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# BMJ Open

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

Journal:	<i>BMJ Open</i>
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

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For peer review only

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3 **1 Anti-Vascular Endothelial Growth Factor Treatment for Retinal Conditions: A Systematic**  
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5 **2**  
6 **Review and Meta-analysis**  
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42  
43 38 **Word count:** 285/300 (Abstract), 3397/4000 (Main text), 1 figure, 4 tables, 2 supplementary  
44  
45 39 files

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4 **40 ABSTRACT**  
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7 **41 Objectives:** To evaluate the comparative effectiveness and safety of intravitreal bevacizumab,  
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10 **42** ranibizumab, and aflibercept for patients with choroidal neovascular age-related macular  
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12 **43** degeneration (cn-AMD), diabetic macular edema (DME), macular edema due to retinal vein  
13  
14 **44** occlusion (RVO-ME) and myopic choroidal neovascularization (m-CNV).  
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16  
17 **45 Design:** Systematic review and random effects meta-analysis.  
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19 **46 Methods:** Multiple databases were searched from inception to August 17th, 2017 (MEDLINE,  
20  
21 **47** Embase, Cochrane Central). Eligible head-to-head randomized controlled trials (RCTs)  
22  
23 **48** comparing the anti-VEGF drugs in patients aged  $\geq 18$  years with the retinal conditions of interest.  
24  
25 **49** Two reviewers independently extracted data and assessed risk of bias using the Cochrane risk-of-  
26  
27 **50** bias tool.  
28

29  
30 **51 Results:** Nineteen RCTs involving 7459 patients with: cn-AMD (n=12), DME (n=3), RVO-ME  
31  
32 **52** (n=2), and m-CNV (n=2) were included. Vision gain was not significantly different in patients  
33  
34 **53** with cn-AMD, DME, RVO-ME, and m-CNV treated with bevacizumab versus ranibizumab.  
35  
36 **54** Similarly, vision gain was not significantly different between cn-AMD patients treated with  
37  
38 **55** aflibercept versus ranibizumab. In DME patients treated for 2 years, vision gain was as likely to  
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40 **56** be attained with aflibercept as with ranibizumab or bevacizumab; however, in the first year of  
41  
42 **57** treatment, patients treated with aflibercept were more likely to attain vision gain than patients  
43  
44 **58** with ranibizumab or bevacizumab. Rates of systemic serious harms were similar among  
45  
46 **59** bevacizumab, ranibizumab, and aflibercept. For cn-AMD patients, compared to monthly  
47  
48 **60** treatment, an as-needed treatment regimen (6-9 injections per year) was associated with a  
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50 **61** mortality increase of 1.8% (RR: 2.0, [1.2, 3.5], 2 RCTs, 1795 patients) in a post-hoc analysis.  
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3 62 **Conclusions:** With few exceptions, intravitreal bevacizumab was a reasonable alternative to  
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5 63 ranibizumab and aflibercept in patients with wet cn-AMD, DME, RVO-ME and m-CNV.  
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7 64 However, the choice of anti-VEGF drugs may depend on the specific retinal condition, baseline  
8  
9 65 visual acuity, and treatment regimen.  
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11

12 66 **Trial registration:** PROSPERO CRD 42015022041  
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16  
17 68 **Keywords:** ranibizumab, bevacizumab, aflibercept, anti-vascular endothelial growth factor, age-  
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19 69 related macular degeneration, diabetic macular edema, retinal vein occlusion, myopic choroidal  
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21 70 neovascularization  
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## 71 STRENGTHS AND LIMITATIONS OF THIS STUDY

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



## 85 BACKGROUND

86 Retinal conditions due to neovascular abnormality are common in older adults. Choroidal  
87 neovascular age-related macular degeneration (cn-AMD) is the leading cause of irreversible  
88 blindness in individuals aged 50 years or older in high-income countries.<sup>1 2</sup> If left untreated,  
89 potentially irreversible visual impairment can also be caused by diabetic macular edema (DME)  
90 and macular edema due to retinal vein occlusion (RVO-ME).<sup>3-5</sup> Choroidal neovascularization  
91 secondary to pathologic myopia (myopic CNV) is another major cause of blindness and visual  
92 impairment worldwide.<sup>6 7</sup> Together, these retinal diseases cause substantial reduction in quality  
93 of life, and are a significant burden on healthcare systems.<sup>8</sup>  
94 Ranibizumab, off-label use of repackaged bevacizumab, and aflibercept are widely used anti-  
95 vascular endothelial growth factor (anti-VEGF) drugs for intravitreal treatment of retinal  
96 conditions. Multiple systematic reviews have evaluated the comparative effectiveness of anti-  
97 VEGF drugs in patients with cn-AMD, DME, RVO-ME, and m-CNV;<sup>9-12</sup> but given the  
98 publication of new trials in patients with RVO-ME<sup>13</sup> and DME,<sup>14</sup> and long-term follow-up data  
99 for patients with cn-AMD,<sup>15</sup> an update is necessary. We aimed to conduct a systematic review to  
100 evaluate the comparative effectiveness and safety of bevacizumab, ranibizumab, and aflibercept  
101 for patients with cn-AMD, DME, RVO-ME, and m-CNV.

## 102 METHODS

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

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3 106 recommendations.<sup>16 17</sup> The report included a meta-analysis of pairwise comparisons of the anti-  
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5 107 VEGF drugs for individual retinal conditions, as well as a network meta-analysis to evaluate the  
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7 108 anti-VEGF drugs in cn-AMD patients. This paper summarizes results of the meta-analysis; a  
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10 109 separate paper is underway for the network meta-analysis results.

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12 110 The current review was conducted using the Cochrane Handbook for Systematic Reviews and  
13  
14 111 reported using the PRISMA statement<sup>18</sup> (Additional file 1). The methods are outlined briefly  
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16 112 below, as they are described in greater detail in Additional file 2: Appendix 1 and a related  
17  
18 113 therapeutic review report.<sup>17</sup>

#### 114 ***Data Sources and Searches:***

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

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

#### 124 ***Study Selection:***

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

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3 127 cn-AMD, DME, RVO-ME or m-CNV. Due to time and resource constraints, we only included  
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5 128 studies published in English.  
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7 129 Eligible RCTs reported one of the following benefits and harms outcomes: vision gain, defined  
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10 130 as a gain in Best-Corrected Visual Acuity (BCVA) letter score of  $\geq 15$  on the Early Treatment  
11  
12 131 Diabetic Retinopathy Study (ETDRS) chart;<sup>21</sup> vision loss, defined as a loss in BCVA letter score  
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14 132 of  $\geq 15$ ; mean change in BCVA from baseline; legal blindness (BCVA of 20/200 or worse  
15  
16 133 measured on a standard Snellen chart, or worse than 20/100 visual acuity measured on ETDRS  
17  
18 134 chart); vision-related function according to the 25-item National Eye Institute Visual Function  
19  
20 135 Questionnaire (NEI-VFQ-25);<sup>22</sup> serious adverse events; all-cause mortality; arterial  
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22 136 thromboembolic events (TEs); venous TEs; bacterial endophthalmitis; and retinal detachment.  
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24 137 All titles/abstracts and potentially relevant full-text articles were screened by two reviewers,  
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26 138 independently. Discrepancies were discussed and if necessary, resolved with input from a third  
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28 139 reviewer. When multiple reports of the same trial were identified, the main report was included,  
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30 140 and the others were treated as companion reports.<sup>23</sup>  
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#### 36 141 ***Data Extraction and Quality Assessment:***

