BMJ Open

Anti–Vascular Endothelial Growth Factor Treatment for Retinal Conditions: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022031
Article Type:	Research
Date Submitted by the Author:	29-Jan-2018
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Keywords:	ranibizumab, bevacizumab, aflibercept, anti-vascular endothelial growth factor, age-related macular degeneration, diabetic macular edema

Anti–Vascular Endothelial Growth Factor Treatment for Retinal Conditions: A Systematic Review and Meta-analysis

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Word count: 285/300 (Abstract), 3397/4000 (Main text), 1 figure, 4 tables, 2 supplementary files

ABSTRACT

Objectives: To evaluate the comparative effectiveness and safety of intravitreal bevacizumab, ranibizumab, and aflibercept for patients with choroidal neovascular age-related macular degeneration (cn-AMD), diabetic macular edema (DME), macular edema due to retinal vein occlusion (RVO-ME) and myopic choroidal neovascularization (m-CNV).

Design: Systematic review and random effects meta-analysis.

Methods: Multiple databases were searched from inception to August 17th, 2017 (MEDLINE, Embase, Cochrane Central). Eligible head-to-head randomized controlled trials (RCTs) comparing the anti-VEGF drugs in patients aged ≥18 years with the retinal conditions of interest. Two reviewers independently extracted data and assessed risk of bias using the Cochrane risk-of-bias tool.

Results: Nineteen RCTs involving 7459 patients with: cn-AMD (n=12), DME (n=3), RVO-ME (n=2), and m-CNV (n=2) were included. Vision gain was not significantly different in patients with cn-AMD, DME, RVO-ME, and m-CNV treated with bevacizumab versus ranibizumab. Similarly, vision gain was not significantly different between cn-AMD patients treated with aflibercept versus ranibizumab. In DME patients treated for 2 years, vision gain was as likely to be attained with aflibercept as with ranibizumab or bevacizumab; however, in the first year of treatment, patients treated with aflibercept were more likely to attain vision gain than patients with ranibizumab or bevacizumab. Rates of systemic serious harms were similar among bevacizumab, ranibizumab, and aflibercept. For cn-AMD patients, compared to monthly treatment, an as-needed treatment regimen (6-9 injections per year) was associated with a mortality increase of 1.8% (RR: 2.0, [1.2, 3.5], 2 RCTs, 1795 patients) in a post-hoc analysis.

Conclusions: With few exceptions, intravitreal bevacizumab was a reasonable alternative to ranibizumab and aflibercept in patients with wet cn-AMD, DME, RVO-ME and m-CNV. However, the choice of anti-VEGF drugs may depend on the specific retinal condition, baseline visual acuity, and treatment regimen.

Trial registration: PROSPERO CRD 42015022041

Keywords: ranibizumab, bevacizumab, aflibercept, anti-vascular endothelial growth factor, age-related macular degeneration, diabetic macular edema, retinal vein occlusion, myopic choroidal neovascularization

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Our systematic review serves as an update to existing systematic reviews of individual retinal conditions, including recent head-to-head trials in patients with RVO-ME and DME, and long-term follow-up data for patients with cn-AMD. We consolidated the evidence for treatment choice of all common retinal conditions, allowing the interpretation of the strength of the evidence of benefits and harms of the anti-VEGF drugs across conditions.
- We summarized information regarding treatment regimens (e.g., 3 initial monthly intravitreal injections and as-needed monthly retreatment, treat and extend), as-needed retreatment criteria, and the reconstitution of bevacizumab. We examined the influence of the choice of treatment regimens on the benefits and harms of the anti-VEGF drugs for specific retinal conditions.
- We limited our review to English studies. We found a limited number of RCTs evaluated the anti-VEGF drugs in patients with RVO-ME and m-CNV. Our sensitivity and subgroup analyses were not specified *a-priori* and should be interpreted with caution.

BACKGROUND

Retinal conditions due to neovascular abnormality are common in older adults. Choroidal neovascular age-related macular degeneration (cn-AMD) is the leading cause of irreversible blindness in individuals aged 50 years or older in high-income countries.[1 2] If left untreated, potentially irreversible visual impairment can also be caused by diabetic macular edema (DME) and macular edema due to retinal vein occlusion (RVO-ME).[3-5] Choroidal neovascularization secondary to pathologic myopia (myopic CNV) is another major cause of blindness and visual impairment worldwide.[6 7] Together, these retinal diseases cause substantial reduction in quality of life, and are a significant burden on healthcare systems.[8]

Ranibizumab, off-label use of repackaged bevacizumab, and aflibercept are widely used anti-vascular endothelial growth factor (anti-VEGF) drugs for intravitreal treatment of retinal conditions. Multiple systematic reviews have evaluated the comparative effectiveness of anti-VEGF drugs in patients with cn-AMD, DME, RVO-ME, and m-CNV;[9-12] but given the publication of new trials in patients with RVO-ME[13] and DME,[14] and long-term follow-up data for patients with cn-AMD,[15] an update is necessary. We aimed to conduct a systematic review to evaluate the comparative effectiveness and safety of bevacizumab, ranibizumab, and aflibercept for patients with cn-AMD, DME, RVO-ME, and m-CNV.

METHODS

A systematic review regarding the comparative efficacy and safety of the anti- VEGF drugs was planned in response to a query from the Canadian Drug Safety and Effectiveness Network (PROSPERO CRD 42015022041), for which a preliminary report was prepared to inform listing

recommendations.[16 17] The report included a meta-analysis of pairwise comparisons of the anti-VEGF drugs for individual retinal conditions, as well as a network meta-analysis to evaluate the anti-VEGF drugs in cn-AMD patients. This paper summarizes results of the meta-analysis; a separate paper is underway for the network meta-analysis results.

The current review was conducted using the Cochrane Handbook for Systematic Reviews and reported using the PRISMA statement[18] (Additional file 1). The methods are outlined briefly below, as they are described in greater detail in Additional file 2: Appendix 1 and a related therapeutic review report.[17]

Data Sources and Searches:

MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were searched. Studies that are not widely available or commercially published (i.e., grey literature), were identified using an established approach.[19] Additional studies were identified by searching reference lists of included studies, and email correspondence with expert clinicians and anti-VEGF drug manufacturers.

An information specialist developed the search strategy, which was peer-reviewed by another information specialist using the PRESS statement.[20] The MEDLINE strategy can be found in Additional file 2: Appendix 1. The search was conducted on May 27th, 2015 and updated on August 17th, 2017.

Study Selection:

Eligible studies were randomized controlled trials (RCTs) that directly compared intravitreal bevacizumab, ranibizumab, and/or aflibercept for the treatment of patients (aged ≥18 years) with

cn-AMD, DME, RVO-ME or m-CNV. Due to time and resource constraints, we only included studies published in English.

Eligible RCTs reported one of the following benefits and harms outcomes: vision gain, defined as a gain in Best-Corrected Visual Acuity (BCVA) letter score of ≥15 on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart;[21] vision loss, defined as a loss in BCVA letter score of ≥15; mean change in BCVA from baseline; legal blindness (BCVA of 20/200 or worse measured on a standard Snellen chart, or worse than 20/100 visual acuity measured on ETDRS chart); vision-related function according to the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25;[22] serious adverse events; all-cause mortality; arterial thromboembolic events (TEs); venous TEs; bacterial endophthalmitis; and retinal detachment. All titles/abstracts and potentially relevant full-text articles were screened by two reviewers, independently. Discrepancies were discussed and if necessary, resolved with input from a third reviewer. When multiple reports of the same trial were identified, the main report was included, and the others were treated as companion reports.[23]

Data Extraction and Quality Assessment:

Data extraction forms were developed with input from three clinicians, pilot-tested, and refined twice. Data extraction was conducted by two reviewers, independently. Discrepancies were discussed and if necessary, resolved with input from a third reviewer. A similar approach was followed for quality assessment using the Cochrane risk-of-bias tool for RCTs.[24]

Synthesis of study results

Study results were synthesized with respect to benefits and harms of treatment, treatment

regimen (e.g., monthly and as-needed regimens), and trends in BCVA improvement over time. With respect to visual acuity improvement, meta-analyses were conducted with studies reporting BCVA letter score as measured on the ETDRS chart. For studies reporting visual acuity in logMAR and decimal values, the values were converted to approximate ETDRS letter scores,[25] with approximate standard deviations.[26] Pairwise comparisons of drugs were assessed at the longest treatment duration, allowing for the inclusion of trials in the meta-analysis that reported outcome data at different time points. Subgroup analyses were conducted at 12 months and 24 months, as these were the most frequently reported time points. A post hoc analysis was conducted to compare different treatment regimens across the drugs. For DME patients, treatment effect estimates were obtained for all patients as well as subgroups based upon baseline BCVA, which were pre-specified in the DRCR.net trial.[27] The meta-analysis was conducted using a random-effects model, as we assumed treatment effects varied across trials. A sensitivity analysis was conducted by restricting results to trials determined to be at low risk of selection bias. Between-study heterogeneity was assessed using the I^2 statistic, with values above 75% indicating substantial heterogeneity.[28]

RESULTS

Literature search

After screening 3176 titles/abstracts and 440 full-text articles, 19 head-to-head RCTs of the anti-VEGF drugs were included, with 7459 patients, including 12 RCTs for cn-AMD, 3 RCTs for DME, 2 RCTs for RVO-ME, and 2 RCTs for m-CNV (Figure 1, Additional file 2: Appendix 1).[27 29-42] Given our inclusion criteria, we excluded RCTs that compared anti-VEGF drugs with placebo or laser photocoagulation.[43-49]

Study and patient characteristics

Studies were completed between 2010 and 2017 with an average sample size of 393 patients per trial (range: 28, 1240) (Table 1, Additional file 2: Appendix 2-3). The mean age ranged from approximately 60 to 80 years, and females accounted for 5% to 76% of the patients. The average follow-up duration was 13 months (range: 6-24 months). RCTs were conducted in Europe (n=8), North America (n=5), Asia (n=4), Africa (n=1) and across multiple continents (n=1); most were multi-centre RCTs (n=13), in addition to 6 single-centre RCTs.

Risk of bias assessment

Random sequence generation and allocation concealment were unclear for 12/19 (63.2%) and 9/19 (47.4%) of the included RCTs, respectively, suggesting the potential for selection bias (Additional file 2: Appendix 4-5). The RCTs were at low risk with respect to blinding of participants and trial personnel 18/19 (94.7%), blinding of outcome assessment 18/19 (94.7%), incomplete outcome data 13/19 (68.4%), and selective reporting 13/19 (68.4%). Two of the 19 RCTs (10.5%) were industry-funded.[38]

Patients with cn-AMD

Comparative effectiveness of bevacizumab and ranibizumab

Results from 10 RCTs (3302 patients) showed that approximately 22% of patients attained vision gain with treatment, and patients treated with bevacizumab were as likely to attain vision gain as those treated with ranibizumab (Risk Ratio (RR): 1.05; [95% confidence interval (CI), 0.93, 1.19], Table 2, Additional file 2: Appendix 6-7). Over an average treatment duration of 16 months, approximately 94% of patients maintained their vision, with no statistical difference

between patients treated with bevacizumab or ranibizumab (RR of vision loss: 0.91 [95% CI, 0.70, 1.19]). Patients treated with bevacizumab or ranibizumab gained an average of 7 letters in terms of mean BCVA with no statistical difference between the drugs (mean difference [MD] 0.03 letters [95% CI, -1.02, 1.08]). Approximately 2-4% patients treated with bevacizumab or ranibizumab became legally blind (RR: 2.04 [95% CI, 0.32 to 12.50], 3 trials, 1823 patients). Overall, the results were consistent across the 10 trials and did not change with the sensitivity analyses restricted to trials determined to be at low risk of selection bias and with different follow-up lengths (Additional file 2: Appendix 6, 8-9).

Treatment regimens

Additional file 2: Appendix 10 provides detailed information regarding the treatment regimens in the included trials, the as-needed re-treatment criteria and the reconstitution of bevacizumab for intravitreal injections. The treatment regimens varied widely, and are summarized in Table 3 along with the mean number of injections per year for each treatment regimen. The number of reported treatment regimens varied by condition (cn-AMD (n=6), DME (n=3), RVO-ME (n=2), and m-CNV (n=1)). In cn-AMD patients, the two most commonly reported regimens for bevacizumab and ranibizumab included monthly injections (~11 injections/year) and 3 monthly injections followed by as-needed treatment (~6 injections/year). Aflibercept was most commonly administered using a monthly regimen (~11 injections/year).

Results of our post hoc analysis comparing as-needed versus monthly treatment in cn-AMD patients are summarized in Table 4. The as-needed treatment regimen with ranibizumab or bevacizumab was less effective than the monthly regimen in improving mean BCVA (MD: -1.9 letters [95% CI, -0.5 to -3.3 letters], 2 RCTs, 1622 patients) and vision gain (RR: 0.73 [95% CI,

0.55 to 0.95]). When the regimens were assessed for non-inferiority at 1 year with an inferiority margin of 5 points, monthly bevacizumab was equivalent to monthly ranibizumab (MD: -0.5 [95% CI, -3.9, 2.9]), as-needed bevacizumab was equivalent to as-needed ranibizumab (MD: -0.8 [95% CI, -4.1, 2.5]), as-needed ranibizumab was equivalent to monthly ranibizumab (MD: -1.7 [95% CI, -4.7, 1.3]) but monthly bevacizumab was not equivalent to as-needed bevacizumab (MD: -2.1 [95% CI, -5.7, 1.6]).[50] Compared to the monthly regimen, the as-needed regimen was associated with a significant increase in mortality of 1.8% (95% CI, 0.1% to 3.4%) [RR, 2.0; 95% CI, 1.2 to 3.5].

Comparative effectiveness of aflibercept and ranibizumab

Results from 2 RCTs (1815 patients; Table 2, and Additional file 2: Appendix 6) showed that approximately 32% of patients attained vision gain with treatment, and patients treated with aflibercept were as likely to attain vision gain as patients treated with ranibizumab (RR: 0.99 [95% CI, 0.81 to 1.22]). Over an average assessment and treatment duration of 12 months, approximately 95% of patients maintained their vision, and aflibercept patients were as likely to maintain vision as ranibizumab patients (RR of vision loss: 0.90 [95% CI, 0.60 to 1.35]). With respect to mean BCVA, patients gained on average 9 letters (MD: -0.05 [95% CI, -2.5, 2.4]). Compared to baseline, patients gained some visual-related function, with an average of 5 points on the NEI-VFQ-25 questionnaire (MD: 2.2 [95% CI, -0.6, 5.1]).

Harms

Over an average of 14 months (range: 12-24 months), mortality was reported in 4% and 3% of patients treated with bevacizumab or ranibizumab, respectively (RR: 1.14 [95% CI, 0.72 to

1.79], 6 RCTs, 2941 patients, Additional file 2: Appendix 6). Serious adverse events were reported in 19 and 18% of patients treated with bevacizumab or ranibizumab, respectively (RR: 1.09 [95% CI, 0.93 to 1.27], 5 RCTs, 3026 patients). Arterial thromboembolic events were reported in 4% and 3%of patients treated with bevacizumab or ranibizumab, respectively (RR: 0.86 [95% CI, 0.51, 1.47], 4 RCTs, 2033 patients). Venous thromboembolic events, bacterial endophthalmitis and retinal detachment were reported in <1% of patients treated with either drug. In the trials evaluating aflibercept and ranibizumab, arterial thromboembolic events were reported in 2% of patients treated with aflibercept or ranibizumab (RR: 0.96 [95% CI, 0.45, 2.04], 2 RCTs, 1818 patients), and venous thromboembolic events were reported in <1% of patients treated with either drug. Data on other harms were not available.

Patients with DME

Comparative effectiveness of ranibizumab, bevacizumab and aflibercept

Results from the trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net trial, 620 patients) showed that over 2 years of treatment, patients were as likely to attain vision gain with ranibizumab (37%), bevacizumab (35%), or aflibercept (39%) - bevacizumab versus ranibizumab: RR: 0.94 [95% CI, 0.72, 1.23]; aflibercept versus bevacizumab: RR: 1.06 [95% CI, 0.80, 1.38]; and aflibercept versus ranibizumab: RR: 1.06 [95% CI, 0.82, 1.37]; Table 2) Over 2 years of treatment, approximately 98% of patients maintained their vision with all 3 drugs. Patients' mean BCVA improved by 13 letters with aflibercept, 10 letters with bevacizumab and 12 letters with ranibizumab (aflibercept versus ranibizumab: MD, 1.4 [95% CI, -1.6, 4.3]; bevacizumab versus aflibercept: MD, -2.7 [95% CI, -5.2 to -0.3]; and bevacizumab versus

ranibizumab: MD, -2.0 [95% CI, -3.9 to -0.1], Table 2).

Treatment regimen

With respect to treatment regimen, the DRCR.net trial treated patients initially with monthly injections until stable visual acuity within 6 months, followed by as-needed treatment (Additional file 2: Appendix 10).[51] The median number of injections administered over a one-year period was 10 in the bevacizumab group, 9 in the aflibercept group, and 10 in the ranibizumab group (Table 3).[51] In the second year, the median number of injections was: 6, 5, and 6 in the bevacizumab, aflibercept, and ranibizumab groups, respectively.[52] Two smaller trials both started treatment with 3 monthly intravitreal injections, followed by varying as-needed retreatment criteria (Table 3).[14 31]

Harms

After 24 months of treatment in the DRCR.net trial,[27] mortality was reported in approximately 6% of bevacizumab patients, 2% of aflibercept patients and 5% of ranibizumab patients (Additional file 2: Appendix 6). Serious adverse events were reported in 21% of bevacizumab patients, 27% of aflibercept patients, and 25% of ranibizumab patients. Arterial thromboembolic events were reported in 4%, 3%, and 5%, of patients treated with bevacizumab, aflibercept, and ranibizumab, respectively. Bacterial endophthalmitis and retinal detachments were reported in <1% of patients treated with any of the drugs.

Patients with RVO-ME

Comparative effectiveness of ranibizumab, bevacizumab, and aflibercept

Results from 1 RCT (77 patients) showed that approximately 59% of patients attained vision gain with bevacizumab and ranibizumab treatment, and no statistical difference was observed between the drugs (RR: 1.0 [95% CI, 0.68 to 1.45]; Table 2 and Additional file 2: Appendix 8).[32] With respect to mean BCVA, patients treated with either drug gained an average of 16 letters (MD -2.5 [95% CI, 8.0 to 5.0]).

Results from the SCORE2 trial (348 patients) showed that approximately 61% of patients treated with bevacizumab or aflibercept attained vision gain, with no statistical difference between the drugs (RR: 1.06 [95% CI, 0.91 to 1.25]; Table 2).[13] With respect to mean BCVA, patients treated with either drug gained an average of 19 letters (MD 1.52 [95% CI, -1.2 to 4.2]).

Treatment regimens

In the SCORE2 trial, patients were treated with monthly intravitreal injections for the first 6 months, with a mean number of 5.8 injections in patients treated with bevacizumab or aflibercept (Table 3 and Additional file 2: Appendix 11).[13] In another trial, patients were treated with one initial intravitreal injection and then as-needed monthly re-treatment over 6 months, with a mean number of 3 injections in patients treated with bevacizumab or ranibizumab.[12 32]

Harms

Serious adverse events were reported in 3% of bevacizumab patients and 5% of ranibizumab patients (RR: 0.5 [95% CI, 0.05 to 5.26], 1 RCT, 74 patients; Additional file 2: Appendix 8).[32] Serious adverse events were reported in 8% of the patients treated with bevacizumab or aflibercept over 6 months (RR: 0.99 [95% CI, 0.49 to 2.00], 1 RCT, 362 patients).[13]

Patients with m-CNV

Comparative effectiveness of ranibizumab and bevacizumab

Results from 1 RCT (32 patients) showed that 62% of patients treated with bevacizumab and 56% of patients treated with ranibizumab attained vision gain (RR: 1.11 [95% CI, 0.63, 1.96], 1 RCT; Table 2 and Additional file 2: Appendix 11).[30] With respect to mean BCVA, patients treated with bevacizumab gained 12 letters and patients treated with ranibizumab gained an average of 13 letters (MD: -1.3 [95% CI, -6.5 to 4.0], 2 RCTs, 80 patients).[29 30] The included trials did not report data on harms.

Treatment regimens

Both trials evaluated ranibizumab and bevacizumab with patients receiving one monthly intravitreal injection and as-needed monthly re-treatment, with a mean number of 3.1 injections in patients treated with bevacizumab and 2.4 injections per year in patients treated with ranibizumab (Table 3 and Additional file 2: Appendix 6).[29 30]

DISCUSSION

This systematic review synthesized results from 19 RCTs to evaluate the comparative effectiveness and safety of intravitreal bevacizumab, ranibizumab, and aflibercept for patients with cn-AMD, DME, RVO-ME and m-CNV. Intravitreal bevacizumab was as effective as ranibizumab in patients with cn-AMD, DME, RVO-ME, and m-CNV for the outcomes we examined. Ranibizumab was as effective as aflibercept in patients with cn-AMD.

In patients with DME that were treated for 2 years, vision gain was equally likely to be attained

with aflibercept, ranibizumab or aflibercept. In the first year of treatment, however, patients treated with aflibercept were more likely to attain vision gain than patients treated with ranibizumab or bevacizumab - differential effects that were observed mainly in patients with initial BCVA < 69 letter scores (equivalent to 20/50 or worse) but not observed in patients with initial BCVA ≥ 69 letter scores (equivalent to 20/40 or better) based on the results from the sub-group analyses. Rates of systemic serious harms were similarly low among the anti-VEGF drugs, across the retinal conditions. In our post hoc analysis, cn-AMD patients and compared to monthly treatment, an as-needed treatment regimen (i.e., 6 to 9 monthly injections per year) was significantly associated with a small loss in visual acuity, but a significant increase in mortality risk of 1.8% (RR: 2.0 [95% CI, 1.2, 3.5]).

Results from the CATT and IVAN trials showed that relative to monthly treatment, patients with cn-AMD receiving as-needed treatment experienced a significant increase in risk of mortality. Whether there are any biological explanations for the increased risk of mortality associated with fewer monthly injections is unclear and this finding may have been attributable to chance. As such, further research should be conducted to verify this result. In DME, RVO-ME and m-CNV trials, patients tended to receive fewer monthly injections per year (Table 3). None of the trials in DME, RVO-ME and m-CNV patients evaluated a monthly treatment regimen, and therefore the safety risk between as-needed and monthly regimens could not be evaluated. This requires further study.

Additional file 2: Appendix 12 displays the mean change in BCVA over time in patients treated with bevacizumab or ranibizumab. For all of the retinal conditions, patients showed improvement in mean BCVA by 3-6 months with initial monthly injections, and maintained a plateau to 24 months in the treatment of cn-AMD patients (average improvement of 6 letters),

DME patients (8 letters), RVO-ME patients (16 letters), and m-CNV patients (11 letters). Comparative outcomes beyond 6 months in patients with RVO-ME and m-CNV were lacking and as such, long-term comparative data of anti-VEGF drugs in these patients are needed.

Our findings are consistent with findings from previous systematic reviews. A meta-analysis of 6 head-to-head trials concluded that bevacizumab and ranibizumab had equivalent efficacy with respect to visual acuity in cn-AMD patients.[11] A meta-analysis of five RCTs suggested no differences in effectiveness between ranibizumab and bevacizumab in DME patients.[53] Other reviews in patients with RVO-ME and m-CNV came to similar conclusions.[9 10 54 55] Although findings were consistent with those in these recent reviews, our review serves as an update (with the inclusion of data up to 2017) while also examining the additional factor of treatment regimen.

There are several limitations worth noting. First, none of our sensitivity and subgroup analyses were specified *a-priori* and as such, these results should be interpreted with caution. This also pertains to our post-hoc analysis on treatment regimen. Secondly, we limited our review to English studies due to time and resources constraints. We believe, however, that the impact of the restrictions is small since our findings are consistent with previous systematic reviews that included RCTs reported in all languages, evaluating the same anti-VEGF drugs for specific retinal conditions,[11 53 56] and results were consistent across studies, so the impact of including additional studies reported in other languages, if any, would be insignificant. We only identified a few RCTs evaluating the anti-VEGF drugs in patients with DME, RVO-ME and m-CNV. Although the rates of reported adverse events were similar across the anti-VEGF drugs, the assessment of harms using comparative trial data is limited. We excluded RCTs which randomized eyes (instead of patients) since the reported analyses failed to adjust for the correlation between the outcomes of eyes from the same individuals.[57] Similarly, we also

excluded one quasi-randomized trial,[58] because we focused on randomized studies.

CONCLUSIONS

With few exceptions, intravitreal bevacizumab was a reasonable alternative to ranibizumab and aflibercept in patients with wet cn-AMD, DME, RVO-ME and m-CNV. The choice of anti-VEGF drug may depend on specific retinal conditions, baseline visual acuity, and treatment regimen.

LIST OF ABBREVIATIONS

Adverse event (AE); Age-related macular degeneration (wet AMD); Arterial thromboembolic events (ATE); Best-corrected visual acuity (BCVA); Bacterial endophthalmitis (BE); Confidence interval (CI); Choroidal neovascularization (CNV); Diabetic macular edema (DME); Early Treatment Diabetic Retinopathy Study (ETDRS); Randomized controlled trial (RCT); Risk ratio (RR); Macular edema due to retinal vein occlusion (RVO-ME); Standardized mean difference (SMD); Vascular endothelial growth factor (VEGF); Venous thromboembolic event (VTE)

ACKNOWLEDGEMENTS

We thank Becky Skidmore for drafting our search strategies, Kelly Farrah for peer reviewing the search strategies (PRESS), and Alissa Epworth for de-duplicating search results and obtaining full-text articles. We thank Meghan Kenny for helping screen studies for inclusion and performing quality appraisal and Jaimie Adams for helping screen studies for inclusion. We would also like to thank Michel Boucher, Sarah Berglas, Hongbo Yuan, and Sarah Jennings for their valuable contribution, insights, and for facilitating the production and dissemination of the synthesized evidence. In addition we would like to thank the clinical experts and stakeholders who provided feedback on the previous therapeutic review report. Finally, we thank Susan Le and Inthuja Selvaratnam for formatting the manuscript for submission.

CONTRIBUTORS

BP screened titles, abstracts, and full-text articles; abstracted and cleaned data, conducted quality assessment; and drafted the manuscript. SMT lead the coordination of the systematic review;

drafted the protocol; screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and helped draft and revise the manuscript. TL screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; helped conduct meta-analysis; and reviewed the manuscript. EL screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the manuscript. JH conducted the analysis and interpretation of data; and reviewed the manuscript. TR helped with conceptualizing the research design, drafting and revising the protocol, interpretation of data; and reviewed the manuscript. GJ helped draft and revise the protocol; screened titles, abstracts, and full-text articles; abstracted data; conducted quality assessment; helped interpret the data; and reviewed the manuscript. AA screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the manuscript. JPS screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the manuscript. AS screened titles, abstracts, and full-text articles; abstracted and cleaned data, conducted quality assessment; and reviewed the manuscript. RW screened titles, abstracts, and full-text articles; abstracted and cleaned data, conducted quality assessment; and reviewed the manuscript. RB abstracted and cleaned data, conducted quality assessment; and reviewed the manuscript. EM screened titles, abstracts, and full-text articles; abstracted and cleaned data; and reviewed the manuscript. SES helped with conceptualizing the research and design; interpretation of data, and reviewed the manuscript. ACT conceptualized the research and design; drafted the protocol; obtained funding; assisted with data acquisition and interpretation; and drafted and revised the manuscript. Authors ACT and BP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

FUNDING

This work was supported by the Canadian Institutes of Health Research/Drug Safety and Effectiveness Network (CIHR/DSEN). SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation. ACT is funded by a Tier 2 Canada Research Chair in Knowledge Synthesis. The therapeutic review was commissioned by the Canadian Agency for Drugs and Technology in Health (CADTH) and funded by a grant from the Canadian Institutes of Health Research Drug Safety and Effectiveness Network. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

COMPETING INTERESTS

All authors declare no competing interests.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DATA SHARING STATEMENT

All datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

MEETING PRESENTATION

The data from the original therapeutic review was presented by ACT and SMT to the Canadian Drug Expert Committee in Ottawa, Ontario, on Nov 17th, 2015.

OPEN ACCESS

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FIGURE LEGENDS

Figure 1. Study Flow

TABLE 1. SUMMARY STUDY CHARACTERISTICS

Study Characteristic	Total No. of trials included (n=19)[a] (%)	No. of studies with cn-AMD (n=12) (%)	No. of studies with DME (n=3) (%)	No. of studies with RVO-ME (n=2) (%)	No. of studies with m-CNV (n=2) (%)
Year of publication					
2010–2011	5 (26.32)	4 (33.33)	0 (0)	0 (0)	1 (50)
2012–2013	6 (31.58)	5 (41.67)	0 (0)	0 (0)	1 (50)
2014–2015	5 (26.32)	2 (16.67)	2 (66.67)	1 (50)	0 (0)
2016	3 (15.79)	1 (8.33)	1 (33.33)	1 (50)	0 (0)
Geographic region					
Europe	8 (42.11)	6 (50)	0 (0)	0 (0)	2 (100)
North America	5 (26.32)	3 (25)	1 (33.33)	1 (50)	0 (0)
Asia	4 (21.05)	2 (16.67)	1 (33.33)	1 (50)	0 (0)
Africa	1 (5.26)	0 (0)	1	0 (0)	0 (0)
Multi-continent	1 (5.26)	1 (8.33)	1 (33.33)	0 (0)	0 (0)
Setting					
Single-Centre	6 (31.58)	2 (16.67)	1 (33.33)	1 (50)	2 (100)
Multi-Centre	12 (63.16)	10 (83.33)	1 (33.33)	1 (50)	0 (0)
NR	1 (5.26)	0 (0)	1 (33.33)	0 (0)	0 (0)
Follow-up duration					
6-12 months	14 (73.68)	9 (75)	2 (66.67)	2 (100)	1 (50)
13-19 months	4 (21.05)	2 (16.67)	1 (33.33)	0	1 (50)
≥20 months	1 (5.26)	1 (8.33)	0	0	0 (0)

Footnotes:
[a] Total number of randomized controlled trials, n=19, from 18 publications

Abbreviations: cn-AMD, choroidal neovascular age-related macular degeneration; DME, diabetic macular edema; m-CNV, myopic choroidal neovascularization; NR, not reported; RVO-ME, macular edema due to retinal vein occlusion.

