Treatment of retinal disease: the impact of Cochrane reviews on decision-making

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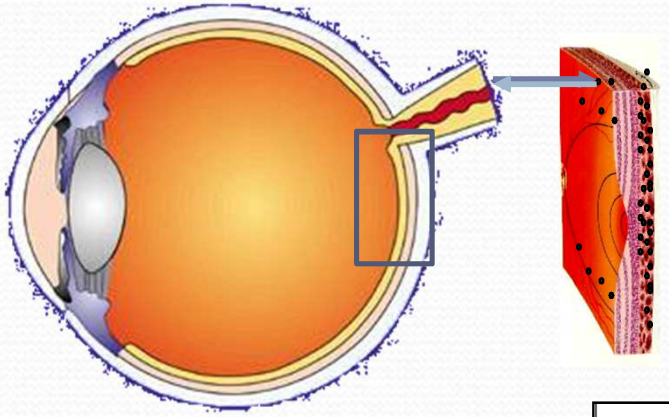
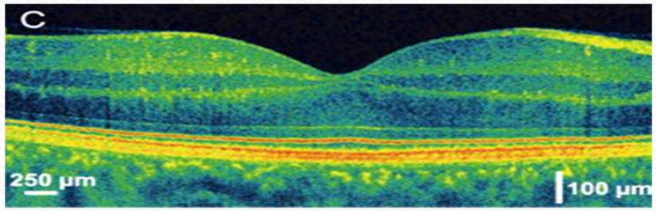
Conflict of interest: none

The case of antiangiogenic (antiVEGF) therapy for age-related macular degeneration (AMD)

bevacizumab vs. ranibizumab for AMD

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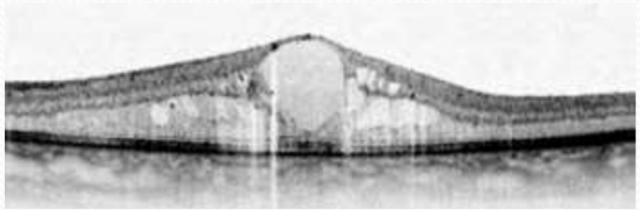

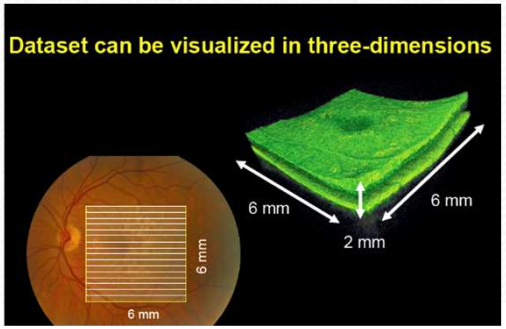
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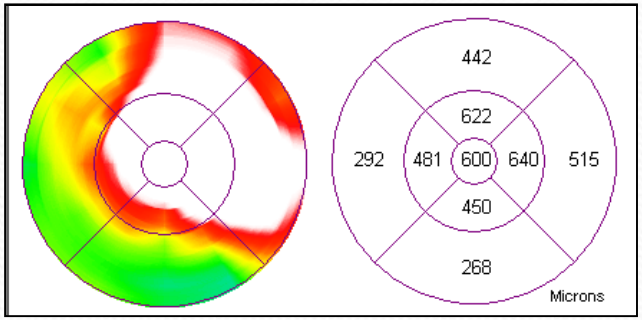
442
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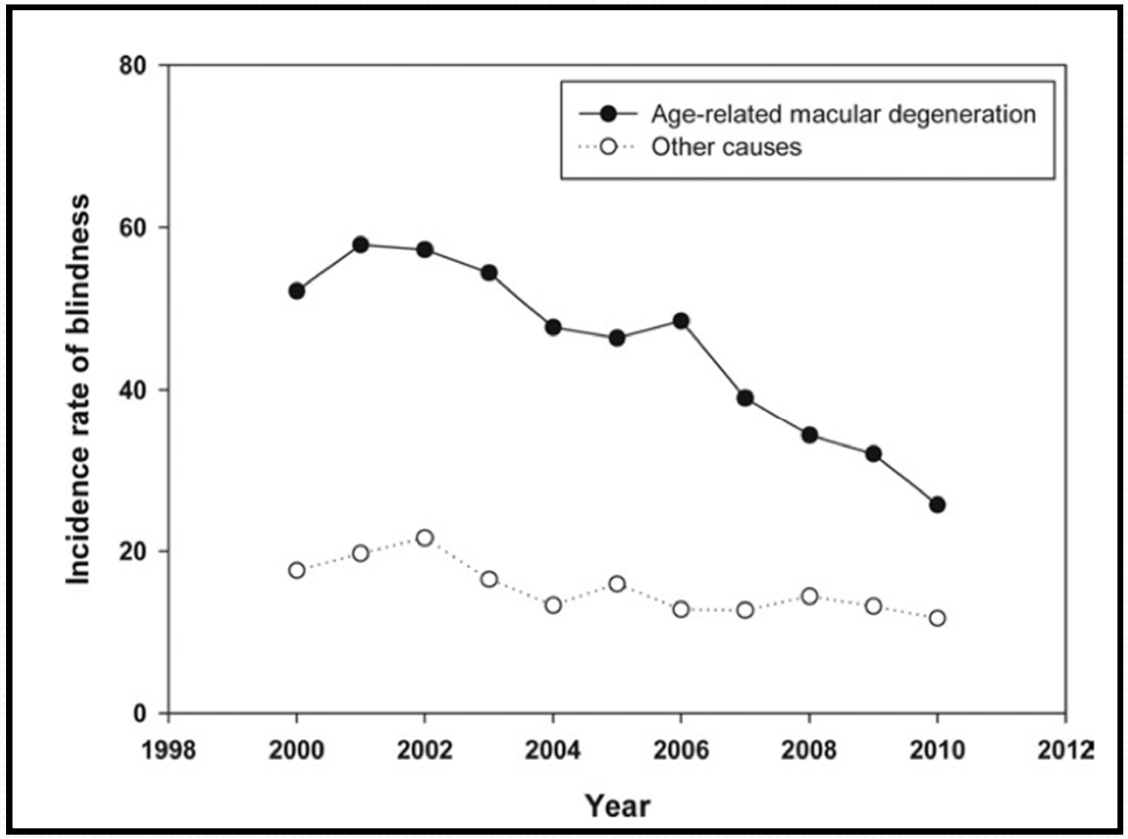
Leaking
blood vessel
JirehDesign.com

