusion criteria:

REVEAL 2015 *(Continued)*

- Concomitant conditions in the study eye that could prevent the improvement in VA on the study treatment in the investigator's opinion
- Active intraocular inflammation or infection in either eye
- Uncontrolled glaucoma in either eye (e.g. IOP > 24 mmHg on medication, or from the investigator's judgement)
- Laser PRP (within 6 months) or focal/grid laser photocoagulation (within 3 months) before study entry
- Treatment with antiangiogenic drugs in the study eye within 3 months before randomisation
- History of stroke
- Systolic BP > 160 mmHg or diastolic BP > 100 mmHg
- Untreated hypertension
- Change in antihypertensive treatment within 3 months preceding baseline

Interventions	Intervention 1: ranibizumab 0.5 mg and sham laser. Injections given on day 1 and monthly until stable vision achieved. Laser administered on day 1 and subsequent laser treatments were readministered according to the ETDRS guidelines at intervals no shorter than 3 months (133 eyes). Intervention 2: ranibizumab 0.5 mg and laser. Injections given on day 1 and monthly until stable vision achieved. Laser administered on day 1 and subsequent laser treatments were readministered according to the ETDRS guidelines at intervals no shorter than 3 months (132 eyes). Comparator: sham injection and laser. Injections given on day 1 and monthly. Laser administered on day 1 and subsequent laser treatments were readministered according to the ETDRS guidelines at intervals no shorter than 3 months (131 eyes).
Outcomes	Primary outcome: • Mean average change in BCVA from baseline over 12 months Secondary outcomes: • Several BCVA expressions • Mean change in central retinal (subfield) thickness • Safety Follow-up: 12 months
Notes	Dates participants enrolled: not reported Funding: Novartis Conflict of interest: study authors reported financial support of Novartis or were Novartis employees Trial registration: NCT00989989

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"At Visit 2, all patients who fulfilled all the inclusion/exclusion criteria were given the lowest available number on the randomization list. This number assigned them to one of the treatment arms. The investigator entered the randomization number on the electronic case report form. A randomization list was produced by, or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio."
Allocation concealment (selection bias)	Low risk	"At Visit 2, all patients who fulfilled all the inclusion/exclusion criteria were given the lowest available number on the randomization list. This number assigned them to one of the treatment arms. The investigator entered the randomization number on the electronic case report form. A randomization list

REVEAL 2015 *(Continued)*

		was produced by, or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To ensure successful masking in this double-masked study, at the start of the study and at each study site, the following site personnel were required to demonstrate their role: BCVA assessor and evaluating investigator (masked to the treatment assignment) and treating investigator (unmasked to the treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To ensure successful masking in this double-masked study, at the start of the study and at each study site, the following site personnel were required to demonstrate their role: BCVA assessor and evaluating investigator (masked to the treatment assignment) and treating investigator (unmasked to the treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Higher proportion of loss to follow-up in the laser group; this can decrease the benefit with anti-VEGF. "Overall, 345 (87.1%) patients completed the study. The proportion of patients who discontinued the study was 7.5% in the ranibizumab arm, 13.6% in the ranibizumab þ active laser treatment arm, and 17.6% in the laser treatment arm (Fig 2, available at www.aaojournal.org). Adverse events (range, 3.0%-6.8%) were the most common reason for discontinuation across all treatment arms (Fig 2, available at www.aaojournal.org). Unsatisfactory therapeutic effect (n= 7 [5.3%]) was reported only in the laser arm."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No other bias identified.
Overall risk of bias	High risk	High risk for two items.

RISE and RIDE 2013

Study characteristics	
Methods	Parallel-group RCT 1 eye per person, unclear how eye selected
Participants	Countries: USA and South America Number of people randomised: 759 (759 eyes) Mean age: 62 (range 21 to 91) years Sex: 43% females Inclusion criteria: • Age ≥18 years • Diabetes mellitus • Decreased vision from DMO (study eye BCVA, 20/40–20/320 Snellen equivalent using ETDRS testing) • Macular oedema (TD-OCT) central subfield thickness ≥ 275 µm Exclusion criteria:

RISE and RIDE 2013 *(Continued)*

- Prior vitreoretinal surgery
- Recent history (within 3 months of screening) of panretinal or macular laser in the study eye
- Intraocular corticosteroids
- Antiangiogenic drugs
- Uncontrolled hypertension
- Uncontrolled diabetes (HbA1c > 12%)
- Recent (within 3 months) cerebrovascular accident, or myocardial infarction

Interventions	**RISE:** Intervention 1: Ranibizumab 0.3mg. Administered monthly for 36 months. Patients who had not discontinued treatment by Month 36 could enter the open-label extension phase to receive ranibizumab 0.5 mg PRN for up to 24 additional months (125 eyes) Intervention 2: Ranibizumab 0.5mg. Administered monthly for 36 months. Patients who had not discontinued treatment by Month 36 could enter the open-label extension phase to receive ranibizumab 0.5 mg PRN for up to 24 additional months (125 eyes) Comparator: Sham injection/ranibizumab 0.5 mg. Injections administered monthly for 24 months. Patients who had not discontinued treatment by Month 24 could choose to receive ranibizumab 0.5 mg monthly administered intravitreally for the subsequent 12 months. Patients who had not discontinued treatment by Month 36 could enter the open-label extension phase to receive ranibizumab 0.5 mg PRN for up to 24 additional months (127 eyes) **RIDE:** Intervention 1: Ranibizumab 0.3mg. Administered monthly for 36 months. Patients who had not discontinued treatment by Month 36 could enter the open-label extension phase to receive ranibizumab 0.5 mg PRN for up to 24 additional months (125 eyes) Intervention 2: Ranibizumab 0.5mg. Administered monthly for 36 months. Patients who had not discontinued treatment by Month 36 could enter the open-label extension phase to receive ranibizumab 0.5 mg PRN for up to 24 additional months (127 eyes) Comparator: Sham injection/ranibizumab 0.5 mg. Injections administered monthly for 24 months. Patients who had not discontinued treatment by Month 24 could choose to receive ranibizumab 0.5 mg monthly administered intravitreally for the subsequent 12 months. Patients who had not discontinued treatment by Month 36 could enter the open-label extension phase to receive ranibizumab 0.5 mg PRN for up to 24 additional months (130 eyes)
Outcomes	Primary outcome: • Gain of 15 or more ETDRS letters in BCVA score from baseline at 24 months (corresponding to 3 lines on the eye chart) Secondary outcomes: • Mean change from baseline BCVA score over time • Proportion of participants with BCVA Snellen equivalent of 20/40 • Mean change from baseline BCVA score over time in participants with focal oedema as assessed on fluorescein angiography • Proportion of participants losing 15 letters in BCVA score from baseline • Mean change from baseline in OCT CFT over time • Proportion of participants with a 3-step progression from baseline in ETDRS retinopathy severity on fundus photography • Proportion of participants with resolution of leakage on FA • Mean number of macular laser treatments Follow-up: 24 months

RISE and RIDE 2013 *(Continued)*

Notes	Dates participants enrolled: June 2007–January 2009 Funding: "This study was supported by Genentech Inc. Support for third-party writing assistance by Ivo Stoilov, MD, CMPP, of Envision Scientific Solutions was provided by Genentech Inc." "The sponsor participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript." Conflict of interest: see page 1121 Trial registration: RIDE NCT00473382, RISE NCT00473330

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was stratified by study eye BCVA (55 vs 55 ETDRS letters), baseline HbA1c (<=8% vs >8%), prior DME therapy in the study eye (yes vs no), and study site. Dynamic randomization was used to obtain approximately a 1:1:1 ratio among groups (Fig 1). Randomization was done via interactive phone system. The sponsor developed the specifications for the randomization, and a third party programmed and held the randomization algorithm."
Allocation concealment (selection bias)	Low risk	"Randomization was stratified by study eye BCVA (55 vs 55 ETDRS letters), baseline HbA1c (<=8% vs >8%), prior DME therapy in the study eye (yes vs no), and study site. Dynamic randomization was used to obtain approximately a 1:1:1 ratio among groups (Fig 1). Randomization was done via interactive phone system. The sponsor developed the specifications for the randomization, and a third party programmed and held the randomization algorithm."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Ocular assessments, including the need for macular laser, were made by evaluating ophthalmologists masked to patients' treatment assignments. Study treatments were administered by treating ophthalmologists unmasked to treatment assignments but masked to ranibizumab dose. To improve patient masking, all patients received subconjunctival anesthesia before sham or active injections (performed as previously described).22 Study site personnel (except treating physicians and assistants), central reading center personnel, and the sponsor and its agents (except drug accountability monitors) were masked to treatment assignment. Treating physicians were masked to the assigned dose of ranibizumab."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Ocular assessments, including the need for macular laser, were made by evaluating ophthalmologists masked to patients' treatment assignments. Study treatments were administered by treating ophthalmologists unmasked to treatment assignments but masked to ranibizumab dose. To improve patient masking, all patients received subconjunctival anesthesia before sham or active injections (performed as previously described).22 Study site personnel (except treating physicians and assistants), central reading center personnel, and the sponsor and its agents (except drug accountability monitors) were masked to treatment assignment. Treating physicians were masked to the assigned dose of ranibizumab."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The 2-year study period was completed by 83.3% of participants in RISE and by 84.6% in RIDE; causes of missingness are balanced.
Selective reporting (reporting bias)	Low risk	All VA cut-offs and secondary outcomes available at 2 years, although not at 1 year, as pre-planned.
Other bias	Low risk	No other bias identified.