TABLE 2. COMPARATIVE EFFECTIVENESS RESULTS

Condition	***Treatment*** vs. ***Comparator***	Outcome[a]	# of RCTs (# of patients)	Baseline ETDRS letters[b] ~Snellen equivalent	***Treatment*** *Effect Mean (Range)*[b]	***Comparator*** effect Mean (Range)[b]	Risk Ratio or *Mean Difference* Estimate (95% CI)	I^{2c}
cn-AMD	Bevacizumab vs. Ranibizumab	Vision gain	9 (3245)	57 (35 to 61) ~ 20/80	22% (12 to 33)	23% (14 to 29)	0.95 (0.84, 1.07)	0%
		Vision loss	10 (3302)	60 (35 to 61) ~ 20/63	6% (0 to 11)	7% (4 to 14)	0.91 (0.7, 1.19)	4%
		BCVA change	8 (3064)	56 (35 to 61) ~ 20/80	7.2 (4.1, 15.2)	5.9 (0.6, 11.4)	*-0.03 (-1.08, 1.02)*	0%
	Aflibercept vs. Ranibizumab	Vision gain	2 (1815)	54 (53 to 55) ~ 20/80	32% (30 to 34)	32% (31 to 34)	0.99 (0.81 to 1.22)	52%
		Vision loss	2 (1815)	54 (53 to 55) ~ 20/80	5% (5 to 5)	6% (5 to 6)	0.90 (0.60 to 1.350)	0%
		BCVA change	2 (1793)	54 (53 to 55) ~ 20/80	8.8 (8.3, 9.4)	8.8 (8.1 to 9.4)	*-0.05 (-2.5, 2.4)*	66%
DME	Bevacizumab vs. Ranibizumab	Vision gain	1 (376)	65 ~ 20/50	35%	37%	0.94 (0.72, 1.23)	NA
		Vision loss	1 (376)	65 ~ 20/50	3%	2%	0.48 (0.12, 1.91)	NA
		BCVA change	2 (456)	59 (54, 65) ~ 20/63	10.3 (10.0, 10.5)	12.1 (11.9 to 12.3)	*-2.0 (-3.9, -0.1)*	0%
	Bevacizumab vs. Aflibercept	Vision gain	1 (386)	65 ~ 20/50	35%	39%	1.06 (0.80, 1.38)	NA
		Vision loss	1 (376)	65 ~ 20/50	2%	3%	2.08 (0.52, 8.33)	NA
		BCVA change	1 (386)	65 ~ 20/50	10.0 (SD: 11.8)	12.8 (SD: 12.4)	*-2.7 (-5.2, -0.3)*	NA
	Aflibercept vs. Ranibizumab	Vision gain	1 (392)	65 ~ 20/50	39%	37%	1.06 (0.73, 1.22)	NA
		Vision loss	1 (392)	65 ~ 20/50	2%	2%	0.63 (0.15, 2.61)	NA
		BCVA change	2 (462)	56 (47, 65) ~ 20/80	16.2 (12.8 to 19.6)	14.0 (12.3 to 15.7)	1.4 (-1.6, 4.3)	27%
RVO-ME	Bevacizumab vs. Ranibizumab	Vision gain	1 (74)	56 ~ 20/80	59%	59%	1.00 (0.68, 1.45)	NA
		BCVA change	1 (77)	56 ~ 20/80	15.6	18.1	*-2.5 (-8.0, 5.0)*	NA
	Bevacizumab vs. Aflibercept	Vision gain	1 (358)	50 ~ 20/100	65%	61%	1.06 (0.91, 1.25)	NA
		BCVA change	1 (348)	50 ~ 20/100	18.6	18.9	*1.5 (-1.2, 4.2)*	NA
m-CNV	Bevacizumab	Vision gain	1 (32)	30 ~ 20/250	62%	56%	1.11 (0.63, 1.96)	NA
		Vision loss	1 (32)	30 ~ 20/250	0%	0%	0%	NA

	vs. Ranibizumab	BCVA change	2 (80)	42 (30, 55) ~ 20/160	12.2 (8.5 to 15.9)	13.4 (9.5 to 17.3)	*-1.3 (-6.5, -4.0)*	0%

Footnotes:

[a] In terms of outcomes, vision gain was defined as a gain in BCVA of ≥15 EDTRS letters, vision loss of ≥15 EDTRS letters, and visual acuity was expressed using ETDRS letters (with conversion, if necessary). The main analysis was conducted with outcomes at the longest follow-up duration for each RCT.

[b] Mean (range) were derived across control groups of the included RCTs.

[c] I^2 <75 was interpreted as low evidence of substantial variation across included RCTs.

Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; cn-AMD, choroidal neovascular age-related macular degeneration; DME, diabetic macular edema; ETDRS, early treatment diabetic retinopathy study; m-CNV, myopic choroidal neovascularization; NA, not applicable; RCT, randomized controlled trials; RVO-ME, macular edema due to retinal vein occlusion.

TABLE 3. SUMMARY OF TREATMENT REGIMENS

Condition	Treatment regimen	# of RCTs	Mean monthly injections per year (range)[a]
cn-AMD	Monthly treatment with ranibizumab	5	11.3 (10.9-11.7)
	Monthly treatment with bevacizumab	3	11.5 (11.0-11.9)
	Treat and extend with ranibizumab	1	8.0
	Treat and extend with bevacizumab	1	8.9
	3 initial monthly treatments + as-needed treatment (every month) with ranibizumab	6	5.7 (4.4-7.1)
	3 initial monthly treatments + as-needed treatment (every month) with bevacizumab	5	6.3 (4.6-7.9)
	3 initial monthly treatments and as-needed treatment (every 3 months) with ranibizumab	1	8.5
	3 initial monthly treatments and as-needed treatment (every 3 months) with bevacizumab	1	8.7
	As-needed monthly treatment with ranibizumab	1	6.9
	As-needed monthly treatment with bevacizumab	1	7.7
	Monthly treatment with aflibercept	2	11.4[b]
	3 initial monthly treatment and as-needed treatment (every 2 months) with aflibercept	2	6.9[b]
DME	3 initial monthly treatments + as-needed treatment (every month) with ranibizumab	1	6.0
	3 initial monthly treatments + as-needed treatment (every month) with aflibercept	1	5.6
	3 initial monthly treatments + as-needed treatment (every month for 3 months) + as-needed treatment (every month) with ranibizumab	1	6.5
	3 initial monthly treatments + as-needed treatment (every month for 3 months) + as-needed treatment (every month) with bevacizumab	1	5.1
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment (every month) with ranibizumab	1	10[c]
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment	1	10[c]

	(every month) with bevacizumab		
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment (every month) with aflibercept	1	9[c]
RVO-ME	1 initial monthly treatment + as-needed treatment (every month) with ranibizumab	1	6.4
	1 initial monthly treatment + as-needed treatment (every month) with bevacizumab	1	6.0
	Monthly treatment with aflibercept	1	11.6
	Monthly treatment with bevacizumab	1	11.5
m-CNV	1 initial monthly treatment + as-needed treatment (every month) with ranibizumab	2	2.4 (1.7-3.1)
	1 initial monthly treatment + as-needed treatment (every month) with bevacizumab	2	3.1 (1.9-4.3)

Footnotes:
[a]Mean and ranges were derived from trial-specific means. Cases, in which a single RCT reported on a regimen, do not have an associated range.
[b]Value was reported once for both trials in Heier et al. 2012.
[c]Reported median values (Wells et al. 2015)

Abbreviations: cn-AMD, choroidal neovascular age-related macular degeneration; DME, diabetic macular edema; m-CNV, myopic choroidal neovascularization; RCT, randomized controlled trial; RVO-ME, macular edema due to retinal vein occlusion.

TABLE 4. COMPARISON OF MONTHLY VERSUS AS NEEDED ANTI-VEGF TREATMENT REGIMENS IN CN-AMD PATIENTS

Comparison	Outcome	# of RCTs[a], # of patients	Baseline ETDRS letters[b] and Snellen equivalent	As-needed regimen Mean (Range)[b]	Monthly Regimen Mean (Range)[b]	Risk Ratio or *Mean Difference* Estimate (95% CI)	I^{2c}
As-Needed Rx vs. Monthly Rx	Vision gain	2/1622	62 (61 to 63) ~ 20/63	20.8% (15.1 to 26.4)	28.9% (25.1 to 32.8)	0.73 (0.55, 0.95)	0%
	BCVA change	2/1622	62 (61 to 63) ~ 20/63	4.9 (3.5, 6.4)	6.9 (5.5, 8.3)	-1.9 (-0.5, -3.3)	0%
	Mortality	2/1795	NA	4.6% (2.6 to 6.6)	2.3% (1.4 to 3.3)	2.00 (1.15, 3.45)	12%

Footnotes:
[a] CATT and IVAN trials.(Martin, 2011; Chakravarthy 2013)
[b] Mean (range) were derived across control groups of the included RCTs.
[c] I^2 <75 was interpreted as low evidence of substantial variation across included RCTs. For each treatment regimen, patients were randomized to be treated with bevacizumab or ranibizumab.

Abbreviations: CI, confidence interval; ETDRS, early treatment diabetic retinopathy study; NA, not applicable; RCT, randomized controlled trials; Rx, treatment.

ADDITIONAL FILES

Additional File 1: PRISMA Checklist

Additional File 2: Supplementary Online Content

Appendix 1: Detailed methods

Appendix 2: Detailed study characteristics

Appendix 3: Detailed patient characteristics

Appendix 4: Cochrane risk of bias results for individual studies

Appendix 5: Risk of bias results

Appendix 6: Treatment effect estimates

Appendix 7: Forest plots for primary outcome in choroidal neovascular age related macular degeneration (cn-AMD) population

Appendix 8: Summary data used in risk of bias results

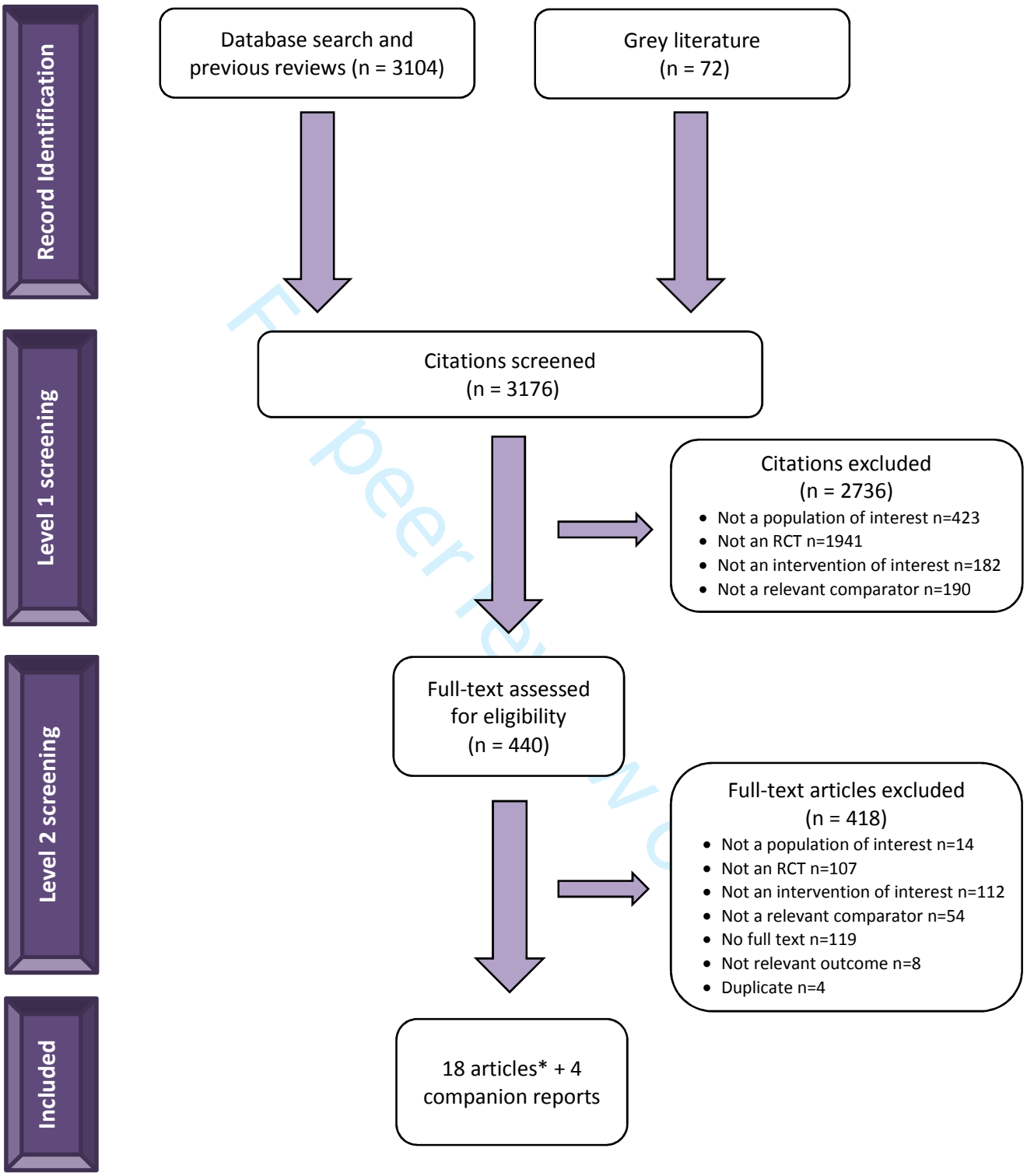
Appendix 9: Sensitivity analysis estimates

Appendix 10: Summary of anti-VEGF treatment protocols

Appendix 11: Summary of results from the DRCR.net trial (Wells 2015[a] and Wells 2016[b])

Appendix 12: Mean change in best-corrected visual acuity letter scores over time in patients treated with bevacizumab or ranibizumab

FIGURE 1: STUDY FLOW



*18 articles describing 19 randomized controlled trials

Supplementary Online Content

Appendix 1: Detailed methods

We conducted a systematic review using methods from the Cochrane Handbook for Systematic Reviews and reported the results using the PRISMA statement.[1] The SR was commissioned by CADTH and funded by a grant from the Canadian Institutes of Health Research Drug Safety and Effectiveness Network. The methods are outlined briefly below, as they are outlined in full in the CADTH report.[2]

Protocol

We drafted a protocol with input from clinical experts, patient advocacy groups, industry stakeholders and CADTH. We posted the draft on the CADTH website to obtain feedback from additional stakeholders, revised the protocol as necessary, and registered the final version with PROSPERO (CRD 42015022041).

Literature Search Strategy

The following bibliographic databases were searched from inception until August 17th 2017, 2015: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; Cochrane Central Register of Controlled Trials via Ovid, and PubMed. Grey literature (i.e., studies that are not widely available or commercially published) was identified by searching relevant websites according to the "Clinical Trials" section of the CADTH Grey Matters checklist.[3] We used Google and other Internet search engines to search for additional web-based materials, including conference abstracts. We obtained additional studies by reviewing the references of all included studies and feedback from clinical experts, patient advocacy groups, and industry stakeholders. In addition, we contacted the three manufacturers of the anti-VEGF drugs to identify further potentially relevant trials.

An experienced information specialist developed the literature search strategy. It was peer-reviewed by another information specialist using the PRESS statement.[4] The final search strategy can be found in Appendix A and the others are available upon request of the corresponding author.

The literature search consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords (see below). The main search concepts were anti-VEGF drugs and the relevant retinal conditions. Validated methodological filters were applied to limit retrieval to RCTs.[5] Where possible, retrieval was limited to humans. Retrieval was not limited by publication year or by language, but non-English language articles were excluded during screening, to increase feasibility of the study.

Keywords

(intravitreal OR intra-vitreal or implant or implanted or implants or inject or injected or injects or injection or injections or Anti-VEGF or antiVEGF or VEGF inhibitor or VEGF antagonist or visudyne or verteporfin or PDT or PDTV or VPDT)

AND

(retinal degeneration OR wet macular degeneration OR wAMD OR neovascular macular degeneration OR exudative macular degeneration or diabetic retinopathy or DRE or Macular Edema or Retinal Vein Occlusion or Choroidal Neovascularization or BRVO or CRVO)

Eligibility Criteria

The inclusion criteria were specified as follows according to the Population, Intervention, Comparator, Outcome, Study design and Time framework (Cochrane Handbook).[5]

- Populations: patients ≥ 18 years of age and with retinal conditions including wet AMD, DME, ME/RVO and myopic CNV.
- Interventions: anti-VEGF drugs in use in Canada, namely ranibizumab, intravitreal bevacizumab and aflibercept
- Comparators: placebo, ranibizumab, intravitreal bevacizumab or aflibercept
- Outcomes: 14 outcomes were selected *a-priori* at the protocol stage according to feedback from the research team, clinical experts, patient advocacy groups, industry stakeholders and CADTH, including five efficacy outcomes and nine safety outcomes (outlined below).
- Study design: parallel- and cluster-RCTs.
- Time: RCTs published at any time; all reports pertaining to an RCT were located to obtain data at the longest follow-up duration.

We excluded studies reporting only results for pediatric patients (<18 years of age), studies evaluating the anti-VEGF drug pegaptanib, as it is no longer licensed for use in Canada, studies that compared an anti-VEGF drug with other comparators (such as intravitreal corticosteroids, grid laser photocoagulation or cataract removal surgery), and studies reported in languages other than English. Studies fulfilling the last two exclusion criteria were excluded to allow for the project timelines to be met, as outlined in the Limitations and Research Implications sections below.

We included the following efficacy outcomes:

1. Vision gain, defined as a gain in Best-Corrected Visual Acuity (BCVA) of ≥15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart,
2. Vision loss, defined as a loss in BCVA of ≥15 ETDRS letters,
3. Change from baseline in BCVA letters,
4. Legal blindness,
5. Vision-related function.

We included the following safety outcomes:

1. All-cause mortality,
2. Arterial venous thromboembolism (VT),
3. Venous VT,
4. Bacterial endophthalmitis (BE),
5. Increased intraocular pressure,
6. Retinal detachment,
7. Adverse events (AEs)
8. Serious AEs,
9. Withdrawals due to AEs

We considered BCVA data derived from Snellen or ETDRS letter charts or the logarithm of the Minimum Angle of Resolution (logMAR) chart for assessing efficacy outcomes 1-3.[6] The Snellen chart is the current standard for measurement of visual acuity in clinical practice.[6-8] The ETDRS chart is the 'gold standard' for measuring visual acuity in clinical trials.[6] The Snellen chart has letters of different sizes arranged from largest at the top to smallest at the bottom, which are read, one eye at a time, at a distance of 6 metres (20 feet). The test-retest variability of the Snellen chart ranges from ±5 to 16.5 letters in normal patients.[9 10] The test-retest variability of the ETDRS charts ranges from ±3.5 to 10 letters.[11] A change of at least 10 letters (or two lines) is required to capture a true clinical

change in visual acuity.[6 12] With respect to vision-related function, we abstracted data from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), which is a self-reported survey questionnaire that assesses the influence of visual impairment on health-related quality of life.[13] Changes in the NEI VFQ overall scores of 10 points or more are associated with clinically relevant changes in vision.[14]

Study selection

Citations from the literature search were imported into an online systematic review software.[15] Also imported were the inclusion criteria, which were used for level-1 screening of citations (titles/abstracts) and level-2 screening of potentially relevant full-text articles. The 14 members of the review team underwent two training exercises; each involved a random sample of 50 citations, which were screened independently by all team members. Level-1 screening proceeded after 80% agreement had been achieved among the reviewers on the second training exercise.[16 17] Paired reviewers conducted the level-1 screening of each citation, independently. The estimated frequency of disagreement was 8%, which was resolved by a third reviewer. We retrieved the full-text articles of potentially relevant citations identified by at least one reviewer for level-2 screening. The team underwent a training exercise using a random sample of 20 full-text articles, which resulted in 70% agreement. Paired reviewers independently screened each full-text article. The estimated frequency of disagreement was 14%, which was resolved by a third reviewer. This reviewer also verified all eligible studies.

Data abstraction

We developed a data abstraction form with inputs from two physicians. We piloted and refined the form two times, each time using five randomly selected studies. Subsequently, paired reviewers conducted the abstraction, independently. Numerical data available only in figures were extracted using WebPlotDigitizer.[18] A third reviewer conducted a quality check on all data, and resolved any remaining discrepancies.

We abstracted data pertaining to study characteristics, patient populations, interventions, and outcomes. Multiple reports of the same trial (hereafter companion reports) were identified using the trial registration identifier, trial name, or a juxtaposition of the author names, treatment comparisons, sample sizes and outcomes, if necessary.[19] We abstracted data from all companion reports, identified differences, and reconciled the differences through discussion. For each set of companion reports, we considered one as the major publication and others as companion reports. We abstracted outcome data from all trial reports and used the data corresponding to the longest duration of follow-up in the meta-analysis.[5]

Risk of bias assessment

The risk of bias in the included trials was appraised using the Cochrane risk-of-bias tool, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases such as funding sources.[20] For selection bias, we assessed the reporting of random sequence generation and allocation concealment. For performance bias, we assessed the reporting of blinding of patients and trial personnel, and for detection bias, the reporting of the blinding of outcome assessors. In the assessment of performance and detection biases, we considered the objectivity of the primary outcome of individual trials in assessing performance and detection biases.

For RCTs that had been registered, the primary outcome was identified from the trial protocol, which was vision gain or change in mean BCVA in the majority of the included RCTs. Otherwise, we identified the primary outcome using an *a-priori* defined algorithm.[21 22] In brief, we selected from the trial report the outcome that was listed in the title or objectives, the most serious clinical outcome among all the trial outcomes, or the first reported outcome in the results section.

Paired reviewers conducted the risk of bias assessment, independently. Discrepancies were resolved by discussion or the involvement of a third reviewer.

Data Analysis in CADTH report

We derived treatment effect estimates using the odds ratio (OR) for binary outcomes such as vision gain, vision loss or the presence or absence of a harmful event. The standardized mean difference (SMD) was used for treatment comparisons involving BCVA data from different visual acuity charts, such as ETDRS or Snellen charts. The SMD expresses the difference in the treatment means in terms of the standard deviations of the measurements. The mean difference (MD) was used for comparison involving BCVA data that were consistently reported using the same measurement scale, either the ETDRS or Snellen chart. This was also the case for vision-related function measurements from the NEI VFQ questionnaire.

The results from multiple arms of the same anti-VEGF drugs at different dosages were combined according to the guidance in the Cochrane handbook.[5] When an RCT did not provide standard deviations for a continuous outcome measure, missing data were imputed from available data from other RCTs using established methods.[23] This was necessary in meta-analyses involving BCVA measures and vision-related functions.

We conducted meta-analyses of pairwise comparisons of all comparators, including the anti-VEGF drugs and placebo. This was done separately for each of the four retinal conditions. The variation across RCTs in any outcome measures was assessed using the I^2 statistic, with values of I^2 >75% indicating substantial statistical heterogeneity.[5] Pooled treatment effect estimates and 95% confidence intervals (CIs) were derived using the meta-analytical random effects model.[23] The meta-analyses were conducted using the "metafor" package in R (version 3.1.1).[24]

Data analysis in manuscript

Study results were synthesized with respect to benefits and harms, trends in BCVA improvement over time, and treatment regimens (e.g., monthly and as-needed regimens). To facilitate the synthesis of results, BCVA values reported in logMAR and decimal measures were converted to approximate ETDRS letter scores,[25] with approximate standard deviations.[26] Pairwise comparisons of drugs were assessed at the longest treatment duration, allowing for the inclusion of trials in the meta-analysis that reported outcome data at different time points. Subgroup analyses were conducted at 12 months and 24 months, as these were the most frequently reported time points. For DME patients, treatment effect estimates were obtained for all patients as well as pre-specified subgroups based upon baseline BCVA, as reported in the DCRC.net trial.[27] The meta-analysis was conducted using a random-effects model, given the assumption of varying treatment effects across trials. A sensitivity analysis was conducted by restricting to trials determined to be at low risk of selection bias. Between-study heterogeneity was assessed using the I^2 statistic, with values above 75% indicating substantial heterogeneity.[5]

Excluded RCT'S

The RCT by Rajagopal et al. 2015[28] (n=98 participants) was excluded because the investigators reported in the results section that an additional nine patients were included in the study but were not randomized to treatment due to financial hardship and were instead assigned to the bevacizumab group. The study by Pece et al. 2014[29] was excluded because the investigators randomized 78 eyes from 80 patients with myopic CNV to treatment with bevacizumab or ranibizumab, and reported eye-based analyses. For this review we were only interested in patient-based analyses.

Medline Literature Search

Interface: Ovid

Databases:

Embase <1974 to 2015 May 26>

MEDLINE Daily and MEDLINE 1946 to present

MEDLINE In-Process & Other Non-Indexed Citations

Cochrane Central Register of Controlled Trials <April 2015>

Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.

Date of Search: May 27, 2015 (Updated November 13, 2015)

Study Types: Randomized controlled trials

Limits: No date or language limits were used

Human filter was applied

Editorials & letters excluded

Search Strategy:

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1 Retinal Degeneration/

2 limit 1 to yr="1973-2009" [EARLIER MESH FOR WET MACULAR DEGENERATION]

3 Macular Degeneration/

4 Wet Macular Degeneration/ [MESH FROM 2010-]

5 ((exudative or neovascular or wet) adj3 ((macula* adj2 degeneration) or (macula* adj2 deterioration) or maculopath* or (macula* adj2 dystroph*))).tw,kw.

6 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.

7 (wAMD or wARMD).tw,kw.

8 Diabetic Retinopathy/

9 ((diabet* or DM) adj3 retinopath*).tw,kw.

10 (PDR or DME or DMO).tw,kw.

11 Macular Edema/

12 ((macula* or retina*) adj3 (edema$1 or oedema$1)).tw,kw.

13 (Irvine-Gass adj3 (edema$1 or oedema$1 or syndrome$1)).tw,kw.

14 (cystoid macula* adj dystroph*).tw,kw.

15 Retinal Vein Occlusion/

16 (retinal vein adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)).tw,kw.

17 (BRVO or CRVO).tw,kw.

18 Choroidal Neovascularization/

19 ((choroid* or subretinal or sub-retinal) adj1 neovasculari#ation*).tw,kw.

20 CNV.tw,kw.

21 or/2-20 [CONDITIONS – MEDLINE]

22 Vascular Endothelial Growth Factor A/ai

23 (anti adj2 VEGF$1).tw,kw.

24 antiVEGF$1.tw,kw.

25 (antivascular endothelial growth factor$1 or anti-vascular endothelial growth factor$1).tw,kw.

26 Antibodies, Monoclonal, Humanized/

27 (monoclonal antibod* and humani#ed).tw,kw.

28 (antibod* adj2 humani#ed).tw,kw.

29 Angiogenesis Inhibitors/

30 (angiogen* adj3 (inhibitor* or antagonist*)).tw,kw.

31 (anti-angiogen* or antiangiogen*).tw,kw.

32 aflibercept.tw,kw.

33 ("AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.

34 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap*).tw,kw.

35 aflibercept.rn.

36 Bevacizumab.tw,kw.

37 (Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.

38 IVB injection$1.tw,kw.

39 Bevacizumab.rn.

40 Pegaptanib.tw,kw.

41 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.

42 Pegaptanib.rn.

43 Ranibizumab.tw,kw.

44 (Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.

45 IVR injection$1.tw,kw.

46 Ranibizumab.rn.

47 or/22-46 [ANTI-VEGF AGENTS – MEDLINE]

48 21 and 47 [ANTI-VEGF AGENTS & CONDITIONS – MEDLINE]

49 exp Photochemotherapy/

50 Photosensitizing Agents/

51 (photochemo* or photo-chemo* or photodynamic* or photo-dynamic* or photosensiti* or photo-sensiti*).tw,kw.

52 PDT.tw,kw.

53 or/49-52

54 verteporfin.tw,kw.

55 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.

56 verteporfin.rn.

57 or/54-56

58 53 and 57

59 (PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.

60 58 or 59 [VISUDYNE PDT – MEDLINE]

61 21 and 60 [VISUDYNE PDT & CONDITIONS – MEDLINE]

62 Triamcinolone Acetonide/

63 ((Triamcinol* adj acet*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog* or Kenlog or "NSC 21916" or Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort* or Triesense or Tristoject or "UNII-F446C597KA" or Volon).tw,kw.

64 triamcinolone acetonide.rn.

65 Glucocorticoids/

66 (glucocorticoid* or glucorticoid*).tw,kw.

67 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or Retaane or "UNII-Y0PC411K4T").tw,kw.

68 anecortave acetate.rn.

69 Pregnadienediols/

70 (dihydroxypregnadiene* or di-hydroxypregnadiene* or pregnadienediol*).tw,kw.

71 exp Dexamethasone/

72 (Dexamethasone or Decaject* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex or Millicorten or Oradexon or Ozurdex).tw,kw.

73 dexamethasone.rn.

74 (intravitreal adj3 (corticoid* or corticosteroid* or steroid*)).tw,kw.

75 or/62-74

76 exp Injections/

77 (depot or implant* or infus* or inject* or intravitreal* or intra-vitreal* or microsphere* or micro-sphere* or suspension*).tw,kw.

78 or/76-77

79 75 and 78 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - MEDLINE]

80 21 and 79 (3513) [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - MEDLINE

81 (controlled clinical trial or randomized controlled trial).pt.

82 clinical trials as topic.sh.

83 (randomi#ed or randomly or RCT$1 or placebo*).tw.

84 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.

85 trial.ti.

86 or/81-85

87 (48 or 61 or 80) and 86

88 exp Animals/ not (exp Animals/ and Humans/)

89 87 not 88

90 (comment or editorial or interview or news).pt.

91 (letter not (letter and randomized controlled trial)).pt.

92 89 not (90 or 91)

93 92 use prmz [MEDLINE RCTS]

94 macular degeneration/

95 age related macular degeneration/

96 wet macular degeneration/

97 ((exudative or neovascular or wet) adj3 ((macula* adj2 degeneration) or (macula* adj2 deterioration) or maculopath* or (macula* adj2 dystroph*))).tw,kw.

98 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.

99 (wAMD or wARMD).tw,kw.

100 diabetic retinopathy/

101 ((diabet* or DM) adj3 retinopath*).tw,kw.

102 diabetic macular edema/

103 (PDR or DME or DMO).tw,kw.

104 exp macular edema/

105 ((macula* or retina*) adj3 (edema$1 or oedema$1)).tw,kw.

106 (Irvine-Gass adj3 (edema$1 or oedema$1 or syndrome$1)).tw,kw.

107 (cystoid macula* adj dystroph*).tw,kw.

108 exp retina vein occlusion/

109 (retinal vein adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)).tw,kw.

110 (BRVO or CRVO).tw,kw.