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39 142 Data extraction forms were developed with input from three clinicians, pilot-tested, and refined  
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41 143 twice. Data extraction was conducted by two reviewers, independently. Discrepancies were  
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43 144 discussed and if necessary, resolved with input from a third reviewer. A similar approach was  
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45 145 followed for quality assessment using the Cochrane risk-of-bias tool for RCTs.<sup>24</sup>  
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#### 49 146 ***Synthesis of study results***

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52 147 Study results were synthesized with respect to benefits and harms of treatment, treatment  
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3 148 regimen (e.g., monthly and as-needed regimens), and trends in BCVA improvement over time.  
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5 149 With respect to visual acuity improvement, meta-analyses were conducted with studies reporting  
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7 150 BCVA letter score as measured on the ETDRS chart. For studies reporting visual acuity in  
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9 151 logMAR and decimal values, the values were converted to approximate ETDRS letter scores,<sup>25</sup>  
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11 152 with approximate standard deviations.<sup>26</sup> Pairwise comparisons of drugs were assessed at the  
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13 153 longest treatment duration, allowing for the inclusion of trials in the meta-analysis that reported  
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15 154 outcome data at different time points. Subgroup analyses were conducted at 12 months and 24  
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17 155 months, as these were the most frequently reported time points. A post hoc analysis was  
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19 156 conducted to compare different treatment regimens across the drugs. For DME patients,  
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21 157 treatment effect estimates were obtained for all patients as well as subgroups based upon baseline  
22  
23 158 BCVA, which were pre-specified in the DRCR.net trial.<sup>27</sup> The meta-analysis was conducted  
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25 159 using a random-effects model, as we assumed treatment effects varied across trials. A sensitivity  
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27 160 analysis was conducted by restricting results to trials determined to be at low risk of selection  
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29 161 bias. Between-study heterogeneity was assessed using the  $I^2$  statistic, with values above 75%  
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31 162 indicating substantial heterogeneity.<sup>28</sup>  
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## 38 163 **RESULTS**

### 39 164 *Literature search*

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42 165 After screening 3176 titles/abstracts and 440 full-text articles, 19 head-to-head RCTs of the anti-  
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44 166 VEGF drugs were included, with 7459 patients, including 12 RCTs for cn-AMD, 3 RCTs for  
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46 167 DME, 2 RCTs for RVO-ME, and 2 RCTs for m-CNV (Figure 1, Additional file 2: Appendix  
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48 168 1).<sup>27 29-42</sup> Given our inclusion criteria, we excluded RCTs that compared anti-VEGF drugs with  
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50 169 placebo or laser photocoagulation.<sup>43-49</sup>  
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3 170 ***Study and patient characteristics***  
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6 171 Studies were completed between 2010 and 2017 with an average sample size of 393 patients per  
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8 172 trial (range: 28, 1240) (Table 1, Additional file 2: Appendix 2-3). The mean age ranged from  
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10 173 approximately 60 to 80 years, and females accounted for 5% to 76% of the patients. The average  
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12 174 follow-up duration was 13 months (range: 6-24 months). RCTs were conducted in Europe (n=8),  
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14 175 North America (n=5), Asia (n=4), Africa (n=1) and across multiple continents (n=1); most were  
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16 176 multi-centre RCTs (n=13), in addition to 6 single-centre RCTs.  
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21 177 ***Risk of bias assessment***  
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23 178 Random sequence generation and allocation concealment were unclear for 12/19 (63.2%) and  
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25 179 9/19 (47.4%) of the included RCTs, respectively, suggesting the potential for selection bias  
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27 180 (Additional file 2: Appendix 4-5). The RCTs were at low risk with respect to blinding of  
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29 181 participants and trial personnel 18/19 (94.7%), blinding of outcome assessment 18/19 (94.7%),  
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31 182 incomplete outcome data 13/19 (68.4%), and selective reporting 13/19 (68.4%). Two of the 19  
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33 183 RCTs (10.5%) were industry-funded.<sup>38</sup>  
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38 184 ***Patients with cn-AMD***  
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41 185 ***Comparative effectiveness of bevacizumab and ranibizumab***  
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45 186 Results from 10 RCTs (3302 patients) showed that approximately 22% of patients attained vision  
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47 187 gain with treatment, and patients treated with bevacizumab were as likely to attain vision gain as  
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49 188 those treated with ranibizumab (Risk Ratio (RR): 1.05; [95% confidence interval (CI), 0.93,  
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51 189 1.19], Table 2, Additional file 2: Appendix 6-7). Over an average treatment duration of 16  
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53 190 months, approximately 94% of patients maintained their vision, with no statistical difference  
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3 191 between patients treated with bevacizumab or ranibizumab (RR of vision loss: 0.91 [95% CI,  
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5 192 0.70, 1.19]). Patients treated with bevacizumab or ranibizumab gained an average of 7 letters in  
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7 193 terms of mean BCVA with no statistical difference between the drugs (mean difference [MD]  
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9 194 0.03 letters [95% CI, -1.02, 1.08]). Approximately 2-4% patients treated with bevacizumab or  
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11 195 ranibizumab became legally blind (RR: 2.04 [95% CI, 0.32 to 12.50], 3 trials, 1823 patients).  
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14 196 Overall, the results were consistent across the 10 trials and did not change with the sensitivity  
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16 197 analyses restricted to trials determined to be at low risk of selection bias and with different  
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18 198 follow-up lengths (Additional file 2: Appendix 6, 8-9).  
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### 22 199 *Treatment regimens*