RISE and RIDE 2013 *(Continued)*

Overall risk of bias	Low risk	Low risk of bias for most items.

Soheilian 2007

Study characteristics	
Methods	Parallel group RCT 1 or 2 eyes per person, in bilateral cases unclear how the second eye allocated
Participants	Country: Iran Number of people randomised: 129 (150 eyes) Mean age: 60.9 (SD 5.6) years Sex: 49% females Inclusion criteria • Clinically significant DMO based on ETDRS criteria Exclusion criteria • Previous PRP or focal laser photocoagulation • Prior intraocular surgery or injection • History of glaucoma or ocular hypertension • VA of 20/40 or better, or worse than 20/300 • Presence of iris neovascularisation • High-risk PDR • Significant media opacity • Monocularity • Pregnancy • Serum creatinine ≥ 3 mg/dL • Uncontrolled diabetes mellitus
Interventions	Intervention 1: bevacizumab 1.25 mg, schedule not reported (50 eyes) Intervention 2: bevacizumab 1.25mg/triamcinolone 2 mg injection, schedule not reported (excluded from this review) Comparator: laser photocoagulation, schedule not reported (50 eyes) Re-treatment was performed at 12-week intervals whenever indicated
Outcomes	Primary outcome: • Change in BCVA (logMAR) at week 24 (data available at 36 weeks) Secondary outcomes: • VA change • CRT change assessed by OCT • Injection-related complications
Notes	Dates participants enrolled: September 2005–May 2007

Soheilian 2007 *(Continued)*

Funding: "Supported by the Ophthalmic Research Center of Shahid Beheshti University (MC) Tehran, Iran."

Conflict of interest: "The author(s) have no proprietary or commercial interest in any materials discussed in this article"

Trial registration: NCT00370669

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using random block permutation method according to a computer-generated randomization list. The block length varied randomly (6, 12). Random allocation sequence was performed by a biostatistician. The detail of series was unknown by the study investigators."
Allocation concealment (selection bias)	Low risk	"Randomization was performed using random block permutation method according to a computer-generated randomization list. The block length varied randomly (6, 12). Random allocation sequence was performed by a biostatistician. The detail of series was unknown by the study investigators."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A sham laser procedure (20 seconds) was performed by aiming the laser beam on the macula for the eyes in the IVB and IVB/IVT groups. In the MPC group, a sham injection was done by a needleless syringe pressed against the conjunctiva. To keep the masking process, patients were prevented from seeing the syringes. All procedures were run by staff members other than the study investigators to preserve investigator masking. Best-corrected VA measurement and OCT were performed by certified examiners masked both to the randomization and to the findings of previous measurements."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A sham laser procedure (20 seconds) was performed by aiming the laser beam on the macula for the eyes in the IVB and IVB/IVT groups. In the MPC group, a sham injection was done by a needleless syringe pressed against the conjunctiva. To keep the masking process, patients were prevented from seeing the syringes. All procedures were run by staff members other than the study investigators to preserve investigator masking. Best-corrected VA measurement and OCT were performed by certified examiners masked both to the randomization and to the findings of previous measurements."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 6 missing eyes out of 50 at 36 weeks in the IVB group and 12 out of 50 in the photocoagulation group, and causes were not clearly unrelated to VA outcome, except for 2 deaths. In a subsequent publication in 2012 the study authors reported 39 (78%) and 38 (76%) eyes in the two arms; 8 participants (12 eyes) missing were dead for causes unrelated to treatment, but other causes of death were not reported.
Selective reporting (reporting bias)	Low risk	The primary outcomes are continuous measures and no arbitrary cutoffs were used.
Other bias	High risk	There was an imbalance of baseline VA in the IVB and photocoagulation groups: 0.71 logMAR versus 0.55 logMAR. Although there was a potential unit of analysis issue (150 eyes of 129 patients, 16% of participants had both eyes included), comparisons were made in a marginal regression model (based on generalised estimating equation methods) adjusted for the baseline values and to eliminate any possible correlation effects between the 2 eyes of participants in bilateral enrolled cases. However, we could not take correlation into account when analysing dichotomous VA definitions.

Soheilian 2007 *(Continued)*

Overall risk of bias	High risk	High or unclear risk of bias for 2 items to a degree that we believe may influence effect estimates.

VIVID and VISTA 2015

Study characteristics	
Methods	2 similarly designed, randomized, phase 3 trials, VISTA and VIVID (100-week results) Only 1 eye per patient was enrolled in the study.
Participants	Countries: Europe, Japan, Australia Number of people randomised: 872 (872 eyes) Mean age: 63 (SD 9.0) years Sex: 42% females Inclusion criteria: • Age ≥ 18 years • Type 1 or 2 diabetes mellitus • Decrease in vision determined to be primarily the result of DME in the study eye • BCVA ETDRS letter score of 73 to 24 (20/40 to 20/320) in the study eye Exclusion criteria: • Laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1 • > 2 previous macular laser treatments in the study eye • Previous use of intraocular or periocular corticosteroids in the study eye within 120 days of day 1 • Previous treatment with anti-angiogenic drugs in the study eye (pegaptanib sodium, bevacizumab, ranibizumab, etc.) within 90 days of day 1 • Active proliferative diabetic retinopathy (PDR) in the study eye • Uncontrolled diabetes mellitus • Only 1 functional eye even if that eye is otherwise eligible for the study
Interventions	**VIVID:** Intervention 1: aflibercept 2 mg injection every 4 weeks (136 eyes) Intervention 2: aflibercept 2 mg injection every 4 weeks for 5 visits followed by every 8 weeks (135 eyes) Comparator: macular laser photocoagulation at baseline and as needed (135 eyes) **VISTA:** Intervention 1: aflibercept 2 mg injection every 4 weeks (156 eyes) Intervention 2: aflibercept 2 mg injection every 4 weeks for 5 visits followed by every 8 weeks (154 eyes) Comparator: macular laser photocoagulation at baseline and as needed (156 eyes)
Outcomes	Primary outcome: • Mean change from baseline in BCVA at week 52 Secondary outcomes:

VIVID and VISTA 2015 *(Continued)*

- Proportion of eyes that gained 10 letters from baseline
- Proportion of eyes that gained 15 letters from baseline
- Proportion of eyes with a 2-step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score
- Change from baseline in CST, as determined by OCT
- Change from baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) near activities subscale score
- Change from baseline in the NEI VFQ-25 distance activities subscale score

Follow-up: 24 months

Notes	Dates participants enrolled: May 2011–May 2014 Funding: not applicable Conflict of interest: not reported Trial registration: VISTA NCT01363440, VIVID NCT01331681

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized by an unmasked investigator via an interactive voice/web response system.
Allocation concealment (selection bias)	Low risk	Patients were randomized by an unmasked investigator via an interactive voice/web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study personnel were both masked and unmasked. Masked and unmasked roles were not interchangeable. Patients, principal investigators, Steering Committee members, and sponsors were masked to the treatment assignments. A masked investigator assessed safety and efficacy and decided on the need for laser re-treatment and additional treatment. The information on laser re-treatment and additional treatment was transferred from the masked to unmasked investigator via the interactive voice/web response system. An unmasked investigator injected intravitreal aflibercept and performed macular laser photocoagulation, sham treatments, laser retreatment, and additional treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masked graders at independent central reading centres evaluated OCT images for CST (Duke Reading Center, Durham, NC for VISTA, and Vienna Reading Center, Vienna, Austria for VIVID) and fundus images including assessment of the DRSS score (Digital Angiography Reading Center, Great Neck, NY for VISTA, and Vienna Reading Center, Vienna, Austria for VIVID).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: VISTA: 4 in intervention 1, 4 in intervention 2, 2 in control; VISTA: 2 in intervention 1, 4 in intervention 2, 1 in control. Discontinued before week 100: VISTA: 31 in intervention 1, 27 in intervention 2, 23 in control; VISTA: 21 in intervention 1, 25 in intervention 2, 30 in control.
Selective reporting (reporting bias)	Low risk	Primary outcome declared and consistent with our review. The primary outcome is the same in the protocol as in the final report.
Other bias	Low risk	No other source of bias identified.
Overall risk of bias	Low risk	Low risk for most items and one unclear risk.