Reduction of legal blindness due to AMD

Annual incidence of legal blindness per 100,000 inhabitants aged ≥50 years in Denmark due to AMD decreased from 52.2 to 25.7 from 2000 to 2010



Bloch SB et al. *Am J Ophthalmol*. 2012

METAANALYSIS OF REAL-WORLD OUTCOMES OF INTRAVITREAL RANIBIZUMAB FOR THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

LEAH N. KIM,* HEMAL MEHTA, MA, FRCOPHTH,*† DANIEL BARTHELMES, PHD, FEBO,*‡
VUONG NGUYEN, PHD,* MARK C. GILLIES, PHD, FRANZCO*

Purpose: To report the efficacy and safety of intravitreal ranibizumab for neovascular age-related macular degeneration (nAMD) in real-world practice.

Methods: Metaanalysis of ~26,360 patients from 42 real-world observational studies reporting outcomes of intravitreal ranibizumab for nAMD published between 2007 and 2015. Baseline demographics, lesion type, and visual acuity (VA) were recorded. The weighted mean was calculated for change in VA and frequency of injections and visits during year 1, year 2, and ≥3 years. Local and systemic adverse events were recorded.

Results: The mean change in VA for patients receiving a treat-and-extend regimen was +8.8 (95% confidence interval [CI]: 5.8 to 11.8), +6.7 (95% CI: 3.2 to 10.1), and +5.4 (95% CI: −4.1 to 14.9) Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 1 year (n = 1,539), 2 years (n = 2,521), and ≥3 years (n = 1,298), in comparison with +3.5 (95% CI: 2.0 to 5.0), +1.3 (95% CI: −1.6 to 4.2), and −1.9 (95% CI: −9.8 to 6.0) ETDRS letters for *pro re nata* at 1 year (n = 20,247), 2 years (n = 14,408), and ≥3 years (n = 11,714). Treat-and-extend patients received on average more injections (6.9 vs. 4.7) but had fewer visits (7.6 vs. 9.2) in the first year. Baseline characteristics were similar between the regimens. The reported rate of endophthalmitis was 17 of 66,176 intravitreal injections (0.026%).

Conclusion: Intravitreal ranibizumab for nAMD prevents severe visual loss in real-world practice. Patients can achieve visual gain from baseline, but the extent to which these are maintained in the long term may depend on the frequency of injections.

RETINA 36:1418–1431, 2016

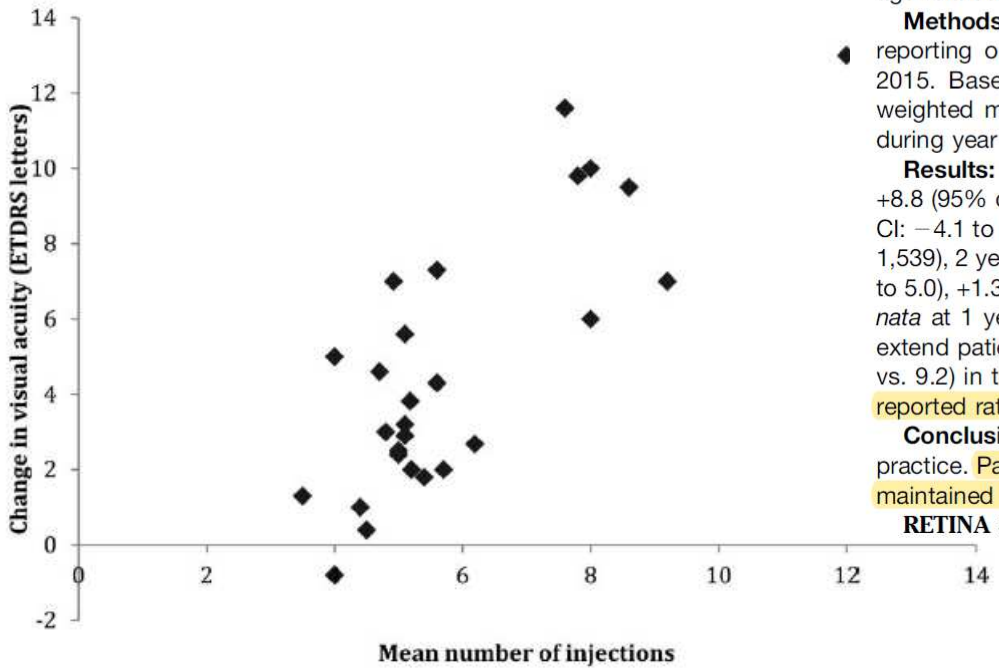


Fig. 2. Mean change in VA versus the mean number of injections administered, in the first year of treatment of included studies.