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26 200 Additional file 2: Appendix 10 provides detailed information regarding the treatment regimens  
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28 201 in the included trials, the as-needed re-treatment criteria and the reconstitution of bevacizumab  
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30 202 for intravitreal injections. The treatment regimens varied widely, and are summarized in Table 3  
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32 203 along with the mean number of injections per year for each treatment regimen. The number of  
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34 204 reported treatment regimens varied by condition (cn-AMD (n=6), DME (n=3), RVO-ME (n=2),  
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36 205 and m-CNV (n=1)). In cn-AMD patients, the two most commonly reported regimens for  
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38 206 bevacizumab and ranibizumab included monthly injections (~11 injections/year) and 3 monthly  
39  
40 207 injections followed by as-needed treatment (~6 injections/year). Aflibercept was most commonly  
41  
42 208 administered using a monthly regimen (~11 injections/year).  
43  
44 209 Results of our post hoc analysis comparing as-needed versus monthly treatment in cn-AMD  
45  
46 210 patients are summarized in Table 4. The as-needed treatment regimen with ranibizumab or  
47  
48 211 bevacizumab was less effective than the monthly regimen in improving mean BCVA (MD: -1.9  
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50 212 letters [95% CI, -0.5 to -3.3 letters], 2 RCTs, 1622 patients) and vision gain (RR: 0.73 [95% CI,  
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3 213 0.55 to 0.95]). When the regimens were assessed for non-inferiority at 1 year with an inferiority  
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5 214 margin of 5 points, monthly bevacizumab was equivalent to monthly ranibizumab (MD: -0.5  
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7 215 [95% CI, -3.9, 2.9]), as-needed bevacizumab was equivalent to as-needed ranibizumab (MD: -0.8  
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9 216 [95% CI, -4.1, 2.5]), as-needed ranibizumab was equivalent to monthly ranibizumab (MD: -1.7  
10  
11 217 [95% CI, -4.7, 1.3]) but monthly bevacizumab was not equivalent to as-needed bevacizumab  
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13 218 (MD: -2.1 [95% CI, -5.7, 1.6]).<sup>50</sup> Compared to the monthly regimen, the as-needed regimen was  
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15 219 associated with a significant increase in mortality of 1.8% (95% CI, 0.1% to 3.4%) [RR, 2.0;  
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17 220 95% CI, 1.2 to 3.5].  
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### 22 *Comparative effectiveness of aflibercept and ranibizumab*

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26 222 Results from 2 RCTs (1815 patients; Table 2, and Additional file 2: Appendix 6) showed that  
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28 223 approximately 32% of patients attained vision gain with treatment, and patients treated with  
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30 224 aflibercept were as likely to attain vision gain as patients treated with ranibizumab (RR: 0.99  
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32 225 [95% CI, 0.81 to 1.22]). Over an average assessment and treatment duration of 12 months,  
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34 226 approximately 95% of patients maintained their vision, and aflibercept patients were as likely to  
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36 227 maintain vision as ranibizumab patients (RR of vision loss: 0.90 [95% CI, 0.60 to 1.35]). With  
37  
38 228 respect to mean BCVA, patients gained on average 9 letters (MD: -0.05 [95% CI, -2.5, 2.4]).  
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40 229 Compared to baseline, patients gained some visual-related function, with an average of 5 points  
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42 230 on the NEI-VFQ-25 questionnaire (MD: 2.2 [95% CI, -0.6, 5.1]).  
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### 47 *Harms*

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51 232 Over an average of 14 months (range: 12-24 months), mortality was reported in 4% and 3% of  
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53 233 patients treated with bevacizumab or ranibizumab, respectively (RR: 1.14 [95% CI, 0.72 to  
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3 234 1.79], 6 RCTs, 2941 patients, Additional file 2: Appendix 6). Serious adverse events were  
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5 235 reported in 19 and 18% of patients treated with bevacizumab or ranibizumab, respectively (RR:  
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7 236 1.09 [95% CI, 0.93 to 1.27], 5 RCTs, 3026 patients). Arterial thromboembolic events were  
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9 237 reported in 4% and 3% of patients treated with bevacizumab or ranibizumab, respectively (RR:  
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11 238 0.86 [95% CI, 0.51, 1.47], 4 RCTs, 2033 patients). Venous thromboembolic events, bacterial  
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13 239 endophthalmitis and retinal detachment were reported in <1% of patients treated with either  
14  
15 240 drug. In the trials evaluating aflibercept and ranibizumab, arterial thromboembolic events were  
16  
17 241 reported in 2% of patients treated with aflibercept or ranibizumab (RR: 0.96 [95% CI, 0.45,  
18  
19 242 2.04], 2 RCTs, 1818 patients), and venous thromboembolic events were reported in <1% of  
20  
21 243 patients treated with either drug. Data on other harms were not available.  
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#### 27 244 ***Patients with DME***

##### 28 29 30 245 *Comparative effectiveness of ranibizumab, bevacizumab and aflibercept*

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32  
33 246 Results from the trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net trial,  
34  
35 247 620 patients) showed that over 2 years of treatment, patients were as likely to attain vision gain  
36  
37 248 with ranibizumab (37%), bevacizumab (35%), or aflibercept (39%) - bevacizumab versus  
38  
39 249 ranibizumab: RR: 0.94 [95% CI, 0.72, 1.23]; aflibercept versus bevacizumab: RR: 1.06 [95% CI,  
40  
41 250 0.80, 1.38]; and aflibercept versus ranibizumab: RR: 1.06 [95% CI, 0.82, 1.37]; Table 2) Over 2  
42  
43 251 years of treatment, approximately 98% of patients maintained their vision with all 3 drugs.  
44  
45 252 Patients' mean BCVA improved by 13 letters with aflibercept, 10 letters with bevacizumab and  
46  
47 253 12 letters with ranibizumab (aflibercept versus ranibizumab: MD, 1.4 [95% CI, -1.6, 4.3];  
48  
49 254 bevacizumab versus aflibercept: MD, -2.7 [95% CI, -5.2 to -0.3]; and bevacizumab versus  
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255 ranibizumab: MD, -2.0 [95% CI, -3.9 to -0.1], Table 2).

### 256 *Treatment regimen*

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

### 265 *Harms*

266 After 24 months of treatment in the DRCR.net trial,<sup>27</sup> mortality was reported in approximately  
267 6% of bevacizumab patients, 2% of aflibercept patients and 5% of ranibizumab patients  
268 (Additional file 2: Appendix 6). Serious adverse events were reported in 21% of bevacizumab  
269 patients, 27% of aflibercept patients, and 25% of ranibizumab patients. Arterial thromboembolic  
270 events were reported in 4%, 3%, and 5%, of patients treated with bevacizumab, aflibercept, and  
271 ranibizumab, respectively. Bacterial endophthalmitis and retinal detachments were reported in  
272 <1% of patients treated with any of the drugs.

### 273 *Patients with RVO-ME*

### 274 *Comparative effectiveness of ranibizumab, bevacizumab, and aflibercept*

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3 275 Results from 1 RCT (77 patients) showed that approximately 59% of patients attained vision  
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5 276 gain with bevacizumab and ranibizumab treatment, and no statistical difference was observed  
6  
7 277 between the drugs (RR: 1.0 [95% CI, 0.68 to 1.45]; Table 2 and Additional file 2: Appendix 8).<sup>32</sup>  
8  
9  
10 278 With respect to mean BCVA, patients treated with either drug gained an average of 16 letters  
11  
12 279 (MD -2.5 [95% CI, 8.0 to 5.0]).