YOSEMITE and RHINE 2022

Study characteristics	
Methods	2 randomised, double-masked, phase 3 trials
Participants	Countries: worldwide Number of people randomised: 1891 (1891 eyes) Mean age: 62.2 (SD 9.9) years Sex: 40% females Inclusion criteria: • At US sites, patients must provide HIPAA authorisation, and in other countries, as applicable according to national laws • Age ≥18 years • Documented diagnosis of diabetes mellitus (type 1 or 2), as defined by the American Diabetes Association or per WHO criteria • Current regular use of insulin or other injectable drugs (e.g. dulaglutide and liraglutide) for the treatment of diabetes, or current regular use of oral anti-hyperglycaemic agents for the treatment of diabetes • HbA1c ≤ 10% within 2 months before day 1 • Ability and willingness to undertake all scheduled visits and assessments • For women of childbearing potential, agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods with a failure rate < 1% per year during the treatment period and for ≥ 3 months after the final dose of study treatment Exclusion criteria: • Currently untreated diabetes mellitus or previously untreated patients who initiated oral or injectable anti-diabetic medication or insulin < 3 months before day 1 • History of allergy or hypersensitivity to aflibercept and any of its excipients, fluorescein, or any study treatment-related mandatory ingredients (e.g. disinfectants, anaesthetics) • History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of faricimab or to aflibercept injections, study treatment procedures, dilating drops, or any of the anaesthetic and antimicrobial preparations used by a patient during the study • Active cancer within the past 12 months, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score ≤ 6 and a stable prostate-specific antigen for > 12 months • Systemic treatment for suspected or active systemic infection. Ongoing use of prophylactic antibiotic therapy may be acceptable but must be discussed with the Medical Monitor. • Renal failure requiring renal transplant, haemodialysis, or peritoneal dialysis, or anticipated to require haemodialysis or peritoneal dialysis at any time during the study • History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, or historical or current clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the faricimab or aflibercept or that might affect interpretation of the results of the study, or renders the patient at high risk for treatment complications in the opinion of the investigator • Uncontrolled BP (systolic >180 mmHg or diastolic >100 mmHg at rest). If a patient's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the screening period. If the patient's blood pressure is controlled by anti-hypertensive medication, the patient should be taking the same medication continuously for ≥ 30 days before day 1. • Stroke (cerebral vascular accident) or myocardial infarction < 6 months before day 1 • Pregnancy or breastfeeding, or intention to become pregnant during the study. Women of childbearing potential must have a negative urine pregnancy test result < 28 days before initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

YOSEMITE and RHINE 2022 *(Continued)*

- Participation in an investigational trial that involves treatment with any drug or device (except vitamins and minerals) < 3 months before day 1
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for peripheral or coronary ischaemia (e.g. limb ischaemia or myocardial infarction) < 3 months or 5 half-lives before day 1
- Inability to comply with study or follow-up procedures
- Requirement for continuous use of any prohibited medications and treatments indicated in the study protocol.

Interventions	**YOSEMITE:** Intervention 1 faricimab every 8 weeks (315 eyes) Intervention 2: faricimab with personalised treatment interval (313 eyes) Comparator: aflibercept 2 mg every 8 weeks (312 eyes) **RHINE:** Intervention 1 faricimab every 8 weeks (317 eyes) Intervention 2: faricimab with personalised treatment interval (319 eyes) Comparator: aflibercept 2 mg every 8 weeks (315 eyes)
Outcomes	Primary outcome: • BCVA outcomes Secondary outcomes: • Anatomical outcome measures using SD-OCT • Diabetic retinopathy severity outcomes • Additional BCVA outcomes • Patient-reported vision-related functioning and quality of life Follow-up: 12 months
Notes	Dates participants enrolled: Sept 2018–Sept 2019 Funding: F Hoffmann-La Roche Conflict of interest: see pages 14–15 Trial registration: YOSEMITE NCT03622580, RHINE NCT03622593

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were screened for eligibility ≤28 days before day 1, and those deemed eligible were assigned a unique randomisation identification number through an interactive voice or web-based response system (IxRS). At the day 1 study visit, eligible patients were randomised 1:1:1 by the IxRS into three treatment arms: intravitreal faricimab 6·0 mg every 8 weeks (Q8W), intravitreal faricimab 6·0 mg per personalised treatment interval (with adjustable dosing up to every 16 weeks), or intravitreal aflibercept 2·0 mg Q8W."
Allocation concealment (selection bias)	Low risk	"Patients were allocated using a permuted-block randomisation scheme, stratified by baseline best-corrected visual acuity (BCVA; <64 vs ≥64 Early Treatment Diabetic Retinopathy Study letters), previous intravitreal anti–vas-

YOSEMITE and RHINE 2022 *(Continued)*

		cular endothelial growth factor therapy (yes vs no), and geographic region (US and Canada, Asia, and rest of the world), as assessed on day 1."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, study site personnel, BCVA examiners, study vendors, central reading centre personnel, and the sponsor and its agents were masked to patient treatment assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"BCVA examiners were additionally masked to the laterality (right vs left) of the study eye. Each site was required to have at least one unmasked treating physician and at least one masked assessing physician; one of each were required to be present at each scheduled study visit. To maintain masking among treatment arms, all patients attended monthly study visits and received sham injections at non–active dosing visits."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Discontinued treatment: 24 in intervention 1, 11 in intervention 2, 19 in control.
Selective reporting (reporting bias)	Low risk	Protocol available.
Other bias	Low risk	No other bias reported.
Overall risk of bias	Low risk	Overall low risk.

BCVA: best-corrected visual acuity; BP: blood pressure; CRT: central retinal thickness; CSFT: central subfield thickness; CSMO: clinically significant macular oedema; CSMT: central subfield mean thickness; CST: central subfield thickness; DMO: diabetic macular oedema (DME: US spelling edema); ECG: electrocardiogram; EQ-5D: EuroQol 5D; ETDRS: Early Treatment Diabetic Retinopathy Study; EZ: ellipsoid zone; FAZ: foveal avascular zone; FFA: fundus fluorescein angiography; GLD: greatest linear dimension; HbA1c: glycated haemoglobin; IOP: intraocular pressure; ITT: intention-to-treat; iv: intravenous; IV: intravitreal injection; IVB: intravitreal bevacizumab; IVT: intravitreal triamcinolone; LOCF: last observation carried forward; logMAR: log of the Minimum Angle of Resolution; NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PFCL: perifoveal capillary loss; PRN: pro re nata (as needed); PRP: panretinal photocoagulation; q8w: eight-week interval; q12w: 12-week interval; RCT: randomised controlled trial; SD: standard deviation; SD-OCT: spectral-domain optical coherence tomography; TD-OCT: time-domain optical coherence tomography; VA: visual acuity; VEGF: vascular endothelial growth factor; WHO: World Health Organization.

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

Study	Reason for exclusion
Afridi 2016 (READ-3)	Wrong dose.
Ahmadieh 2008	24-week follow-up.
Ahmadieh 2013	Not an RCT.
Azad 2012	6-month follow-up.
BOULEVARD 2019	Follow-up at 36 weeks only.
BRDME 2020	Follow-up at 6 months only.
Chen 2016	Abstract only.
ChiCTR-TRC-12002417	No update since 2012.

Study	Reason for exclusion
Cornish 2018 (BEVORDEX)	Wrong comparator.
CRFB002DFR08 (LUDIC)	Single-arm study.
CRFB002DGB14 (RELIGHT)	Single-arm study.
CRFB002DNO02 (PTIMAL)	Single-arm study.
Ding 2015	Wrong intervention.
DRCRnet 2007	Follow-up at 12 weeks only.
DRCRnet 2011	Follow-up at 14 weeks only. RCT comparing ranibizumab (2 injections) and triamcinolone (1 injection) to sham in participants with DMO undergoing grid and panretinal laser photocoagulation.
DRCRnet 2012	Follow-up of DRCRnet 2010 comparing prompt to deferred laser in participants treated for ranibizumab for DMO: does not report on comparison of ranibizumab with laser.
Eichenbaum 2018	Small sample size, 10 per group.
Faghihi 2008	Follow-up at 16 weeks only.
Fang 2016	Wrong outcomes.
Fouda 2017	Authors contacted – no response. Unable to use data in analyses.
Gillies 2014 (BEVORDEX)	Wrong comparator.
Gillies 2015 (BEVORDEX)	Wrong comparator.
Huang 2016	6 months only.
Ishibashi 2014	24-week follow-up.
Jovanovic 2015	Results were not provided at desired fixed follow-up times by each randomisation group.
Lafuente 2017	Wrong intervention.
Li 2015	Wrong outcomes.
Lopez-Galvez 2014	Available as an abstract only.
Macugen 2005	Drug not commercially available.
Macugen 2011	Drug not commercially available.
NCT00387582	No results reported.
NCT00997191 (IBeTA)	No results reported.
NCT01445899 (MATISSE)	No results posted.
NCT01565148 (IDEAL)	Not commercially available and Phase 2 study. Drug not evaluated in Phase 3.