111 subretinal neovascularization/

112 ((choroid* or subretinal or sub-retinal) adj1 neovasculari#ation*).tw,kw.

113 CNV.tw,kw.

114 or/94-113 [CONDITIONS – EMBASE]

115 vasculotropin inhibitor/

116 (anti adj2 VEGF$1).tw,kw.

117 antiVEGF$1.tw,kw.

118 (antivascular endothelial growth factor$1 or anti-vascular endothelial growth factor$1).tw,kw.

119 monoclonal antibody/

120 (monoclonal antibod* and humani#ed).tw,kw.

121 (antibod* adj2 humani#ed).tw,kw.

122 angiogenesis inhibitor/

123 (angiogen* adj3 (inhibitor* or antagonist*)).tw,kw.

124 (anti-angiogen* or antiangiogen*).tw,kw.

125 aflibercept/

126 (aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.

127 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap*).tw,kw.

128 aflibercept.rn.

129 bevacizumab/

130 (bevacizumab or Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.

131 IVB injection$1.tw,kw.

132 Bevacizumab.rn.

133 pegaptanib/

134 (Pegaptanib or "EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.

135 Pegaptanib.rn.

136 ranibizumab/

137 (Ranibizumab or Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.

138 IVR injection$1.tw,kw.

139 Ranibizumab.rn.

140 or/115-139 [ANTI-VEGF AGENTS – EMBASE]

141 114 and 140 [ANTI-VEGF AGENTS & CONDITIONS – EMBASE]

142 photodynamic therapy/

143 photosensitizing agent/

144 (photochemo* or photo-chemo* or photodynamic* or photo-dynamic* or photosensiti* or photo-sensiti*).tw,kw.

145 PDT.tw,kw.

146 or/142-145

147 verteporfin/

148 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.

149 verteporfin.rn.

150 or/147-149

151 146 and 150

152 (PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.

153 151 or 152 [VISUDYNE PDT – EMBASE]

154 114 and 153 [VISUDYNE PDT & CONDITIONS – EMBASE]

155 triamcinolone/

156 triamcinolone acetonide/

157 ((Triamcinol* adj acet*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog* or Kenlog or "NSC 21916" or Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort* or Triesense or Tristoject or "UNII-F446C597KA" or Volon).tw,kw.

158 triamcinolone.rn.

159 triamcinolone acetonide.rn.

160 exp glucocorticoid/

161 (glucocorticoid* or glucorticoid*).tw,kw.

162 anecortave/

163 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or Retaane or "UNII-Y0PC411K4T").tw,kw.

164 anecortave.rn.

165 pregnane derivative/

166 (dihydroxypregnadiene* or di-hydroxypregnadiene* or pregnadienediol*).tw,kw.

167 dexamethasone/

168 dexamethasone isonicotinate/

169 (Dexamethasone or Decaject* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex or Millicorten or Oradexon or Ozurdex).tw,kw.

170 dexamethasone.rn.

171 dexamethasone isonicotinate.rn.

172 (intravitreal adj3 (corticoid* or corticosteroid* or steroid*)).tw,kw.

173 or/155-172

174 exp injection/

175 intravitreal drug administration/

176 vi.fs. [EMBASE FLOATING SUBJECT HEADING FOR INTRAVITREAL DRUG ADMIN]

177 (depot or implant* or infus* or inject* or intravitreal* or intra-vitreal* or microsphere* or micro-sphere* or suspension*).tw,kw.

178 or/174-177

179 173 and 178 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - EMBASE]

180 114 and 179 [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - EMBASE]

181 randomized controlled trial/ or controlled clinical trial/

182 exp "clinical trial (topic)"/

183 (randomi#ed or randomly or RCT$1 or placebo*).tw.

184 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.

185 trial.ti.

186 or/181-185

187 (141 or 154 or 180) and 186

188 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/

189 exp humans/ or exp human experimentation/ or exp human experiment/

190 188 not 189

191 187 not 190

192 editorial.pt.

193 letter.pt. not (letter.pt. and randomized controlled trial/)

194 191 not (192 or 193)

195 194 use emczd [EMBASE RCTS]

196 93 or 195 [MEDLINE / EMBASE RCTS]

197 remove duplicates from 196 [TOTAL UNIQUE HITS]

198 197 use prmz [UNIQUE MEDLINE]

199 197 use emczd [UNIQUE EMBASE]

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Appendix 2: Detailed study characteristics

First author	Year of publication	Trial name	Trial identifier	Country	Study design	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
cn-AMD (n = 12)									
Schauwvlieghe[30]	2016	BRAMD	Netherlands Trial Register: NTR1704	Netherlands	Parallel RCT	Jan 2009 - Dec 2011	Multi	332	12
Berg[31]	2015	LUCAS	NCT01127360	Norway	Parallel RCT	Mar 2009 - Jul 2012	Multi	441	12
Scholler[32]	2014	NR	EK-07-192-1007 / EudraCT Nr. 2007-005157-33	Austria	Parallel RCT	2008 - 2011	Single	55	12
Chakravarthy[33]	2013	IVAN	ISRCTN92166560	UK	Parallel RCT	Mar 27, 2008 - Oct 15, 2010	Multi	610	24
Kodjikian[34]	2013	GEFAL	NCT01170767	France	Parallel RCT	2009 - 2012	Multi	501	12
Krebs[35]	2013	MANTA	NCT00710229	Austria	Parallel RCT	2008 - 2011	Multi	321	12
Heier[36]	2012	VIEW 1	NCT00509795	US, Canada	Parallel RCT	Aug 2007 - Sep 2010	Multi	1217	12
Heier[36]	2012	VIEW 2	NCT00637377	Argentina, Australia, Austria, Belgium, Brazil, Colombia, Czech Republic, France, Germany,	Parallel RCT	Apr 2008 - Sep 2010	Multi	1240	12

First author	Year of publication	Trial name	Trial identifier	Country	Study design	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
				Hungary, India, Israel, Italy, Japan, Republic of Korea, Latvia, Mexico, Netherlands, Poland, Portugal, Singapore, Slovakia, Spain, Sweden, Switzerland, United Kingdom					
Biswas[37]	2011a	NR	NR	India	Parallel RCT	2007 - 2009	Multi	60	18
Biswas[38]	2011b	NR	NR	India	Parallel RCT	NA	Multi	120	18
Martin[39]	2011	CATT	NCT00593450	US	Parallel RCT	2008 - 2010	Multi	1208	12
Subramanian[40]	2010	NR	ISRCTN73359806	US	Parallel RCT	2007 - 2009	Single	28	12
DME (n = 3)									
Fouda[41]	2017	NR	NR	Egypt	Parallel RCT	NR	Single	42	15
Wells[27]	2015	NR	NCT01627249	US	Parallel	Aug 2012	Multi	660	12

First author	Year of publication	Trial name	Trial identifier	Country	Study design	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
					RCT	- Oct 2014			
Ekinci[42]	2014	NR	NR	Turkey	Parallel RCT	2011 - 2014	NR	100	12
RVO-ME (n = 2)									
Scott[43]	2017	SCORE2	NCT01969708	US	Parallel RCT	Sep 2014 - Dec 2016	MULTI	362	6
Narayanan[44]	2015	MARVEL	CTRI/2012/01/003120	India	Parallel RCT	Jan 2012 - Feb 2013	Single	75	6
m-CNV (n = 2)									
Iacono[45]	2012	NR	NR	Italy	Parallel RCT	Apr 2006 - Jul 2007	Single	55	18
Gharbiya[46]	2010	NR	ISRCTN49803272	Italy	Parallel RCT	Feb 2008 - Dec 2008	Single	32	6

Abbreviations: cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; NR – not reported; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion

Appendix 3: Detailed patient characteristics

First author & year	# of eyes	Overall mean age	Overall mean age variance type	Overall mean age variance value	TX 1 - mean age	TX 1 - mean age var value	TX 2 - mean age	TX 2 - mean age var value	TX 3 - mean age	TX 3 - mean age var value	TX 4 - mean age	TX 4 - mean age var value	% female	% of patients with diabetes	Mean A1C value	% of patients with A1C >8.5%	% of patients with hypertension	Lens status of patients
cn-AMD (n = 12)																		
Schauwvlieghe 2016[30]	332	78	SD	7	79	7	78	7	NR	NR	NR	NR	56	NR	NR	NR	NR	40 % pseudophakic
Berg 2015[31]	NR	NR	SD	NR	78.7	7.6	78	8.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Scholler 2014[32]	55	NR	SD	NR	79.5	6.8	80.8	6.6	NR	NR	NR	NR	70.9	NR	NR	NR	NR	NR
Chakravarthy 2013[33]	NR	77.7	SD	7.4	77.8	7.6	77.7	7.3	NR	NR	NR	NR	60	NR	NR	NR	NR	NR
Kodjikian 2013[34]	501	NR	NR	NR	79.6	6.9	78.7	7.3	NR	NR	NR	NR	66	NR	NR	NR	57	NR
Krebs 2013[35]	317	NR	SD	NR	76.7	7.8	77.6	8.1	NR	NR	NR	NR	63.7	0	NR	NR	NR	NR
Heier 2012 – VIEW 1[36]	1210	NR	SD	NR	78.2	7.6	77.7	7.9	78.4	8.1	77.9	8.4	58.8	NR	NR	NR	NR	NR
Heier 2012 – VIEW 2[36]	1202	NR	SD	NR	73	9	74.1	8.5	74.7	8.6	73.8	8.6	55.5	NR	NR	NR	NR	NR
Biswas 2011a[37]	60	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Biswas 2011b[38]	104	NR	NR	NR	63.5	NR	64.4	NR	NR	NR	NR	NR	52	NR	NR	NR	NR	NR
Martin 2011[39]	1208	NR	NR	NR	79.2	7.4	80.1	7.3	78.4	7.8	79.3	7.6	62	NR	NR	NR	NR	NR
Subramanian 2010[40]	28	78.6	SD	NR	78	NR	80	NR	NR	NR	NR	NR	4.6	NR	NR	NR	NR	NR
DME (n = 3)																		
Fouda 2017[41]	70	NR	SD	NR	55.1	4.7	56.6	5.8	NA	NA	NA	NA	NR	100	NR	NR	NR	NR
Wells 2015[27]	660	61	SD	10	60	10	62	10	60	11	NR	NR	47	100	NR	NR	NR	NR
Ekinci 2014[42]	100	NR	NR	NR	68	9	65	14	NR	NR	NR	NR	68	100	NR	0	NR	NR
RVO-ME (n = 2)																		

First author & year	# of eyes	Overall mean age	Overall mean age variance type	Overall mean age variance value	TX 1 - mean age	TX 1 - mean age var value	TX 2 - mean age	TX 2 - mean age var value	TX 3 - mean age	TX 3 - mean age var value	TX 4 - mean age	TX 4 - mean age var value	% female	% of patients with diabetes	Mean A1C value	% of patients with A1C >8.5%	% of patients with hypertension	Lens status of patients
Scott 2017[43]	362	69	SD	12	69	11	69	13	NA	NA	NA	NA	43.4	31.5	NR	NR	76.8	83.1 % cataract
Narayanan 2015[44]	75	NR	NR	NR	53	NR	50	NR	NR	NR	NR	NR	45.3	17	NR	NR	50	NR
m-CNV (n = 2)																		
Iacono 2012[45]	55	NR	SD	NR	65	12	61	11	NR	NR	NR	NR	76.4	NR	NR	NR	NR	NR
Gharbiya 2010[46]	32	NR	SD	NR	60.6	10.5	59.1	11.4	NR	NR	NR	NR	68.8	NR	NR	NR	NR	NR

Abbreviations: cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; NA – not applicable; NR – not reported; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion; SD – standard deviation; TX – treatment

Appendix 4: Cochrane risk of bias results for individual studies

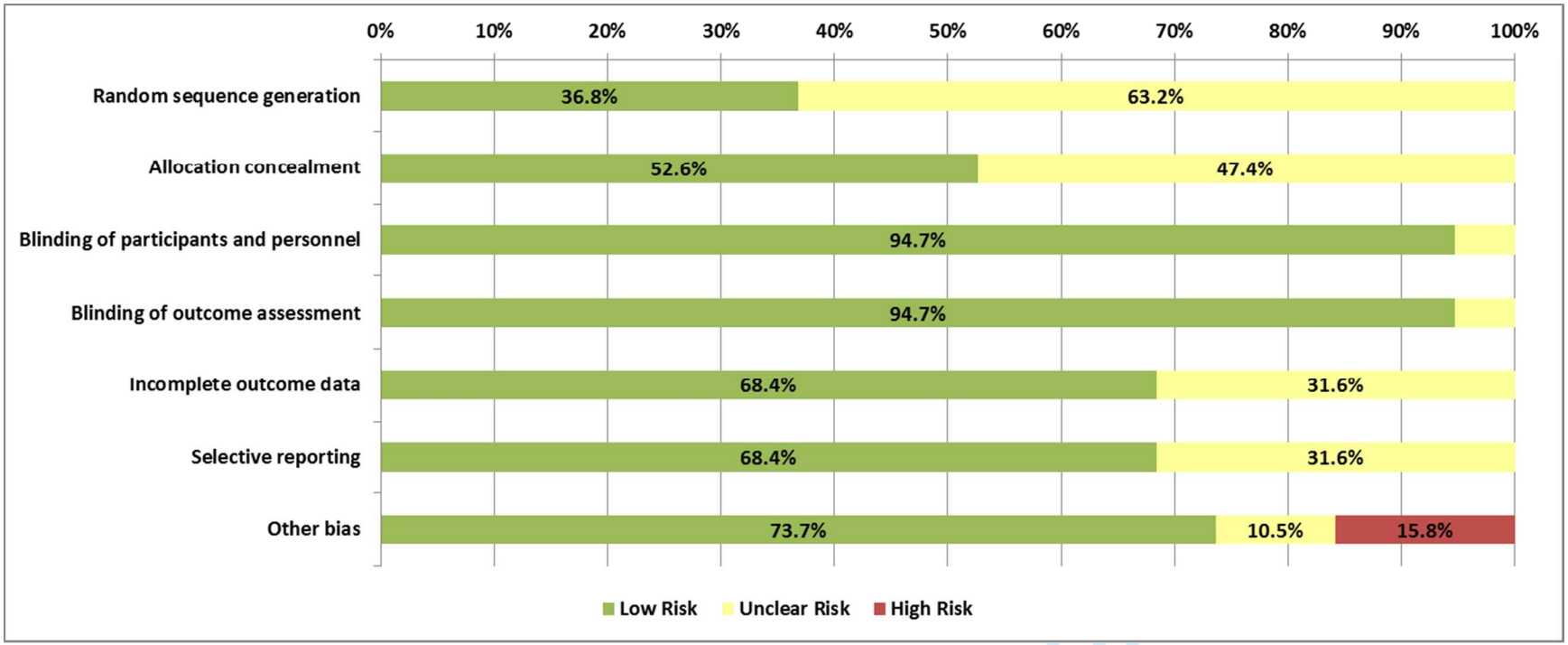
STUDY	Cochrane ROB item						
	1	2	3	4	5	6	7
cn-AMD (n = 12)							
Schauwvlieghe 2016[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Berg 2015[31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Scholler 2014[32]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Chakravarthy 2013[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kodjikian 2013[34]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Krebs 2013[35]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Heier 2012 – VIEW 1[36]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Heier 2012 – VIEW 2[36]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Biswas 2011a[37]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Biswas 2011b[38]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Martin 2011[39]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Subramanian 2010[40]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
DME (n = 3)							
Fouda 2017[41]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Wells 2015[27]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ekinci 2014[42]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
RVO-ME (n = 2)							
Scott 2017[43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Narayanan 2015[44]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
m-CNV (n = 2)							
Iacono 2012[45]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Gharbiya 2010[46]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk

Note: The legend for the ROB table is as follows:
1: Random sequence generation
2: Allocation concealment
3: Blinding of patients & personnel
4: Blinding of outcome assessment

5: Incomplete outcome data
6: Selective reporting
7: Other bias

Abbreviations: cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; RVO-ME – macular edema due to retinal vein occlusion

Appendix 5: Risk of bias results



Appendix 6: Treatment effect estimates

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
Treatment Effects in choroidal neovascular Age-related Macular Degeneration								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	2	1815	0.32 [0.3, 0.34]	0.32 [0.31, 0.34]	0.99 (0.81-1.22)	-0.21 (-6.82, 6.4)	52%[b]
	Bevacizumb vs. Ranibizumab	9	3245	0.22 [0.12, 0.33]	0.23 [0.14, 0.29]	0.95 (0.84-1.08)	-1.62 (-4.86, 1.62)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	2	1815	0.05 [0.05, 0.05]	0.06 [0.05, 0.06]	0.9 (0.6-1.35)	-0.51 (-2.75, 1.72)	0%
	Bevacizumb vs. Ranibizumab	10	3302	0.06 [0, 0.11]	0.07 [0.04, 0.14]	1.1 (0.84-1.43)	0.39 (-1.46, 2.23)	4%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mean change in BCVA (MD in # letters)	Aflibercept vs. Ranibizumab	2	1793	8.83 [8.25, 9.41]	8.75 [8.1, 9.4]	NA	0.05 (-2.36, 2.46)	66%
	Bevacizumb vs. Ranibizumab	8	3064	7.24 [4.1, 15.2]	5.85 [0.6, 11.43]	NA	0.03 (-1.02, 1.08)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision-related function	Aflibercept vs. Ranibizumab	2	1632	5.32 ± 14.46	5.60 ± 14.40	NA	-2.23 (-5.07, 0.61)	73%
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs.	3	1823	0.04 [0, 0.12]	0.02 [0, 0.06]	2.04 (0.32-12.5)	0.11 (-0.25, 0.47)	0%

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Ranibizumab							
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	6	2941	0.04 [0.01, 0.12]	0.03 [0.01, 0.06]	1.14 (0.72-1.79)	0.31 (-0.74, 0.36)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Serious adverse events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	5	3026	0.19 [0.12, 0.28]	0.18 [0.09, 0.28]	1.09 (0.93-1.27)	0.02 (-0.01, 0.05)	12%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Arterial thromboembolic events	Aflibercept vs. Ranibizumab	2	1818	0.02 [0.01, 0.02]	0.02 [0.02, 0.02]	0.96 (0.45-2.04)	-0.07 (-1.32, 1.18)	0%
	Bevacizumb vs. Ranibizumab	4	2033	0.03 [0, 0.05]	0.04 [0, 0.08]	0.86 (0.51-1.47)	-0.03 (-0.97, 0.9)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Venous thromboembolic events	Aflibercept vs. Ranibizumab	1	913	0.0033	0	0.25 (0.01-7.69)	-0.25 (-0.93, 0.44)	NA
	Bevacizumb vs. Ranibizumab	3	2135	0 [0, 0.01]	0 [0, 0.01]	1.59 (0.42-5.88)	0.18 (-0.43, 0.79)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	3	2011	0 [0, 0.01]	0 [0, 0]	1.75 (0.44-6.67)	0.18 (-0.40, 0.77)	0%

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Retinal detachment	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	2	1526	0.01 [0.01, 0.01]	0 [0, 0.01]	2.33 (0.31-16.67)	0.38 (-0.2, 0.96)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Treatment Effects in Diabetic Macular Edema								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	1	392	0.39	0.37	1.06 (0.82-1.37)	2.16 (-7.44, 11.75)	NA
	Bevacizumb vs. Ranibizumab	1	376	0.35	0.37	0.94 (0.72-1.23)	2.05 (-7.62, 11.73)	NA
	Bevacizumb vs. Aflibercept	1	386	0.35	0.37	0.94 (0.72, 1.24)	-2.05 (-11.73, 7.62)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	1	392	0.02	0.02	1.59 (0.38-6.67)	0.92 (-1.87, 3.7)	NA
	Bevacizumb vs. Ranibizumab	1	376	0.03	0.02	2.08 (0.52-8.33)	1.67 (-1.43, 4.78)	NA
	Bevacizumb vs. Aflibercept	1	376	0.02	0.03	0.48 (0.12, 1.91)	-1.67 (-4.78, 1.43)	NA
Mean change in BCVA letters	Aflibercept vs. Ranibizumab	2	462	16.22 (12.8, 19.64)	13.97 (12.3, 15.65)	NA	1.36 (-1.59, 4.31)	27%
	Bevacizumb vs. Ranibizumab	2	456	10.27 (10.0, 10.54)	12.08 (11.87, 12.3)	NA	-2.0 (-3.90, -0.09)	0%
	Bevacizumb vs. Aflibercept	1	386	10.0 ± 11.8	12.8 ± 12.4	NA	-2.7 (-0.3, -5.2)	NA
Vision-related function	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	2	513	0.02 (0.01, 0.02)	0.03 (0.01, 0.05)	0.47 (0.17-1.28)	-2.00 (-4.95, 0.94)	NA
	Bevacizumb vs. Ranibizumab	1	436	0.06	0.05	1.18 (0.54-2.56)	0.92 (-3.36, 5.2)	NA
	Bevacizumb vs. Aflibercept	1	436	0.05	0.06	0.85 (0.39, 1.85)	-0.92 (-5.2, 3.36)	NA
Serious adverse events	Aflibercept vs. Ranibizumab	2	507	0.14 (0.01 , 0.27)	0.13 (0.01, 0.25)	1.08 (0.78-1.47)	0.56 (-4.00 , 5.13)	0%
	Bevacizumb vs. Ranibizumab	1	436	0.21	0.25	0.83 (0.59-1.18)	-4.13 (-12.04, 3.78)	NA
	Bevacizumb vs. Aflibercept	1	436	0.25	0.21	1.2 (0.85, 1.69)	4.13 (-3.78, 12.04)	NA
Arterial thromboembolic events	Aflibercept vs. Ranibizumab	1	436	0.05	0.03	0.6 (0.22-1.61)	-1.83 (-5.36, 1.69)	NA
	Bevacizumb vs. Ranibizumab	1	436	0.05	0.04	0.9 (0.37-2.17)	-0.46 (-4.29, 3.37)	NA
	Bevacizumb vs. Aflibercept	1	436	0.05	0.04	1.11 (0.46, 2.68)	0.46 (-3.37, 4.29)	NA
Venous thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs.	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Aflibercept							
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	2	512	0	0	NE	NE	NE
	Bevacizumb vs. Ranibizumab	1	436	0.01	0	3.03 (0.12-100)	0.46 (-0.81, 1.72)	NA
	Bevacizumb vs. Aflibercept	1	436	0.01	0	0.33 (0.01, 8.14)	-0.46 (-1.72, 0.81)	NA
Retinal detachment	Aflibercept vs. Ranibizumab	2	512	0.004 (0, 0.01)	0	1.61 (0.21-12.5)	0.4 (-1.06, 1.87)	0%
	Bevacizumb vs. Ranibizumab	1	436	0.0092	0.0046	2 (0.18-20)	NR	NA
	Bevacizumb vs. Aflibercept	1	436	0.0046	0.0092	0.5 (0.05, 5.47)	-0.46 (-2.01, 1.09)	NA
Treatment Effects in Retinal Vein Occlusion – Macular Edema								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	74	0.59	0.59	1 (0.68-1.45)	0 (-22.37, 22.37)	NA
	Bevacizumb vs. Aflibercept	1	358	0.65	0.61	1.06 (0.91, 1.25)	3.87 (-6.25 , 14)	NR
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mean change in BCVA (MD in # letters)	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	77	15.6	18.1	NA	-2.5 (-8.0, 5.0)	NA
	Bevacizumb vs.	1	362	18.6	18.9	NA	-1.5 (-4.2, 1.2)	NA

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Aflibercept							
Vision-related function	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0.0056	0.0055	1.01 (0.06, 16.04)	0.01 (-1.52 , 1.53)	NR
Serious adverse events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	74	0.03	0.05	0.5 (0.05-5.26)	-2.7 (-11.67, 6.26)	NA
	Bevacizumb vs. Aflibercept	1	362	0.079	0.0769	1.01 (0.5, 2.06)	0.09 (-5.42, 5.59)	NR
Arterial thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0.0056	0.011	0.51 (0.05, 5.53)	-0.54 (-2.41, 1.32)	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
Venous thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0	0.006	0.34 (0.01, 8.22)	-0.54 (-2.06, 0.97)	NR
Retinal detachment	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0	0	NE	NE	NA
Treatment Effects in Myopic Choroidal Neovascularization								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	32	0.62	0.56	1.11 (0.63-1.96)	6.25 (-27.71, 40.21)	NA
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	32	0	0	NA	NA	NA
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
Mean change in BCVA (MD in # letters)	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	2	80	12.18 (8.5, 15.87)	13.4 (9.5, 17.31)	NA	-1.26 (-6.52, 4.00)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision-related function	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Serious adverse events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Arterial	Aflibercept vs.	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
thromboembolic events	Ranibizumab							
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Venous thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Retinal detachment	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR

Footnotes:

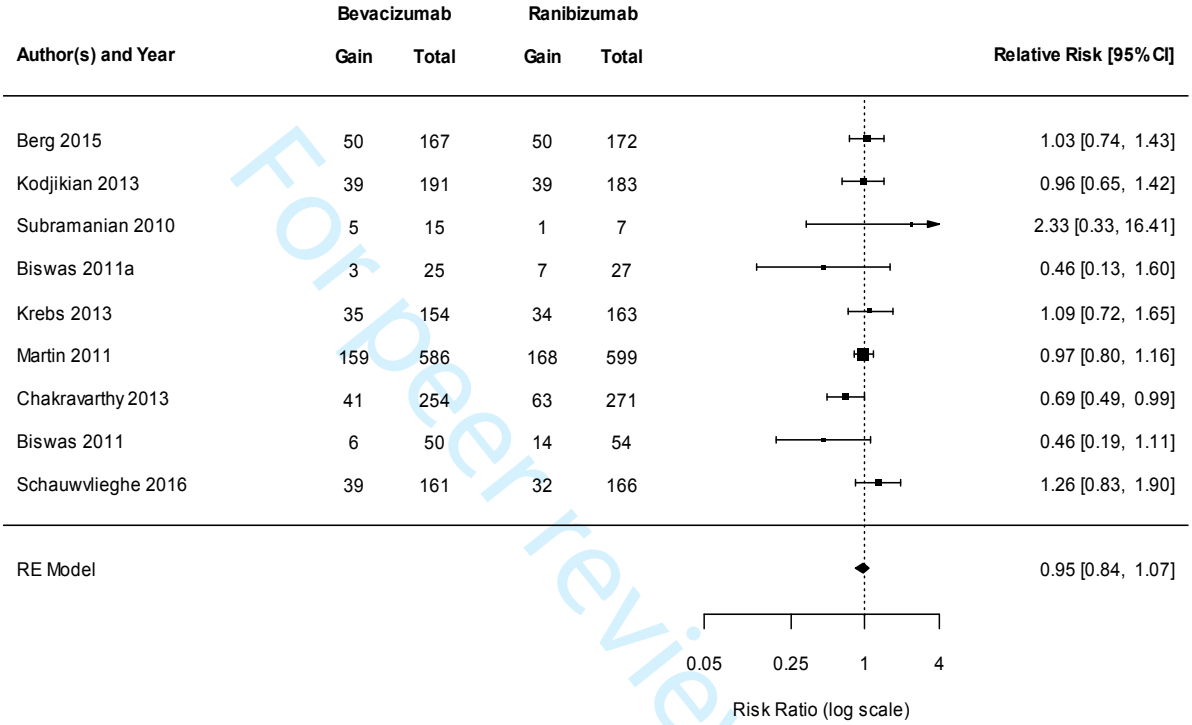
[a] Meta-analysis was not conducted for comparisons with 1 RCT; the point estimate and 95% confidence interval were calculated using data from a single trial.

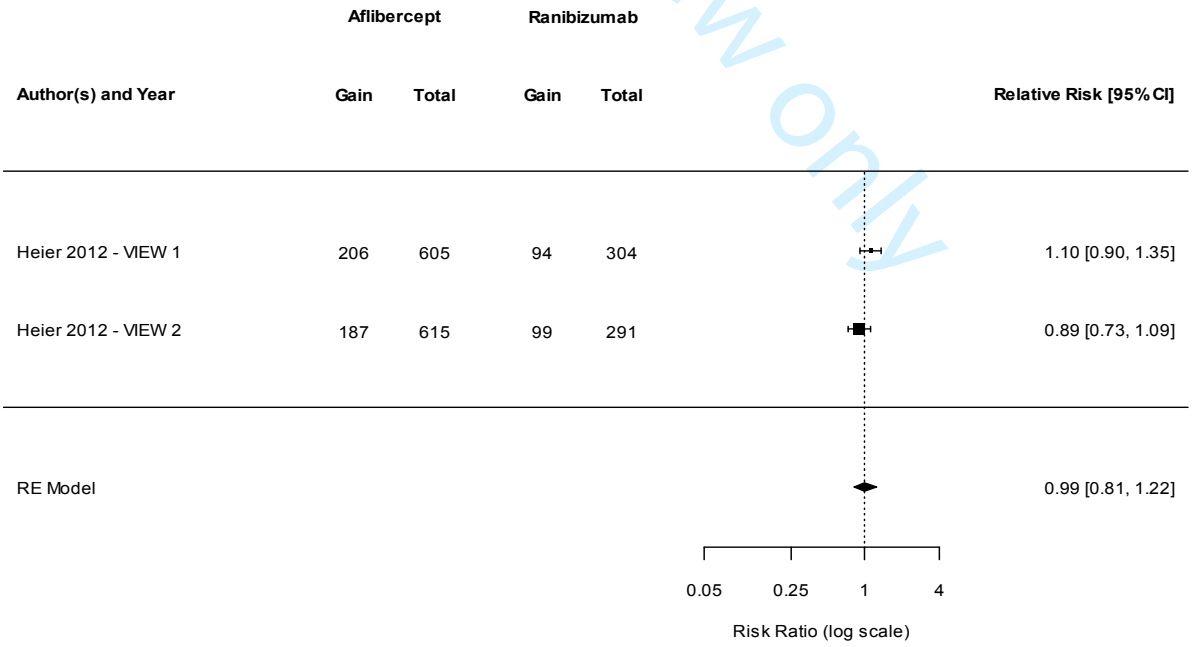
[b] The summary statistics were derived by taking the mean and range across estimates from included studies.