13  
14 280 Results from the SCORE2 trial (348 patients) showed that approximately 61% of patients treated  
15  
16 281 with bevacizumab or aflibercept attained vision gain, with no statistical difference between the  
17  
18 282 drugs (RR: 1.06 [95% CI, 0.91 to 1.25]; Table 2).<sup>13</sup> With respect to mean BCVA, patients treated  
19  
20 283 with either drug gained an average of 19 letters (MD 1.52 [95% CI, -1.2 to 4.2]).  
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#### 24 284 *Treatment regimens*

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28 285 In the SCORE2 trial, patients were treated with monthly intravitreal injections for the first 6  
29  
30 286 months, with a mean number of 5.8 injections in patients treated with bevacizumab or aflibercept  
31  
32 287 (Table 3 and Additional file 2: Appendix 11).<sup>13</sup> In another trial, patients were treated with one  
33  
34 288 initial intravitreal injection and then as-needed monthly re-treatment over 6 months, with a mean  
35  
36 289 number of 3 injections in patients treated with bevacizumab or ranibizumab.<sup>12 32</sup>  
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#### 40 290 *Harms*

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44 291 Serious adverse events were reported in 3% of bevacizumab patients and 5% of ranibizumab  
45  
46 292 patients (RR: 0.5 [95% CI, 0.05 to 5.26], 1 RCT, 74 patients; Additional file 2: Appendix 8).<sup>32</sup>  
47  
48 293 Serious adverse events were reported in 8% of the patients treated with bevacizumab or  
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50 294 aflibercept over 6 months (RR: 0.99 [95% CI, 0.49 to 2.00], 1 RCT, 362 patients).<sup>13</sup>  
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3 295 ***Patients with m-CNV***

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6 296 *Comparative effectiveness of ranibizumab and bevacizumab*

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10 297 Results from 1 RCT (32 patients) showed that 62% of patients treated with bevacizumab and  
11  
12 298 56% of patients treated with ranibizumab attained vision gain (RR: 1.11 [95% CI, 0.63, 1.96], 1  
13  
14 299 RCT; Table 2 and Additional file 2: Appendix 11).<sup>30</sup> With respect to mean BCVA, patients  
15  
16 300 treated with bevacizumab gained 12 letters and patients treated with ranibizumab gained an  
17  
18 301 average of 13 letters (MD: -1.3 [95% CI, -6.5 to 4.0], 2 RCTs, 80 patients).<sup>29 30</sup> The included  
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20 302 trials did not report data on harms.

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24 303 *Treatment regimens*

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28 304 Both trials evaluated ranibizumab and bevacizumab with patients receiving one monthly  
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30 305 intravitreal injection and as-needed monthly re-treatment, with a mean number of 3.1 injections  
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32 306 in patients treated with bevacizumab and 2.4 injections per year in patients treated with  
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34 307 ranibizumab (Table 3 and Additional file 2: Appendix 6).<sup>29 30</sup>

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38 308 **DISCUSSION**

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41 309 This systematic review synthesized results from 19 RCTs to evaluate the comparative  
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43 310 effectiveness and safety of intravitreal bevacizumab, ranibizumab, and aflibercept for patients  
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45 311 with cn-AMD, DME, RVO-ME and m-CNV. Intravitreal bevacizumab was as effective as  
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47 312 ranibizumab in patients with cn-AMD, DME, RVO-ME, and m-CNV for the outcomes we  
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49 313 examined. Ranibizumab was as effective as aflibercept in patients with cn-AMD.  
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52 314 In patients with DME that were treated for 2 years, vision gain was equally likely to be attained

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3 315 with aflibercept, ranibizumab or aflibercept. In the first year of treatment, however, patients  
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5 316 treated with aflibercept were more likely to attain vision gain than patients treated with  
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7 317 ranibizumab or bevacizumab - differential effects that were observed mainly in patients with  
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9 318 initial BCVA < 69 letter scores (equivalent to 20/50 or worse) but not observed in patients with  
10  
11 319 initial BCVA  $\geq$  69 letter scores (equivalent to 20/40 or better) based on the results from the sub-  
12  
13 320 group analyses. Rates of systemic serious harms were similarly low among the anti-VEGF drugs,  
14  
15 321 across the retinal conditions. In our post hoc analysis, cn-AMD patients and compared to  
16  
17 322 monthly treatment, an as-needed treatment regimen (i.e., 6 to 9 monthly injections per year) was  
18  
19 323 significantly associated with a small loss in visual acuity, but a significant increase in mortality  
20  
21 324 risk of 1.8% (RR: 2.0 [95% CI, 1.2, 3.5]).

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24 325 Results from the CATT and IVAN trials showed that relative to monthly treatment, patients with  
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26 326 cn-AMD receiving as-needed treatment experienced a significant increase in risk of mortality.  
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28 327 Whether there are any biological explanations for the increased risk of mortality associated with  
29  
30 328 fewer monthly injections is unclear and this finding may have been attributable to chance. As  
31  
32 329 such, further research should be conducted to verify this result. In DME, RVO-ME and m-CNV  
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34 330 trials, patients tended to receive fewer monthly injections per year (Table 3). None of the trials in  
35  
36 331 DME, RVO-ME and m-CNV patients evaluated a monthly treatment regimen, and therefore the  
37  
38 332 safety risk between as-needed and monthly regimens could not be evaluated. This requires  
39  
40 333 further study.

41  
42 334 Additional file 2: Appendix 12 displays the mean change in BCVA over time in patients treated  
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44 335 with bevacizumab or ranibizumab. For all of the retinal conditions, patients showed  
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46 336 improvement in mean BCVA by 3-6 months with initial monthly injections, and maintained a  
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48 337 plateau to 24 months in the treatment of cn-AMD patients (average improvement of 6 letters),

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3 338 DME patients (8 letters), RVO-ME patients (16 letters), and m-CNV patients (11 letters).  
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5 339 Comparative outcomes beyond 6 months in patients with RVO-ME and m-CNV were lacking  
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7 340 and as such, long-term comparative data of anti-VEGF drugs in these patients are needed.  
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9  
10 341 Our findings are consistent with findings from previous systematic reviews. A meta-analysis of 6  
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12 342 head-to-head trials concluded that bevacizumab and ranibizumab had equivalent efficacy with  
13  
14 343 respect to visual acuity in cn-AMD patients.<sup>11</sup> A meta-analysis of five RCTs suggested no  
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16 344 differences in effectiveness between ranibizumab and bevacizumab in DME patients.<sup>53</sup> Other  
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18 345 reviews in patients with RVO-ME and m-CNV came to similar conclusions.<sup>9 10 54 55</sup> Although  
19  
20 346 findings were consistent with those in these recent reviews, our review serves as an update (with  
21  
22 347 the inclusion of data up to 2017) while also examining the additional factor of treatment regimen.  
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24 348 There are several limitations worth noting. First, none of our sensitivity and subgroup analyses  
25  
26 349 were specified *a-priori* and as such, these results should be interpreted with caution. This also  
27  
28 350 pertains to our post-hoc analysis on treatment regimen. Secondly, we limited our review to  
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30 351 English studies due to time and resources constraints. We believe, however, that the impact of  
31  
32 352 the restrictions is small since our findings are consistent with previous systematic reviews that  
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34 353 included RCTs reported in all languages, evaluating the same anti-VEGF drugs for specific  
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36 354 retinal conditions,<sup>11 53 56</sup> and results were consistent across studies, so the impact of including  
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38 355 additional studies reported in other languages, if any, would be insignificant. We only identified  
39  
40 356 a few RCTs evaluating the anti-VEGF drugs in patients with DME, RVO-ME and m-CNV.  
41  
42 357 Although the rates of reported adverse events were similar across the anti-VEGF drugs, the  
43  
44 358 assessment of harms using comparative trial data is limited. We excluded RCTs which  
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46 359 randomized eyes (instead of patients) since the reported analyses failed to adjust for the  
47  
48 360 correlation between the outcomes of eyes from the same individuals.<sup>57</sup> Similarly, we also