Study	Reason for exclusion
NCT01635790 (BRDME)	6-month follow-up.
NCT02348918	24-week follow-up.
NCT02645734	6-month follow-up.
NCT02712008	12- and 36-week follow-up.
NCT02985619 (BEVATAAC)	Triamcinolone as comparator, unpublished study.
Paccola 2008	Single injection of intravitreal triamcinolone acetonide (4 mg/0.1 mL) compared to single injection of intravitreal bevacizumab (1.5 mg/0.06 mL). Duration: 24 weeks.
Payne 2021	Wrong comparator.
Soheilian 2015	Wrong outcomes.
Solaiman 2010	Single intravitreal injection of bevacizumab (inadequate dose); follow-up 6 months.
Turkoglu 2015	6-month follow-up.
Wiley 2016	36-week follow-up.
Zehetner 2013	Physiological study of anti-VEGF levels only

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

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

NCT04108156 (PAGODA)

Study name	PAGODA
Methods	This study will evaluate the efficacy, safety, and pharmacokinetics of the Port Delivery System with Ranibizumab (PDS) in Participants with Diabetic Macular Edema (DME) when treated every 24 weeks (Q24W) compared with intravitreal ranibizumab 0.5 mg every 4 weeks (Q4W).
Participants	643 participants
Interventions	Intervention 1: PDS Implant Pre-Filled with 100 mg/mL Ranibizumab Intervention 2: Intravitreal Ranibizumab 0.5 mg Injection
Outcomes	Primary outcomes: change in BCVA from baseline to week 64
Starting date	30 September 2019
Contact information	Hoffmann-La Roche Investigators
Notes	Updated 2023

NCT04611152 (GLEAM) and NCT04603937 (GLIMMER)

Study name	GLEAM and GLIMMER
Methods	This phase 3 study will evaluate the efficacy, durability, and safety of KSI-301 compared to aflibercept in participants with treatment-naïve DME.
Participants	GLEAM: 460 participants GLIMMER: 459 participants
Interventions	Participants will be randomized 1:1 to 1 of 2 treatment arms: KSI-301 or aflibercept.
Outcomes	Primary outcome: non-inferiority of KSI-301 to Aflibercept measured by changes in BCVA (time frame: Day 1–year 1)
Starting date	30 September 2020
Contact information	Pablo Velazquez-Martin, MD Kodiak Sciences Inc
Notes	Updated 2023

NCT05885503 (RHONE-X)

Study name	RHONE-X
Methods	This is a multicentre long-term extension study designed to evaluate the long-term safety and tolerability of faricimab administered by intravitreal (IVT) injection at a personalised treatment interval (PTI) to participants who enrolled in and completed one of the two Phase III studies, GR40349 (NCT03622580) or GR40398 (NCT03622593), also referred to as the parent studies.
Participants	1479 participants
Interventions	Intervention 1: faricimab Intervention 2: sham procedure
Outcomes	Primary outcomes: • Incidence and severity of ocular adverse events (time frame: ≤ 2 years) • Incidence and severity of systemic (non-ocular) adverse events (time frame: ≤ 2 years) • Number of participants with presence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study (time frame: ≤ 2 years from baseline)
Starting date	5 August 2020
Contact information	Hoffmann-La Roche
Notes	Updated 2023

BCVA: best-corrected visual acuity; CRT: central retinal thickness; CSFT: central subfield thickness; DM: diabetes mellitus; DME: diabetic macular edema (American English spelling); DMO: diabetic macular oedema; PRN: pro re nata (as required in the circumstances); RCT: randomised controlled trial; VFQ: Visual Function Questionnaire-25.

DATA AND ANALYSES

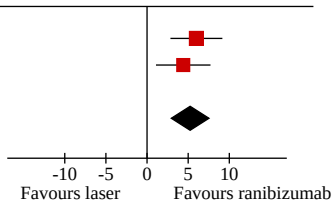
Comparison 1. Ranibizumab versus laser photocoagulation at 6 to 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Quality of life: NEI-VFQ composite score at 6 to 12 months	2	342	Mean Difference (IV, Fixed, 95% CI)	5.24 [2.95, 7.52]

Analysis 1.1. Comparison 1: Ranibizumab versus laser photocoagulation at 6 to 12 months, Outcome 1: Quality of life: NEI-VFQ composite score at 6 to 12 months

Study or Subgroup	Mean Difference	SE	Ranibizumab Total	Laser Total	Weight	Mean Difference IV, Fixed, 95% CI
RESPOND 2013	6	1.61	75	72	52.4%	6.00 [2.84 , 9.16]
RESTORE 2011	4.4	1.69	99	96	47.6%	4.40 [1.09 , 7.71]
Total (95% CI)			**174**	**168**	**100.0%**	**5.24 [2.95 , 7.52]**

Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 4.49 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Mean change in best-corrected visual acuity from baseline to 24 months: direct estimates (upper-right triangle) and mixed estimates (lower-left triangle)

Laser	**-0.07 (-0.12, -0.02)**	**-0.12 (-0.18, -0.06)**	-0.05 (-0.16, 0.06)		**-0.15 (-0.25, -0.05)**	**-0.19 (-0.23, -0.15)**
0.10 (0.03, 0.17)	**Ranibizumab + PL**	-0.04 (-0.10, 0.02)	0.00 (-0.04, 0.042)			
0.13 (0.03, 0.22)	0.03 (-0.07, 0.13)	**Ranibizumab + DL**				
0.13 (0.06, 0.20)	0.03 (-0.04, 0.09)	-0.00 (-0.11, 0.10)	**Ranibizumab**		0.05 (0.00, 0.09)	-0.01 (-0.06, 0.04)
0.14 (0.03, 0.25)	0.04 (-0.07, 0.17)	0.01 (-0.13, 0.11)	0.01 (-0.10, 0.13)	**Brolucizumab**		-0.04 (-0.09, 0.01)
0.13 (0.07, 0.19)	0.03 (-0.05, 0.11)	0.00 (-0.11, 0.11)	0.00 (-0.07, 0.08)	-0.01 (-0.13, 0.11)	**Beva-cizumab**	**-0.06 (-0.10, -0.01)**
0.18 (0.12, 0.23)	**0.08 (0.00, 0.16)**	0.05 (-0.06, 0.16)	0.05 (-0.02, 0.12)	0.04 (-0.06, 0.13)	0.05 (-0.02, 0.12)	**Aflibercept**

DL: deferred laser; PL: prompt laser.
Values in the table are mean differences (logMAR) with 95% confidence intervals. Values in **bold** are those where the 95% confidence intervals do not include 0 (null effect).

Table 2. Mean change in best-corrected visual acuity from baseline to 12 months: direct estimates (upper-right triangle) and mixed estimates (lower-left triangle)

Laser	**−0.11 (−0.13 to −0.08)**	**−0.12 (−0.16 to −0.08)**	**−0.12 (−0.13 to −0.09)**	**−0.17 (−0.22 to −0.12)**		**−0.20 −0.28 to −0.12)**	**−0.20 (−0.24 to −0.17)**
0.11 (0.09, 0.13)	**Ranibizumab + PL**	0.00 (−0.05 to 0.05)	−0.01 (−0.01 to * −0.03)				
0.11 (0.07, 0.16)	0.01 (-0.04, 0.05)	**Ranibizumab + DL**					
0.12 (0.10, 0.14)	0.01 (-0.01, 0.03)	0.01 (-0.04, 0.05)	**Ranibizumab**			0.00 (−0.04, 0.04)	
0.20 (0.17, 0.24)	**0.10 (0.06, 0.13)**	**0.09 (0.04, 0.14)**	**0.08 (0.05, 0.12)**	**Faricimab**			0.01 (−0.01, 0.04)
0.17 (0.12, 0.22)	**0.06 (0.00, 0.12)**	0.06 (-0.01, 0.12)	0.05 (-0.01, 0.11)	-0.03 (-0.10, 0.03)	**Conbercept**		
0.19 (0.15, 0.22)	**0.08 (0.04, 0.12)**	**0.07 (0.02, 0.13)**	**0.07 (0.03, 0.10)**	-0.02 (-0.05, 0.02)	0.02 (-0.05, 0.08)	**Brolu-cizumab**	0.00 (-0.05, 0.05)
0.13 (0.10, 0.16)	0.02 (-0.01, 0.05)	0.01 (-0.04, 0.06)	**0.01 (0.02, 0.04)**	**-0.08 (-0.12, -0.04)**	-0.04 (-0.10, 0.02)	-0.06 (-0.10, -0.02)	**Bevacizum-ab**	−0.07 (−0.11, 0.03)
0.19 (0.16, 0.21)	**0.08 (0.05, 0.11)**	**0.08 (0.03, 0.12)**	**0.07 (0.04, 0.10)**	-0.01 (-0.04, 0.01)	0.02 (-0.04, 0.08)	0.00 (-0.02, 0.03)	**0.06 (0.03 to 0.09)**	**Aflibercept**

DL: deferred laser; PL: prompt laser.
Values in the table are mean differences (logMAR) and 95% confidence intervals. Values in **bold** are those where the 95% confidence intervals do not include 0 (null effect).