Abbreviations: BCVA - best-corrected visual acuity; CI - confidence interval; Ctrl - control; ETDRS - Early Treatment Diabetic Retinopathy Study; MD - mean difference; NA - not applicable; NE - not estimable; NR - not reported; RCT - randomized controlled trials; Rx - treatment; SMD - standardized mean difference

Appendix 7: Forest plots for primary outcome in choroidal neovascular age related macular degeneration (cn-AMD) population

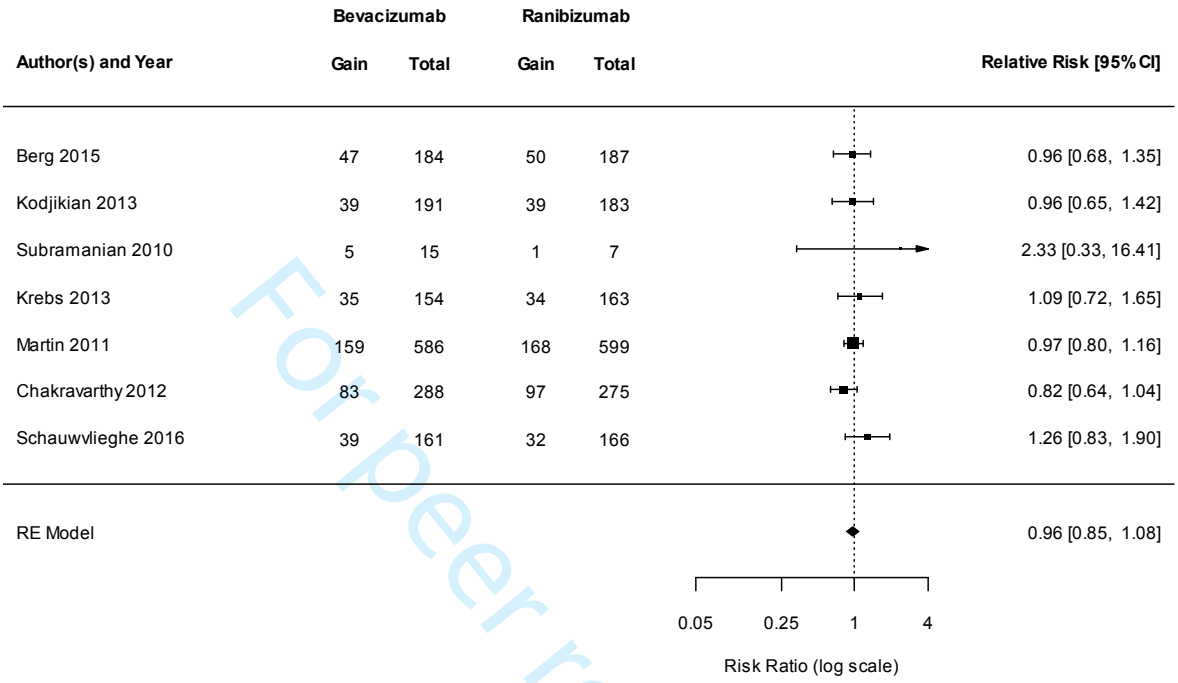
A: Vision gain in cn-AMD population



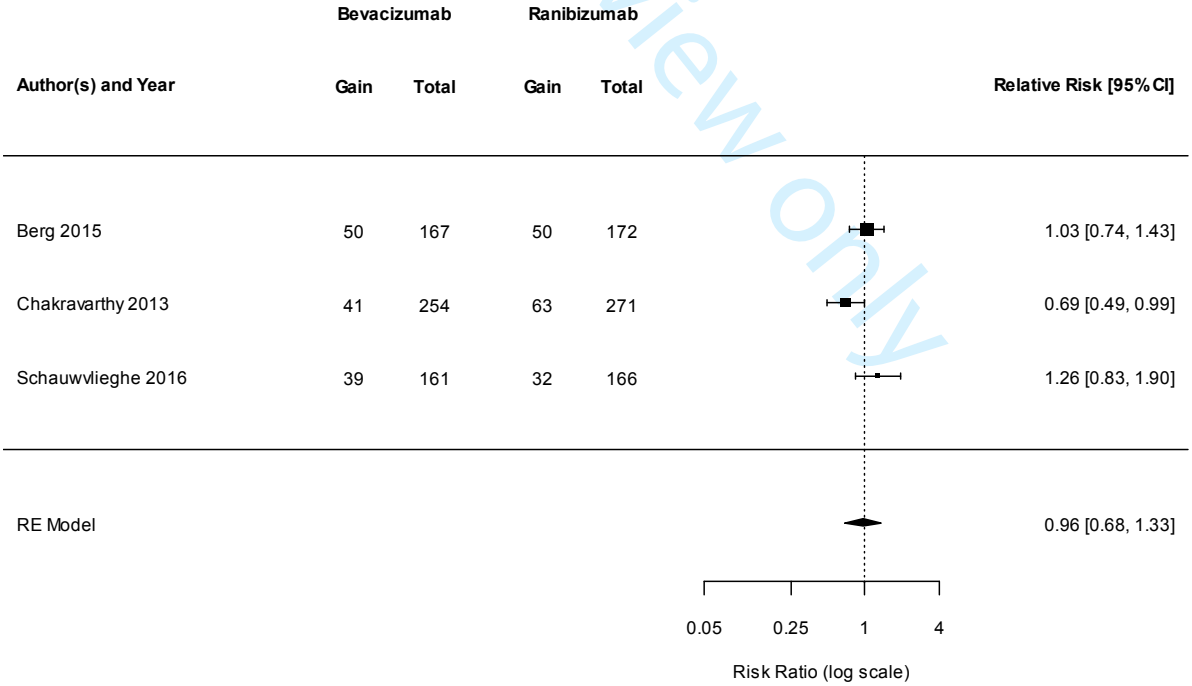


B: Sensitivity analyses for vision gain in cn-AMD population

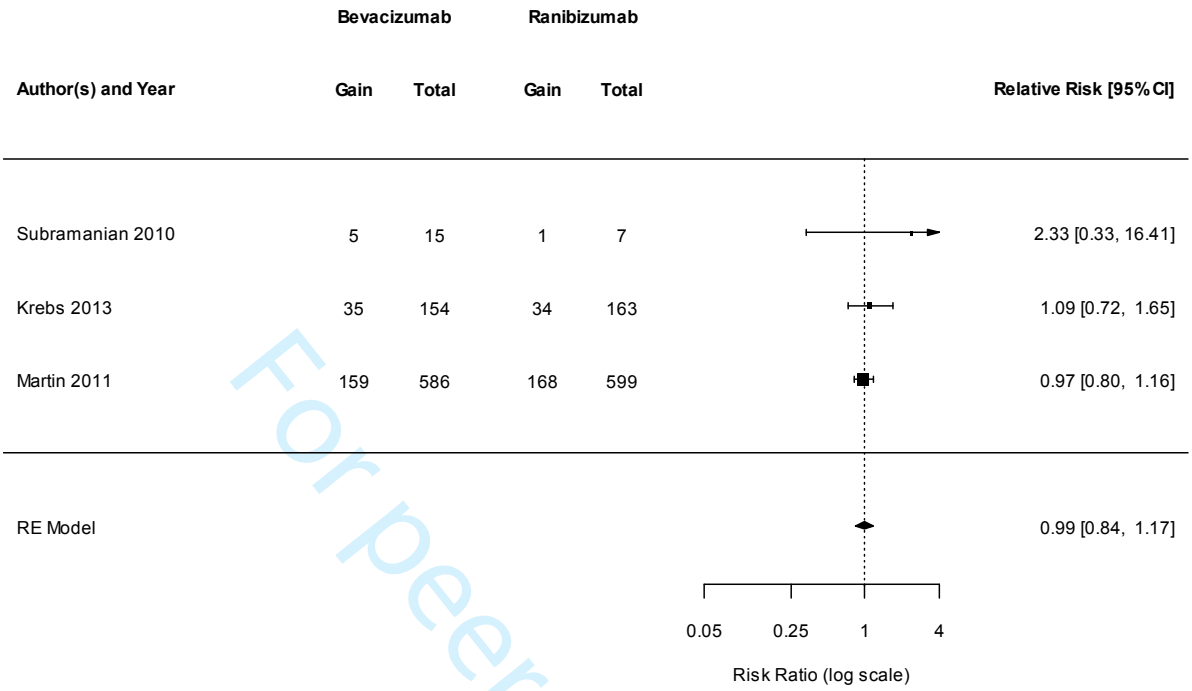
Sensitivity Analysis: 1 Year Follow-Up



Sensitivity Analysis: Low Risk of Selection Bias



Sensitivity Analysis: De Novo Patients



Appendix 8: Summary data used in risk of bias results

		Length of follow-up (months)							
		1	**3**	**4**	**6**	**8**	**12**	**18**	**24**
Mean improvement in BCVA letter score (SEM)	**cn-AMD**								
	# of RCTs	0	4	0	4	0	8	0	2
	Bevacizumab	NA	5.14 (0.45)	NA	5.66 (0.45)	NA	6.35 (0.52)	NA	5.84 (1.85)
	Ranibizumab	NA	5.19 (0.43)	NA	6.02 (0.38)	NA	6.23 (0.8)	NA	6.10 (1.30)
	DME								
	# of RCTs	1	0	1	0	1	2	0	1
	Bevacizumab	4.48 (0.19)	NA	7.90 (0.45)	NA	9.30 (0.59)	10.06 (0.60)	NA	10.00 (0.75)
	Ranibizumab	4.46 (0.24)	NA	9.05 (0.24)	NA	10.44 (0.36)	11.37 (0.58)	NA	12.30 (0.52)
	RVO-ME								
	# of RCTs	0	1	0	1	0	0	0	0
	Bevacizumab	NA	13.23 (0.35)	NA	15.60 (0.35)	NA	NA	NA	NA
	Ranibizumab	NA	15.91 (0.42)	NA	18.10 (0.42)	NA	NA	NA	NA
	m-CNV								
	# of RCTs	0	2	0	2	0	1	1	0
	Bevacizumab	NA	10.28 (31.00)	NA	10.42 (33.00)	NA	28.00 (35.00)	28.00 (37.00)	NA
	Ranibizumab	NA	11.09 (30.00)	NA	12.38 (32.00)	NA	27.00 (34.00)	27.00 (36.00)	NA

Abbreviations: BCVA - best-corrected visual acuity; cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; NA – not applicable; RCT – randomized controlled trial; RVO-ME – macular edema due to retinal vein occlusion; SEM – standard error of the mean

Appendix 9: Sensitivity analysis estimates

Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate[Range]	Mean comparator effect estimate[a] [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I^2
					Sensitivity Analyses of Bevacizumab vs. Ranibizumab in choroidal neovascular age-related macular degeneration (cn-AMD)			
Vision gain in BCVA of ≥15 EDTRS letters	Main - Longest follow-up duration	9	3245	0.22 [0.12, 0.33]	0.23 [0.14, 0.29]	0.95 (0.84, 1.08,)	-1.62 (-4.86, 1.62,)	0%
	SA - Follow-up for 12 months	7	3159	0.26 [0.2, 0.33]	0.24 [0.14, 0.35]	0.96 (0.85, 1.08)	-0.67 (-3.72, 2.38,)	0%
	SA - Trials with low risk of selection bias (random-effects model)	3	1191	0.23 [0.16, 0.3]	0.24 [0.19, 0.29]	0.95 (0.68, 1.33)	-0.97 (-8.42,6.49,)	61%
	SA - Trials with low risk of selection bias (fixed-effects model)	3	1191	0.23 [0.16, 0.3]	0.24 [0.19, 0.29]	0.94 (0.77, 1.16)	-1.87 (-6.58, 2.85,)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Main - Longest follow-up duration	10	3302	0.06 [0, 0.11]	0.07 [0.04, 0.14]	1.10 (0.84, 1.43)	0.39 (-1.46, 2.23,)	4%
	SA - Follow-up for 12 months	8	3214	0.06 [0, 0.11]	0.07 [0.03, 0.14]	1.18 (0.86, 1.54)	0.57 (-0.98, (2.11)	2%
	SA - Trials with low risk of selection bias (random-effects model)	3	1191	0.09 [0.08, 0.11]	0.08 [0.05, 0.1]	1.18 (0.65, 2.13)	1.42 (6.34, -3.5, 6.34)	59%
	SA - Trials with low risk of selection bias (fixed-effects model)	3	1191	0.09 [0.08, 0.11]	0.08 [0.05, 0.1]	1.14 (0.78, 1.67)	1.4 (-1.79, 4.59)	NA
Mean change in BCVA	Main - Longest follow-up duration	8	3064	7.24 [4.1, 15.2]	5.85 [0.6, 11.43]	NA	0.03 (-1.02, 1.08)	0%

Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate[Range]	Mean comparator effect estimate[a] [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I^2
	SA - Follow-up for 12 months	8	3134	7.33 [4.7, 15.2]	6.12 [0.6, 11.43]	NA	-0.30 (0.70, -1.29, 0.70)	2%
	SA - Trials with low risk of selection bias (random-effects model)	3	1191	5.95 [4.1, 7.8]	6.36 [4.9, 7.5]	NA	-0.52 (-2.14, 1.10)	0%
	SA - Trials with low risk of selection bias (fixed-effects model)	3	1191	5.95 [4.1, 7.8]	6.36 [4.9, 7.5]	NA	-0.52 (-2.14, 1.10)	NA

Footnote:
[a] The summary statistics were derived by taking the mean and range across estimates from included studies.

Abbreviations: BCVA - best-corrected visual acuity; CI - confidence interval; ETDRS - Early Treatment Diabetic Retinopathy Study; NA - not applicable; RCT - randomized controlled trials; SA - sensitivity analysis

Appendix 10: Summary of anti-VEGF treatment protocols

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
cn-AMD (n = 12)				
Schauwvlieghe 2016[30]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Monthly injections for 12 months.	None	Yes
Berg 2015[31]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Treat-and-extend protocol: Monthly injections till no signs of active AMD were found. Subsequently, injection intervals can be extended by 2 wks to max 12 wks, or shortened by 2 wks depending on AMD activities. Follow-up for 12 months. Initial injections and repeated injections as needed (treat-and-extend)	Sign of recurrence	Yes
Scholler 2014[32]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up duration for 9 months.	loss of VA of ≥5 letters with OCT evidence of fluid in the macula; increase in OCT central retinal thickness of at least 100 um; new area of nAMD; new macular haemorrhage; persistent fluid on OCT at least 1 month after the previous intravitreal injection.	No

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Chakravarthy 2013[33]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml TX 3: ranibizumab 0.5 mg/0.05 ml TX 4: bevacizumab 1.25 mg/0.05 ml	TX 1 & TX 2: 3 monthly injections + monthly injections for 24 months. TX 3 & TX 4: 3 monthly injections + repeated 3 monthly injections as needed treatment criteria.	Prespecified clinical and OCT criteria for active disease were met.	Yes
Kodjikian 2013[34]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 9 months.	loss of ≥5 letters from the previous visit with no obvious atrophy or subretinal fibrosis and with fluid on OCT; and/or active exudation on OCT; and/or increased CNV area or persistence of leakage on angiography since the previous visit; and/or new or persistent subretinal or intraretinal macular hemorrhage.	Yes
Krebs 2013[35]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 12 months.	visual acuity loss of at least 5 letters with OCT or fluorescein angiographic evidence of fluid in the macula; an increase in OCT central retinal thickness of at least 100 um; new macular haemorrhage; new area of classic CNV; or evidence of persistent fluid on OCT at least 1 month after the previous injection.	Yes

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Heier 2012 – VIEW 1[36]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: aflibercept 0.5 mg/0.05 ml TX 3: aflibercept 2 mg/0.05 ml TX 4: aflibercept 2 mg/0.05 ml	TX 1, 2, & 3: Approximately monthly injections for 12 months. TX 4: 3 monthly injections and every bimonthly injections for 12 months.	None	NA
Heier 2012 – VIEW 2[36]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: aflibercept 0.5 mg/0.05 ml TX 3: aflibercept 2 mg/0.05 ml TX 4: aflibercept 2 mg/0.05 ml	TX 1, 2, & 3: Approximately monthly injections for 12 months. TX 4: 3 monthly injections and every bimonthly injections for 12 months.	None	NA
Biswas 2011a[37]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 18 months.	an increase in CMT of more than 100 um or a fall in BCVA by more than 5 ETDRS letters	No
Biswas 2011b[38]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 18 months.	an increase in CMT of more than 100 um or a fall in BCVA by more than 5 ETDRS letters	No

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Martin 2011[39]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml TX 3: ranibizumab 0.5 mg/0.05 ml TX 4: bevacizumab 1.25 mg/0.05 ml	TX 1 & TX 2: monthly injections for 12 months. TX 3 & TX 4: monthly injections as needed treatment criteria.	Fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on fluorescein angiography.	Yes
Subramanian 2010[40]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 12 months.	Patients returned monthly to undergo visual acuity measurements (ETDRS chart, OCT and clinical exam) If patients showed a qualitative increase in intraretinal fluid or subretinal fluid by OCT	Yes
DME (n = 3)				
Fouda 2017[41]	TX 1: ranibizumab 0.5 mg/0.05 ml Tx 2: aflibercept 2 mg/0.05 ml	The drugs were injected into the study eyes at baseline and then every 1 month until the 3rd month (loading dose of three injections). During the follow-up period, the drug re-injection was considered on monthly basis	Re-injection if macular edema persisted or worsened and visual acuity worsened in comparison with the preceding visit. The treatment was withheld if there was no change of macular thickness or visual acuity for two successive visits but was reinstated once vision or macular edema worsened again. Improvement or worsening of macular edema was defined as a 10% change of CMT in comparison with last visit while 0.1 change of visual acuity in comparison with last visit was considered a significant change.	None

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Wells 2015[27]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml TX 3: aflibercept 2 mg/0.05 ml	Monthly injections until stable visual acuity within 6 months. Subsequently, irrespective of visual acuity and central subfield thickness, an injection was withheld if there was no improvement or worsening after two consecutive injections, but treatment was reinitiated if the visual-acuity letter score or the central subfield thickness worsened. Laser PCT was initiated at or after the 24 week visit for persistent DME. Follow-up for 12 months.	Patients were injected at baseline and then every month unless visual acuity was 20/20 or better with a central subfield thickness below the eligibility threshold and there was no improvement or worsening in response to the past two injections. Starting at 6 months, irrespective of visual acuity and central subfield thickness, an injection was withheld if there was no improvement or worsening after two consecutive injections, but treatment was reinitiated if the visual-acuity letter score or the central subfield thickness worsened.	Yes
Ekinci 2014[42]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Start with 3 monthly injections. Subsequently, 3 additional monthly injections as needed. After 6 injections, additional injections were used till stable visual acuity was obtained. Follow-up for 12 months.	Central macular thickness was >275 um or if there was an increase in BCVA of at least 3 letters compared with baseline	No
RVO-ME (n = 2)				
Scott 2017[43]	TX 1: aflibercept 2 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Monthly injections for 6 months	Not applicable	No

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Narayanan 2015[44]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Initial injection. Repeated monthly injections according to as needed treatment criteria for 6 months. Macular grid laser photocoagulation was allowed concurrently with injections after 3 months.	>50um increase in CRT compared with the thinnest previous measurement; new or persistent cystoid retinal changes or sub-retinal fluid on OCT; loss of >5 letters from the best previous VA measurement in conjunction with any increase in CRT; increase in VA of >5 letters between the current and most recent visits.	No
m-CNV (n = 2)				
Iacono 2012[45]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Initial injection. Repeated monthly injections according to as needed treatment criteria for 18 months.	subretinal/intraretinal fluid on OCT, leakage on FA or appearance of a new hemorrhage.	Yes
Gharbiya 2010[46]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Initial injection. Repeated monthly injections according to as needed treatment criteria for 6 months.	Monthly additional injections were performed until absence of fluorescein leakage from the CNV and absence of any fluid collections on OCT were obtained.	Yes

Abbreviations: BCVA – Best-corrected visual acuity; cn-AMD – choroidal neovascular age-related macular degeneration; CRT – central retinal thickness; DME – diabetic macular oedema; ETDRS – Early Treatment Diabetic Retinopathy Study; m-CNV – myopic choroidal neovascularization; NA – not applicable; NR – not reported; OCT – optical coherence tomography; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion; SD – standard deviation; TX – treatment; VA – visual acuity

Appendix 11: Summary of results from the DRCR.net trial (Wells 2015[a] and Wells 2016[b])

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate [Range]	Mean comparator effect estimateb [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I^2
Subgroup Analysis of Anti-VEGF Treatment Effects in Diabetic Macular Edema (DME) According to the DRCR.net RCT								
Aflibercept vs. Ranibizumab								
Vision gain in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	392	0.37	0.39	1.06 (0.82, 1.37)	2.16 (- 7.44, 11.75)	NA
	Participants with baseline BCVA < 69 letters	1	192	0.55	0.58	1.05 (0.82, 1.35)	2.84 (-11.17, 16.86)	NA
	Participants with baseline BCVA ≥ 69 letters	1	200	0.19	0.2	1.10 (0.63, 1.92)	1.83 (-9.14, 12.8)	NA
	Follow-up for 12 months	1	414	0.32	0.42	**1.30 (1.01, 1.69)**	**10.1 (1.00, 19.00)**	NA
	Participants with baseline BCVA < 69 letters	1	203	0.50	0.67	**1.35 (1.06, 1.72)**	**17.16 (3.79, 30.53)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	211	0.15	0.18	1.18 (0.64, 2.17)	2.69 (- 7.34, 12.72)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	392	0.02	0.02	1.59 (0.38, 6.67)	0.92 (-1.87, 3.7)	NA
	Follow-up for 12 months	1	414	0.01	0.01	0.99 (0.20, 4.76)	0 (-2.00, 2.02)	NA
Mean change in BCVA (SMD)	Follow-up for 24 months	1	392	12.3 ± 10.5	12.8 ± 12.4	NA	0.7 (-1.3, 2.8)	NA
	Participants with baseline BCVA < 69 letters	1	192	16.1 ± 12.1	18.1 ± 13.8	NA	2.3 (-1.1, 5.6)	NA

	Participants with baseline BCVA ≥ 69 letters	1	200	8.6 ± 7.0	7.8 ± 8.4	NA	-0.7 (-2.9, 1.5)	NA
	Follow-up for 12 months	1	414	11.2 ± 9.4	13.3 ± 11.1	NA	**2.1 (0.1, 4.2)**	NA
	Participants with baseline BCVA < 69 letters	1	203	14.2 ± 10.6	18.9 ± 11.5	NA	**4.7 (1.4, 8.0)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	211	8.3 ± 6.8	8.0 ± 7.6	NA	-0.4 (-2.3, 1.5)	NA
Bevacizumab vs Aflibercept								
Vision gain in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	386	0.35	0.39	0.89 (0.69, 1.16)	-4.21 (-13.82, 5.4)	NA
	Participants with baseline BCVA < 69 letters	1	190	0.52	0.58	0.9 (0.69, 1.16)	-5.99 (-20.12, 8.14)	NA
	Participants with baseline BCVA ≥ 69 letters	1	196	0.17	0.2	0.84 (0.47, 1.52)	-3.18 (-14.11, 7.74)	NA
	Follow-up for 12 months	1	414	0.29	0.42	**0.68 (0.52, 0.89)**	**-14.0 (-23.00, -4.04)**	NA
	Participants with baseline BCVA < 69 letters	1	204	0.41	0.67	**0.62 (0.47, 0.81)**	**-25.49 (-38.72, -12.26)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	210	0.16	0.18	0.91 (0.5, 1.65)	-1.58 (-11.77, 8.61)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	386	0.03	0.02	1.3 (0.4, 4.2)	0.76 (-2.58, 4.1)	NA
	SA - Follow-up for 12 months	1	412	0.01	0.01	1 (0.2, 4.9)	0 (-2.02, 2.00)	NA
Mean change in BCVA (SMD)	Follow-up for 24 months	1	386	10.0 ± 11.8	12.8 ± 12.4	NA	**-2.7 (-5.2, -0.3)**	NA
	Participants with baseline BCVA < 69 letters	1	190	13.3 ± 13.4	18.1 ± 13.8	NA	**-4.7 (-8.8, -0.5)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	196	6.8 ± 8.8	7.8 ± 8.4	NA	-1.1 (-3.4, 1.1)	NA

	Follow-up for 12 months	1	414	9.7 ± 10.1	13.3 ± 11.1	NA	**-3.5 (-1.4, -5.7)**	NA
	Participants with baseline BCVA < 69 letters	1	204	11.8 ± 12.0	18.9 ± 11.5	NA	**-6.5 (-10.1, -2.9)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	210	7.5 ± 7.4	8.0 ± 7.6	NA	-0.7 (-2.7, 1.3)	NA

Footnote: Bolded estimates indicate statistical significance.

[a] Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193-1203.

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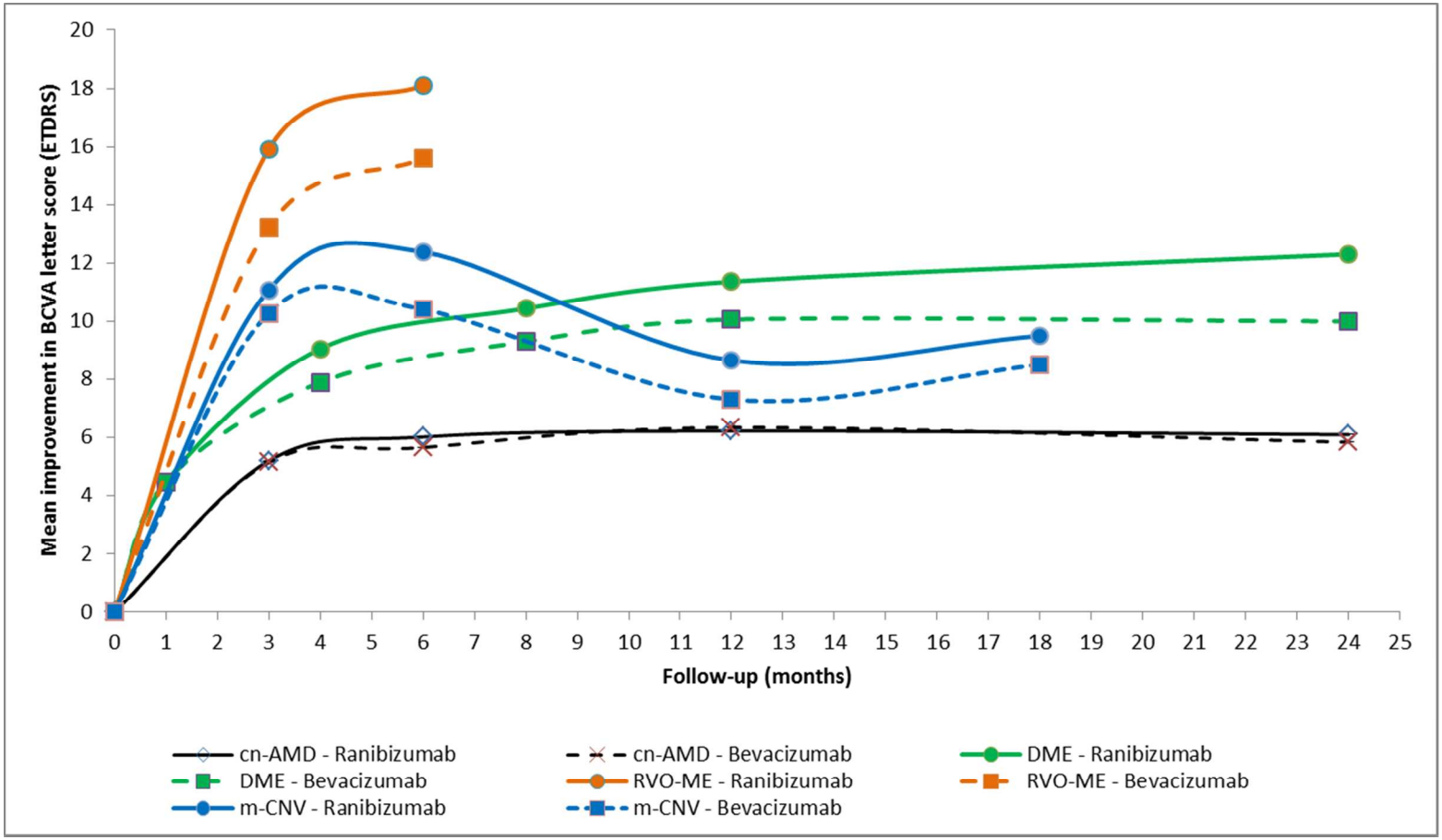
Abbreviations: BCVA - best-corrected visual acuity; CI - confidence interval; ETDRS - Early Treatment Diabetic Retinopathy Study; NA - not applicable; RCT - randomized controlled trials; Rx - treatment; SA - sensitivity analysis; SMD - standardized mean difference

Appendix 12: Mean change in best-corrected visual acuity letter scores over time in patients treated with bevacizumab or ranibizumab



Abbreviations: BCVA – Best-corrected visual acuity; cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; ETDRS – Early Treatment Diabetic Retinopathy Study; m-CNV – myopic choroidal neovascularization; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion

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PRISMA Checklist

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

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8, Appendix 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8; Appendix 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9; Appendix 1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9; Appendix 1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8; Appendix 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9; Appendix 1
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9; Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10; Appendix 2-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10; Appendix 4-5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-16, Appendix 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10; Appendix 4-5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-16, Appendix 9
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

BMJ Open

Anti–Vascular Endothelial Growth Factor Treatment for Retinal Conditions: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022031.R1
Article Type:	Research
Date Submitted by the Author:	27-Nov-2018
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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	ranibizumab, bevacizumab, aflibercept, anti-vascular endothelial growth factor, age-related macular degeneration, diabetic macular edema

Anti–Vascular Endothelial Growth Factor Treatment for Retinal Conditions: A Systematic Review and Meta-analysis

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Word count: 300/300 (Abstract), 3955/4000 (Main text), 1 figure, 4 tables, 2 supplementary files

ABSTRACT

Objectives: To evaluate the comparative effectiveness and safety of intravitreal bevacizumab, ranibizumab, and aflibercept for patients with choroidal neovascular age-related macular degeneration (cn-AMD), diabetic macular edema (DME), macular edema due to retinal vein occlusion (RVO-ME) and myopic choroidal neovascularization (m-CNV).

Design: Systematic review and random-effects meta-analysis.

Methods: Multiple databases were searched from inception to August 17th, 2017. Eligible head-to-head randomized controlled trials (RCTs) comparing the anti-VEGF drugs in adult patients aged ≥18 years with the retinal conditions of interest. Two reviewers independently screened studies, extracted data and assessed risk of bias.