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3 361 excluded one quasi-randomized trial,<sup>58</sup> because we focused on randomized studies.  
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5

6 362 **CONCLUSIONS**  
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10 363 With few exceptions, intravitreal bevacizumab was a reasonable alternative to ranibizumab and  
11  
12 364 aflibercept in patients with wet ex-AMD, DME, RVO-ME and m-CNV. The choice of anti-  
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14 365 VEGF drug may depend on specific retinal conditions, baseline visual acuity, and treatment  
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16 366 regimen.  
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## 367 LIST OF ABBREVIATIONS

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

## 374 ACKNOWLEDGEMENTS

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

## 384 CONTRIBUTORS

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

1  
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4  
5 388 conducted quality assessment; and helped draft and revise the manuscript. TL screened titles,  
6  
7 389 abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment;  
8  
9  
10 390 helped conduct meta-analysis; and reviewed the manuscript. EL screened titles, abstracts, and  
11  
12 391 full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the  
13  
14 392 manuscript. JH conducted the analysis and interpretation of data; and reviewed the manuscript.  
15  
16 393 TR helped with conceptualizing the research design, drafting and revising the protocol,  
17  
18 394 interpretation of data; and reviewed the manuscript. GJ helped draft and revise the protocol;  
19  
20 395 screened titles, abstracts, and full-text articles; abstracted data; conducted quality assessment;  
21  
22 396 helped interpret the data; and reviewed the manuscript. AA screened titles, abstracts, and full-  
23  
24 397 text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the  
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26 398 manuscript. JPS screened titles, abstracts, and full-text articles; abstracted and cleaned data;  
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28 399 conducted quality assessment; and reviewed the manuscript. AS screened titles, abstracts, and  
29  
30 400 full-text articles; abstracted and cleaned data, conducted quality assessment; and reviewed the  
31  
32 401 manuscript. RW screened titles, abstracts, and full-text articles; abstracted and cleaned data,  
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34 402 conducted quality assessment; and reviewed the manuscript. RB abstracted and cleaned data,  
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38 404 full-text articles; abstracted and cleaned data; and reviewed the manuscript. SES helped with  
39  
40 405 conceptualizing the research and design; interpretation of data, and reviewed the manuscript.  
41  
42 406 ACT conceptualized the research and design; drafted the protocol; obtained funding; assisted  
43  
44 407 with data acquisition and interpretation; and drafted and revised the manuscript. Authors ACT  
45  
46 408 and BP had full access to all the data in the study and takes responsibility for the integrity of the  
47  
48 409 data and the accuracy of the data analysis.



**410 FUNDING**

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

**419 COMPETING INTERESTS**

420 All authors declare no competing interests.

**421 PROVENANCE AND PEER REVIEW**

422 Not commissioned; externally peer reviewed.

**423 DATA SHARING STATEMENT**

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

**426 MEETING PRESENTATION**

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

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590 **FIGURE LEGENDS**

591 *Figure 1. Study Flow*

For peer review only



TABLE 1. SUMMARY STUDY CHARACTERISTICS

Study Characteristic	Total No. of trials included (n=19) <sup>a</sup> (%)	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) (%)
<b>Year of publication</b>					
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)
<b>Geographic region</b>					
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)
<b>Setting</b>					
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)
<b>Follow-up duration</b>					
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:**

<sup>a</sup> 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.



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**TABLE 2. COMPARATIVE EFFECTIVENESS RESULTS**

Condition	Treatment vs. Comparator	Outcome <sup>a</sup>	# of RCTs (# of patients)	Baseline ETDRS letters <sup>b</sup> ~Snellen equivalent	Treatment Effect Mean (Range) <sup>b</sup>	Comparator effect Mean (Range) <sup>b</sup>	Risk Ratio or Mean Difference Estimate (95% CI)	I <sup>2c</sup>
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
	Aflibercept vs. Ranibizumab	BCVA change	1 (386)	65 ~ 20/50	10.0 (SD: 11.8)	12.8 (SD: 12.4)	-2.7 (-5.2, -0.3)	NA
		Vision gain	1 (392)	65 ~ 20/50	39%	37%	1.06 (0.73, 1.22)	NA
	Aflibercept vs. Ranibizumab	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%
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**Footnotes:**

<sup>a</sup> In terms of outcomes, vision gain was defined as a gain in BCVA of  $\geq 15$  EDTRS letters, vision loss of  $\geq 15$  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.

<sup>b</sup> Mean (range) were derived across control groups of the included RCTs.

<sup>c</sup>  $I^2 < 75$  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) <sup>a</sup>
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 <sup>b</sup>
	3 initial monthly treatment and as-needed treatment (every 2 months) with aflibercept	2	6.9 <sup>b</sup>
	DME	3 initial monthly treatments + as-needed treatment (every month) with ranibizumab	1
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 <sup>c</sup>
As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment		1	10 <sup>c</sup>

	(every month) with bevacizumab		
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment (every month) with aflibercept	1	9 <sup>c</sup>
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:**

<sup>a</sup>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.

<sup>b</sup>Value was reported once for both trials in Heier et al. 2012.

<sup>c</sup>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 <sup>a</sup> , # of patients	Baseline ETDRS letters <sup>b</sup> and Snellen equivalent	As-needed regimen Mean (Range) <sup>b</sup>	Monthly Regimen Mean (Range) <sup>b</sup>	Risk Ratio or <i>Mean Difference</i> Estimate (95% CI)	I <sup>2c</sup>
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:**

<sup>a</sup> CATT and IVAN trials.(Martin, 2011; Chakravarthy 2013)

<sup>b</sup> Mean (range) were derived across control groups of the included RCTs.

<sup>c</sup> I<sup>2</sup> <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.