Table 3. Gain of three or more lines of visual acuity at 24 months: direct estimates (upper-right triangle) and mixed estimates (lower-left triangle)

Laser	**1.61 (1.12, 2.32)**	**1.60 (1.08, 2.38)**	1.37 (0.54, 3.53)			**2.56 (1.80, 3.62)**
0.35 (0.19, 0.65)	**Ranibizumab + PL**	0.98 (0.67, 1.43)	0.92 (0.40, 2.09)			
0.34 (0.18, 0.64)	0.95 (0.62, 1.47)	**Ranibizumab + DL**				
0.50 (0.31, 0.80)	1.41 (0.94, 2.11)	1.48 (0.95, 2.30)	**Ranibizumab**			
0.40 (0.26, 0.62)	1.13 (0.62, 2.03)	1.18 (0.64, 2.18)	0.80 (0.52, 1.22)	**Brolucizumab**		0.92 (0.71, 1.19)
0.51 (0.31, 0.83)	1.43 (0.83, 2.45)	1.50 (0.85, 2.65)	1.01 (0.71, 1.45)	1.27 (0.83, 1.95)	**Bevacizumab**	
0.43 (0.30, 0.62)	1.22 (0.71, 2.10)	1.28 (0.73, 2.26)	0.87 (0.61, 1.24)	1.09 (0.85, 1.38)	0.86 (0.60, 1.22)	**Aflibercept**

DL: deferred laser; PL: prompt laser.
Values in the table are risk ratios and 95% confidence intervals. Values in **bold** are those where the 95% confidence intervals do not include 1 (null effect).

Table 4. Mean change in central retinal thickness at 24 months: direct estimates (upper-right triangle) and mixed estimates (lower-left triangle)

Laser	−3 (−36, 39)	−12 (−43, 19)			−27 (−70, 16)	**−109 (−134, −83)**
3 (−30, 35)	**Ranibizumab + PL**					
12 (−19, 43)	9 (−26, 44)	**Ranibizumab + DL**				
75 (42, 109)	**72 (25, 119)**	**63 (17, 109)**	**Ranibizumab**			−22 (−50, 6)
98 (59, 137)	**95 (44, 146)**	**86 (36, 136)**	**23 (-19, 64)**	**Brolucizumab**		-3 (-35, 28)
47 (19.76)	**44 (1, 88)**	35 (−7, 78)	−28 (−56, 0)	**−73 (−106, −40)**	**Bevacizumab**	
101 (79, 124)	**98 (58, 139)**	**89 (51, 128)**	26 (−1, 53)	−19 (−41, 2)	**54 (29, 79)**	**Aflibercept**

DL: deferred laser; PL: prompt laser.
Values in the table are mean differences (microns) and 95% confidence intervals. Values in **bold** are those where the 95% confidence intervals do not include 0 (null effect).

Table 5. All-cause mortality at longest available follow-up: direct estimates (upper-right triangle) and mixed estimates (lower-left triangle)

Control[a]			0.33 (0.01-8.04)		0.44 (0.16, 1.25)	**1.90 (1.11, 3.31)**

Table 5. All-cause mortality at longest available follow-up: direct estimates (upper-right triangle) and mixed estimates (lower-left triangle) *(Continued)*

0.79 (0.43, 1.47)	**Ranibizumab**				1.12 (0.55, 2.53)	
0.52 (0.13, 2.20)	0.66 (0.15, 2.99)	**Faricimab**				0.77 (0.24, 2.48)
3.02 (0.11, 80.60)	3.81 (0.13, 107.66)	5.76 (0.16, 207.28)	**Conbercept**			
0.34 (0.08, 1.47)	0.43 (0.09, 2.00)	0.65 (0.10, 4.13)	0.11 (0.00, 4.11)	**Brolucizumab**		0.51 (0.15, 1.68)
0.48 (0.17, 1.33)	0.60 (0.23, 1.57)	0.91 (0.17, 4.78)	0.16 (0.01, 4.92)	1.39 (0.26, 7.49)	**Bevacizumab**	0.37 (0.14, 1.03)
0.67 (0.36, 1.26)	0.85 (0.39, 1.85)	1.29 (0.35, 4.68)	0.22 (0.01 to 6.31)	1.97 (0.53, 7.37)	1.42 (0.50, 4.03)	**Aflibercept**

Values in the table are risk ratios and 95% confidence intervals. Values in **bold** are those where the 95% confidence intervals do not include 1 (null effect).
[a]Laser, observation, or sham.

Table 6. Arterial thromboembolic events at the longest available follow-up: direct estimates (upper-right triangle) and mixed estimates (lower-left triangle)

Control[a]	1.55 (0.95, 2.50)		0.99 (0.25, 3.88)		1.11 (0.13, 9.05)	0.70 (0.48, 1.02)
0.79 (0.37, 1.69)	**Ranibizumab**				1.85 (0.92, 2.95)	**2.18 (1.14, 4.16)**
1.01 (0.26, 3.94)	2.53 (1.00, 6.38)	**Faricimab**				0.84 (0.34, 2.07)
1.54 (0.62, 3.84)	3.21 (0.67, 15.27)	1.27 (0.27, 6.03)	**Conbercept**			
0.48 (0.21, 1.08)	4.89 (1.69, 14.14)	1.94 (0.67, 5.57)	1.53 (0.30, 7.88)	**Brolucizumab**		0.45 (0.16, 1.25)
2.30 (0.29, 18.30)	1.53 (0.85, 2.74)	0.61 (0.23, 1.59)	0.48 (0.10, 2.33)	0.31 (0.10, 0.94)	**Bevacizumab**	1.41 (0.60, 3.28)
0.70 (0.48, 1.02)	2.23 (1.15, 4.30)	0.88 (0.46, 1.69)	0.69 (0.17, 2.86)	0.45 (0.20, 1.05)	1.46 (0.71, 2.98)	**Aflibercept**

Values in the table are risk ratios and 95% confidence intervals. Values in **bold** are those where the 95% confidence intervals do not include 1 (null effect).
[a]Laser, observation, or sham.

Table 7. Similarities among studies: baseline values and number of injections

Study		No. of participants	Interventions	Mean no. of injections	BCVA (logMAR)	CRT (µm)	HbA1c (%)	Study sponsor
Baker 2019[b]		702	Aflibercept 2 mg (n = 236)	8.3	0	306	7.6[a]	Public
			Laser (n = 240)	1.5	0	314	7.6[a]	
BOLT 2010[b]		80	Bevacizumab 1.25 mg (n = 42)	13[a]	0.59	507	7.6 (1.4)	Public
			Laser (n = 38)	4[a]	0.61	481	7.5 (1.2)	
Chatzirallis 2020		112	Ranibizumab 0.5 mg (n = 54)	9.2	0.57	424.2	NR	Public
			Aflibercept 2 mg n = 58)	7.6	0.52	429.5		
DA VINCI 2011		221	Aflibercept 2 mg (n = 131)	7.4	0.55	427	8.0	Industry
			Laser (n = 44)	NA	0.55	441	7.9	
DRCRnet 2010[b]		668	Laser (n = 293)	3[a]	0.38	407[a]	7.4[a]	Public
			Ranibizumab 0.5 mg + DL (n = 188)	9[a]	0.39	382[a]	7.5[a]	
			Ranibizumab 0.5 mg + PL (n = 187)	8[a]	0.38	371[a]	7.3[a]	
DRCRnet 2015[b]		660	Aflibercept 2 mg (n = 224)	9.2	0.40	412	7.6[a]	Public
			Bevacizumab 1.25 mg (n = 218)	9.7	0.40	414	7.7[a]	
			Ranibizumab 0.3 mg (n = 218)	9.4	0.40	407	7.8[a]	
Ekinci 2014		100	Bevacizumab 1.25 mg (n = 50)	5.1	0.22	484	7.2	Public
			Ranibizumab 0.5 mg (n = 50)	6.5	0.24	490	7.4	
KITE and KESTREL 2022[b]	**KESTREL**	566	Brolucizumab 6 mg (n = 189)	6.8	0.37	453	7.7 (1.1)	Industry
			Aflibercept 2 mg (n = 187)	8.5	0.40	476	7.4 (1.1)	
	KITE	360	Brolucizumab 6 mg (n = 179)	7	0.38	481	7.6 (1.2)	

Table 7. Similarities among studies: baseline values and number of injections *(Continued)*

		Aflibercept 2 mg (n = 181)	8.5	0.43	484	7.5 (1.2)	
Li 2019 (REFINE)	384	Ranibizumab 0.5 mg (n = 307)	7.9	0.51	473.4	7.4	Public
		Laser (n = 77)	2.1	0.54	475.0	7.3	
Liu 2022	251	Conbercept 0.5 mg (n = 126)	9.5	0.57	480.0	7.1	NR
		Laser (n= 125)		0.55	470.0	7.1	
LUCIDATE 2014	33	Laser (n = 11)	2.6	0.42	489	7.3	NR
		Ranibizumab 0.5 mg (n = 22)	9	0.30	455	7.9	
RELATION 2012	128	Laser (n = 43)	NR	NR	NR	NR	Industry
		Ranibizumab 0.5 mg + PL (n = 85)					
Nepomuceno 2013	45 (60 eyes)	Bevacizumab 1.5 mg (n = 32 eyes)	9.8	0.60	451	8.6	Public
		Ranibizumab 0.5 mg (n = 28 eyes)	7.7	0.63	421	8.7	
READ2 2009[b]	126	Laser (n = 42)	4.4	0.60	228	7.8	Industry
		Ranibizumab 0.5 mg (n = 42)	5.3	0.54	199	7.4	
		Ranibizumab 0.5 mg + PL (n = 42)	2.9	0.60	263	7.6	
RESOLVE 2010	151	Ranibizumab 0.3 or 0.5 mg (n = 102)	10.2	0.50	455	7.4	Industry
		Sham (n = 49)	8.9	0.48	449	7.5	
RESPOND 2013	239	Laser (n = 81)	NA	0.46	458	NR	Industry
		Ranibizumab 0.5 mg (n = 80)	9.2	0.44	448		
		Ranibizumab 0.5 mg + PL (n=78)	8.8	0.40	422		
RESTORE 2011	345	Laser (n = 111)	7.3	0.46	412	NR	Industry
		Ranibizumab 0.5 mg (n = 116)	7	0.40	427		