The debate on the ***efficacy and safety of bevacizumab vs. ranibizumab for AMD*** started ***after CATT trial*** (an NIH sponsored RCT comparing ranibuizumab and bevacizumab published **in 2011**) found a similar efficacy of the two drugs but **more Severe Systemic Adverse Events (SSAEs) with bevacizumab**

At the time, ***bevacizumab (off-label) cost 40$ and ranibizumab (approved) 2000$***

This supported **Genentech and Novartis' claim that only on-label drugs should be used**

EDITORIAL

Emerging Evidence Concerning Systemic Safety of Anti-VEGF Agents – Should Ophthalmologists Be Concerned?

LAURENCE S. LIM, CHUI MING GEMMY CHEUNG, PAUL MITCHELL, AND TIEN Y. WONG

CATT STUDY
NIH 2011

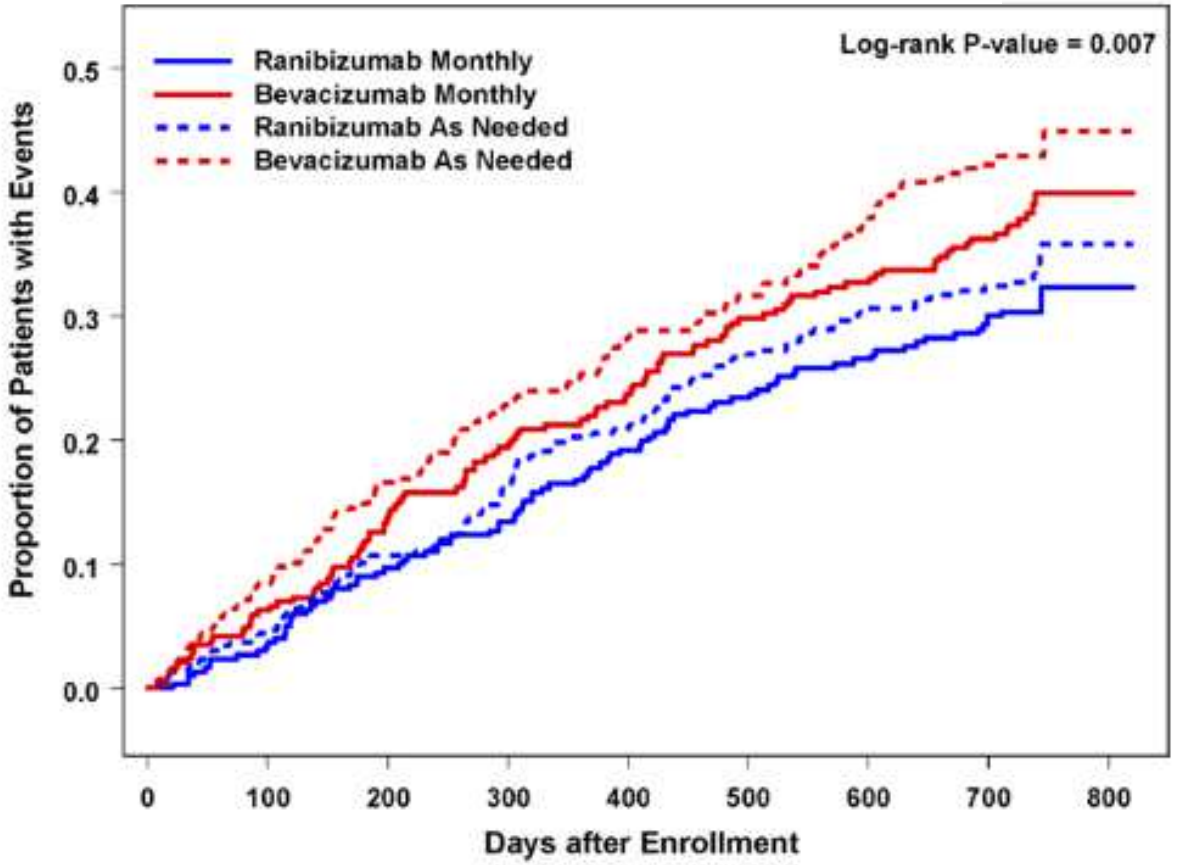


Figure 8. The cumulative proportion of patients with 1 or more systemic serious adverse events by originally assigned dosing regimen and drug.

EDITORIAL

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Bevacizumab: not as good with more adverse reactions?

Safety Implications of Vascular Endothelial Growth Factor Blockade for Subjects Receiving Intravitreal Anti–Vascular Endothelial Growth Factor Therapies