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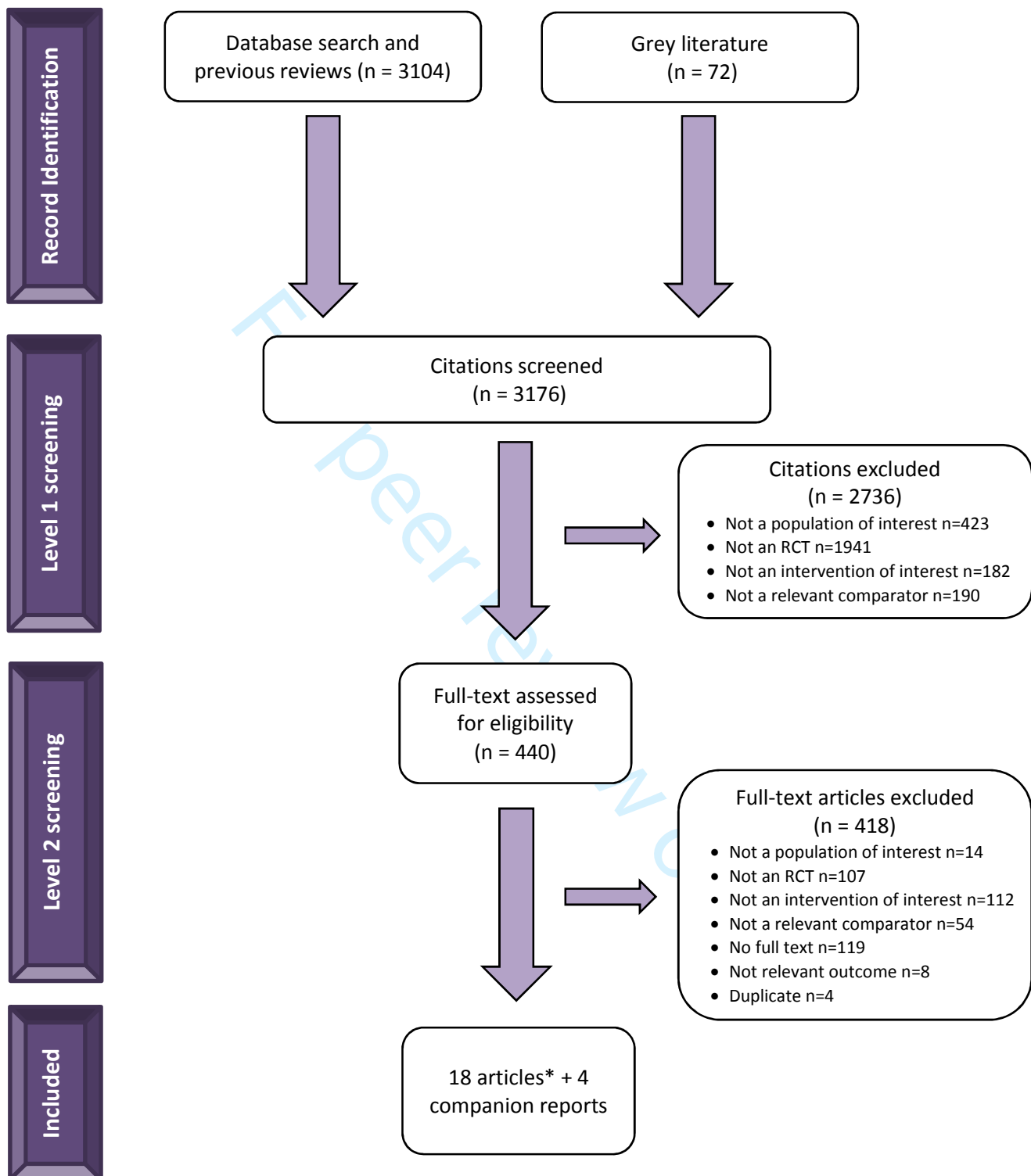
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FIGURE 1: STUDY FLOW



\*18 articles describing 19 randomized controlled trials

## Supplementary Online Content

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## 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.<sup>1</sup> 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.<sup>2</sup>

### *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 17<sup>th</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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-vitreous 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).<sup>5</sup>

- Populations: patients  $\geq 18$  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  $\geq 15$  letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart,
2. Vision loss, defined as a loss in BCVA of  $\geq 15$  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.<sup>6</sup> The Snellen chart is the current standard for measurement of visual acuity in clinical practice.<sup>6-8</sup> The ETDRS chart is the 'gold standard' for measuring visual acuity in clinical trials.<sup>6</sup> 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  $\pm 5$  to 16.5 letters in normal patients.<sup>9</sup> <sup>10</sup> The test-retest variability of the ETDRS charts ranges from  $\pm 3.5$  to 10 letters.<sup>11</sup> A change of at least 10 letters (or two lines) is required to capture a true clinical

1  
2  
3 change in visual acuity.<sup>6 12</sup> With respect to vision-related function, we abstracted data from the 25-item National  
4 Eye Institute Visual Function Questionnaire (NEI VFQ-25), which is a self-reported survey questionnaire that  
5 assesses the influence of visual impairment on health-related quality of life.<sup>13</sup> Changes in the NEI VFQ overall  
6 scores of 10 points or more are associated with clinically relevant changes in vision.<sup>14</sup>  
7

### 8 ***Study selection***

9

10 Citations from the literature search were imported into an online systematic review software.<sup>15</sup> Also imported were  
11 the inclusion criteria, which were used for level-1 screening of citations (titles/abstracts) and level-2 screening of  
12 potentially relevant full-text articles. The 14 members of the review team underwent two training exercises; each  
13 involved a random sample of 50 citations, which were screened independently by all team members. Level-1  
14 screening proceeded after 80% agreement had been achieved among the reviewers on the second training exercise.<sup>16</sup>  
15 <sup>17</sup> Paired reviewers conducted the level-1 screening of each citation, independently. The estimated frequency of  
16 disagreement was 8%, which was resolved by a third reviewer. We retrieved the full-text articles of potentially  
17 relevant citations identified by at least one reviewer for level-2 screening. The team underwent a training exercise  
18 using a random sample of 20 full-text articles, which resulted in 70% agreement. Paired reviewers independently  
19 screened each full-text article. The estimated frequency of disagreement was 14%, which was resolved by a third  
20 reviewer. This reviewer also verified all eligible studies.  
21  
22

### 23 ***Data abstraction***

24

25 We developed a data abstraction form with inputs from two physicians. We piloted and refined the form two times,  
26 each time using five randomly selected studies. Subsequently, paired reviewers conducted the abstraction,  
27 independently. Numerical data available only in figures were extracted using WebPlotDigitizer.<sup>18</sup> A third reviewer  
28 conducted a quality check on all data, and resolved any remaining discrepancies.  
29