Table 7. Similarities among studies: baseline values and number of injections *(Continued)*

			Ranibizumab 0.5 mg-PL (n = 118)	6.8	0.42	416		
RETAIN 2016[b]		372	T&E Ranibizumab 0.5 mg + Laser (n = 121)	12	0.47	480.7	7.8	Industry
			T&E Ranibizumab 0.5 mg (n = 123)	12	0.42	452.4	7.9	
			Ranibizumab 0.5 mg only (n = 128)	10	0.41	432.5	8.0	
REVEAL 2015		396	Laser (n = 131)	1.9	0.54	395	7.5	Industry
			Ranibizumab 0.5 mg (n = 133)	7.8	0.52	419	7.5	
			Ranibizumab 0.5 mg + PL (n = 132)	7	0.52	430	7.4	
RISE and RIDE 2013[c]	**RISE**	377	Sham injection (n = 127)	20.0	0.56	467.3	7.7	Industry
			Ranibizumab 0.5 mg (n = 125)	20.9	0.56	463.8	7.7	
	RIDE	382	Sham injection (n = 130)	20.8	0.55	447.4	7.6	
			Ranibizumab 0.5 mg (n = 127)	21.9	0.56	463.8	7.6	
Soheilian 2007[b]		129 (150 eyes)	Bevacizumab 1.25 mg (n = 50 eyes)	NR	0.78	352	NR	Public
			Laser (n = 50 eyes)		0.50	319		
VIVID and VISTA 2015[b]	**VIVID**	403	Laser (n = 132)	NA	0.48	540	7.7	Industry
			Aflibercept 2mg 2q4 (n = 136)	12.2	0.48	502	7.8	
			Aflibercept 2mg 2q8 (n = 135)	8.7	0.52	518	7.7	
	VISTA	459	Laser (n = 154)	NA	0.51	483	7.6	
			Aflibercept 2mg 2q4 (n = 154)	11.8	0.52	485	7.9	
			Aflibercept 2mg 2q8 (n = 151)	8.4	0.51	479	7.9	
YOSEMITE and RHINE 2022	**YOSEMITE**	940	Faricimab 6 mg/8 weeks (n = 315)	10	0.46	492.3	7.6	Industry
			Faricimab PTI (n = 313)	NA	0.46	485.8	7.7	

Table 7. Similarities among studies: baseline values and number of injections *(Continued)*

		Aflibercept 2 mg (n = 312)	9	0.46	484.5	7.6
RHINE	951	Faricimab 6 mg /8 weeks (n = 317)	10	0.46	466.2	7.6
		Faricimab PTI (n = 319)	NA	0.45	471.3	7.7
		Aflibercept 2 mg (n = 315)	9	0.46	477.3	7.7

2q4: 2 mg every four weeks; 2q8: 2 mg every eight weeks after five initial monthly doses; BCVA: best-corrected visual acuity; CRT: central retinal thickness; DL: deferred laser; NA: not applicable; NR: not reported; PTI: personalised treatment interval; PL: prompt laser.

[a] Median, not mean, available and reported.

[b] 24 months' follow-up.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Macular Edema] explode all trees
#2 macula* near/3 oedema
#3 macula* near/3 edema
#4 maculopath*
#5 CME or CSME or CMO or CSMO
#6 DMO or DME
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Diabetes Mellitus] explode all trees
#9 MeSH descriptor: [Diabetic Retinopathy] this term only
#10 MeSH descriptor: [Diabetes Complications] this term only
#11 diabet*
#12 retinopath*
#13 #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees
#15 MeSH descriptor: [Angiogenesis Inducing Agents] this term only
#16 MeSH descriptor: [Endothelial Growth Factors] this term only
#17 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees
#18 macugen or pegaptanib or lucentis or rhufab or ranibizumab or bevacizumab or avastin or aflibercept or conbercept or OPT 302 or Opthea or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol
#19 anti near/2 VEGF*
#20 anti near/1 angiogen*
#21 endothelial near/2 growth near/2 factor*
#22 VEGF TRAP*
#23 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24 #7 AND #13 AND #23

Appendix 2. MEDLINE Ovid search strategy

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

30. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin$ or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol).tw.
31. (anti adj2 VEGF$).tw.
32. (anti adj1 angiogen$).tw.
33. (endothelial adj2 growth adj2 factor$).tw.
34. VEGF TRAP$.tw.
35. or/26-34
36. 19 and 25 and 35

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

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. diabetic macular edema/
34. (diabet$ adj2 macula$ adj2 oedema).tw.
35. (diabet$ adj2 macula$ adj2 edema).tw.
36. maculopath$.tw.
37. (DMO or DME).tw.
38. or/33-37
39. angiogenesis/
40. angiogenesis inhibitors/
41. angiogenesis factor/
42. monoclonal antibody/
43. exp endothelial cell growth factor/
44. vasculotropin/
45. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin$ or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol).tw.
46. (anti adj2 VEGF$).tw.
47. (endothelial adj2 growth adj2 factor$).tw.
48. (anti adj1 angiogen$).tw.

49. VEGF TRAP$.tw.
50. or/39-49
51. 38 and 50
52. 32 and 51

Appendix 4. LILACS search strategy

macula$ edema or macula$ oedema or DMO or DME or CMO or CME or CSMO and angiogenesis or endothelial growth factor or macugen $ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept$ or conbercept or opthea or RTH258 or faricimab or brolucizumab or leizumabor or abicipar pegol

Appendix 5. ISRCTN search strategy

(diabetic macular edema OR DMO OR DME)

Appendix 6. ClinicalTrials.gov search strategy

(diabetic macular edema OR DMO OR DME) AND (Ranibizumab OR Bevacizumab OR Avastin OR Aflibercept OR Conbercept OR OPT 302 OR Opthea OR RTH258 OR faricimab OR brolucizumab OR leizumabor OR abicipar pegol) AND random

Appendix 7. WHO ICTRP search strategy

diabetic macular edema = Condition AND Ranibizumab OR Bevacizumab OR Avastin OR Aflibercept OR Conbercept OR OPT 302 OR Opthea OR RTH258 OR faricimab OR brolucizumab OR leizumabor OR abicipar pegol = Intervention

F E E D B A C K

Feedback, 25 June 2013

Summary

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

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

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

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

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

6. In the 'Characteristics of included studies' table for RISE and RIDE 2013, the 'outcomes' section should be completed.

7. In Tables 2, 5, 6, 7, 8 and 9 'bevacacizumab' should be corrected to 'bevacizumab'.

Reply

We thank Ruth Ubago Pérez for her comments submitted through the Feedback system in *The Cochrane Library*.

1. In the 'Characteristics of excluded studies' table, we have added that not only Paccola 2008, but also Lim 2012 were excluded because another Cochrane review focuses on the use of intravitreal steroids in people with diabetic macular oedema.

2. We will include quality of life data in the next review update.

3. We have removed this sentence.

4 and 5. We have added these references.

6. We have completed the 'Outcomes' section.

7. We have corrected these typos.

Contributors

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

Feedback, 2 July 2018

Summary

Comment: We think that the results regarding the differences between drugs at one year (in favour to aflibercept) should be interpreted considering the Minimal Clinically Important Difference, which is generally assumed to be 1 line (0.1 logMAR or 5 letters) in medical retina research. In addition, a "Summary of Findings" table should be offered to grade the certainty of evidence at two years, despite the fact that this is based on a single, but large, directly comparative study and no NMA is possible. In fact, longer term data are critical for decision makers, since DMO is a chronic condition. The results at 2 years should be used as primary outcome, as results at one year are suggestive but might be associated with a rapid decay effect.

Reviewers also need to consider what Bressler wrote in Jama 2017 on macular edema due to CRVO (Another Score for Repackaged Bevacizumab): "[…] Thus, given the substantial cost differential between aflibercept and repackaged bevacizumab for intravitreal injections, an important remaining question is whether bevacizumab results in outcomes that are no worse than aflibercept for treatment of macular edema due to a central retinal or hemiretinal vein occlusion.[…]." In the Netherlands, as well as being used for wet AMD, bevacizumab had become standard treatment for diabetic macular oedema—the most common eye condition treated with anti-VEGFs—on the basis of cost (Schauwvlieghe AM, et. BMC Ophthalmol 2015).

Finally David Hambleton and Deborah Cohen commented on recent implications of laws at EU level: actual rules do not allow drug companies to restrict the ability of the NHS to offer patients a choice between products with an approved indication and other products used off-label (if evidence supports off label use). This interpretation was released by the European Court of Justice handed down in September 2017: "The choice between three clinically effective drugs should be one for NHS clinicians and patients to make together, not for drug companies."
With these improvements, the network meta-analysis might better serve public health decision making in the field of diabetes care.