Results: Nineteen RCTs involving 7459 patients with cn-AMD (n=12), DME (n=3), RVO-ME (n=2), and m-CNV (n=2) were included. Vision gain was not significantly different in patients with cn-AMD, DME, RVO-ME, and m-CNV treated with bevacizumab versus ranibizumab. Similarly, vision gain was not significantly different between cn-AMD patients treated with aflibercept versus ranibizumab. Patients with DME treated with aflibercept experienced significantly higher vision gain at 12 months than patients receiving ranibizumab or bevacizumab, however this difference was not significant at 24 months. Rates of systemic serious harms were similar across anti-VEGF agents. Post-hoc analyses revealed that an as-needed treatment regimen (6-9 injections per year) was associated with a mortality increase of 1.8% (RR: 2.0, [1.2, 3.5], 2 RCTs, 1795 patients) compared to monthly treatment in cn-AMD patients.

Conclusions: Intravitreal bevacizumab was a reasonable alternative to ranibizumab and aflibercept in patients with cn-AMD, DME, RVO-ME and m-CNV. The only exception was for patients with DME and low visual acuity (<69 ETDRS letters), where treatment with aflibercept was associated with significantly higher vision gain (≥15 ETDRS letters) than bevacizumab or ranibizumab at 12 months; but the significant effects were not maintained at 24 months. The choice of anti-VEGF drugs may depend on the specific retinal condition, baseline visual acuity, and treatment regimen.

Trial registration: PROSPERO CRD 42015022041

Keywords: ranibizumab, bevacizumab, aflibercept, anti-vascular endothelial growth factor, age-related macular degeneration, diabetic macular edema, retinal vein occlusion, myopic choroidal neovascularization

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We consolidated the evidence for treatment choice of all common retinal conditions, allowing the interpretation of the strength of the evidence of benefits and harms of the anti-VEGF drugs across conditions.
- We summarized information regarding treatment regimens (e.g., 3 initial monthly intravitreal injections and as-needed monthly retreatment, treat and extend), as-needed retreatment criteria, and the reconstitution of bevacizumab, and examined the influence of the choice of treatment regimens on the benefits and harms of the anti-VEGF drugs for specific retinal conditions.
- We limited our review to English studies, and found that very few RCTs evaluated the anti-VEGF drugs in patients with RVO-ME and m-CNV.
- Our sensitivity and subgroup analyses were not specified *a-priori* and should be interpreted with caution.

BACKGROUND

Retinal conditions due to neovascular abnormality are common in older adults. Choroidal neovascular age-related macular degeneration (cn-AMD) is the leading cause of irreversible blindness in individuals aged 50 years or older in high-income countries.[1, 2] If left untreated, potentially irreversible visual impairment can also be caused by diabetic macular edema (DME) and macular edema due to retinal vein occlusion (RVO-ME).[3-5] Choroidal neovascularization secondary to pathologic myopia (myopic CNV) is another major cause of blindness and visual impairment worldwide.[6, 7] Together, these retinal diseases cause substantial reduction in quality of life, and are a significant burden on healthcare systems.[8]

Ranibizumab, off-label use of repackaged bevacizumab, and aflibercept are widely used anti-vascular endothelial growth factor (anti-VEGF) drugs for intravitreal treatment of retinal conditions. Multiple systematic reviews have evaluated the comparative effectiveness of anti-VEGF drugs in patients with cn-AMD, DME, RVO-ME, and m-CNV;[9-12] but given the publication of new trials in patients with RVO-ME[13] and DME,[14] and long-term follow-up data for patients with cn-AMD,[15] an update is necessary. We aimed to conduct a systematic review to evaluate the comparative effectiveness and safety of bevacizumab, ranibizumab, and aflibercept for patients with cn-AMD, DME, RVO-ME, and m-CNV.

METHODS

A systematic review regarding the comparative efficacy and safety of the anti- VEGF drugs was planned in response to a query from the Canadian Drug Safety and Effectiveness Network (PROSPERO CRD 42015022041), for which a preliminary report was prepared to inform listing

recommendations.[16, 17] The report included a meta-analysis of pairwise comparisons of the anti-VEGF drugs for individual retinal conditions, as well as a network meta-analysis to evaluate the anti-VEGF drugs in cn-AMD patients. This paper summarizes results of the meta-analysis; a separate paper is underway for the network meta-analysis results.

The current review was conducted using the Cochrane Handbook for Systematic Reviews and reported using the PRISMA statement[18] (Additional file 1). The methods are outlined briefly below, as they are described in greater detail in Additional file 2: Appendix 1 and a related therapeutic review report.[17]

Data Sources and Searches:

MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were searched. Studies that are not widely available or commercially published (i.e., grey literature), were identified using an established approach.[19] Additional studies were identified by searching reference lists of included studies, and email correspondence with expert clinicians and anti-VEGF drug manufacturers.

An information specialist developed the search strategy, which was peer-reviewed by another information specialist using the PRESS statement.[20] The MEDLINE strategy can be found in Additional file 2: Appendix 1. The search was conducted on May 27th, 2015 and updated on August 17th, 2017.

Study Selection and Outcome Definitions:

Eligible studies were randomized controlled trials (RCTs) that directly compared intravitreal bevacizumab, ranibizumab, and/or aflibercept for the treatment of patients (aged ≥18 years) with

cn-AMD, DME, RVO-ME or m-CNV. We excluded RCTs comparing anti-VEGF drugs with other comparators, such as photodynamic therapy, intravitreal corticosteroids, and grid laser photocoagulation (Appendix 1). Due to time and resource constraints, we only included studies published in English.

Eligible RCTs reported one of the following benefits and harms outcomes: vision gain, defined as a gain in Best-Corrected Visual Acuity (BCVA) letter score of ≥15 on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart;[21] vision loss, defined as a loss in BCVA letter score of ≥15; mean change in BCVA from baseline; legal blindness (BCVA of 20/200 or worse measured on a standard Snellen chart, or worse than 20/100 visual acuity measured on ETDRS chart); vision-related function according to the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25);[22] serious adverse events; all-cause mortality; arterial thromboembolic events (TEs); venous TEs; bacterial endophthalmitis; and retinal detachment. All titles/abstracts and potentially relevant full-text articles were screened by two reviewers, independently. Discrepancies were discussed and if necessary, resolved with input from a third reviewer. When multiple reports of the same trial were identified, the main report was included, and the others were treated as companion reports.[23]

Data Extraction and Quality Assessment:

Data extraction forms were developed with input from three clinicians, pilot-tested, and refined twice. Data extraction was conducted by two reviewers, independently. Discrepancies were discussed and if necessary, resolved with input from a third reviewer. A similar approach was followed for quality assessment using the Cochrane risk-of-bias tool for RCTs.[24]

Patient and Public Involvement

There was no patient or public involvement in the conduct of this study.

Synthesis of study results

Study results were synthesized with respect to benefits and harms of treatment, treatment regimen (e.g., monthly and as-needed regimens), and trends in BCVA improvement over time. With respect to visual acuity improvement, meta-analyses were conducted with studies reporting BCVA letter score as measured on the ETDRS chart. For studies reporting visual acuity in logMAR and decimal values, the values were converted to approximate ETDRS letter scores,[25] with approximate standard deviations.[26] Pairwise comparisons of drugs were assessed at the longest treatment duration, allowing for the inclusion of trials in the meta-analysis that reported outcome data at different time points. Subgroup analyses were conducted at 12 months and 24 months, as these were the most frequently reported time points. A post hoc analysis was conducted to compare different treatment regimens across the drugs. For DME patients, treatment effect estimates were obtained for all patients as well as subgroups based upon baseline BCVA, which were pre-specified in the DRCR.net trial.[27] The meta-analysis was conducted using a random-effects model, as we assumed treatment effects varied across trials. A sensitivity analysis was conducted by restricting results to trials determined to be at low risk of selection bias. Between-study heterogeneity was assessed using the I^2 statistic, with values above 75% indicating substantial heterogeneity.[28]

RESULTS

Literature search

After screening 3176 titles/abstracts and 440 full-text articles, 19 head-to-head RCTs of the anti-

VEGF drugs were included, with 7459 patients, including 12 RCTs for cn-AMD, 3 RCTs for DME, 2 RCTs for RVO-ME, and 2 RCTs for m-CNV (Figure 1, Additional file 2: Appendix 1).[27, 29-42] Given our inclusion criteria, we excluded RCTs that compared anti-VEGF drugs with placebo or laser photocoagulation.[43-49]

Study and patient characteristics

Studies were completed between 2010 and 2017 with an average sample size of 393 patients per trial (range: 28, 1240) (Table 1, Additional file 2: Appendix 2-3). The mean age ranged from approximately 60 to 80 years, and females accounted for 5% to 76% of the patients. The average follow-up duration was 13 months (range: 6-24 months). RCTs were conducted in Europe (n=8), North America (n=5), Asia (n=4), Africa (n=1) and across multiple continents (n=1); most were multi-centre RCTs (n=13), in addition to 6 single-centre RCTs.

Risk of bias assessment

Random sequence generation and allocation concealment were unclear for 12/19 (63.2%) and 9/19 (47.4%) of the included RCTs, respectively, suggesting the potential for selection bias (Additional file 2: Appendix 4-5). The RCTs were at low risk with respect to blinding of participants and trial personnel 18/19 (94.7%), blinding of outcome assessment 18/19 (94.7%), incomplete outcome data 13/19 (68.4%), and selective reporting 13/19 (68.4%). Two of the 19 RCTs (10.5%) were industry-funded.[38]

Patients with cn-AMD

Comparative effectiveness of bevacizumab and ranibizumab

Results from 10 RCTs (3302 patients) showed that approximately 22% of patients attained vision gain of ≥15 BCVA letter scores with treatment, and patients treated with bevacizumab were as likely to attain vision gain as those treated with ranibizumab (Risk Ratio (RR): 1.05; [95% confidence interval (CI), 0.93, 1.19], Table 2, Additional file 2: Appendix 6-7). Over an average treatment duration of 16 months, approximately 94% of patients maintained their vision, with no statistical difference between patients treated with bevacizumab or ranibizumab (RR of vision loss: 0.91 [95% CI, 0.70, 1.19]). Patients treated with bevacizumab or ranibizumab gained an average of 7 letters in terms of mean BCVA with no statistical difference between the drugs (mean difference [MD] 0.03 letters [95% CI, -1.02, 1.08]). Approximately 2-4% patients treated with bevacizumab or ranibizumab became legally blind (RR: 2.04 [95% CI, 0.32 to 12.50], 3 trials, 1823 patients). Overall, the results were consistent across the 10 trials and did not change with the sensitivity analyses restricted to trials determined to be at low risk of selection bias and with different follow-up lengths (Additional file 2: Appendix 6, 8-9).

Comparative effectiveness of aflibercept and ranibizumab

Results from 2 RCTs (1815 patients; Table 2, and Additional file 2: Appendix 6) showed that approximately 32% of patients attained vision gain with treatment, and patients treated with aflibercept were as likely to attain vision gain as patients treated with ranibizumab (RR: 0.99 [95% CI, 0.81 to 1.22]). Over an average assessment and treatment duration of 12 months, approximately 95% of patients maintained their vision, and aflibercept patients were as likely to maintain vision as ranibizumab patients (RR of vision loss: 0.90 [95% CI, 0.60 to 1.35]). With respect to mean BCVA, patients gained on average 9 letters (MD: -0.05 [95% CI, -2.5, 2.4]). Compared to baseline, patients gained some visual-related function, with an average of 5 points

on the NEI-VFQ-25 questionnaire (MD: 2.2 [95% CI, -0.6, 5.1]).

Comparative effectiveness of bevacizumab and aflibercept

There were no RCTs that directly compared bevacizumab and aflibercept (Table 2, and Additional file 2: Appendix 6).Regarding BCVA change, the *mean difference between bevacizumab and ranibizumab was -0.03 (95% CI: -1.08, 1.02) whereas the mean difference between aflibercept and ranibizumab was -0.05 (95% CI: -2.5, 2.4), suggesting a mean difference between bevacizumab and aflibercept of 0.02 (95% CI: -2.60, 2.64)*[50]. For vision gain, the corresponding risk ratio estimate was 0.95 (95% CI: 0.84*, 1.07)* for bevacizumab versus ranibizumab and 0.99 (95% CI: 0.81, 1.22) for bevacizumab versus ranibizumab, suggesting a risk ratio estimate of 0.96 (95% CI: 0.75, 1.22) between bevacizumab and aflibercept.

Treatment regimens

Additional file 2: Appendix 10 provides detailed information regarding the treatment regimens in the included trials, the as-needed re-treatment criteria and the reconstitution of bevacizumab for intravitreal injections. The treatment regimens varied widely, and are summarized in Table 3 along with the mean number of injections per year for each treatment regimen. The number of reported treatment regimens varied by condition (cn-AMD (n=6), DME (n=3), RVO-ME (n=2), and m-CNV (n=1)). In cn-AMD patients, the two most commonly reported regimens for bevacizumab and ranibizumab included monthly injections (~11 injections/year) and 3 monthly injections followed by as-needed treatment (~6 injections/year). Aflibercept was most commonly administered using a monthly regimen (~11 injections/year).

Results of our posthoc analysis comparing as-needed versus monthly treatment in cn-AMD

patients are summarized in Table 4. The as-needed treatment regimen with ranibizumab or bevacizumab was less effective than the monthly regimen in improving mean BCVA (MD: -1.9 letters [95% CI, -3.3 to -0.5 letters], 2 RCTs, 1622 patients) and vision gain (RR: 0.73 [95% CI, 0.55 to 0.95]). When the regimens were assessed for non-inferiority at 1 year with an inferiority margin of 5 points, monthly bevacizumab was equivalent to monthly ranibizumab (MD: -0.5 [95% CI, -3.9, 2.9]), as-needed bevacizumab was equivalent to as-needed ranibizumab (MD: -0.8 [95% CI, -4.1, 2.5]), as-needed ranibizumab was equivalent to monthly ranibizumab (MD: -1.7 [95% CI, -4.7, 1.3]) but monthly bevacizumab was not equivalent to as-needed bevacizumab (MD: -2.1 [95% CI, -5.7, 1.6]).[51] Compared to the monthly regimen, the as-needed regimen was associated with a significant increase in mortality of 1.8% (95% CI, 0.1% to 3.4%, meta-analysis of mortality data reported in 2 RCTs, 1795 patients) [RR, 2.0; 95% CI, 1.2 to 3.5].[35, 51]

Harms

Over an average of 14 months (range: 12-24 months), mortality was reported in 4% and 3% of patients treated with bevacizumab or ranibizumab, respectively (RR: 1.14 [95% CI, 0.72 to 1.79], 6 RCTs, 2941 patients, Additional file 2: Appendix 6). Serious adverse events were reported in 19% and 18% of patients treated with bevacizumab or ranibizumab, respectively (RR: 1.09 [95% CI, 0.93 to 1.27], 5 RCTs, 3026 patients). Arterial thromboembolic events were reported in 4% and 3%of patients treated with bevacizumab or ranibizumab, respectively (RR: 0.86 [95% CI, 0.51, 1.47], 4 RCTs, 2033 patients). Venous thromboembolic events, bacterial endophthalmitis and retinal detachment were reported in <1% of patients treated with either drug. In the trials evaluating aflibercept and ranibizumab, arterial thromboembolic events were reported in 2% of patients treated with aflibercept or ranibizumab (RR: 0.96 [95% CI, 0.45,

2.04], 2 RCTs, 1818 patients), and venous thromboembolic events were reported in <1% of patients treated with either drug. Data on other harms were not available.

Patients with DME

Comparative effectiveness of ranibizumab, bevacizumab and aflibercept

Results from the trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net trial, 620 patients) showed that over 2 years of treatment, patients were as likely to attain vision gain with ranibizumab (37%), bevacizumab (35%), or aflibercept (39%) - bevacizumab versus ranibizumab: RR: 0.94 [95% CI, 0.72, 1.23]; aflibercept versus bevacizumab: RR: 1.06 [95% CI, 0.80, 1.38]; and aflibercept versus ranibizumab: RR: 1.06 [95% CI, 0.82, 1.37]; Table 2). Over 2 years of treatment, approximately 98% of patients maintained their vision with all 3 drugs. Besides the DRCR.net RCT, two small single-centered RCTs reported BCVA data, one comparing aflibercept with ranibizumab[14], and another comparing bevacizumab and ranibizumab[31]. Patients' mean BCVA improved by approximately 13 letters with aflibercept, 10 letters with bevacizumab and 12 letters with ranibizumab (aflibercept versus ranibizumab: MD, 1.4 [95% CI, -1.6, 4.3]; bevacizumab versus aflibercept: MD, -2.7 [95% CI, -5.2 to -0.3]; and bevacizumab versus ranibizumab: MD, -2.0 [95% CI, -3.9 to -0.1], Table 2).

The DRCR.net trial reported results stratified by baseline visual acuity at 12 and 24 months (Appendix 11). In patients with high baseline visual acuity (BCVA ≥ 69 letters), approximately 16% of patients treated with bevacizumab, 15% of patients treated with ranibizumab and 18% of patients treated with aflibercept attained vision gain at 12 months (RR of bevacizumab versus aflibercept: 0.91 [95% CI: 0.50, 1.65]; RR of aflibercept versus ranibizumab: 1.18 [95% CI:

0.64, 2.17]). Vision gain at 24 months was 17% with bevacizumab, 19% with ranibizumab and 20% with aflibercept (RR of bevacizumab versus aflibercept: 0.84 [95% CI: 0.47, 1.52]; RR of aflibercept versus ranibizumab: 1.10 [95% CI: 0.63, 1.92]). In patients with low baseline visual acuity (BCVA < 69 letters), approximately 41% of patients treated with bevacizumab, 50% of patients treated with ranibizumab and 67% of patients treated with aflibercept attained vision gain at 12 months (RR of bevacizumab versus aflibercept: 0.62 [95% CI: 0.47, 0.81]; RR of aflibercept versus ranibizumab: 1.35 [95% CI: 1.06, 1.72]). At 24 months, vision gain was 52% with bevacizumab, 55% with ranibizumab and 58% with aflibercept (RR of bevacizumab versus aflibercept: 0.90 [95% CI: 0.69, 1.16]; RR of aflibercept versus ranibizumab: 1.05 [95% CI: 0.82, 1.35]).

Treatment regimen

With respect to treatment regimen, the DRCR.net trial treated patients initially with monthly injections until stable visual acuity within 6 months, followed by as-needed treatment (Additional file 2: Appendix 10).[52] The median number of injections administered over a one-year period was 10 in the bevacizumab group, 9 in the aflibercept group, and 10 in the ranibizumab group (Table 3).[52] In the second year, the median number of injections was: 6, 5, and 6 in the bevacizumab, aflibercept, and ranibizumab groups, respectively.[53] Two smaller trials both started treatment with 3 monthly intravitreal injections, followed by monthly re-treatment with persistence of macular edema, thickening of central macular or worsening of visual acuity (Table 3 and Appendix 10 – Summary of treatment protocols).[14, 31]

Harms

After 24 months of treatment in the DRCR.net trial,[27] mortality was reported in approximately 6% of bevacizumab patients, 2% of aflibercept patients and 5% of ranibizumab patients (Additional file 2: Appendix 6). Serious adverse events were reported in 21% of bevacizumab patients, 27% of aflibercept patients, and 25% of ranibizumab patients. Arterial thromboembolic events were reported in 4%, 3%, and 5%, of patients treated with bevacizumab, aflibercept, and ranibizumab, respectively. Bacterial endophthalmitis and retinal detachments were reported in <1% of patients treated with any of the drugs.

Patients with RVO-ME

Comparative effectiveness of ranibizumab, bevacizumab, and aflibercept

Results from one randomized, double-blind, controlled and non-inferiority trial conducted in India (including 77 patients with ME due to branch RVO) showed that approximately 59% of patients attained vision gain with bevacizumab and ranibizumab treatment, and no statistical difference was observed between the drugs (RR: 1.0 [95% CI, 0.68 to 1.45]; Table 2 and Additional file 2: Appendix 8).[32] With respect to mean BCVA, patients treated with either drug gained an average of 16 letters (MD -2.5 [95% CI, -8.0 to 5.0]).

Results from the SCORE2 randomized non-inferiority trial conducted in 66 centers in the United States (348 patients with ME due to central RVO) showed that approximately 61% of patients treated with bevacizumab or aflibercept attained vision gain, with no statistical difference between the drugs (RR: 1.06 [95% CI, 0.91 to 1.25]; Table 2).[13] With respect to mean BCVA, patients treated with either drug gained an average of 19 letters (MD 1.52 [95% CI, -1.2 to 4.2]).

Treatment regimens

In the SCORE2 trial, patients were treated with monthly intravitreal injections for 6 months, with a mean number of 5.8 injections in patients treated with bevacizumab or aflibercept (Table 3 and Additional file 2: Appendix 11).[13] In the other trial, patients were treated with one initial intravitreal injection and then as-needed monthly re-treatment over 6 months, with a mean number of 3 injections in patients treated with bevacizumab or ranibizumab.[13, 32]

Harms

Serious adverse events were reported in 3% of bevacizumab patients and 5% of ranibizumab patients (RR: 0.5 [95% CI, 0.05 to 5.26], 1 RCT, 74 patients; Additional file 2: Appendix 8).[32] Serious adverse events were reported in 8% of the patients treated with bevacizumab or aflibercept over 6 months (RR: 0.99 [95% CI, 0.49 to 2.00], 1 RCT, 362 patients).[13]

Patients with m-CNV

Comparative effectiveness of ranibizumab and bevacizumab

Two small RCTs both conducted in Italy evaluated ranibizumab and bevacizumab for patients with m-CNV. Results from one RCT (32 patients) showed that 62% of patients treated with bevacizumab and 56% of patients treated with ranibizumab attained vision gain (RR: 1.11 [95% CI, 0.63, 1.96], 1 RCT; Table 2 and Additional file 2: Appendix 11).[30] The other RCT (55 patients) only report BCVA results.[29] With respect to mean BCVA, patients treated with bevacizumab gained 12 letters and patients treated with ranibizumab gained 13 letters (MD: -1.3 [95% CI, -6.5 to 4.0], 2 RCTs, 80 patients).[29, 30] The included trials did not report data on harms.

Treatment regimens

Both trials evaluated ranibizumab and bevacizumab with patients receiving one monthly intravitreal injection and as-needed monthly re-treatment for 18 and 6 months, respectively, with a mean number of 3.1 injections per year in patients treated with bevacizumab and 2.4 injections in patients treated with ranibizumab (Table 3 and Additional file 2: Appendix 6).[29, 30]

DISCUSSION

This systematic review synthesized results from 19 RCTs to evaluate the comparative effectiveness and safety of intravitreal bevacizumab, ranibizumab, and aflibercept for patients with cn-AMD, DME, RVO-ME and m-CNV. Intravitreal bevacizumab was as effective as ranibizumab in patients with cn-AMD, DME, RVO-ME, and m-CNV for the outcomes we examined. Ranibizumab was as effective as aflibercept in patients with cn-AMD.

In patients with DME that were treated for 2 years, vision gain was equally likely to be attained with aflibercept, ranibizumab or aflibercept. In the first year of treatment, however, patients treated with aflibercept were more likely to attain vision gain than patients treated with ranibizumab or bevacizumab - differential effects that were observed mainly in patients with initial BCVA < 69 letter scores (equivalent to 20/50 or worse) but not observed in patients with initial BCVA ≥ 69 letter scores (equivalent to 20/40 or better) based on the results from the sub-group analyses. Rates of systemic serious harms were similarly low among the anti-VEGF drugs, across the retinal conditions. None of the included RCTs were designed with sufficient statistical power to detect significant differences between the treatments with respect to the incidence of harms. In our post-hoc analysis, cn-AMD patients and compared to monthly treatment, an as-needed treatment regimen (i.e., 6 to 9 monthly injections per year) was significantly associated with a small loss in visual acuity, but a significant increase in mortality risk of 1.8% (RR: 2.0

[95% CI, 1.2, 3.5]).

Results from the CATT and IVAN trials showed that relative to monthly treatment, patients with cn-AMD receiving as-needed treatment experienced a significant increase in risk of mortality. Whether there are any biological explanations for the increased risk of mortality associated with fewer monthly injections is unclear and this finding may have been attributable to chance. As such, further research should be conducted to verify this result. In DME, RVO-ME and m-CNV trials, patients tended to receive fewer monthly injections per year (Table 3). None of the trials in DME, RVO-ME and m-CNV patients evaluated a monthly treatment regimen, and therefore the safety risk between as-needed and monthly regimens could not be evaluated. This requires further study.

Additional file 2: Appendix 12 displays the mean change in BCVA over time in patients treated with bevacizumab or ranibizumab. For all of the retinal conditions, patients showed improvement in mean BCVA by 3-6 months with initial monthly injections, and maintained a plateau to 24 months in the treatment of cn-AMD patients (average improvement of 6 letters), DME patients (8 letters), RVO-ME patients (16 letters), and m-CNV patients (11 letters). Comparative outcomes beyond 6 months in patients with RVO-ME and m-CNV were lacking and as such, long-term comparative data of anti-VEGF drugs in these patients are needed.

Our findings are consistent with findings from previous systematic reviews. A meta-analysis of 6 head-to-head trials concluded that bevacizumab and ranibizumab had equivalent efficacy with respect to visual acuity in cn-AMD patients.[11] A meta-analysis of five RCTs suggested no differences in effectiveness between ranibizumab and bevacizumab in DME patients.[54] Other reviews in patients with RVO-ME and m-CNV came to similar conclusions.[9, 10, 55, 56] Although

findings were consistent with those in these recent reviews, our review serves as an update (with the inclusion of data up to 2017) while also examining the additional factor of treatment regimen. There are several limitations worth noting. First, none of our sensitivity and subgroup analyses were specified *a-priori* and as such, these results should be interpreted with caution. This also pertains to our post-hoc analysis on treatment regimen. Secondly, we limited our review to English studies due to time and resources constraints. We believe, however, that the impact of the restrictions is small since our findings are consistent with previous systematic reviews that included RCTs reported in all languages, evaluating the same anti-VEGF drugs for specific retinal conditions, [11, 54, 57] and results were consistent across studies, so the impact of including additional studies reported in other languages, if any, would be insignificant. We only identified a few RCTs evaluating the anti-VEGF drugs in patients with DME, RVO-ME and m-CNV. We did not include ziv-aflibercept (a low-cost anti-VEGF alternative to aflibercept and bevacizumab[58]), the old anti-VEGF pegaptanib, or the newest anti-VEGF brolucizumab. Although the rates of reported adverse events were similar across the anti-VEGF drugs, the assessment of harms using comparative trial data is limited. We excluded RCTs which randomized eyes (instead of patients) since the reported analyses failed to adjust for the correlation between the outcomes of eyes from the same individuals.[59] Similarly, we also excluded one quasi-randomized trial,[60] because we focused on randomized studies.

CONCLUSIONS

Intravitreal bevacizumab was a reasonable alternative to ranibizumab and aflibercept in patients with cn-AMD, DME, RVO-ME and m-CNV. The only exception was for patients with DME and low visual acuity (<69 ETDRS letters, 20/50 or worse), where treatment with aflibercept was

associated with significantly higher vision gain (≥15 ETDRS letters) than bevacizumab or ranibizumab at 12 months; but the significant effects were not maintained at 24 months. The choice of anti-VEGF drug may depend on specific retinal conditions, baseline visual acuity, and treatment regimen.

LIST OF ABBREVIATIONS

Adverse event (AE); Age-related macular degeneration (wet AMD); Arterial thromboembolic events (ATE); Best-corrected visual acuity (BCVA); Bacterial endophthalmitis (BE); Confidence interval (CI); Choroidal neovascularization (CNV); Diabetic macular edema (DME); Early Treatment Diabetic Retinopathy Study (ETDRS); Randomized controlled trial (RCT); Risk ratio (RR); Macular edema due to retinal vein occlusion (RVO-ME); Standardized mean difference (SMD); Vascular endothelial growth factor (VEGF); Venous thromboembolic event (VTE)

ACKNOWLEDGEMENTS

We thank Becky Skidmore for drafting our search strategies, Kelly Farrah for peer reviewing the search strategies (PRESS), and Alissa Epworth for de-duplicating search results and obtaining full-text articles. We thank Meghan Kenny for helping screen studies for inclusion and performing quality appraisal and Jaimie Adams for helping screen studies for inclusion. We would also like to thank Michel Boucher, Sarah Berglas, Hongbo Yuan, and Sarah Jennings for their valuable contribution, insights, and for facilitating the production and dissemination of the synthesized evidence. In addition we would like to thank the clinical experts and stakeholders who provided feedback on the previous therapeutic review report. Finally, we thank Susan Le, Inthuja Selvaratnam, Katrina Chiu, and Krystle Amog for preparing tables and formatting the manuscript for submission.

CONTRIBUTORS

BP screened titles, abstracts, and full-text articles; abstracted and cleaned data, conducted quality assessment; and drafted the manuscript. SMT lead the coordination of the systematic review; drafted the protocol; screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and helped draft and revise the manuscript. TL screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; helped conduct meta-analysis; and reviewed the manuscript. EL screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the manuscript. JH conducted the analysis and interpretation of data; and reviewed the manuscript. TR helped with conceptualizing the research design, drafting and revising the protocol, interpretation of data; and reviewed the manuscript. GJ helped draft and revise the protocol; screened titles, abstracts, and full-text articles; abstracted data; conducted quality assessment; helped interpret the data; and reviewed the manuscript. AA screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the manuscript. JPS screened titles, abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the manuscript. AS screened titles, abstracts, and full-text articles; abstracted and cleaned data, conducted quality assessment; and reviewed the manuscript. RW screened titles, abstracts, and full-text articles; abstracted and cleaned data, conducted quality assessment; and reviewed the manuscript. RB abstracted and cleaned data, conducted quality assessment; and reviewed the manuscript. EM screened titles, abstracts, and full-text articles; abstracted and cleaned data; and reviewed the manuscript. SES helped with conceptualizing the research and design; interpretation of data, and reviewed the manuscript.

ACT conceptualized the research and design; drafted the protocol; obtained funding; assisted with data acquisition and interpretation; and drafted and revised the manuscript. Authors ACT and BP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

FUNDING

This work was supported by the Canadian Institutes of Health Research/Drug Safety and Effectiveness Network (CIHR/DSEN). SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation. ACT is funded by a Tier 2 Canada Research Chair in Knowledge Synthesis. The therapeutic review was commissioned by the Canadian Agency for Drugs and Technology in Health (CADTH) and funded by a grant from the Canadian Institutes of Health Research Drug Safety and Effectiveness Network. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

COMPETING INTERESTS

All authors declare no competing interests.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DATA SHARING STATEMENT

All datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

MEETING PRESENTATION

The data from the original therapeutic review was presented by ACT and SMT to the Canadian Drug Expert Committee in Ottawa, Ontario, on Nov 17th, 2015.