30 We abstracted data pertaining to study characteristics, patient populations, interventions, and outcomes. Multiple  
31 reports of the same trial (hereafter companion reports) were identified using the trial registration identifier, trial  
32 name, or a juxtaposition of the author names, treatment comparisons, sample sizes and outcomes, if necessary.<sup>19</sup> We  
33 abstracted data from all companion reports, identified differences, and reconciled the differences through discussion.  
34 For each set of companion reports, we considered one as the major publication and others as companion reports. We  
35 abstracted outcome data from all trial reports and used the data corresponding to the longest duration of follow-up in  
36 the meta-analysis.<sup>5</sup>  
37  
38

### 39 ***Risk of bias assessment***

40

41 The risk of bias in the included trials was appraised using the Cochrane risk-of-bias tool, including selection bias,  
42 performance bias, detection bias, attrition bias, reporting bias, and other biases such as funding sources.<sup>20</sup> For  
43 selection bias, we assessed the reporting of random sequence generation and allocation concealment. For  
44 performance bias, we assessed the reporting of blinding of patients and trial personnel, and for detection bias, the  
45 reporting of the blinding of outcome assessors. In the assessment of performance and detection biases, we  
46 considered the objectivity of the primary outcome of individual trials in assessing performance and detection biases.  
47

48 For RCTs that had been registered, the primary outcome was identified from the trial protocol, which was vision  
49 gain or change in mean BCVA in the majority of the included RCTs. Otherwise, we identified the primary outcome  
50 using an *a-priori* defined algorithm.<sup>21 22</sup> In brief, we selected from the trial report the outcome that was listed in the  
51 title or objectives, the most serious clinical outcome among all the trial outcomes, or the first reported outcome in  
52 the results section.  
53

54 Paired reviewers conducted the risk of bias assessment, independently. Discrepancies were resolved by discussion or  
55 the involvement of a third reviewer.  
56  
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### ***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.<sup>5</sup> 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.<sup>23</sup> 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.<sup>5</sup> Pooled treatment effect estimates and 95% confidence intervals (CIs) were derived using the meta-analytical random effects model.<sup>23</sup> The meta-analyses were conducted using the "metafor" package in R (version 3.1.1).<sup>24</sup>

### ***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,<sup>25</sup> with approximate standard deviations.<sup>26</sup> 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.<sup>27</sup> 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.<sup>5</sup>

### ***Excluded RCT'S***

The RCT by Rajagopal et al. 2015<sup>28</sup> (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<sup>29</sup> 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>

1  
2  
3 MEDLINE Daily and MEDLINE 1946 to present

4 MEDLINE In-Process & Other Non-Indexed Citations

5  
6 Cochrane Central Register of Controlled Trials <April 2015>

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

9  
10 Date of Search: May 27, 2015 (Updated November 13, 2015)

11 Study Types: Randomized controlled trials

12 Limits: No date or language limits were used

13 Human filter was applied

14 Editorials & letters excluded

15  
16  
17 Search Strategy:  
18  
19  
20  
21

22 -----  
23 1 Retinal Degeneration/  
24 2 limit 1 to yr="1973-2009" [EARLIER MESH FOR WET MACULAR DEGENERATION]  
25 3 Macular Degeneration/  
26 4 Wet Macular Degeneration/ [MESH FROM 2010-]  
27 5 ((exudative or neovascular or wet) adj3 ((macula\* adj2 degeneration) or (macula\* adj2 deterioration) or  
28 maculopath\* or (macula\* adj2 dystroph\*))).tw,kw.  
29 6 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.  
30 7 (wAMD or wARMD).tw,kw.  
31 8 Diabetic Retinopathy/  
32 9 ((diabet\* or DM) adj3 retinopath\*).tw,kw.  
33 10 (PDR or DME or DMO).tw,kw.  
34 11 Macular Edema/  
35 12 ((macula\* or retina\*) adj3 (edema\$1 or oedema\$1)).tw,kw.  
36 13 (Irvine-Gass adj3 (edema\$1 or oedema\$1 or syndrome\$1)).tw,kw.  
37 14 (cystoid macula\* adj dystroph\*).tw,kw.  
38 15 Retinal Vein Occlusion/  
39 16 (retinal vein adj3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or embolism\*)).tw,kw.  
40 17 (BRVO or CRVO).tw,kw.  
41 18 Choroidal Neovascularization/  
42 19 ((choroid\* or subretinal or sub-retinal) adj1 neovasculari#ation\*).tw,kw.  
43 20 CNV.tw,kw.  
44 21 or/2-20 [CONDITIONS – MEDLINE]  
45 22 Vascular Endothelial Growth Factor A/ai

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2  
3 23 (anti adj2 VEGF\$1).tw,kw.  
4  
5 24 antiVEGF\$1.tw,kw.  
6  
7 25 (antivascular endothelial growth factor\$1 or anti-vascular endothelial growth factor\$1).tw,kw.  
8  
9 26 Antibodies, Monoclonal, Humanized/  
10  
11 27 (monoclonal antibod\* and humani#ed).tw,kw.  
12  
13 28 (antibod\* adj2 humani#ed).tw,kw.  
14  
15 29 Angiogenesis Inhibitors/  
16  
17 30 (angiogen\* adj3 (inhibitor\* or antagonist\*)).tw,kw.  
18  
19 31 (anti-angiogen\* or antiangiogen\*).tw,kw.  
20  
21 32 aflibercept.tw,kw.  
22  
23 33 ("AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-  
24  
25 15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.  
26  
27 34 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap\*).tw,kw.  
28  
29 35 aflibercept.rn.  
30  
31 36 Bevacizumab.tw,kw.  
32  
33 37 (Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.  
34  
35 38 IVB injection\$1.tw,kw.  
36  
37 39 Bevacizumab.rn.  
38  
39 40 Pegaptanib.tw,kw.  
40  
41 41 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.  
42  
43 42 Pegaptanib.rn.  
44  
45 43 Ranibizumab.tw,kw.  
46  
47 44 (Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.  
48  
49 45 IVR injection\$1.tw,kw.  
50  
51 46 Ranibizumab.rn.  
52  
53 47 or/22-46 [ANTI-VEGF AGENTS – MEDLINE]  
54  
55 48 21 and 47 [ANTI-VEGF AGENTS & CONDITIONS – MEDLINE]  
56  
57 49 exp Photochemotherapy/  
58  
59 50 Photosensitizing Agents/  
60  
61 51 (photochemo\* or photo-chemo\* or photodynamic\* or photo-dynamic\* or photosensiti\* or photo-  
62  
63 sensiti\*).tw,kw.  
64  
65 52 PDT.tw,kw.  
66  
67 53 or/49-52  
68  
69 54 verteporfin.tw,kw.  
70  
71 55 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.  
72  
73 56 verteporfin.rn.