Reply

We thank Annalisa Campomori for her comment.

We agree that the minimum clinical important difference for visual acuity is generally agreed to be around 1 line on a logMAR chart. However, we partly based our conclusions on the findings for vision improvement (gain of 3 or more letters). We downgraded for imprecision to reflect the uncertainty around these estimates.

The Cochrane Review aims to present data that might be useful for decision makers i.e. to present the best estimate of the size and certainty of the comparative effects so that healthcare decision makers can weigh up the cost-effectiveness of these agents specific to their own context. However, we are reliant on individual trials to collect and report data on longer term follow-up. After discussion, we have decided not to amend our protocol and change the primary outcome of the review, however, in response to your comment we have amended the conclusions of the Abstract and in the Implications for research to make it clearer that data on long-term effects are needed.

Cost-effectiveness evaluations are used to make decisions on the trade-off between benefits and costs. Whether the apparent relative benefit seen with aflibercept at one year is value for money is a matter of balance between health benefit and resource use, and is also dependent on the setting of the evaluation and the resulting acceptability of cost-effectiveness thresholds for willingness-to-pay. These judgements are not part of the remit for this Cochrane Review.

We agree with this statement “The choice between three clinically effective drugs should be one for NHS clinicians and patients to make together, not for drug companies.”

Contributors

Comment from: Annalisa Campomori, PharmD, Hospital Pharmacy, Trento General Hospital, Health Trust of the Autonomous Province of Trento, Italy. Role: Hospital Pharmacy, Chief
Annalise Campomori does not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of her comment.
Reply from: Gianni Virgili and Jennifer Evans (authors of the review)

Feedback, 27 September 2022

Summary

Content peer reviewer: Winfried Amoaku
This review is important and welcome in understanding DMO clinical treatments with the various approved anti-VEGF drugs. However, the manuscript can be enhanced further.

Methods peer reviewer: Riaz Qureshi

- This review presents an update on a previous Cochrane review assessing the comparative effectiveness of various anti-vascular endothelial growth factor (anti-VEGF) medications for improving best-corrected visual acuity among people with diabetic macular edema, particularly at longer follow up periods (e.g., 24 months).* The authors appear to have addressed previous feedback and comments.* The review changes the primary outcome of interest from the protocol and previous versions, however this change is clearly specified and justified.
- The description of methods for searching, assessing studies for various aspects of synthesis, data extraction, and data synthesis are appropriate and thorough.
- The Summary of Findings table and description of the quality of evidence are consistent with the results and clear.
- Forest plots and data appear correct and accurate.

Reply

We thank the reviewers for their comments. We have addressed all comments as outlined below:

1. Several abbreviations have been used without first stating the full wording, either in the Abstract or main manuscript. These need to be corrected. Examples are 'NMA' and 'SUCRA'. This need to be addressed.

Author response: Thank you for highlighting this, we have made the corrections throughout the manuscript.

2. It is gratifying that a reference has been provided for SUCRA in the main manuscript (Salanti 2012) (under 'Methods for indirect and mixed comparisons'). However, I believe a short explanation of what SUCRA (+stated values) mean will be good for readers who are not experts in NMA (including ophthalmologist as well service commissioners). This would be similar (or slightly more) to the short summary provided for CINeMA in the section on 'Summary of findings….'.

Author response: We have added an explanation of the SUCRA, together with a caveat on its interpretation based on a new reference: “In the 'Summary of Findings' table we also present SUCRA (Surface Under the Cumulative RAnking curve) values. SUCRA is a summary of the rank distribution, which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. It should be interpreted considering the corresponding certainty of evidence for each outcome and how close the values are across all treatments (Mbuagbaw 2017).”

3. There must be consistency with the use of 'anti-VEGF' throughout the document. Currently some places have it as 'antiVEGF' and others as 'anti-VEGF'. The correct one is 'anti-VEGF'.
Author response: Thank you. We have not corrected to anti-VEGF throughout the manuscript.

4. There are several typos, including spacing in the summary of findings tables: e.g. 'patients with'; 'brolucizumab' has been misspelt a few times, e.g in line 11 under 'Types of intervention', and 'Types of intervention'.
Author response: Thank you, we have corrected the spelling of brolucizumab.

5.Start of para 4 under 'Description of condition' would read better as 'Over the past few decades…..' instead of 'During the last decades…' or something similar.

Author response: Thank you, this correction has now been made.
6. Para 2 under 'Description of intervention', please revise to read…'in all patients with DMO, particularly those with centre-involving DMO'…. or something similar.

Author response: This correction has been made, thank you.

7. Overall the results, summary of findings table look good. However, extra details should be added as ff: Kite and Kestrel (Brown et al, 2022) adopted a 'disease activity assessment' strategy which allowed extension of treatment intervals up to 12 weeks. This (although a secondary outcome) needs to be included, with the numbers achieving q12w. Similarly for the Yosemite and Rhine PTI, the % of eyes treated with faricimab achieving q12w and q16w need to be included.

Author response: In KESTREL and KITE, 104 (55.1%) and 90 (50.3%) of brolucizumab 6mg subjects were maintained on a q12w interval to week 52. Under the condition that a brolucizumab-treated eye successfully completed the first q12w interval with no observed disease activity, the probabilities for remaining on q12w dosing up to Week 52 increased to 87.6% for brolucizumab 6 mg in KESTREL and 95.1% for brolucizumab 6 mg in KITE. At the week 52 visit, 60 (21%) patients in YOSEMITE and 62 (20%) patients in RHINE achieved faricimab dosing q12w and 151 (53%) patients in YOSEMITE and 157 (51%) patients in RHINE achieved dosing q16w. Approximately two-thirds of patients reached q12w or q16w dosing at week 52 without an interval reduction below every 12 weeks during year 1 (YOSEMITE n=194 (68%) and RHINE n=198 (64%)).

8. These points should be included in the Discussion as well.

Author response: More than half of patients to be treated with brolucizumab 6mg were maintained on a q12w interval at one year. Two-thirds of patients treated with faricimab reached q12w or q16w intervals at one year.

9. The last para in 'Summary of main results' should include a statement explaining that some of the findings were only identified during post marketing authorisation. As such observational studies (including registries) would be the plausible way to collect such information. That statement is supported by the last sentence with the Khanani, 2022 reference.

Author response: We have remarked the need of large-scale observational studies when commenting on the risk of death, which is followed by the statement reported above:**“**We suggest all this evidence is inconclusive and needs further studies, such as observational studies based on large electronic databases with a specific focus on high-risk patient subgroups, such as those with previous stroke or major cardiovascular events.**”**

10. The implications for practice is appropriate and reads well. The implications for research are apt, especially the recommendation for a systematic data collection on systemic and ocular safety, and longer term outcomes of anti-VEGF comparisons. These could be achieved through large registries. Evidence for effects of switching anti-VEGF therapies are limited.

Author response: The Implications for research section has been slightly expanded as follows:**“**The evidence used to build the NMA was much more sparse at 24 months compared to 12 months, which is due to the fact that most trials become open-label after one year. There is a need to generate more evidence on the long-term (two years or longer) comparative effects of these anti-VEGF agents, including the switch between different drugs. Systemic and ocular safety should be investigated in observational studies, particularly in patients with diabetes at higher cardiovascular risk. These goals could be achieved with observational studies based on large electronic databases or registries.**”**

11. I believe under 'Types of interventions', consistency in citing the pivotal references (as with others) should be maintained such that the brolucizumab phase III study should be referred to as Kite and Kestrel (rather than Brown et al, 2022). The authors need to define which 'Brown, 2022' is referred to in paragraph 3 under 'Included studies'. Similarly, the use of comas or abbreviations after references must be consistent. "Only nine maintained the randomisation scheme at two years' follow-up (BOLT 2010; DRCRnet 2010; DRCRnet 2015; READ2 2009; RISE and RIDE 2013, Brown 2022, RETAIN 2016, Soheilian 2007, VIVID and VISTA 2015)."

Author response: Thank you, we changed the reference by Brown 2022 to KITE and KESTREL 2022, and used made the abbreviations more consistent throughout.

12. *In the Plain Language Summary "Key messages", is it important to note there were no increases in the risk of death, or would a more common harm that may be severe (but not as serious) be more appropriate to include? There should be some statement of the harms in the key messages, but I am not sure that risk of death is a general expected concern with these medications and wonder if a different statement may be more appropriate.

Author response: We have added to death the risk of “major cardiovascular events ”, to be consistent with choices made in the SoF.
13. "Types of interventions" section, second sentence: consider changing "The reasons for selecting treatments of direct and indirect treatment have been discussed…" to "The reasons for selecting both direct and indirect treatments have been discussed…"

Author response: Thank you, we have made this amendment.

14. "Sensitivity analysis" section: typo "… which di not change our …"

Author response: Thank you for highlighting this typo, we have now amended.

15. Related to the above comment and the sensitivity analyses section, were any of the previous reviews' sensitivity analyses carried over and should they be described here as well?