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FIGURE LEGENDS

Figure 1. Study Flow

TABLE 1. SUMMARY STUDY CHARACTERISTICS

Study Characteristic	Total No. of trials included (n=19)[a] (%)	No. of studies with cn-AMD (n=12) (%)	No. of studies with DME (n=3) (%)	No. of studies with RVO-ME (n=2) (%)	No. of studies with m-CNV (n=2) (%)
Year of publication					
2010–2011	5 (26.32)	4 (33.33)	0 (0)	0 (0)	1 (50)
2012–2013	6 (31.58)	5 (41.67)	0 (0)	0 (0)	1 (50)
2014–2015	5 (26.32)	2 (16.67)	2 (66.67)	1 (50)	0 (0)
2016	3 (15.79)	1 (8.33)	1 (33.33)	1 (50)	0 (0)
Geographic region					
Europe	8 (42.11)	6 (50)	0 (0)	0 (0)	2 (100)
North America	5 (26.32)	3 (25)	1 (33.33)	1 (50)	0 (0)
Asia	4 (21.05)	2 (16.67)	1 (33.33)	1 (50)	0 (0)
Africa	1 (5.26)	0 (0)	1	0 (0)	0 (0)
Multi-continent	1 (5.26)	1 (8.33)	1 (33.33)	0 (0)	0 (0)
Setting					
Single-Centre	6 (31.58)	2 (16.67)	1 (33.33)	1 (50)	2 (100)
Multi-Centre	12 (63.16)	10 (83.33)	1 (33.33)	1 (50)	0 (0)
NR	1 (5.26)	0 (0)	1 (33.33)	0 (0)	0 (0)
Follow-up duration					
6-12 months	14 (73.68)	9 (75)	2 (66.67)	2 (100)	1 (50)
13-19 months	4 (21.05)	2 (16.67)	1 (33.33)	0	1 (50)
≥20 months	1 (5.26)	1 (8.33)	0	0	0 (0)

Footnotes:
[a] Total number of randomized controlled trials, n=19, from 18 publications

Abbreviations: cn-AMD, choroidal neovascular age-related macular degeneration; DME, diabetic macular edema; m-CNV, myopic choroidal neovascularization; NR, not reported; RVO-ME, macular edema due to retinal vein occlusion.

TABLE 2. COMPARATIVE EFFECTIVENESS RESULTS

Condition	***Treatment*** vs. ***Comparator***	Outcome[a]	# of RCTs (# of patients)	Baseline ETDRS letters[b] ~Snellen equivalent	***Treatment*** *Effect Mean (Range)*[b]	***Comparator*** effect Mean (Range)[b]	Risk Ratio or *Mean Difference* Estimate (95% CI)	I^{2c}
cn-AMD	Bevacizumab vs. Ranibizumab	Vision gain	9 (3245)	57 (35 to 61) ~ 20/80	22% (12 to 33)	23% (14 to 29)	0.95 (0.84, 1.07)	0%
		Vision loss	10 (3302)	60 (35 to 61) ~ 20/63	6% (0 to 11)	7% (4 to 14)	0.91 (0.7, 1.19)	4%
		BCVA change	8 (3064)	56 (35 to 61) ~ 20/80	7.2 (4.1, 15.2)	5.9 (0.6, 11.4)	*-0.03 (-1.08, 1.02)*	0%
	Aflibercept vs. Ranibizumab	Vision gain	2 (1815)	54 (53 to 55) ~ 20/80	32% (30 to 34)	32% (31 to 34)	0.99 (0.81 to 1.22)	52%
		Vision loss	2 (1815)	54 (53 to 55) ~ 20/80	5% (5 to 5)	6% (5 to 6)	0.90 (0.60 to 1.350)	0%
		BCVA change	2 (1793)	54 (53 to 55) ~ 20/80	8.8 (8.3, 9.4)	8.8 (8.1 to 9.4)	*-0.05 (-2.5, 2.4)*	66%
DME	Bevacizumab vs. Ranibizumab	Vision gain	1 (376)	65 ~ 20/50	35%	37%	0.94 (0.72, 1.23)	NA
		Vision loss	1 (376)	65 ~ 20/50	3%	2%	0.48 (0.12, 1.91)	NA
		BCVA change	2 (456)	59 (54, 65) ~ 20/63	10.3 (10.0, 10.5)	12.1 (11.9 to 12.3)	*-2.0 (-3.9, -0.1)*	0%
	Bevacizumab vs. Aflibercept	Vision gain	1 (386)	65 ~ 20/50	35%	39%	1.06 (0.80, 1.38)	NA
		Vision loss	1 (376)	65 ~ 20/50	2%	3%	2.08 (0.52, 8.33)	NA
		BCVA change	1 (386)	65 ~ 20/50	10.0 (SD: 11.8)	12.8 (SD: 12.4)	*-2.7 (-5.2, -0.3)*	NA
	Aflibercept vs. Ranibizumab	Vision gain	1 (392)	65 ~ 20/50	39%	37%	1.06 (0.73, 1.22)	NA
		Vision loss	1 (392)	65 ~ 20/50	2%	2%	0.63 (0.15, 2.61)	NA
		BCVA change	2 (462)	56 (47, 65) ~ 20/80	16.2 (12.8 to 19.6)	14.0 (12.3 to 15.7)	1.4 (-1.6, 4.3)	27%
RVO-ME	Bevacizumab vs. Ranibizumab	Vision gain	1 (74)	56 ~ 20/80	59%	59%	1.00 (0.68, 1.45)	NA
		BCVA change	1 (77)	56 ~ 20/80	15.6	18.1	*-2.5 (-8.0, 5.0)*	NA
	Bevacizumab vs. Aflibercept	Vision gain	1 (358)	50 ~ 20/100	65%	61%	1.06 (0.91, 1.25)	NA
		BCVA change	1 (348)	50 ~ 20/100	18.6	18.9	*1.5 (-1.2, 4.2)*	NA
m-CNV	Bevacizumab vs. Ranibizumab	Vision gain	1 (32)	30 ~ 20/250	62%	56%	1.11 (0.63, 1.96)	NA
		Vision loss	1 (32)	30 ~ 20/250	0%	0%	0%	NA
		BCVA change	2 (80)	42 (30, 55) ~ 20/160	12.2 (8.5 to 15.9)	13.4 (9.5 to 17.3)	*-1.3 (-6.5, -4.0)*	0%

Footnotes:

[a] In terms of outcomes, vision gain was defined as a gain in BCVA of ≥15 EDTRS letters, vision loss of ≥15 EDTRS letters, and visual acuity was expressed using ETDRS letters (with conversion, if necessary). The main analysis was conducted with outcomes at the longest follow-up duration for each RCT.

[b] Mean (range) were derived across control groups of the included RCTs.

[c] I^2 <75 was interpreted as low evidence of substantial variation across included RCTs.

Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; cn-AMD, choroidal neovascular age-related macular degeneration; DME, diabetic macular edema; ETDRS, early treatment diabetic retinopathy study; m-CNV, myopic choroidal neovascularization; NA, not applicable; RCT, randomized controlled trials; RVO-ME, macular edema due to retinal vein occlusion.

TABLE 3. SUMMARY OF TREATMENT REGIMENS

Condition	Treatment regimen	# of RCTs	Mean monthly injections per year (range)[a]
cn-AMD	Monthly treatment with ranibizumab	5	11.3 (10.9-11.7)
	Monthly treatment with bevacizumab	3	11.5 (11.0-11.9)
	Treat and extend with ranibizumab	1	8.0
	Treat and extend with bevacizumab	1	8.9
	3 initial monthly treatments + as-needed treatment (every month) with ranibizumab	6	5.7 (4.4-7.1)
	3 initial monthly treatments + as-needed treatment (every month) with bevacizumab	5	6.3 (4.6-7.9)
	3 initial monthly treatments and as-needed treatment (every 3 months) with ranibizumab	1	8.5
	3 initial monthly treatments and as-needed treatment (every 3 months) with bevacizumab	1	8.7
	As-needed monthly treatment with ranibizumab	1	6.9
	As-needed monthly treatment with bevacizumab	1	7.7
	Monthly treatment with aflibercept	2	11.4[b]
	3 initial monthly treatment and as-needed treatment (every 2 months) with aflibercept	2	6.9[b]
DME	3 initial monthly treatments + as-needed treatment (every month) with ranibizumab	1	6.0
	3 initial monthly treatments + as-needed treatment (every month) with aflibercept	1	5.6
	3 initial monthly treatments + as-needed treatment (every month for 3 months) + as-needed treatment (every month) with ranibizumab	1	6.5
	3 initial monthly treatments + as-needed treatment (every month for 3 months) + as-needed treatment (every month) with bevacizumab	1	5.1
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment (every month) with ranibizumab	1	10[c]
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment	1	10[c]

	(every month) with bevacizumab		
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment (every month) with aflibercept	1	9[c]
RVO-ME	1 initial monthly treatment + as-needed treatment (every month) with ranibizumab	1	6.4
	1 initial monthly treatment + as-needed treatment (every month) with bevacizumab	1	6.0
	Monthly treatment with aflibercept	1	11.6
	Monthly treatment with bevacizumab	1	11.5
m-CNV	1 initial monthly treatment + as-needed treatment (every month) with ranibizumab	2	2.4 (1.7-3.1)
	1 initial monthly treatment + as-needed treatment (every month) with bevacizumab	2	3.1 (1.9-4.3)

Footnotes:
[a]Mean and ranges were derived from trial-specific means. Cases, in which a single RCT reported on a regimen, do not have an associated range.
[b]Value was reported once for both trials in Heier et al. 2012.
[c]Reported median values (Wells et al. 2015)

Abbreviations: cn-AMD, choroidal neovascular age-related macular degeneration; DME, diabetic macular edema; m-CNV, myopic choroidal neovascularization; RCT, randomized controlled trial; RVO-ME, macular edema due to retinal vein occlusion.

TABLE 4. COMPARISON OF MONTHLY VERSUS AS NEEDED ANTI-VEGF TREATMENT REGIMENS IN CN-AMD PATIENTS

Comparison	Outcome	# of RCTs[a], # of patients	Baseline ETDRS letters[b] and Snellen equivalent	As-needed regimen Mean (Range)[b]	Monthly Regimen Mean (Range)[b]	Risk Ratio or *Mean Difference* Estimate (95% CI)	I^{2c}
As-Needed Rx vs. Monthly Rx	Vision gain	2/1622	62 (61 to 63) ~ 20/63	20.8% (15.1 to 26.4)	28.9% (25.1 to 32.8)	0.73 (0.55, 0.95)	0%
	BCVA change	2/1622	62 (61 to 63) ~ 20/63	4.9 (3.5, 6.4)	6.9 (5.5, 8.3)	-1.9 (-0.5, -3.3)	0%
	Mortality	2/1795	NA	4.6% (2.6 to 6.6)	2.3% (1.4 to 3.3)	2.00 (1.15, 3.45)	12%

Footnotes:

[a] CATT and IVAN trials.(Martin, 2011; Chakravarthy 2013)

[b] Mean (range) were derived across control groups of the included RCTs.

[c] I^2 <75 was interpreted as low evidence of substantial variation across included RCTs. For each treatment regimen, patients were randomized to be treated with bevacizumab or ranibizumab.

Abbreviations: CI, confidence interval; ETDRS, early treatment diabetic retinopathy study; NA, not applicable; RCT, randomized controlled trials; Rx, treatment.

ADDITIONAL FILES

Additional File 1: PRISMA Checklist

Additional File 2: Supplementary Online Content

Appendix 1: Detailed methods

Appendix 2: Detailed study characteristics

Appendix 3: Detailed patient characteristics

Appendix 4: Cochrane risk of bias results for individual studies

Appendix 5: Risk of bias results

Appendix 6: Treatment effect estimates

Appendix 7: Forest plots for primary outcome in choroidal neovascular age related macular degeneration (cn-AMD) population

Appendix 8: Summary data used in risk of bias results

Appendix 9: Sensitivity analysis estimates

Appendix 10: Summary of anti-VEGF treatment protocols

Appendix 11: Summary of results from the DRCR.net trial (Wells 2015[a] and Wells 2016[b])

Appendix 12: Mean change in best-corrected visual acuity letter scores over time in patients treated with bevacizumab or ranibizumab

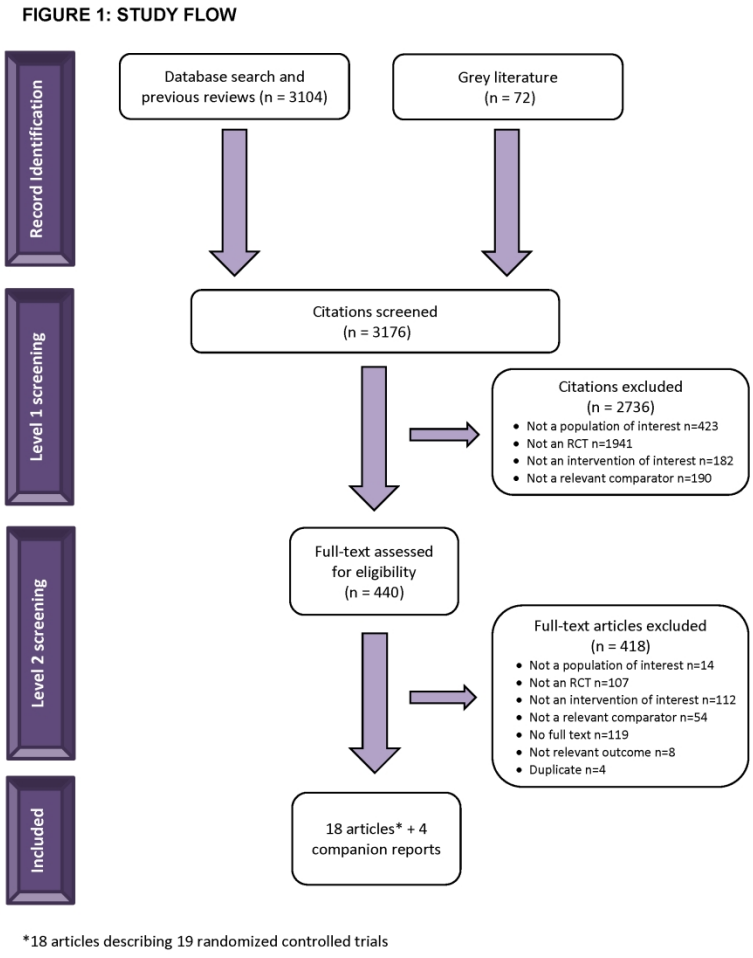

Figure 1. Study Flow

215x279mm (300 x 300 DPI)

PRISMA Checklist

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

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8, Appendix 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8; Appendix 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9; Appendix 1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9; Appendix 1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8; Appendix 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9; Appendix 1
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9; Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10; Appendix 2-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10; Appendix 4-5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-18, Appendix 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10; Appendix 4-5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-16, Appendix 9
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Online Content

Appendix 1: Detailed methods

We conducted a systematic review using methods from the Cochrane Handbook for Systematic Reviews and reported the results using the PRISMA statement.[1] The SR was commissioned by CADTH and funded by a grant from the Canadian Institutes of Health Research Drug Safety and Effectiveness Network. The methods are outlined briefly below, as they are outlined in full in the CADTH report.[2]

Protocol

We drafted a protocol with input from clinical experts, patient advocacy groups, industry stakeholders and CADTH. We posted the draft on the CADTH website to obtain feedback from additional stakeholders, revised the protocol as necessary, and registered the final version with PROSPERO (CRD 42015022041).

Literature Search Strategy

The following bibliographic databases were searched from inception until August 17th 2017, 2015: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; Cochrane Central Register of Controlled Trials via Ovid, and PubMed. Grey literature (i.e., studies that are not widely available or commercially published) was identified by searching relevant websites according to the "Clinical Trials" section of the CADTH Grey Matters checklist.[3] We used Google and other Internet search engines to search for additional web-based materials, including conference abstracts. We obtained additional studies by reviewing the references of all included studies and feedback from clinical experts, patient advocacy groups, and industry stakeholders. In addition, we contacted the three manufacturers of the anti-VEGF drugs to identify further potentially relevant trials.

An experienced information specialist developed the literature search strategy. It was peer-reviewed by another information specialist using the PRESS statement.[4] The final search strategy can be found in Appendix A and the others are available upon request of the corresponding author.

The literature search consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords (see below). The main search concepts were anti-VEGF drugs and the relevant retinal conditions. Validated methodological filters were applied to limit retrieval to RCTs.[5] Where possible, retrieval was limited to humans. Retrieval was not limited by publication year or by language, but non-English language articles were excluded during screening, to increase feasibility of the study.

Keywords

(intravitreal OR intra-vitreal or implant or implanted or implants or inject or injected or injects or injection or injections or Anti-VEGF or antiVEGF or VEGF inhibitor or VEGF antagonist or visudyne or verteporfin or PDT or PDTV or VPDT)

AND

(retinal degeneration OR wet macular degeneration OR wAMD OR neovascular macular degeneration OR exudative macular degeneration or diabetic retinopathy or DRE or Macular Edema or Retinal Vein Occlusion or Choroidal Neovascularization or BRVO or CRVO)

Eligibility Criteria

The inclusion criteria were specified as follows according to the Population, Intervention, Comparator, Outcome, Study design and Time framework (Cochrane Handbook).[5]

- Populations: patients ≥ 18 years of age and with retinal conditions including wet AMD, DME, ME/RVO and myopic CNV.
- Interventions: anti-VEGF drugs in use in Canada, namely ranibizumab, intravitreal bevacizumab and aflibercept
- Comparators: placebo, ranibizumab, intravitreal bevacizumab or aflibercept
- Outcomes: 14 outcomes were selected *a-priori* at the protocol stage according to feedback from the research team, clinical experts, patient advocacy groups, industry stakeholders and CADTH, including five efficacy outcomes and nine safety outcomes (outlined below).
- Study design: parallel- and cluster-RCTs.
- Time: RCTs published at any time; all reports pertaining to an RCT were located to obtain data at the longest follow-up duration.

We excluded studies reporting only results for pediatric patients (<18 years of age), studies evaluating the anti-VEGF drug pegaptanib, as it is no longer licensed for use in Canada, studies that compared an anti-VEGF drug with other comparators (such as intravitreal corticosteroids, grid laser photocoagulation or cataract removal surgery), and studies reported in languages other than English. Studies fulfilling the last two exclusion criteria were excluded to allow for the project timelines to be met, as outlined in the Limitations and Research Implications sections below.

We included the following efficacy outcomes:

1. Vision gain, defined as a gain in Best-Corrected Visual Acuity (BCVA) of ≥15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart,
2. Vision loss, defined as a loss in BCVA of ≥15 ETDRS letters,
3. Change from baseline in BCVA letters,
4. Legal blindness,
5. Vision-related function.

We included the following safety outcomes:

1. All-cause mortality,
2. Arterial venous thromboembolism (VT),
3. Venous VT,
4. Bacterial endophthalmitis (BE),
5. Increased intraocular pressure,
6. Retinal detachment,
7. Adverse events (AEs)
8. Serious AEs,
9. Withdrawals due to AEs

We considered BCVA data derived from Snellen or ETDRS letter charts or the logarithm of the Minimum Angle of Resolution (logMAR) chart for assessing efficacy outcomes 1-3.[6] The Snellen chart is the current standard for measurement of visual acuity in clinical practice.[6-8] The ETDRS chart is the 'gold standard' for measuring visual acuity in clinical trials.[6] The Snellen chart has letters of different sizes arranged from largest at the top to smallest at the bottom, which are read, one eye at a time, at a distance of 6 metres (20 feet). The test-retest variability of the Snellen chart ranges from ±5 to 16.5 letters in normal patients.[9 10] The test-retest variability of the ETDRS charts ranges from ±3.5 to 10 letters.[11] A change of at least 10 letters (or two lines) is required to capture a true clinical

change in visual acuity.[6 12] With respect to vision-related function, we abstracted data from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), which is a self-reported survey questionnaire that assesses the influence of visual impairment on health-related quality of life.[13] Changes in the NEI VFQ overall scores of 10 points or more are associated with clinically relevant changes in vision.[14]

Study selection

Citations from the literature search were imported into an online systematic review software.[15] Also imported were the inclusion criteria, which were used for level-1 screening of citations (titles/abstracts) and level-2 screening of potentially relevant full-text articles. The 14 members of the review team underwent two training exercises; each involved a random sample of 50 citations, which were screened independently by all team members. Level-1 screening proceeded after 80% agreement had been achieved among the reviewers on the second training exercise.[16 17] Paired reviewers conducted the level-1 screening of each citation, independently. The estimated frequency of disagreement was 8%, which was resolved by a third reviewer. We retrieved the full-text articles of potentially relevant citations identified by at least one reviewer for level-2 screening. The team underwent a training exercise using a random sample of 20 full-text articles, which resulted in 70% agreement. Paired reviewers independently screened each full-text article. The estimated frequency of disagreement was 14%, which was resolved by a third reviewer. This reviewer also verified all eligible studies.

Data abstraction

We developed a data abstraction form with inputs from two physicians. We piloted and refined the form two times, each time using five randomly selected studies. Subsequently, paired reviewers conducted the abstraction, independently. Numerical data available only in figures were extracted using WebPlotDigitizer.[18] A third reviewer conducted a quality check on all data, and resolved any remaining discrepancies.

We abstracted data pertaining to study characteristics, patient populations, interventions, and outcomes. Multiple reports of the same trial (hereafter companion reports) were identified using the trial registration identifier, trial name, or a juxtaposition of the author names, treatment comparisons, sample sizes and outcomes, if necessary.[19] We abstracted data from all companion reports, identified differences, and reconciled the differences through discussion. For each set of companion reports, we considered one as the major publication and others as companion reports. We abstracted outcome data from all trial reports and used the data corresponding to the longest duration of follow-up in the meta-analysis.[5]

Risk of bias assessment

The risk of bias in the included trials was appraised using the Cochrane risk-of-bias tool, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases such as funding sources.[20] For selection bias, we assessed the reporting of random sequence generation and allocation concealment. For performance bias, we assessed the reporting of blinding of patients and trial personnel, and for detection bias, the reporting of the blinding of outcome assessors. In the assessment of performance and detection biases, we considered the objectivity of the primary outcome of individual trials in assessing performance and detection biases.

For RCTs that had been registered, the primary outcome was identified from the trial protocol, which was vision gain or change in mean BCVA in the majority of the included RCTs. Otherwise, we identified the primary outcome using an *a-priori* defined algorithm.[21 22] In brief, we selected from the trial report the outcome that was listed in the title or objectives, the most serious clinical outcome among all the trial outcomes, or the first reported outcome in the results section.

Paired reviewers conducted the risk of bias assessment, independently. Discrepancies were resolved by discussion or the involvement of a third reviewer.

Data Analysis in CADTH report

We derived treatment effect estimates using the odds ratio (OR) for binary outcomes such as vision gain, vision loss or the presence or absence of a harmful event. The standardized mean difference (SMD) was used for treatment comparisons involving BCVA data from different visual acuity charts, such as ETDRS or Snellen charts. The SMD expresses the difference in the treatment means in terms of the standard deviations of the measurements. The mean difference (MD) was used for comparison involving BCVA data that were consistently reported using the same measurement scale, either the ETDRS or Snellen chart. This was also the case for vision-related function measurements from the NEI VFQ questionnaire.

The results from multiple arms of the same anti-VEGF drugs at different dosages were combined according to the guidance in the Cochrane handbook.[5] When an RCT did not provide standard deviations for a continuous outcome measure, missing data were imputed from available data from other RCTs using established methods.[23] This was necessary in meta-analyses involving BCVA measures and vision-related functions.

We conducted meta-analyses of pairwise comparisons of all comparators, including the anti-VEGF drugs and placebo. This was done separately for each of the four retinal conditions. The variation across RCTs in any outcome measures was assessed using the I^2 statistic, with values of I^2 >75% indicating substantial statistical heterogeneity.[5] Pooled treatment effect estimates and 95% confidence intervals (CIs) were derived using the meta-analytical random effects model.[23] The meta-analyses were conducted using the "metafor" package in R (version 3.1.1).[24]

Data analysis in manuscript

Study results were synthesized with respect to benefits and harms, trends in BCVA improvement over time, and treatment regimens (e.g., monthly and as-needed regimens). To facilitate the synthesis of results, BCVA values reported in logMAR and decimal measures were converted to approximate ETDRS letter scores,[25] with approximate standard deviations.[26] Pairwise comparisons of drugs were assessed at the longest treatment duration, allowing for the inclusion of trials in the meta-analysis that reported outcome data at different time points. Subgroup analyses were conducted at 12 months and 24 months, as these were the most frequently reported time points. For DME patients, treatment effect estimates were obtained for all patients as well as pre-specified subgroups based upon baseline BCVA, as reported in the DCRC.net trial.[27] The meta-analysis was conducted using a random-effects model, given the assumption of varying treatment effects across trials. A sensitivity analysis was conducted by restricting to trials determined to be at low risk of selection bias. Between-study heterogeneity was assessed using the I^2 statistic, with values above 75% indicating substantial heterogeneity.[5]

Excluded RCT'S

The RCT by Rajagopal et al. 2015[28] (n=98 participants) was excluded because the investigators reported in the results section that an additional nine patients were included in the study but were not randomized to treatment due to financial hardship and were instead assigned to the bevacizumab group. The study by Pece et al. 2014[29] was excluded because the investigators randomized 78 eyes from 80 patients with myopic CNV to treatment with bevacizumab or ranibizumab, and reported eye-based analyses. For this review we were only interested in patient-based analyses.

Medline Literature Search

Interface: Ovid

Databases:

Embase <1974 to 2015 May 26>

MEDLINE Daily and MEDLINE 1946 to present

MEDLINE In-Process & Other Non-Indexed Citations

Cochrane Central Register of Controlled Trials <April 2015>

Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.

Date of Search: May 27, 2015 (Updated November 13, 2015)

Study Types: Randomized controlled trials

Limits: No date or language limits were used

Human filter was applied

Editorials & letters excluded

Search Strategy:

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1 Retinal Degeneration/

2 limit 1 to yr="1973-2009" [EARLIER MESH FOR WET MACULAR DEGENERATION]

3 Macular Degeneration/

4 Wet Macular Degeneration/ [MESH FROM 2010-]

5 ((exudative or neovascular or wet) adj3 ((macula* adj2 degeneration) or (macula* adj2 deterioration) or maculopath* or (macula* adj2 dystroph*))).tw,kw.

6 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.

7 (wAMD or wARMD).tw,kw.

8 Diabetic Retinopathy/

9 ((diabet* or DM) adj3 retinopath*).tw,kw.

10 (PDR or DME or DMO).tw,kw.

11 Macular Edema/

12 ((macula* or retina*) adj3 (edema$1 or oedema$1)).tw,kw.

13 (Irvine-Gass adj3 (edema$1 or oedema$1 or syndrome$1)).tw,kw.

14 (cystoid macula* adj dystroph*).tw,kw.

15 Retinal Vein Occlusion/

16 (retinal vein adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)).tw,kw.

17 (BRVO or CRVO).tw,kw.

18 Choroidal Neovascularization/

19 ((choroid* or subretinal or sub-retinal) adj1 neovasculari#ation*).tw,kw.

20 CNV.tw,kw.

21 or/2-20 [CONDITIONS – MEDLINE]

22 Vascular Endothelial Growth Factor A/ai

23 (anti adj2 VEGF$1).tw,kw.

24 antiVEGF$1.tw,kw.

25 (antivascular endothelial growth factor$1 or anti-vascular endothelial growth factor$1).tw,kw.

26 Antibodies, Monoclonal, Humanized/

27 (monoclonal antibod* and humani#ed).tw,kw.

28 (antibod* adj2 humani#ed).tw,kw.

29 Angiogenesis Inhibitors/

30 (angiogen* adj3 (inhibitor* or antagonist*)).tw,kw.

31 (anti-angiogen* or antiangiogen*).tw,kw.

32 aflibercept.tw,kw.

33 ("AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.

34 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap*).tw,kw.

35 aflibercept.rn.

36 Bevacizumab.tw,kw.

37 (Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.

38 IVB injection$1.tw,kw.

39 Bevacizumab.rn.

40 Pegaptanib.tw,kw.

41 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.

42 Pegaptanib.rn.

43 Ranibizumab.tw,kw.

44 (Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.

45 IVR injection$1.tw,kw.

46 Ranibizumab.rn.

47 or/22-46 [ANTI-VEGF AGENTS – MEDLINE]

48 21 and 47 [ANTI-VEGF AGENTS & CONDITIONS – MEDLINE]

49 exp Photochemotherapy/

50 Photosensitizing Agents/

51 (photochemo* or photo-chemo* or photodynamic* or photo-dynamic* or photosensiti* or photo-sensiti*).tw,kw.

52 PDT.tw,kw.

53 or/49-52

54 verteporfin.tw,kw.

55 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.

56 verteporfin.rn.

57 or/54-56

58 53 and 57

59 (PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.

60 58 or 59 [VISUDYNE PDT – MEDLINE]

61 21 and 60 [VISUDYNE PDT & CONDITIONS – MEDLINE]

62 Triamcinolone Acetonide/

63 ((Triamcinol* adj acet*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog* or Kenlog or "NSC 21916" or Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort* or Triesense or Tristoject or "UNII-F446C597KA" or Volon).tw,kw.

64 triamcinolone acetonide.rn.

65 Glucocorticoids/

66 (glucocorticoid* or glucorticoid*).tw,kw.

67 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or Retaane or "UNII-Y0PC411K4T").tw,kw.

68 anecortave acetate.rn.

69 Pregnadienediols/

70 (dihydroxypregnadiene* or di-hydroxypregnadiene* or pregnadienediol*).tw,kw.

71 exp Dexamethasone/

72 (Dexamethasone or Decaject* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex or Millicorten or Oradexon or Ozurdex).tw,kw.

73 dexamethasone.rn.

74 (intravitreal adj3 (corticoid* or corticosteroid* or steroid*)).tw,kw.

75 or/62-74

76 exp Injections/

77 (depot or implant* or infus* or inject* or intravitreal* or intra-vitreal* or microsphere* or micro-sphere* or suspension*).tw,kw.

78 or/76-77

79 75 and 78 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - MEDLINE]

80 21 and 79 (3513) [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - MEDLINE

81 (controlled clinical trial or randomized controlled trial).pt.

82 clinical trials as topic.sh.

83 (randomi#ed or randomly or RCT$1 or placebo*).tw.

84 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.

85 trial.ti.