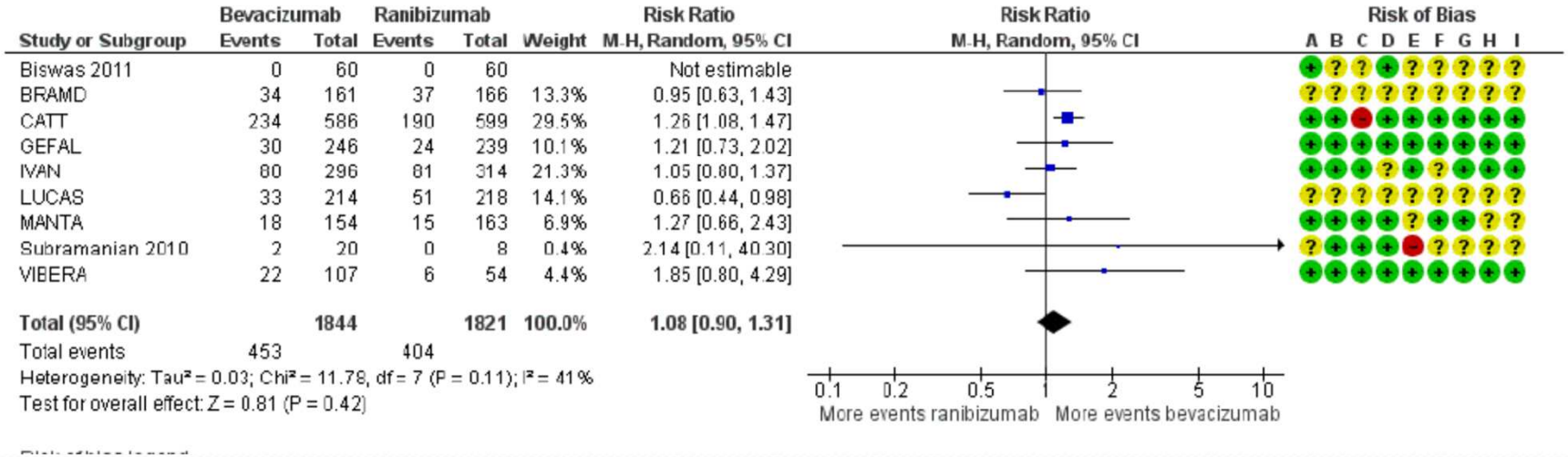
KARL CSAKY AND DIANA V. DO

Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration (Review)

Moja L, Lucenteforte E, Kwag KH, Bertele V, Campomori A, Chakravarthy U, D'Amico R, Dickersin K, Kodjikian L, Lindsley K, Loke Y, Maguire M, Martin DF, Mugelli A, Mühlbauer B, Püntmann I, Reeves B, Rogers C, Schmucker C, Subramanian ML, Virgili G

2014

Figure 4. Forest plot of comparison: 1 Bevacizumab versus ranibizumab, longest follow-up, outcome: 1.2 All serious systemic adverse events.



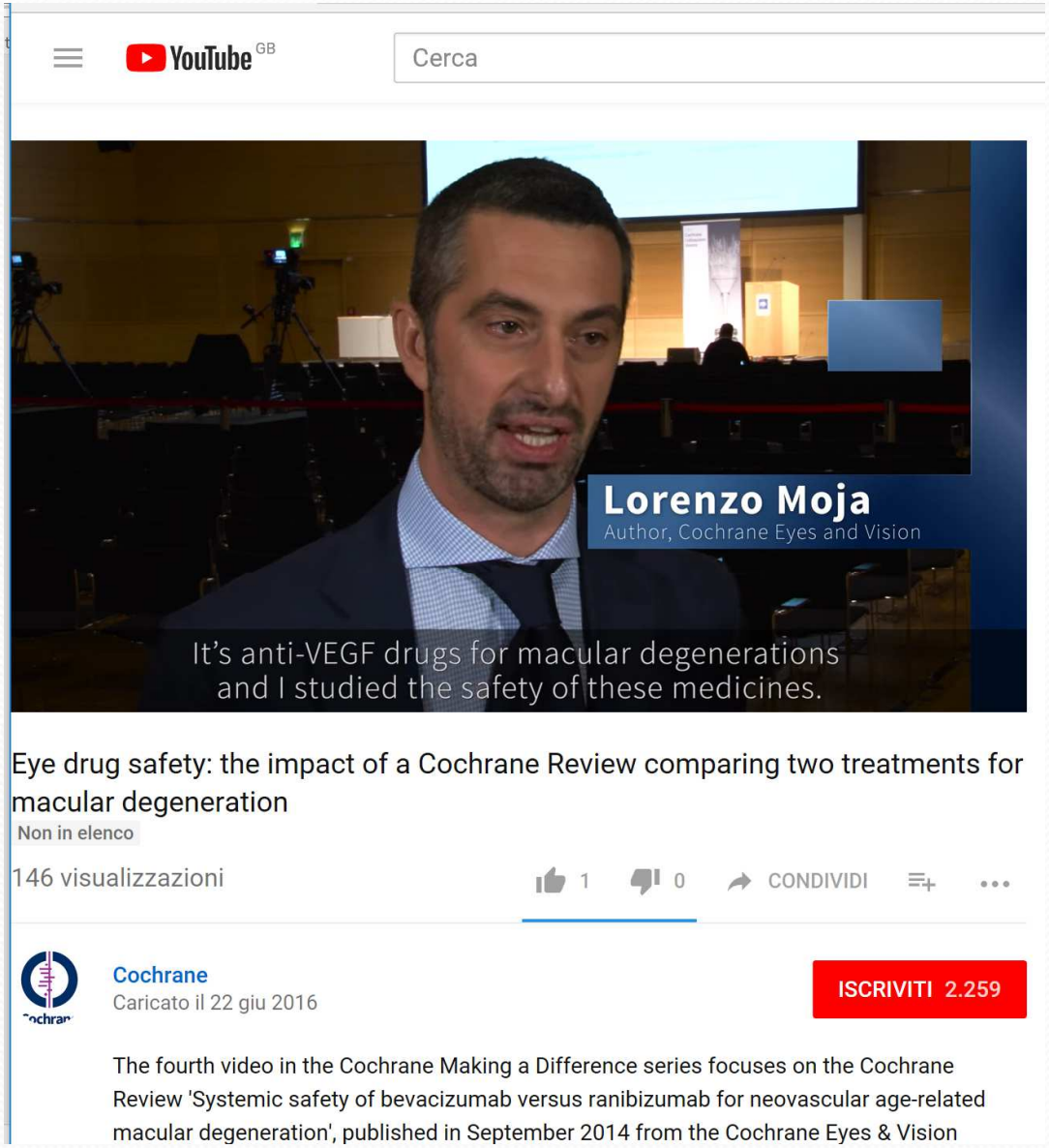
Bevacizumab compared with ranibizumab for neovascular age-related macular degeneration