Author response: We suggest the current statement in the corresponding section of the Methods is complete: “In the previous update of this review (Virgili 2018) we conducted post-hoc sensitivity analyses excluding studies at high risk of bias, which did not change our conclusions. In this version of the review there were too few trials with data at 24 months to conduct such analyses**”**

16. CINeMA was not used in the previous version of the review. It would be good to include a note for why CINeMA was chosen to aid in assessing the risk of bias in the section on assessing the certainty of evidence.

Author response: In order not to lengthen this Methods section, we have given this explanation in the Differences between protocol and review section: “In this update we graded the certainty of the evidence for mixed estimates using the CINeMA platform (Nikolakopoulou 2020), which provides detailed guidance for its implementation.”

17. "Summary of findings and assessment of the certainty of the evidence" section: typo "… in the CINeMA framework, refer to extent to which the …"

Author response: Thank you, this typo has been modified.

18. Although the end of the methods noted assessing the transitivity assumption, I did not see any results specifically about the transitivity assessment for the various comparisons.

Author response: The section ‘Similarity between studies’ supports pooling data in NMAs, with the exception of one study on early DMO:**“**Table 7 shows baseline characteristics (BCVA, CRT) and the number of injections across study and treatment arms. Overall, most studies included participants with mean BCVA about 20/60 and CRT between 400 and 500 micron, which we believe sufficiently homogeneous, with the exception of Baker 2019, which included patients with normal vision and borderline DMO, and was excluded from meta-analyses.**”**

19. "Summary of main results" section: typo "…found no evidence that any anti-VEGF drug increase all-cause death or arterial …"

Author response: Corrected, thank you.

20. The risk of bias assessment seems quite favourable as most studies are of low or moderate risk of bias. Some discussion about this might be nice as it is unusual for such a small proportion of high risk of bias studies.

Author response: We added the following introduction to the RoB section: “As seen in the section 'Risk of bias in included studies' and in Figure 2, the number of trials with high risk of bias domains was small in this review. This was likely due to the exclusion of trials with short follow-up and inclusion of phase III trials using established research methods.

21. The description of assessment of heterogeneity should be expanded to include considerations for network meta-analysis. Specifically, heterogeneity should be discussed in the context of assessing the transitivity assumption and beyond statistical investigations (i.e., the "subgroup analysis and investigation of heterogeneity" section notes only that there were too few studies to conduct subgroup analyses of efficacy at 24 months, but a qualitative description of why the studies were heterogenous would be good).

Author response: Most studies at 24 months had BCVA between 0.35 and 0.8, and CRT between 400 and 500, except for Baker 2019 (excluded) and READ2 (CRT <300).

22. The review descriptively summarizes some specific adverse events. The review should specify in the methods the reasons for focusing on these harms and clarify whether any other harms from included studies are discussed or not reported. Specifically, if any harms are noted in primary studies but not reported in the review, the reviewers should specify their selection criteria.

Author response: In the Methods, Outcomes, we have added that “Most large studies reported a large number of adverse events, often grouped by ocular anatomic district, or, if systemic, by MedDRA system organ class. Based on the experience made in the previous version of this review we decided to report on adverse events for which we believed further evidence should be collected (Khanani 2022; Reibaldi 2022).”

Contributors

Comments from: Winfried Amoaku and Riaz Qureshi

Reply from: Gianni Virgili, Katie Curran and Mariacristina Parravano (authors of the review)

WHAT'S NEW

Date	Event	Description
26 June 2023	New citation required but conclusions have not changed	8 studies included in previous version of the review now excluded. 8 new studies included (Baker 2019; Chatzirallis 2020; KITE and KESTREL 2022; Li 2019 (REFINE); Liu 2022; RETAIN 2016; VIVID and VISTA 2015; YOSEMITE and RHINE 2022).
26 June 2023	New search has been performed	Primary outcome timeframe now at 2 years; evidence on brolucizumab and faricimab incorporated.

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 4, 2009

Date	Event	Description
31 August 2018	New citation required and conclusions have changed	Issue 9, 2018: Authors' conclusions in the Abstract and Implications for research have been edited
31 August 2018	Amended	Issue 9, 2018: The review has been amended in light of Feedback received
2 May 2017	New citation required and conclusions have changed	Issue 6, 2017: Searches updated and six new studies added (DRCRnet 2015, Ishibashi 2014, Lopez-Galvez 2014, REVEAL 2015, Turkoglu 2015, Wiley 2016) and conclusions changed
2 May 2017	New search has been performed	Issue 6, 2017: Updated protocol: objectives revised as comparing different antiangiogenic drugs using network meta-analysis technique
4 November 2014	Amended	Plain language summary title has been amended
17 October 2014	New citation required but conclusions have not changed	Issue 10, 2014: Five new studies (Azad 2012; Ekinci 2014; Nepomuceno 2013; RELATION 2012; RESPOND 2013) have been included in the update.
17 October 2014	New search has been performed	Issue 10, 2014: Electronic searches updated.
4 November 2013	Feedback has been incorporated	The authors have made some edits to the review in response to feedback received. See 'Feedback 1' for further details.
14 March 2013	Amended	The abstract has been amended to focus on the comparison with laser and presenting absolute effects.
11 November 2012	New citation required and conclusions have changed	Inclusion of seven new studies has changed the conclusions to this review from the previous version.
11 November 2012	New search has been performed	Updated searches yielded seven new trials for inclusion. One trial that had previously been included was excluded. An economic section has been added. One new author Massimo Brunetti has been added to the review team.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: GV, KC, EL, MP
Designing the review: GV, KC, EL, MP
Co-ordinating the review: GV
Designing search strategies: IG
Undertaking searches: Iris Gordon (search specialist, not an author)
Screening search results: KC, MP
Organising retrieval of papers:
Screening retrieved papers against inclusion criteria: GV, Cochrane Eyes and Vision
Appraising quality of papers: KC, MP
Extracting data from papers: KC, EL, MP
Writing to authors of papers for additional information: KC, TP
Obtaining and screening data on unpublished studies: GV, Cochrane Eyes and Vision
Entering data into Review Manager 5: GV, KC, EL, MP
Analysis of data: GV, EL
Providing a methodological perspective: GV, EL
Providing a clinical perspective: GV, MP
Providing a policy perspective: GV, EL, MP
Providing a consumer perspective: none
Writing the review: GV, EL, MP

DECLARATIONS OF INTEREST

GV: none known
KC: none known
EL: none known
TP: received honoraria for advisory board and lecture fees from Bayer, Allergan, B-I, Sandoz, Roche, Novartis, Heidelberg, Zeiss, and Optos
MP: received payment for participating on the Advisory Board for Allergan, Bayer and Novartis.
Jennifer Evans (methods guide, not an author): none known
Iris Gordon (search specialist, not an author): none known

SOURCES OF SUPPORT

Internal sources

- Azienda Ospedaliero-Universitaria Careggi & University of Florence, based on funding by the Tuscany Region, Italy

External sources

- Public Health Agency, UK

  The HSC Research and Development (R&D) Division of the Public Health Agency funds the Cochrane Eyes and Vision editorial base at Queen's University Belfast.
- Queen's University Belfast, UK

  Gianni Virgili, Co-ordinating Editor for Cochrane Eyes and Vision's work is funded by the Centre for Public Health, Queen's University of Belfast, Northern Ireland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See Parravano 2008 (original protocol).

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

We added LILACS to the list of electronic databases. We used a sensitivity analysis for the robustness of results in comparisons including only one trial according to a statistical technique derived from Borm 2009.

Changes in 2012 update compared to protocol and previous version of review

- We specified that we will also include studies comparing different anti-VEGF drugs, but will exclude intravitreal steroids as they are the subject of another Cochrane Review. Moreover, we decided not to consider the comparison of bevacizumab with bevacizumab plus triamcinolone, which included two studies; in fact, this comparison investigates the additional effect of triamcinolone rather than the benefit of anti-VEGF drugs.

- We computed indirect comparison odds ratios (OR) of a gain of 3+ and 2+ lines for bevacizumab and pegaptanib versus ranibizumab as the reference drug using random-effects model logistic regression.

Changes in 2014 update compared to protocol and previous version of review

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

Changes in 2018 update compared to protocol and previous version of review

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

Changes in update, 2023 compared to the protocol of the previous version

- We changed the primary outcome from proportion of participants gaining three lines of vision to mean change in BCVA from baseline to 24 months
- We removed systemic serious adverse events and replaced with ocular serious adverse events.
- In this update, we graded the certainty of the evidence for mixed estimates using the CINeMA platform (Nikolakopoulou 2020), which provides detailed guidance for its implementation.

INDEX TERMS

Medical Subject Headings (MeSH)

Bevacizumab [therapeutic use]; *Diabetes Mellitus [drug therapy]; *Diabetic Retinopathy [complications] [drug therapy]; Endothelial Growth Factors [therapeutic use]; Laser Coagulation [methods]; *Macular Edema [drug therapy] [etiology] [surgery]; Network Meta-Analysis; Ranibizumab [therapeutic use]; Vascular Endothelial Growth Factor A

MeSH check words

Humans