86 or/81-85

87 (48 or 61 or 80) and 86

88 exp Animals/ not (exp Animals/ and Humans/)

89 87 not 88

90 (comment or editorial or interview or news).pt.

91 (letter not (letter and randomized controlled trial)).pt.

92 89 not (90 or 91)

93 92 use prmz [MEDLINE RCTS]

94 macular degeneration/

95 age related macular degeneration/

96 wet macular degeneration/

97 ((exudative or neovascular or wet) adj3 ((macula* adj2 degeneration) or (macula* adj2 deterioration) or maculopath* or (macula* adj2 dystroph*))).tw,kw.

98 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.

99 (wAMD or wARMD).tw,kw.

100 diabetic retinopathy/

101 ((diabet* or DM) adj3 retinopath*).tw,kw.

102 diabetic macular edema/

103 (PDR or DME or DMO).tw,kw.

104 exp macular edema/

105 ((macula* or retina*) adj3 (edema$1 or oedema$1)).tw,kw.

106 (Irvine-Gass adj3 (edema$1 or oedema$1 or syndrome$1)).tw,kw.

107 (cystoid macula* adj dystroph*).tw,kw.

108 exp retina vein occlusion/

109 (retinal vein adj3 (occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)).tw,kw.

110 (BRVO or CRVO).tw,kw.

111 subretinal neovascularization/

112 ((choroid* or subretinal or sub-retinal) adj1 neovasculari#ation*).tw,kw.

113 CNV.tw,kw.

114 or/94-113 [CONDITIONS – EMBASE]

115 vasculotropin inhibitor/

116 (anti adj2 VEGF$1).tw,kw.

117 antiVEGF$1.tw,kw.

118 (antivascular endothelial growth factor$1 or anti-vascular endothelial growth factor$1).tw,kw.

119 monoclonal antibody/

120 (monoclonal antibod* and humani#ed).tw,kw.

121 (antibod* adj2 humani#ed).tw,kw.

122 angiogenesis inhibitor/

123 (angiogen* adj3 (inhibitor* or antagonist*)).tw,kw.

124 (anti-angiogen* or antiangiogen*).tw,kw.

125 aflibercept/

126 (aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.

127 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap*).tw,kw.

128 aflibercept.rn.

129 bevacizumab/

130 (bevacizumab or Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.

131 IVB injection$1.tw,kw.

132 Bevacizumab.rn.

133 pegaptanib/

134 (Pegaptanib or "EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.

135 Pegaptanib.rn.

136 ranibizumab/

137 (Ranibizumab or Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.

138 IVR injection$1.tw,kw.

139 Ranibizumab.rn.

140 or/115-139 [ANTI-VEGF AGENTS – EMBASE]

141 114 and 140 [ANTI-VEGF AGENTS & CONDITIONS – EMBASE]

142 photodynamic therapy/

143 photosensitizing agent/

144 (photochemo* or photo-chemo* or photodynamic* or photo-dynamic* or photosensiti* or photo-sensiti*).tw,kw.

145 PDT.tw,kw.

146 or/142-145

147 verteporfin/

148 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.

149 verteporfin.rn.

150 or/147-149

151 146 and 150

152 (PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.

153 151 or 152 [VISUDYNE PDT – EMBASE]

154 114 and 153 [VISUDYNE PDT & CONDITIONS – EMBASE]

155 triamcinolone/

156 triamcinolone acetonide/

157 ((Triamcinol* adj acet*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog* or Kenlog or "NSC 21916" or Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort* or Triesense or Tristoject or "UNII-F446C597KA" or Volon).tw,kw.

158 triamcinolone.rn.

159 triamcinolone acetonide.rn.

160 exp glucocorticoid/

161 (glucocorticoid* or glucorticoid*).tw,kw.

162 anecortave/

163 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or Retaane or "UNII-Y0PC411K4T").tw,kw.

164 anecortave.rn.

165 pregnane derivative/

166 (dihydroxypregnadiene* or di-hydroxypregnadiene* or pregnadienediol*).tw,kw.

167 dexamethasone/

168 dexamethasone isonicotinate/

169 (Dexamethasone or Decaject* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex or Millicorten or Oradexon or Ozurdex).tw,kw.

170 dexamethasone.rn.

171 dexamethasone isonicotinate.rn.

172 (intravitreal adj3 (corticoid* or corticosteroid* or steroid*)).tw,kw.

173 or/155-172

174 exp injection/

175 intravitreal drug administration/

176 vi.fs. [EMBASE FLOATING SUBJECT HEADING FOR INTRAVITREAL DRUG ADMIN]

177 (depot or implant* or infus* or inject* or intravitreal* or intra-vitreal* or microsphere* or micro-sphere* or suspension*).tw,kw.

178 or/174-177

179 173 and 178 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - EMBASE]

180 114 and 179 [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - EMBASE]

181 randomized controlled trial/ or controlled clinical trial/

182 exp "clinical trial (topic)"/

183 (randomi#ed or randomly or RCT$1 or placebo*).tw.

184 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.

185 trial.ti.

186 or/181-185

187 (141 or 154 or 180) and 186

188 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/

189 exp humans/ or exp human experimentation/ or exp human experiment/

190 188 not 189

191 187 not 190

192 editorial.pt.

193 letter.pt. not (letter.pt. and randomized controlled trial/)

194 191 not (192 or 193)

195 194 use emczd [EMBASE RCTS]

196 93 or 195 [MEDLINE / EMBASE RCTS]

197 remove duplicates from 196 [TOTAL UNIQUE HITS]

198 197 use prmz [UNIQUE MEDLINE]

199 197 use emczd [UNIQUE EMBASE]

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Appendix 2: Detailed study characteristics

First author	Year of publication	Trial name	Trial identifier	Country	Study design	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
cn-AMD (n = 12)									
Schauwvlieghe[30]	2016	BRAMD	Netherlands Trial Register: NTR1704	Netherlands	Parallel RCT	Jan 2009 - Dec 2011	Multi	332	12
Berg[31]	2015	LUCAS	NCT01127360	Norway	Parallel RCT	Mar 2009 - Jul 2012	Multi	441	12
Scholler[32]	2014	NR	EK-07-192-1007 / EudraCT Nr. 2007-005157-33	Austria	Parallel RCT	2008 - 2011	Single	55	12
Chakravarthy[33]	2013	IVAN	ISRCTN92166560	UK	Parallel RCT	Mar 27, 2008 - Oct 15, 2010	Multi	610	24
Kodjikian[34]	2013	GEFAL	NCT01170767	France	Parallel RCT	2009 - 2012	Multi	501	12
Krebs[35]	2013	MANTA	NCT00710229	Austria	Parallel RCT	2008 - 2011	Multi	321	12
Heier[36]	2012	VIEW 1	NCT00509795	US, Canada	Parallel RCT	Aug 2007 - Sep 2010	Multi	1217	12
Heier[36]	2012	VIEW 2	NCT00637377	Argentina, Australia, Austria, Belgium, Brazil, Colombia, Czech Republic, France, Germany,	Parallel RCT	Apr 2008 - Sep 2010	Multi	1240	12

First author	Year of publication	Trial name	Trial identifier	Country	Study design	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
				Hungary, India, Israel, Italy, Japan, Republic of Korea, Latvia, Mexico, Netherlands, Poland, Portugal, Singapore, Slovakia, Spain, Sweden, Switzerland, United Kingdom					
Biswas[37]	2011a	NR	NR	India	Parallel RCT	2007 - 2009	Multi	60	18
Biswas[38]	2011b	NR	NR	India	Parallel RCT	NA	Multi	120	18
Martin[39]	2011	CATT	NCT00593450	US	Parallel RCT	2008 - 2010	Multi	1208	12
Subramanian[40]	2010	NR	ISRCTN73359806	US	Parallel RCT	2007 - 2009	Single	28	12
DME (n = 3)									
Fouda[41]	2017	NR	NR	Egypt	Parallel RCT	NR	Single	42	15
Wells[27]	2015	NR	NCT01627249	US	Parallel	Aug 2012	Multi	660	12

First author	Year of publication	Trial name	Trial identifier	Country	Study design	Study period	Setting (multi/single centre)	Overall sample size	Study duration (months)
					RCT	- Oct 2014			
Ekinci[42]	2014	NR	NR	Turkey	Parallel RCT	2011 - 2014	NR	100	12
RVO-ME (n = 2)									
Scott[43]	2017	SCORE2	NCT01969708	US	Parallel RCT	Sep 2014 - Dec 2016	MULTI	362	6
Narayanan[44]	2015	MARVEL	CTRI/2012/01/003120	India	Parallel RCT	Jan 2012 - Feb 2013	Single	75	6
m-CNV (n = 2)									
Iacono[45]	2012	NR	NR	Italy	Parallel RCT	Apr 2006 - Jul 2007	Single	55	18
Gharbiya[46]	2010	NR	ISRCTN49803272	Italy	Parallel RCT	Feb 2008 - Dec 2008	Single	32	6

Abbreviations: cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; NR – not reported; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion

Appendix 3: Detailed patient characteristics

First author & year	# of eyes	Overall mean age	Overall mean age variance type	Overall mean age variance value	TX 1 - mean age	TX 1 - mean age var value	TX 2 - mean age	TX 2 - mean age var value	TX 3 - mean age	TX 3 - mean age var value	TX 4 - mean age	TX 4 - mean age var value	% female	% of patients with diabetes	Mean A1C value	% of patients with A1C >8.5%	% of patients with hypertension	Lens status of patients
cn-AMD (n = 12)																		
Schauwvlieghe 2016[30]	332	78	SD	7	79	7	78	7	NR	NR	NR	NR	56	NR	NR	NR	NR	40 % pseudophakic
Berg 2015[31]	NR	NR	SD	NR	78.7	7.6	78	8.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Scholler 2014[32]	55	NR	SD	NR	79.5	6.8	80.8	6.6	NR	NR	NR	NR	70.9	NR	NR	NR	NR	NR
Chakravarthy 2013[33]	NR	77.7	SD	7.4	77.8	7.6	77.7	7.3	NR	NR	NR	NR	60	NR	NR	NR	NR	NR
Kodjikian 2013[34]	501	NR	NR	NR	79.6	6.9	78.7	7.3	NR	NR	NR	NR	66	NR	NR	NR	57	NR
Krebs 2013[35]	317	NR	SD	NR	76.7	7.8	77.6	8.1	NR	NR	NR	NR	63.7	0	NR	NR	NR	NR
Heier 2012 – VIEW 1[36]	1210	NR	SD	NR	78.2	7.6	77.7	7.9	78.4	8.1	77.9	8.4	58.8	NR	NR	NR	NR	NR
Heier 2012 – VIEW 2[36]	1202	NR	SD	NR	73	9	74.1	8.5	74.7	8.6	73.8	8.6	55.5	NR	NR	NR	NR	NR
Biswas 2011a[37]	60	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Biswas 2011b[38]	104	NR	NR	NR	63.5	NR	64.4	NR	NR	NR	NR	NR	52	NR	NR	NR	NR	NR
Martin 2011[39]	1208	NR	NR	NR	79.2	7.4	80.1	7.3	78.4	7.8	79.3	7.6	62	NR	NR	NR	NR	NR
Subramanian 2010[40]	28	78.6	SD	NR	78	NR	80	NR	NR	NR	NR	NR	4.6	NR	NR	NR	NR	NR
DME (n = 3)																		
Fouda 2017[41]	70	NR	SD	NR	55.1	4.7	56.6	5.8	NA	NA	NA	NA	NR	100	NR	NR	NR	NR
Wells 2015[27]	660	61	SD	10	60	10	62	10	60	11	NR	NR	47	100	NR	NR	NR	NR
Ekinci 2014[42]	100	NR	NR	NR	68	9	65	14	NR	NR	NR	NR	68	100	NR	0	NR	NR
RVO-ME (n = 2)																		

First author & year	# of eyes	Overall mean age	Overall mean age variance type	Overall mean age variance value	TX 1 - mean age	TX 1 - mean age var value	TX 2 - mean age	TX 2 - mean age var value	TX 3 - mean age	TX 3 - mean age var value	TX 4 - mean age	TX 4 - mean age var value	% female	% of patients with diabetes	Mean A1C value	% of patients with A1C >8.5%	% of patients with hypertension	Lens status of patients
Scott 2017[43]	362	69	SD	12	69	11	69	13	NA	NA	NA	NA	43.4	31.5	NR	NR	76.8	83.1 % cataract
Narayanan 2015[44]	75	NR	NR	NR	53	NR	50	NR	NR	NR	NR	NR	45.3	17	NR	NR	50	NR
m-CNV (n = 2)																		
Iacono 2012[45]	55	NR	SD	NR	65	12	61	11	NR	NR	NR	NR	76.4	NR	NR	NR	NR	NR
Gharbiya 2010[46]	32	NR	SD	NR	60.6	10.5	59.1	11.4	NR	NR	NR	NR	68.8	NR	NR	NR	NR	NR

Abbreviations: cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; NA – not applicable; NR – not reported; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion; SD – standard deviation; TX – treatment

Appendix 4: Cochrane risk of bias results for individual studies

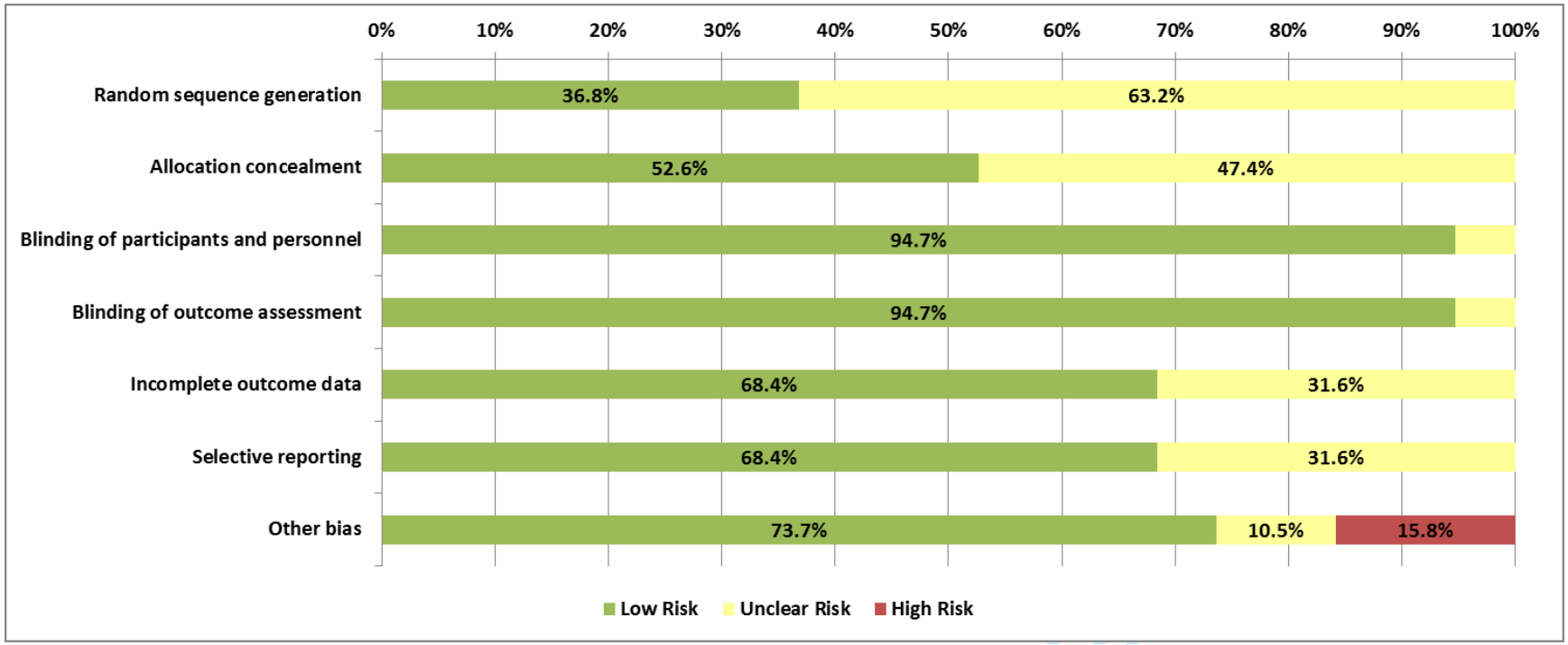
STUDY	Cochrane ROB item						
	1	2	3	4	5	6	7
cn-AMD (n = 12)							
Schauwvlieghe 2016[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Berg 2015[31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Scholler 2014[32]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Chakravarthy 2013[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kodjikian 2013[34]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Krebs 2013[35]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Heier 2012 – VIEW 1[36]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Heier 2012 – VIEW 2[36]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Biswas 2011a[37]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Biswas 2011b[38]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Martin 2011[39]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Subramanian 2010[40]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
DME (n = 3)							
Fouda 2017[41]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Wells 2015[27]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ekinci 2014[42]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
RVO-ME (n = 2)							
Scott 2017[43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Narayanan 2015[44]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
m-CNV (n = 2)							
Iacono 2012[45]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Gharbiya 2010[46]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk

Note: The legend for the ROB table is as follows:
1: Random sequence generation
2: Allocation concealment
3: Blinding of patients & personnel
4: Blinding of outcome assessment

5: Incomplete outcome data
6: Selective reporting
7: Other bias

Abbreviations: cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; RVO-ME – macular edema due to retinal vein occlusion

Appendix 5: Risk of bias results



Appendix 6: Treatment effect estimates

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
Treatment Effects in choroidal neovascular Age-related Macular Degeneration								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	2	1815	0.32 [0.3, 0.34]	0.32 [0.31, 0.34]	0.99 (0.81-1.22)	-0.21 (-6.82, 6.4)	52%[b]
	Bevacizumb vs. Ranibizumab	9	3245	0.22 [0.12, 0.33]	0.23 [0.14, 0.29]	0.95 (0.84-1.08)	-1.62 (-4.86, 1.62)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	2	1815	0.05 [0.05, 0.05]	0.06 [0.05, 0.06]	0.9 (0.6-1.35)	-0.51 (-2.75, 1.72)	0%
	Bevacizumb vs. Ranibizumab	10	3302	0.06 [0, 0.11]	0.07 [0.04, 0.14]	1.1 (0.84-1.43)	0.39 (-1.46, 2.23)	4%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mean change in BCVA (MD in # letters)	Aflibercept vs. Ranibizumab	2	1793	8.83 [8.25, 9.41]	8.75 [8.1, 9.4]	NA	0.05 (-2.36, 2.46)	66%
	Bevacizumb vs. Ranibizumab	8	3064	7.24 [4.1, 15.2]	5.85 [0.6, 11.43]	NA	0.03 (-1.02, 1.08)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision-related function	Aflibercept vs. Ranibizumab	2	1632	5.32 ± 14.46	5.60 ± 14.40	NA	-2.23 (-5.07, 0.61)	73%
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs.	3	1823	0.04 [0, 0.12]	0.02 [0, 0.06]	2.04 (0.32-12.5)	0.11 (-0.25, 0.47)	0%

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Ranibizumab							
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	6	2941	0.04 [0.01, 0.12]	0.03 [0.01, 0.06]	1.14 (0.72-1.79)	0.31 (-0.74, 0.36)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Serious adverse events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	5	3026	0.19 [0.12, 0.28]	0.18 [0.09, 0.28]	1.09 (0.93-1.27)	0.02 (-0.01, 0.05)	12%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Arterial thromboembolic events	Aflibercept vs. Ranibizumab	2	1818	0.02 [0.01, 0.02]	0.02 [0.02, 0.02]	0.96 (0.45-2.04)	-0.07 (-1.32, 1.18)	0%
	Bevacizumb vs. Ranibizumab	4	2033	0.03 [0, 0.05]	0.04 [0, 0.08]	0.86 (0.51-1.47)	-0.03 (-0.97, 0.9)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Venous thromboembolic events	Aflibercept vs. Ranibizumab	1	913	0.0033	0	0.25 (0.01-7.69)	-0.25 (-0.93, 0.44)	NA
	Bevacizumb vs. Ranibizumab	3	2135	0 [0, 0.01]	0 [0, 0.01]	1.59 (0.42-5.88)	0.18 (-0.43, 0.79)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	3	2011	0 [0, 0.01]	0 [0, 0]	1.75 (0.44-6.67)	0.18 (-0.40, 0.77)	0%

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Retinal detachment	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	2	1526	0.01 [0.01, 0.01]	0 [0, 0.01]	2.33 (0.31-16.67)	0.38 (-0.2, 0.96)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Treatment Effects in Diabetic Macular Edema								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	1	392	0.39	0.37	1.06 (0.82-1.37)	2.16 (-7.44, 11.75)	NA
	Bevacizumb vs. Ranibizumab	1	376	0.35	0.37	0.94 (0.72-1.23)	2.05 (-7.62, 11.73)	NA
	Bevacizumb vs. Aflibercept	1	386	0.35	0.37	0.94 (0.72, 1.24)	-2.05 (-11.73, 7.62)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	1	392	0.02	0.02	1.59 (0.38-6.67)	0.92 (-1.87, 3.7)	NA
	Bevacizumb vs. Ranibizumab	1	376	0.03	0.02	2.08 (0.52-8.33)	1.67 (-1.43, 4.78)	NA
	Bevacizumb vs. Aflibercept	1	376	0.02	0.03	0.48 (0.12, 1.91)	-1.67 (-4.78, 1.43)	NA
Mean change in BCVA letters	Aflibercept vs. Ranibizumab	2	462	16.22 (12.8, 19.64)	13.97 (12.3, 15.65)	NA	1.36 (-1.59, 4.31)	27%
	Bevacizumb vs. Ranibizumab	2	456	10.27 (10.0, 10.54)	12.08 (11.87, 12.3)	NA	-2.0 (-3.90, -0.09)	0%
	Bevacizumb vs. Aflibercept	1	386	10.0 ± 11.8	12.8 ± 12.4	NA	-2.7 (-0.3, -5.2)	NA
Vision-related function	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	2	513	0.02 (0.01, 0.02)	0.03 (0.01, 0.05)	0.47 (0.17-1.28)	-2.00 (-4.95, 0.94)	NA
	Bevacizumb vs. Ranibizumab	1	436	0.06	0.05	1.18 (0.54-2.56)	0.92 (-3.36, 5.2)	NA
	Bevacizumb vs. Aflibercept	1	436	0.05	0.06	0.85 (0.39, 1.85)	-0.92 (-5.2, 3.36)	NA
Serious adverse events	Aflibercept vs. Ranibizumab	2	507	0.14 (0.01 , 0.27)	0.13 (0.01, 0.25)	1.08 (0.78-1.47)	0.56 (-4.00 , 5.13)	0%
	Bevacizumb vs. Ranibizumab	1	436	0.21	0.25	0.83 (0.59-1.18)	-4.13 (-12.04, 3.78)	NA
	Bevacizumb vs. Aflibercept	1	436	0.25	0.21	1.2 (0.85, 1.69)	4.13 (-3.78, 12.04)	NA
Arterial thromboembolic events	Aflibercept vs. Ranibizumab	1	436	0.05	0.03	0.6 (0.22-1.61)	-1.83 (-5.36, 1.69)	NA
	Bevacizumb vs. Ranibizumab	1	436	0.05	0.04	0.9 (0.37-2.17)	-0.46 (-4.29, 3.37)	NA
	Bevacizumb vs. Aflibercept	1	436	0.05	0.04	1.11 (0.46, 2.68)	0.46 (-3.37, 4.29)	NA
Venous thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs.	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Aflibercept							
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	2	512	0	0	NE	NE	NE
	Bevacizumb vs. Ranibizumab	1	436	0.01	0	3.03 (0.12-100)	0.46 (-0.81, 1.72)	NA
	Bevacizumb vs. Aflibercept	1	436	0.01	0	0.33 (0.01, 8.14)	-0.46 (-1.72, 0.81)	NA
Retinal detachment	Aflibercept vs. Ranibizumab	2	512	0.004 (0, 0.01)	0	1.61 (0.21-12.5)	0.4 (-1.06, 1.87)	0%
	Bevacizumb vs. Ranibizumab	1	436	0.0092	0.0046	2 (0.18-20)	NR	NA
	Bevacizumb vs. Aflibercept	1	436	0.0046	0.0092	0.5 (0.05, 5.47)	-0.46 (-2.01, 1.09)	NA
Treatment Effects in Retinal Vein Occlusion – Macular Edema								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	74	0.59	0.59	1 (0.68-1.45)	0 (-22.37, 22.37)	NA
	Bevacizumb vs. Aflibercept	1	358	0.65	0.61	1.06 (0.91, 1.25)	3.87 (-6.25 , 14)	NR
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mean change in BCVA (MD in # letters)	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	77	15.6	18.1	NA	-2.5 (-8.0, 5.0)	NA
	Bevacizumb vs.	1	362	18.6	18.9	NA	-1.5 (-4.2, 1.2)	NA

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
	Aflibercept							
Vision-related function	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0.0056	0.0055	1.01 (0.06, 16.04)	0.01 (-1.52 , 1.53)	NR
Serious adverse events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	74	0.03	0.05	0.5 (0.05-5.26)	-2.7 (-11.67, 6.26)	NA
	Bevacizumb vs. Aflibercept	1	362	0.079	0.0769	1.01 (0.5, 2.06)	0.09 (-5.42, 5.59)	NR
Arterial thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0.0056	0.011	0.51 (0.05, 5.53)	-0.54 (-2.41, 1.32)	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
Venous thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0	0.006	0.34 (0.01, 8.22)	-0.54 (-2.06, 0.97)	NR
Retinal detachment	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	1	362	0	0	NE	NE	NA
Treatment Effects in Myopic Choroidal Neovascularization								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	32	0.62	0.56	1.11 (0.63-1.96)	6.25 (-27.71, 40.21)	NA
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision loss in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	1	32	0	0	NA	NA	NA
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
Mean change in BCVA (MD in # letters)	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	2	80	12.18 (8.5, 15.87)	13.4 (9.5, 17.31)	NA	-1.26 (-6.52, 4.00)	0%
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Vision-related function	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Blindness	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Mortality	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Serious adverse events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Arterial	Aflibercept vs.	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
thromboembolic events	Ranibizumab							
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Venous thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR
Retinal detachment	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept	NR	NR	NR	NR	NR	NR	NR

Footnotes:

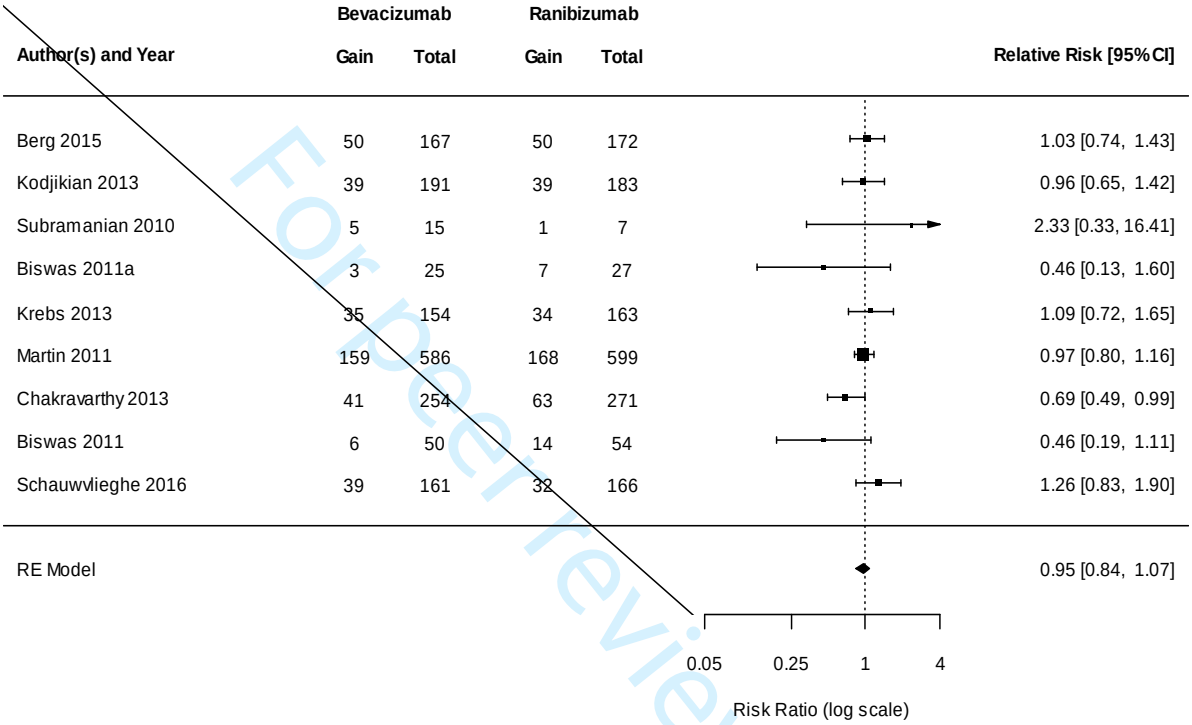
[a] Meta-analysis was not conducted for comparisons with 1 RCT; the point estimate and 95% confidence interval were calculated using data from a single trial.

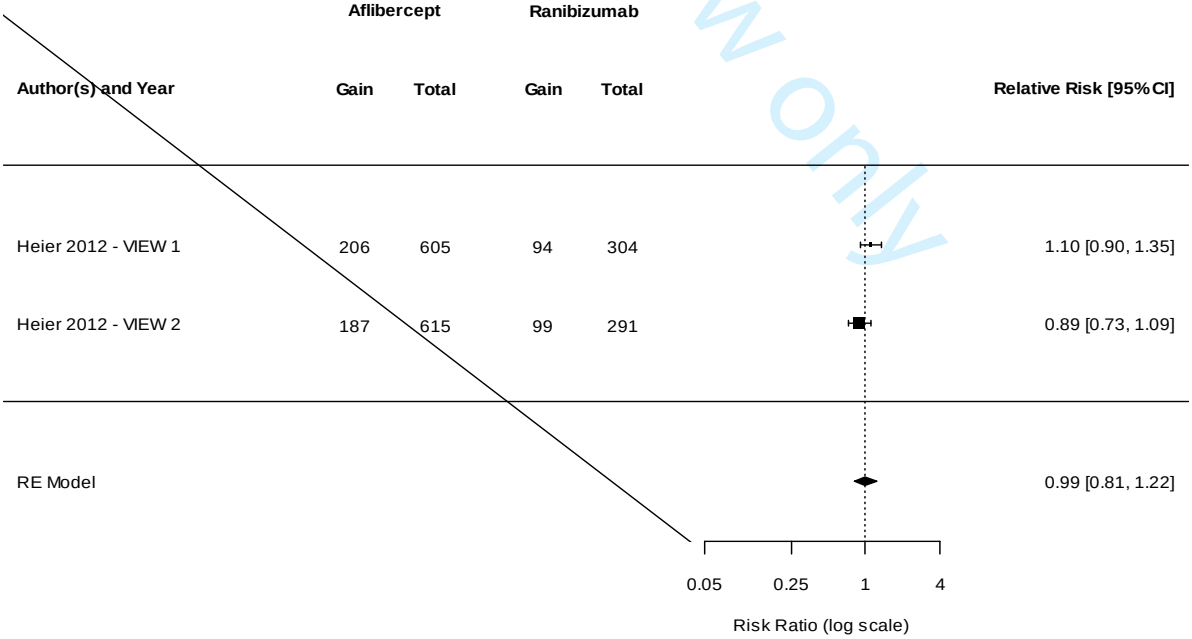
[b] The summary statistics were derived by taking the mean and range across estimates from included studies.