Patient or population: patients with neovascular age-related macular degeneration
Intervention: bevacizumab
Comparison: ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Ranibizumab	Bevacizumab			
All-cause death Follow-up: 1 to 2 years	**34 per 1000**	**37 per 1000** (27 to 53)	**RR 1.10** (0.78 to 1.57)	3338 (8)	⊕⊕⊕◯ **moderate** 1,2,3
All serious systemic adverse events Follow-up: 1 to 2 years	**222 per 1000**	**240 per 1000** (200 to 291)	**RR 1.08** (0.90 to 1.31)	3665 (9)	⊕⊕◯◯ **low** 1,2,3,4
Infection	**37 per 1000**	**50 per 1000** (36 to 69)	**RR 1.34** (0.97 to 1.86)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3
Arterial thromboembolic event	**35 per 1000**	**32 per 1000** (21 to 47)	**RR 0.92** (0.62 to 1.37)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3
Myocardial infarction	**14 per 1000**	**12 per 1000** (6 to 23)	**RR 0.84** (0.42 to 1.66)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3
Stroke	**11 per 1000**	**9 per 1000** (5 to 19)	**RR 0.83** (0.42 to 1.66)	3190 (6)	⊕⊕⊕◯ **moderate** 1,2,3
Gastrointestinal disorders MedDRA class	**16 per 1000**	**29 per 1000** (16 to 50)	**RR 1.82** (1.04 to 3.19)	3190 (6)	⊕⊕⊕◯ **moderate** 1,4,5

http://www.cochrane.org/news/eye-drug-safety-impact-cochrane-review-comparing-two-treatments-macular-degeneration

https://youtu.be/PyfRW2zHNBI



BMJ 2014;349:g6887 doi: 10.1136/bmj.g6887 (Published 19 November 2014)

EDITORIALS

What is stopping the NHS from using bevacizumab for macular degeneration and other retinal disorders?

Government must act to remove the hurdles

Andrew Lotery *professor*[1], Carrie MacEwen *president*[2]

BMJ 2012;344:e3162 doi: 10.1136/bmj.e3162 (Published 2 May 2012)

EDITOR'S CHOICE

Avastin versus Lucentis

Fiona Godlee *editor, BMJ*

2014-2015

BMJ 2015;350:h2050 doi: 10.1136/bmj.h2050 (Published 16 April 2015)

NEWS

Minister rules out use of Avastin over Lucentis for wet AMD

Zosia Kmietowicz

The BMJ

A UK government minister has ruled that it is illegal and against the wider public interest to use the cheaper drug bevacizumab (Avastin) to treat wet age related macular degeneration (AMD) instead of the more expensive ranibizumab (Lucentis).

However, a barrister with expertise in healthcare law has criticised the ruling as "confused and illogical" and that the minister is acting outside his remit.

But an investigation by *The BMJ* pointed out that bevacizumab was neither unlicensed nor generic, as was the situation with the drugs in the Polish case, and questioned the relevance of this case law to the prescribing of bevacizumab in the United Kingdom.[2]

David Lock QC rebuked the minister's response to the situation. He told *The BMJ*, "It is unfortunate that the minister appears

BMJ 2015;350:h1981 doi: 10.1136/bmj.h1981 (Published 13 April 2015)

NEWS

GMC is criticised for refusing to disclose reasons behind its advice to support prescribing for Lucentis rather than Avastin for wet AMD

Deborah Cohen

The BMJ

Doctors, commissioners, and drug safety experts have criticised the UK General Medical Council for a lack of transparency over its prescribing guidance and for conflating European laws governing drug marketing with laws governing drug prescribing.

authorisation," he said, adding, "It seems a pity that law intended for one purpose is used for another."

How the GMC's position compares with positions in other European countries is unclear. Ophthalmologists from Ireland,

World Health Organization
REGIONAL OFFICE FOR Europe

Who on regulatory issues

Access to new medicines in Europe:

technical review of policy initiatives and opportunities for collaboration and research

4.2.5. Off-label policies: drug registration versus effectiveness

In Italy the outcry following a verdict of the Competition Authority in February 2014 around bevacizumab resulted in the Italian Medicines Agency readmitting it as a therapeutic option for AMD. More generally, however, a further result was a change in legislation to allow the off-label use of drugs, provided that strong evidence on their effectiveness and safety is available (Decree Law 36/2014 of 20 March 2014). Specifically, the Authority fined the multinational drug companies commercializing the two drugs €182 million for cartelizing the sales of two major ophthalmic drugs (bevacizumab and ranibizumab) in order to channel demand towards the more expensive of the two *(118)*. Following the case in Italy an investigation started in France, and a law was passed to reallow the use of the less expensive drug *(119)*.

WHO has expressed a clear position regarding off-label uses: the listing of only those drugs that have been registered was challenged in its model essential medicines list (EML), which considers "evidence of efficacy and safety and demonstrable public health importance as the main criteria for inclusion … rather than the indications having been approved by regulatory authorities in national settings" *(120)*. In fact, bevacizumab was included in the EML for the treatment of AMD in April 2013. National drug policies could consider following the WHO position towards the evidence-based (and not registration-based) reimbursement of drugs, in order to facilitate access to effective drugs and affordability of treatments.

Commentary: NHS patients should have a choice of drug for wet age-related macular degeneration, despite pressure from pharma

2017-2018

David Hambleton *chief officer*

South Tyneside Clinical Commissioning Group, Jarrow, UK

CCGs face legal threat for offering off-label drug for wet AMD

INVESTIGATION

Are the odds shifting against pharma in the fight for cheaper treatment for macular degeneration?

Doctors plan to prescribe bevacizumab despite legal threats from drug companies, and against GMC and NICE guidance. Responses to the policy and new legal rulings hint at a turning point in a long-running battle in which £0.5bn potential NHS savings are at stake, reports **Deborah Cohen**

Deborah Cohen *associate editor, The BMJ*

Ophthalmologists should be able to prescribe bevacizumab, says royal college

Deborah Cohen

BMJ

Doctors are cleared to prescribe cheaper drug for wet AMD

Deborah Cohen

Court of Justice of the European Union
PRESS RELEASE No 06/18
Luxembourg, 23 January 2018

Judgment in Case C-179/16
F. Hoffmann-La Roche Ltd and Others v Autorità Garante della Concorrenza e del Mercato

Press and Information

The agreement between the pharmaceutical groups Roche and Novartis designed to reduce the use of Avastin in ophthalmology and to increase the use of Lucentis might constitute a restriction of competition 'by object'

The Court recalls that, in principle, medicinal products that may be used for the same therapeutic indications belong to the same market. However, the fact that pharmaceutical products are manufactured or sold unlawfully prevents them from being regarded as substitutable with products manufactured and sold lawfully. Nevertheless, the EU rules governing pharmaceutical matters prohibit neither the prescription of a medicinal product outside the conditions laid down in its marketing authorisation (MA) nor its repackaging for such off-label use, provided that they comply with certain conditions. It is not for the AGCM but for the national courts or the competent authorities to verify that those conditions are satisfied. The Court then notes that, for the treatment of eye diseases, there is a specific relationship of substitutability between Lucentis and Avastin when used off label.

BMJ 2018;360:k511 doi: 10.1136/bmj.k511 (Published 31 January 2018)

NEWS

Off-label drugs directly compete with licensed drugs for same use, rules European court

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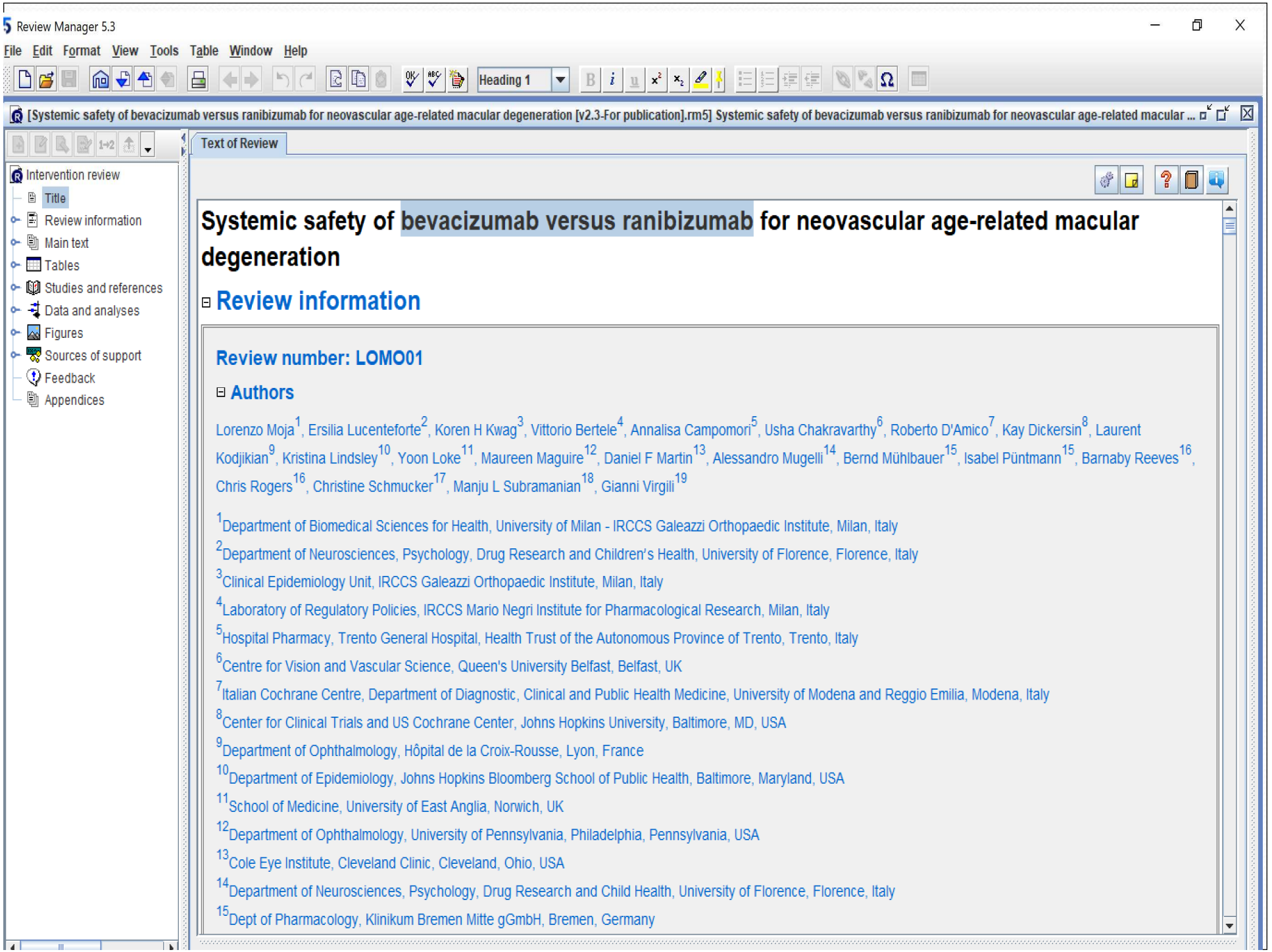
RCOphth welcomes EU Court of Justice Advocate General's new opinion on the use of 'off-label' drug Avastin