Abbreviations: BCVA - best-corrected visual acuity; CI - confidence interval; Ctrl - control; ETDRS - Early Treatment Diabetic Retinopathy Study; MD - mean difference; NA - not applicable; NE - not estimable; NR - not reported; RCT - randomized controlled trials; Rx - treatment; SMD - standardized mean difference

Appendix 7: Forest plots for primary outcome in choroidal neovascular age related macular degeneration (cn-AMD) population

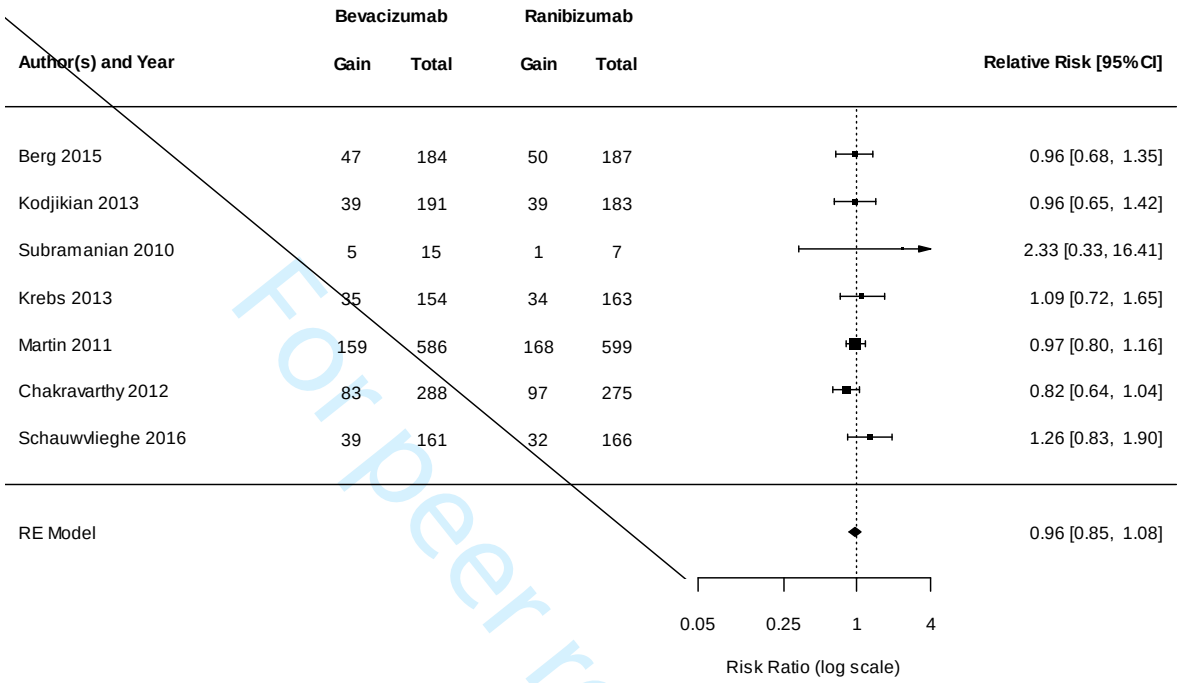
A: Vision gain in cn-AMD population



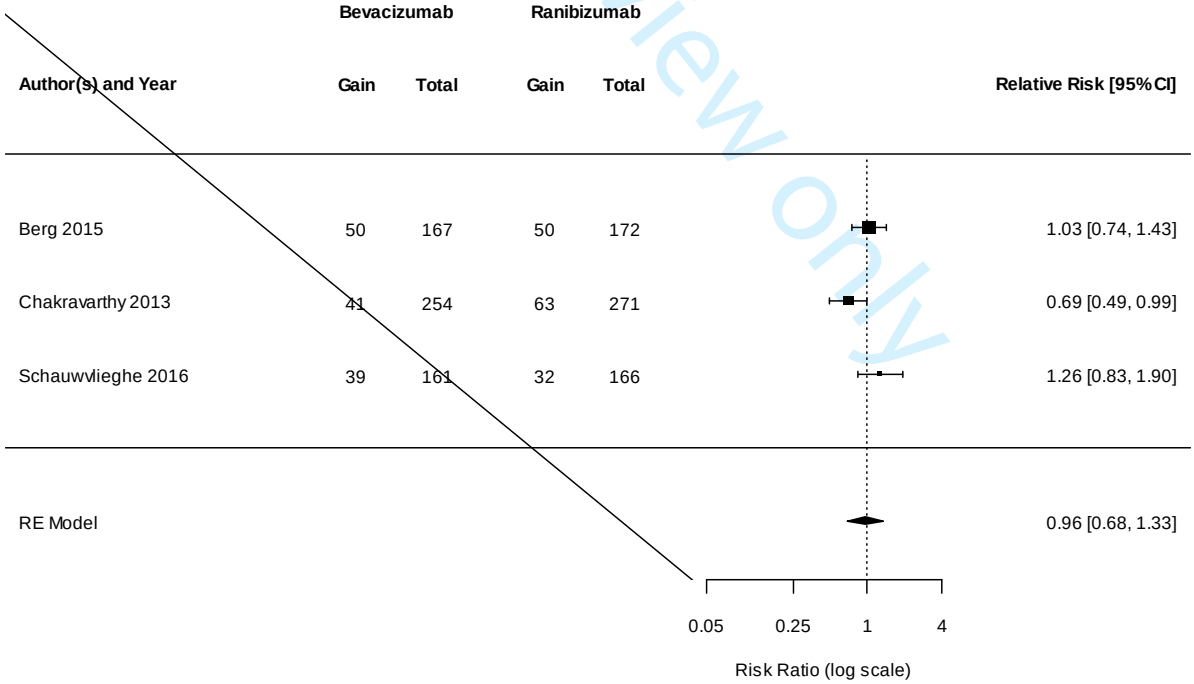


B: Sensitivity analyses for vision gain in cn-AMD population

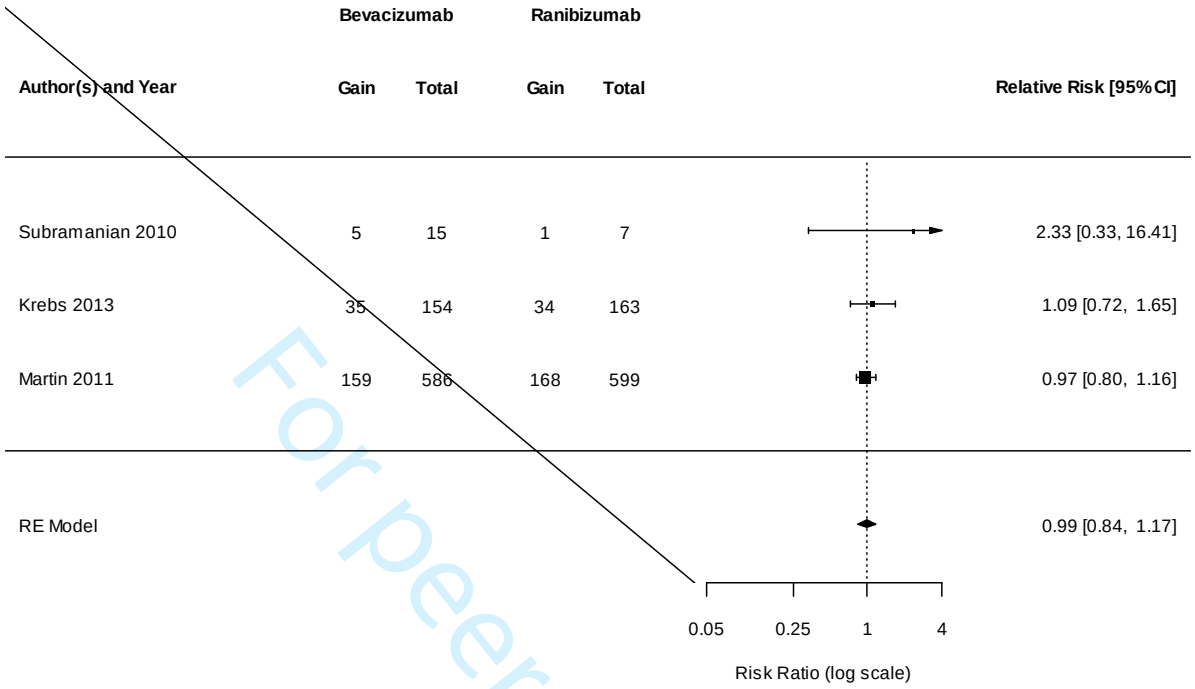
Sensitivity Analysis: 1 Year Follow-Up



Sensitivity Analysis: Low Risk of Selection Bias



Sensitivity Analysis: De Novo Patients



Appendix 8: Summary data used in risk of bias results

		Length of follow-up (months)							
		1	**3**	**4**	**6**	**8**	**12**	**18**	**24**
Mean improvement in BCVA letter score (SEM)	**cn-AMD**								
	# of RCTs	0	4	0	4	0	8	0	2
	Bevacizumab	NA	5.14 (0.45)	NA	5.66 (0.45)	NA	6.35 (0.52)	NA	5.84 (1.85)
	Ranibizumab	NA	5.19 (0.43)	NA	6.02 (0.38)	NA	6.23 (0.8)	NA	6.10 (1.30)
	DME								
	# of RCTs	1	0	1	0	1	2	0	1
	Bevacizumab	4.48 (0.19)	NA	7.90 (0.45)	NA	9.30 (0.59)	10.06 (0.60)	NA	10.00 (0.75)
	Ranibizumab	4.46 (0.24)	NA	9.05 (0.24)	NA	10.44 (0.36)	11.37 (0.58)	NA	12.30 (0.52)
	RVO-ME								
	# of RCTs	0	1	0	1	0	0	0	0
	Bevacizumab	NA	13.23 (0.35)	NA	15.60 (0.35)	NA	NA	NA	NA
	Ranibizumab	NA	15.91 (0.42)	NA	18.10 (0.42)	NA	NA	NA	NA
	m-CNV								
	# of RCTs	0	2	0	2	0	1	1	0
	Bevacizumab	NA	10.28 (31.00)	NA	10.42 (33.00)	NA	28.00 (35.00)	28.00 (37.00)	NA
	Ranibizumab	NA	11.09 (30.00)	NA	12.38 (32.00)	NA	27.00 (34.00)	27.00 (36.00)	NA

Abbreviations: BCVA - best-corrected visual acuity; cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; m-CNV – myopic choroidal neovascularization; NA – not applicable; RCT – randomized controlled trial; RVO-ME – macular edema due to retinal vein occlusion; SEM – standard error of the mean

Appendix 9: Sensitivity analysis estimates

Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate[Range]	Mean comparator effect estimate[a] [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I^2
Sensitivity Analyses of Bevacizumab vs. Ranibizumab in choroidal neovascular age-related macular degeneration (cn-AMD)								
Vision gain in BCVA of ≥15 EDTRS letters	Main - Longest follow-up duration	9	3245	0.22 [0.12, 0.33]	0.23 [0.14, 0.29]	0.95 (0.84, 1.08,)	-1.62 (-4.86, 1.62,)	0%
	SA - Follow-up for 12 months	7	3159	0.26 [0.2, 0.33]	0.24 [0.14, 0.35]	0.96 (0.85, 1.08)	-0.67 (-3.72, 2.38,)	0%
	SA - Trials with low risk of selection bias (random-effects model)	3	1191	0.23 [0.16, 0.3]	0.24 [0.19, 0.29]	0.95 (0.68, 1.33)	-0.97 (-8.42,6.49,)	61%
	SA - Trials with low risk of selection bias (fixed-effects model)	3	1191	0.23 [0.16, 0.3]	0.24 [0.19, 0.29]	0.94 (0.77, 1.16)	-1.87 (-6.58, 2.85,)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Main - Longest follow-up duration	10	3302	0.06 [0, 0.11]	0.07 [0.04, 0.14]	1.10 (0.84, 1.43)	0.39 (-1.46, 2.23,)	4%
	SA - Follow-up for 12 months	8	3214	0.06 [0, 0.11]	0.07 [0.03, 0.14]	1.18 (0.86, 1.54)	0.57 (-0.98, (2.11)	2%
	SA - Trials with low risk of selection bias (random-effects model)	3	1191	0.09 [0.08, 0.11]	0.08 [0.05, 0.1]	1.18 (0.65, 2.13)	1.42 (6.34, -3.5, 6.34)	59%
	SA - Trials with low risk of selection bias (fixed-effects model)	3	1191	0.09 [0.08, 0.11]	0.08 [0.05, 0.1]	1.14 (0.78, 1.67)	1.4 (-1.79, 4.59)	NA
Mean change in BCVA	Main - Longest follow-up duration	8	3064	7.24 [4.1, 15.2]	5.85 [0.6, 11.43]	NA	0.03 (-1.02, 1.08)	0%

Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate[Range]	Mean comparator effect estimate[a] [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I^2
	SA - Follow-up for 12 months	8	3134	7.33 [4.7, 15.2]	6.12 [0.6, 11.43]	NA	-0.30 (0.70, -1.29, 0.70)	2%
	SA - Trials with low risk of selection bias (random-effects model)	3	1191	5.95 [4.1, 7.8]	6.36 [4.9, 7.5]	NA	-0.52 (-2.14, 1.10)	0%
	SA - Trials with low risk of selection bias (fixed-effects model)	3	1191	5.95 [4.1, 7.8]	6.36 [4.9, 7.5]	NA	-0.52 (-2.14, 1.10)	NA

Footnote:
[a] The summary statistics were derived by taking the mean and range across estimates from included studies.

Abbreviations: BCVA - best-corrected visual acuity; CI - confidence interval; ETDRS - Early Treatment Diabetic Retinopathy Study; NA - not applicable; RCT - randomized controlled trials; SA - sensitivity analysis

Appendix 10: Summary of anti-VEGF treatment protocols

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
cn-AMD (n = 12)				
Schauwvlieghe 2016[30]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Monthly injections for 12 months.	None	Yes
Berg 2015[31]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Treat-and-extend protocol: Monthly injections till no signs of active AMD were found. Subsequently, injection intervals can be extended by 2 wks to max 12 wks, or shortened by 2 wks depending on AMD activities. Follow-up for 12 months. Initial injections and repeated injections as needed (treat-and-extend)	Sign of recurrence	Yes
Scholler 2014[32]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up duration for 9 months.	loss of VA of ≥5 letters with OCT evidence of fluid in the macula; increase in OCT central retinal thickness of at least 100 um; new area of nAMD; new macular haemorrhage; persistent fluid on OCT at least 1 month after the previous intravitreal injection.	No

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Chakravarthy 2013[33]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml TX 3: ranibizumab 0.5 mg/0.05 ml TX 4: bevacizumab 1.25 mg/0.05 ml	TX 1 & TX 2: 3 monthly injections + monthly injections for 24 months. TX 3 & TX 4: 3 monthly injections + repeated 3 monthly injections as needed treatment criteria.	Prespecified clinical and OCT criteria for active disease were met.	Yes
Kodjikian 2013[34]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 9 months.	loss of ≥5 letters from the previous visit with no obvious atrophy or subretinal fibrosis and with fluid on OCT; and/or active exudation on OCT; and/or increased CNV area or persistence of leakage on angiography since the previous visit; and/or new or persistent subretinal or intraretinal macular hemorrhage.	Yes
Krebs 2013[35]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 12 months.	visual acuity loss of at least 5 letters with OCT or fluorescein angiographic evidence of fluid in the macula; an increase in OCT central retinal thickness of at least 100 um; new macular haemorrhage; new area of classic CNV; or evidence of persistent fluid on OCT at least 1 month after the previous injection.	Yes

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Heier 2012 – VIEW 1[36]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: aflibercept 0.5 mg/0.05 ml TX 3: aflibercept 2 mg/0.05 ml TX 4: aflibercept 2 mg/0.05 ml	TX 1, 2, & 3: Approximately monthly injections for 12 months. TX 4: 3 monthly injections and every bimonthly injections for 12 months.	None	NA
Heier 2012 – VIEW 2[36]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: aflibercept 0.5 mg/0.05 ml TX 3: aflibercept 2 mg/0.05 ml TX 4: aflibercept 2 mg/0.05 ml	TX 1, 2, & 3: Approximately monthly injections for 12 months. TX 4: 3 monthly injections and every bimonthly injections for 12 months.	None	NA
Biswas 2011a[37]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 18 months.	an increase in CMT of more than 100 um or a fall in BCVA by more than 5 ETDRS letters	No
Biswas 2011b[38]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 18 months.	an increase in CMT of more than 100 um or a fall in BCVA by more than 5 ETDRS letters	No

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Martin 2011[39]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml TX 3: ranibizumab 0.5 mg/0.05 ml TX 4: bevacizumab 1.25 mg/0.05 ml	TX 1 & TX 2: monthly injections for 12 months. TX 3 & TX 4: monthly injections as needed treatment criteria.	Fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on fluorescein angiography.	Yes
Subramanian 2010[40]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	3 monthly injections. Repeated injections as needed treatment criteria. Follow-up for 12 months.	Patients returned monthly to undergo visual acuity measurements (ETDRS chart, OCT and clinical exam) If patients showed a qualitative increase in intraretinal fluid or subretinal fluid by OCT	Yes
DME (n = 3)				
Fouda 2017[41]	TX 1: ranibizumab 0.5 mg/0.05 ml Tx 2: aflibercept 2 mg/0.05 ml	The drugs were injected into the study eyes at baseline and then every 1 month until the 3rd month (loading dose of three injections). During the follow-up period, the drug re-injection was considered on monthly basis	Re-injection if macular edema persisted or worsened and visual acuity worsened in comparison with the preceding visit. The treatment was withheld if there was no change of macular thickness or visual acuity for two successive visits but was reinstated once vision or macular edema worsened again. Improvement or worsening of macular edema was defined as a 10% change of CMT in comparison with last visit while 0.1 change of visual acuity in comparison with last visit was considered a significant change.	None

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Wells 2015[27]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml TX 3: aflibercept 2 mg/0.05 ml	Monthly injections until stable visual acuity within 6 months. Subsequently, irrespective of visual acuity and central subfield thickness, an injection was withheld if there was no improvement or worsening after two consecutive injections, but treatment was reinitiated if the visual-acuity letter score or the central subfield thickness worsened. Laser PCT was initiated at or after the 24 week visit for persistent DME. Follow-up for 12 months.	Patients were injected at baseline and then every month unless visual acuity was 20/20 or better with a central subfield thickness below the eligibility threshold and there was no improvement or worsening in response to the past two injections. Starting at 6 months, irrespective of visual acuity and central subfield thickness, an injection was withheld if there was no improvement or worsening after two consecutive injections, but treatment was reinitiated if the visual-acuity letter score or the central subfield thickness worsened.	Yes
Ekinci 2014[42]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Start with 3 monthly injections. Subsequently, 3 additional monthly injections as needed. After 6 injections, additional injections were used till stable visual acuity was obtained. Follow-up for 12 months.	Central macular thickness was >275 um or if there was an increase in BCVA of at least 3 letters compared with baseline	No
RVO-ME (n = 2)				
Scott 2017[43]	TX 1: aflibercept 2 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Monthly injections for 6 months	Not applicable	No

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Narayanan 2015[44]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Initial injection. Repeated monthly injections according to as needed treatment criteria for 6 months. Macular grid laser photocoagulation was allowed concurrently with injections after 3 months.	>50um increase in CRT compared with the thinnest previous measurement; new or persistent cystoid retinal changes or sub-retinal fluid on OCT; loss of >5 letters from the best previous VA measurement in conjunction with any increase in CRT; increase in VA of >5 letters between the current and most recent visits.	No
m-CNV (n = 2)				
Iacono 2012[45]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Initial injection. Repeated monthly injections according to as needed treatment criteria for 18 months.	subretinal/intraretinal fluid on OCT, leakage on FA or appearance of a new hemorrhage.	Yes
Gharbiya 2010[46]	TX 1: ranibizumab 0.5 mg/0.05 ml TX 2: bevacizumab 1.25 mg/0.05 ml	Initial injection. Repeated monthly injections according to as needed treatment criteria for 6 months.	Monthly additional injections were performed until absence of fluorescein leakage from the CNV and absence of any fluid collections on OCT were obtained.	Yes

Abbreviations: BCVA – Best-corrected visual acuity; cn-AMD – choroidal neovascular age-related macular degeneration; CRT – central retinal thickness; DME – diabetic macular oedema; ETDRS – Early Treatment Diabetic Retinopathy Study; m-CNV – myopic choroidal neovascularization; NA – not applicable; NR – not reported; OCT – optical coherence tomography; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion; SD – standard deviation; TX – treatment; VA – visual acuity

Appendix 11: Summary of results from the DRCR.net trial (Wells 2015[a] and Wells 2016[b])

Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate [Range]	Mean comparator effect estimate[b] [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I^2
Subgroup Analysis of Anti-VEGF Treatment Effects in Diabetic Macular Edema (DME) According to the DRCR.net RCT								
Aflibercept vs. Ranibizumab								
Vision gain in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	392	0.37	0.39	1.06 (0.82, 1.37)	2.16 (- 7.44, 11.75)	NA
	Participants with baseline BCVA < 69 letters	1	192	0.55	0.58	1.05 (0.82, 1.35)	2.84 (-11.17, 16.86)	NA
	Participants with baseline BCVA ≥ 69 letters	1	200	0.19	0.2	1.10 (0.63, 1.92)	1.83 (-9.14, 12.8)	NA
	Follow-up for 12 months	1	414	0.32	0.42	**1.30 (1.01, 1.69)**	**10.1 (1.00, 19.00)**	NA
	Participants with baseline BCVA < 69 letters	1	203	0.50	0.67	**1.35 (1.06, 1.72)**	**17.16 (3.79, 30.53)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	211	0.15	0.18	1.18 (0.64, 2.17)	2.69 (- 7.34, 12.72)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	392	0.02	0.02	1.59 (0.38, 6.67)	0.92 (-1.87, 3.7)	NA
	Follow-up for 12 months	1	414	0.01	0.01	0.99 (0.20, 4.76)	0 (-2.00, 2.02)	NA
Mean change in BCVA (SMD)	Follow-up for 24 months	1	392	12.3 ± 10.5	12.8 ± 12.4	NA	0.7 (-1.3, 2.8)	NA
	Participants with baseline BCVA < 69 letters	1	192	16.1 ± 12.1	18.1 ± 13.8	NA	2.3 (-1.1, 5.6)	NA

	Participants with baseline BCVA ≥ 69 letters	1	200	8.6 ± 7.0	7.8 ± 8.4	NA	-0.7 (-2.9, 1.5)	NA
	Follow-up for 12 months	1	414	11.2 ± 9.4	13.3 ± 11.1	NA	**2.1 (0.1, 4.2)**	NA
	Participants with baseline BCVA < 69 letters	1	203	14.2 ± 10.6	18.9 ± 11.5	NA	**4.7 (1.4, 8.0)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	211	8.3 ± 6.8	8.0 ± 7.6	NA	-0.4 (-2.3, 1.5)	NA
Bevacizumab vs Aflibercept								
Vision gain in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	386	0.35	0.39	0.89 (0.69, 1.16)	-4.21 (-13.82, 5.4)	NA
	Participants with baseline BCVA < 69 letters	1	190	0.52	0.58	0.9 (0.69, 1.16)	-5.99 (-20.12, 8.14)	NA
	Participants with baseline BCVA ≥ 69 letters	1	196	0.17	0.2	0.84 (0.47, 1.52)	-3.18 (-14.11, 7.74)	NA
	Follow-up for 12 months	1	414	0.29	0.42	**0.68 (0.52, 0.89)**	**-14.0 (-23.00, -4.04)**	NA
	Participants with baseline BCVA < 69 letters	1	204	0.41	0.67	**0.62 (0.47, 0.81)**	**-25.49 (-38.72, -12.26)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	210	0.16	0.18	0.91 (0.5, 1.65)	-1.58 (-11.77, 8.61)	NA
Vision loss in BCVA of ≥15 EDTRS letters	Follow-up for 24 months	1	386	0.03	0.02	1.3 (0.4, 4.2)	0.76 (-2.58, 4.1)	NA
	SA - Follow-up for 12 months	1	412	0.01	0.01	1 (0.2, 4.9)	0 (-2.02, 2.00)	NA
Mean change in BCVA (SMD)	Follow-up for 24 months	1	386	10.0 ± 11.8	12.8 ± 12.4	NA	**-2.7 (-5.2, -0.3)**	NA
	Participants with baseline BCVA < 69 letters	1	190	13.3 ± 13.4	18.1 ± 13.8	NA	**-4.7 (-8.8, -0.5)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	196	6.8 ± 8.8	7.8 ± 8.4	NA	-1.1 (-3.4, 1.1)	NA

	Follow-up for 12 months	1	414	9.7 ± 10.1	13.3 ± 11.1	NA	**-3.5 (-1.4, -5.7)**	NA
	Participants with baseline BCVA < 69 letters	1	204	11.8 ± 12.0	18.9 ± 11.5	NA	**-6.5 (-10.1, -2.9)**	NA
	Participants with baseline BCVA ≥ 69 letters	1	210	7.5 ± 7.4	8.0 ± 7.6	NA	-0.7 (-2.7, 1.3)	NA

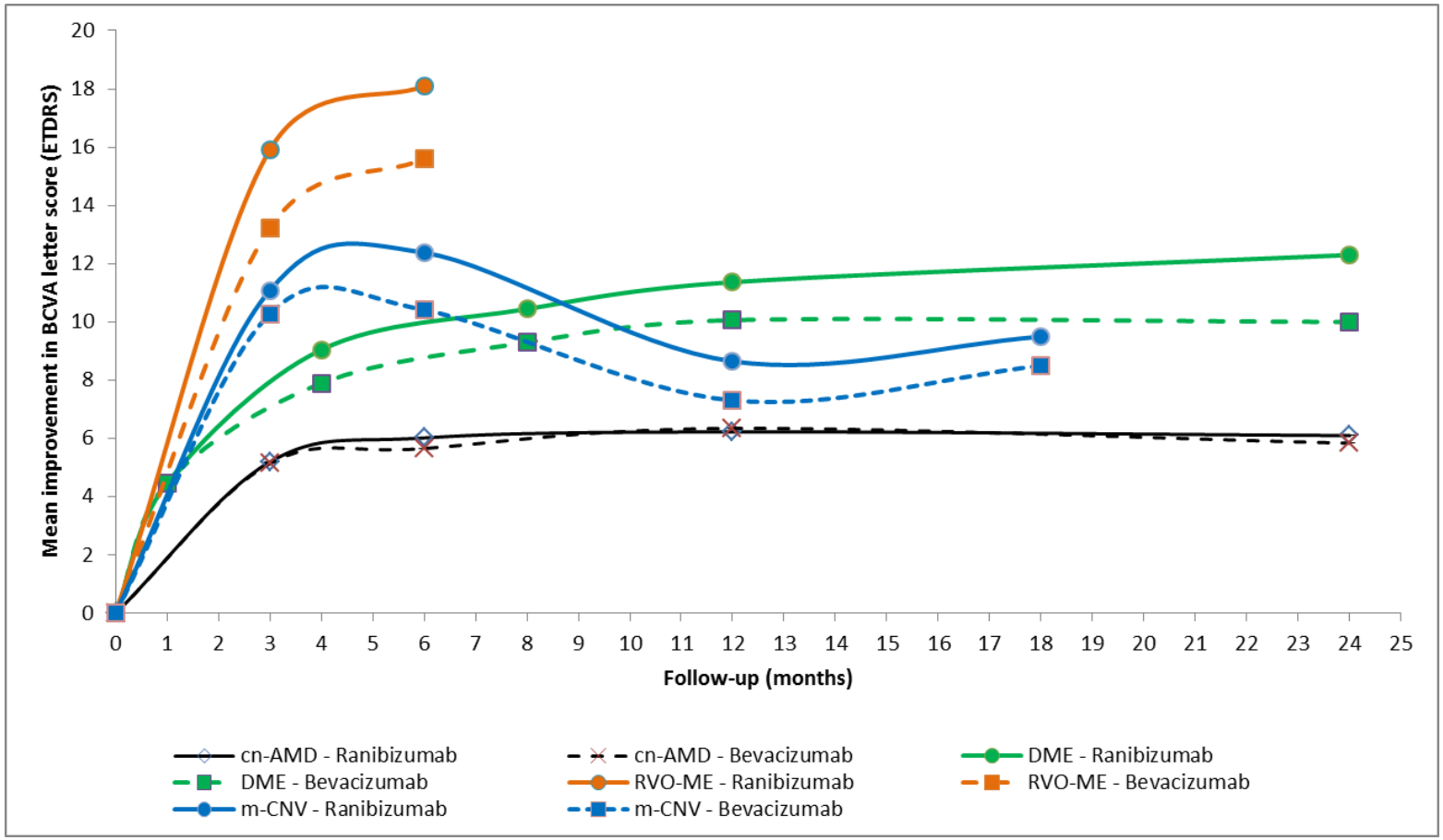
Footnote: Bolded estimates indicate statistical significance.

[a] Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193-1203.

[b] Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016;123(6):1351-1359.

Abbreviations: BCVA - best-corrected visual acuity; CI - confidence interval; ETDRS - Early Treatment Diabetic Retinopathy Study; NA - not applicable; RCT - randomized controlled trials; Rx - treatment; SA - sensitivity analysis; SMD - standardized mean difference

Appendix 12: Mean change in best-corrected visual acuity letter scores over time in patients treated with bevacizumab or ranibizumab



Abbreviations: BCVA – Best-corrected visual acuity; cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic macular oedema; ETDRS – Early Treatment Diabetic Retinopathy Study; m-CNV – myopic choroidal neovascularization; RCT – randomized controlled trials; RVO-ME – macular edema due to retinal vein occlusion

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