31 October 2017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Text of Review
Intervention review
Title
Review information
Main text
Tables
Studies and references
Data and analyses
Figures
Sources of support
Feedback
Appendices
Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration
Review information
Review number: LOMO01
Authors
Lorenzo Moja[1], Ersilia Lucenteforte[2], Koren H Kwag[3], Vittorio Bertele[4], Annalisa Campomori[5], Usha Chakravarthy[6], Roberto D'Amico[7], Kay Dickersin[8], Laurent Kodjikian[9], Kristina Lindsley[10], Yoon Loke[11], Maureen Maguire[12], Daniel F Martin[13], Alessandro Mugelli[14], Bernd Mühlbauer[15], Isabel Püntmann[15], Barnaby Reeves[16], Chris Rogers[16], Christine Schmucker[17], Manju L Subramanian[18], Gianni Virgili[19]
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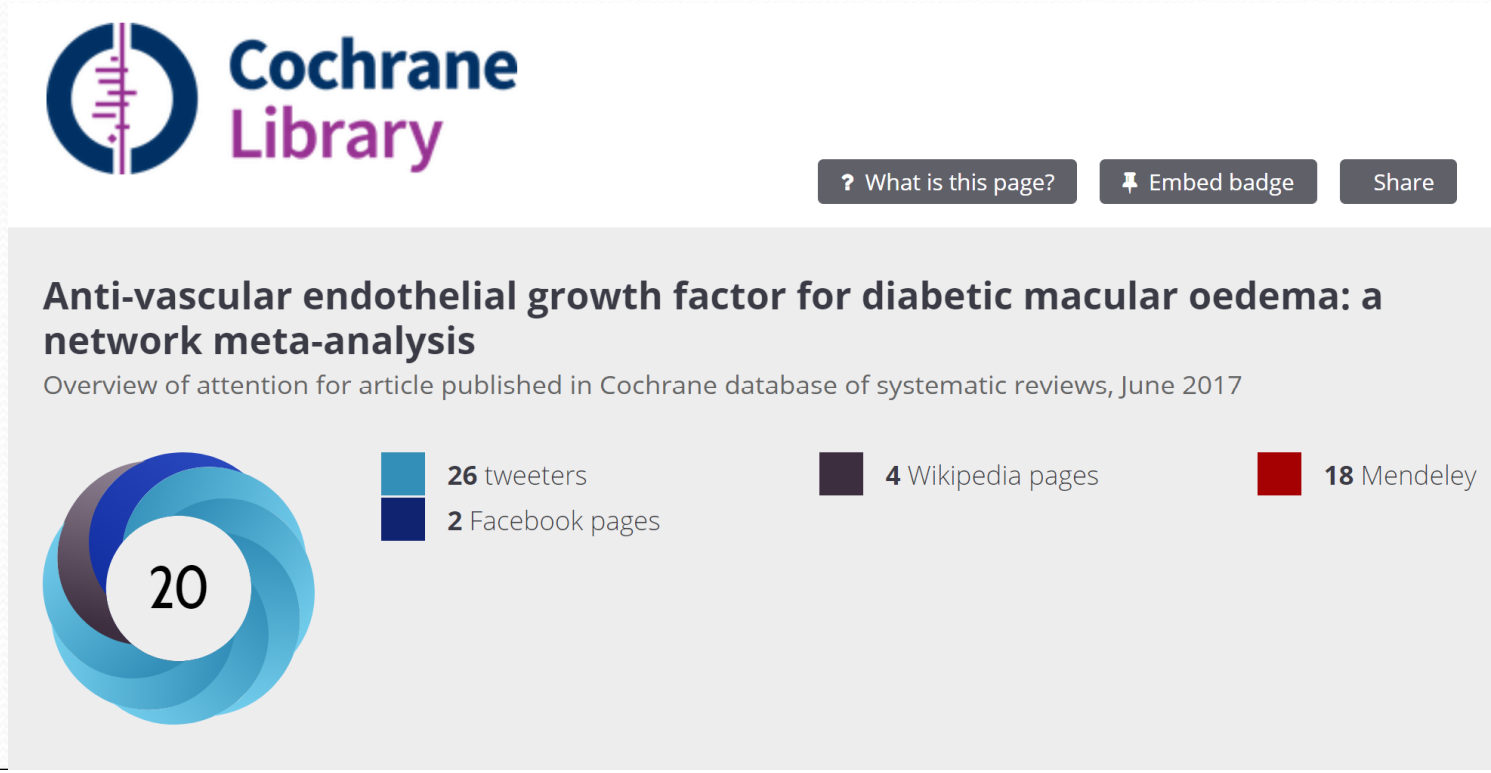
Authors' conclusions

This systematic review of **non-industry sponsored RCTs could not determine a difference between intravitreal bevacizumab and ranibizumab for deaths, All SSAEs, or specific subsets of SSAEs in the first two years of treatment**, with the exception of gastrointestinal disorders. The current evidence is imprecise and might vary across levels of patient risks, but overall suggests that if a difference exists, it is likely to be small. **Health policies for the utilisation of ranibizumab instead of bevacizumab as a routine intervention for neovascular AMD for reasons of systemic safety are not sustained by evidence.** The main results and quality of evidence should be verified once all trials are fully published.

Last year another CEV review and **network meta-analysis on antiangiogenic drugs for diabetic macular oedema** found **some advantage in terms of visual acuity at one year with aflibercept over ranibizumab and bevacizumab,** but **data at two years were limited to the single largest study**, which found similar efficacy or very small differences among the three drugs.
This is a limitation of evidence production and no (network) meta-analysis was possible at 2 years.



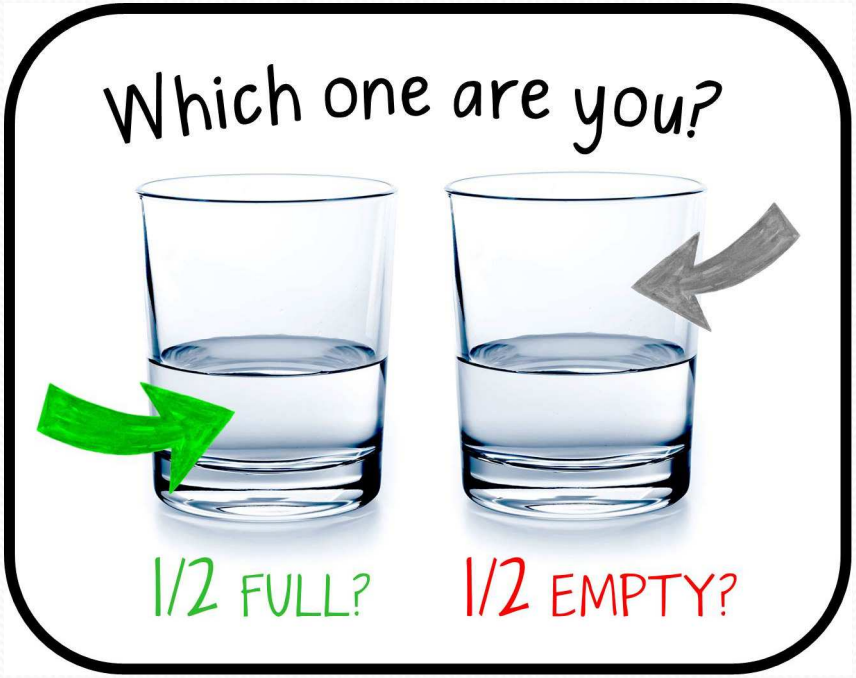
Authors' conclusions

Anti-VEGF drugs are effective at improving vision in people with DMO with three to four in every 10 people likely to experience an improvement of 3 or more lines VA at one year. There is moderate-certainty evidence that aflibercept confers some advantage over ranibizumab and bevacizumab in people with DMO at one year in visual and anatomic terms.

Relative effects among anti-VEGF drugs at two years are less well known, since most studies were short term. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often under-treated and under-monitored.

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

A small difference with the newest drug?



The three drugs are about the same?

Conclusion. **Words matter, even in science (especially in the abstract)**, and a 'neutral' statement on efficacy and safety in highly debated topics may be difficult for review authors to formulate (also think of flu vaccine).

Question. Should public stakeholders views be considered formally when formulating conclusions of potentially high-impact reviews?

Antiangiogenic therapy versus control

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

Outcomes	Assumed risk*	Corresponding risk and relative risk** (95% CI), mixed evidence			Certainty of evidence and reason for downgrading
	Laser photocoagulation	Aflibercept	Bevacizumab	Ranibizumab	
Gain 3+ lines of visual acuity at 1 year	100 per 1000	366 per 1000 (279 to 479) RR: 3.66 (2.79 to 4.79)	247 per 1000 (181 to 337) RR: 2.47 (1.81 to 3.37)	276 per 1000 (212 to 359) RR: 2.76 (2.12 to 3.59)	⊕⊕⊕⊕ high
Visual acuity change at 1 year Measured on the logMAR scale, range −0.3 to 1.3. Higher values represent worse visual acuity.	On average visual acuity improved by −0.01 logMAR units in the laser group between the start of treatment and 1 year (effectively no change)	Average change in visual acuity was −0.20 (−0.22 to −0.17) logMAR units better with aflibercept compared with laser photocoagulation	Average change in visual acuity was −0.12 (−0.15 to −0.09) logMAR units better with bevacizumab compared with laser photocoagulation	Average change in visual acuity was −0.12 (−0.14 to −0.10) logMAR units better with ranibizumab compared with laser photocoagulation	⊕⊕⊕⊕ high for aflibercept and ranibizumab ⊕⊕⊕ moderate for bevacizumab (−1 for inconsistency of indirect versus direct evidence)