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3 57 or/54-56  
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5 58 53 and 57  
6 59 (PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.  
7  
8 60 58 or 59 [VISUDYNE PDT – MEDLINE]  
9  
10 61 21 and 60 [VISUDYNE PDT & CONDITIONS – MEDLINE]  
11  
12 62 Triamcinolone Acetonide/  
13 ((Triamcinol\* adj acet\*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS  
14 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog\* or Kenlog or "NSC 21916" or  
15 Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort\* or Triesense or Tristoject or "UNII-  
16 F446C597KA" or Volon).tw,kw.  
17 64 triamcinolone acetonide.rn.  
18  
19 65 Glucocorticoids/  
20 66 (glucocorticoid\* or glucorticoid\*).tw,kw.  
21  
22 67 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or Retaane  
23 or "UNII-Y0PC411K4T").tw,kw.  
24 68 anecortave acetate.rn.  
25  
26 69 Pregnadienediols/  
27 70 (dihydroxypregnadiene\* or di-hydroxypregnadiene\* or pregnadienediol\*).tw,kw.  
28  
29 71 exp Dexamethasone/  
30 72 (Dexamethasone or Decaject\* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex  
31 or Millicorten or Oradexon or Ozurdex).tw,kw.  
32  
33 73 dexamethasone.rn.  
34 74 (intravitreal adj3 (corticoid\* or corticosteroid\* or steroid\*).tw,kw.  
35  
36 75 or/62-74  
37  
38 76 exp Injections/  
39 77 (depot or implant\* or infus\* or inject\* or intravitreal\* or intra-vitreal\* or microsphere\* or micro-sphere\* or  
40 suspension\*).tw,kw.  
41  
42 78 or/76-77  
43 79 75 and 78 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - MEDLINE]  
44  
45 80 21 and 79 (3513) [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - MEDLINE]  
46 81 (controlled clinical trial or randomized controlled trial).pt.  
47  
48 82 clinical trials as topic.sh.  
49 83 (randomi#ed or randomly or RCT\$1 or placebo\*).tw.  
50  
51 84 ((singl\* or doubl\* or trebl\* or tripl\*) adj (mask\* or blind\* or dumm\*)).tw.  
52 85 trial.ti.  
53  
54 86 or/81-85  
55 87 (48 or 61 or 80) and 86



- 1  
2  
3 88 exp Animals/ not (exp Animals/ and Humans/)  
4  
5 89 87 not 88  
6 90 (comment or editorial or interview or news).pt.  
7  
8 91 (letter not (letter and randomized controlled trial)).pt.  
9  
10 92 89 not (90 or 91)  
11 93 92 use prmz [MEDLINE RCTS]  
12 94 macular degeneration/  
13  
14 95 age related macular degeneration/  
15 96 wet macular degeneration/  
16  
17 97 ((exudative or neovascular or wet) adj3 ((macula\* adj2 degeneration) or (macula\* adj2 deterioration) or  
18 maculopath\* or (macula\* adj2 dystroph\*))).tw,kw.  
19 98 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.  
20  
21 99 (wAMD or wARMD).tw,kw.  
22  
23 100 diabetic retinopathy/  
24 101 ((diabet\* or DM) adj3 retinopath\*).tw,kw.  
25 102 diabetic macular edema/  
26 103 (PDR or DME or DMO).tw,kw.  
27  
28 104 exp macular edema/  
29  
30 105 ((macula\* or retina\*) adj3 (edema\$1 or oedema\$1)).tw,kw.  
31 106 (Irvine-Gass adj3 (edema\$1 or oedema\$1 or syndrome\$1)).tw,kw.  
32 107 (cystoid macula\* adj dystroph\*).tw,kw.  
33  
34 108 exp retina vein occlusion/  
35  
36 109 (retinal vein adj3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or embolism\*)).tw,kw.  
37 110 (BRVO or CRVO).tw,kw.  
38  
39 111 subretinal neovascularization/  
40 112 ((choroid\* or subretinal or sub-retinal) adj1 neovasculari#ation\*).tw,kw.  
41 113 CNV.tw,kw.  
42  
43 114 or/94-113 [CONDITIONS – EMBASE]  
44 115 vasculotropin inhibitor/  
45 116 (anti adj2 VEGF\$1).tw,kw.  
46 117 antiVEGF\$1.tw,kw.  
47 118 (antivascular endothelial growth factor\$1 or anti-vascular endothelial growth factor\$1).tw,kw.  
48 119 monoclonal antibody/  
49 120 (monoclonal antibod\* and humani#ed).tw,kw.  
50 121 (antibod\* adj2 humani#ed).tw,kw.  
51 122 angiogenesis inhibitor/  
52  
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2  
3 123 (angiogen\* adj3 (inhibitor\* or antagonist\*)).tw,kw.  
4  
5 124 (anti-angiogen\* or antiangiogen\*).tw,kw.  
6  
7 125 aflibercept/  
8 126 (aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or  
9 Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.  
10  
11 127 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap\*).tw,kw.  
12  
13 128 aflibercept.rn.  
14  
15 129 bevacizumab/  
16 130 (bevacizumab or Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-  
17 2S9ZZM9Q9V").tw,kw.  
18  
19 131 IVB injection\$1.tw,kw.  
20  
21 132 Bevacizumab.rn.  
22  
23 133 pegaptanib/  
24 134 (Pegaptanib or "EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-  
25 3HP012Q0FH").tw,kw.  
26  
27 135 Pegaptanib.rn.  
28  
29 136 ranibizumab/  
30 137 (Ranibizumab or Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.  
31  
32 138 IVR injection\$1.tw,kw.  
33  
34 139 Ranibizumab.rn.  
35  
36 140 or/115-139 [ANTI-VEGF AGENTS – EMBASE]  
37  
38 141 114 and 140 [ANTI-VEGF AGENTS & CONDITIONS – EMBASE]  
39  
40 142 photodynamic therapy/  
41  
42 143 photosensitizing agent/  
43  
44 144 (photochemo\* or photo-chemo\* or photodynamic\* or photo-dynamic\* or photosensiti\* or photo-  
45 sensiti\*).tw,kw.  
46  
47 145 PDT.tw,kw.  
48  
49 146 or/142-145  
50  
51 147 verteporfin/  
52  
53 148 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.  
54  
55 149 verteporfin.rn.  
56  
57 150 or/147-149  
58  
59 151 146 and 150  
60  
61 152 (PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.  
62  
63 153 151 or 152 [VISUDYNE PDT – EMBASE]  
64  
65 154 114 and 153 [VISUDYNE PDT & CONDITIONS – EMBASE]  
66  
67 155 triamcinolone/

- 1  
2  
3 156 triamcinolone acetone/
- 4  
5 157 ((Triamcinol\* adj acet\*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS  
6 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog\* or Kenlog or "NSC 21916" or  
7 Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort\* or Triesense or Tristoject or "UNII-  
8 F446C597KA" or Volon).tw,kw.
- 9  
10 158 triamcinolone.rn.
- 11 159 triamcinolone acetone.rn.
- 12  
13 160 exp glucocorticoid/
- 14 161 (glucocorticoid\* or glucorticoid\*).tw,kw.
- 15  
16 162 anecortave/
- 17 163 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or  
18 Retaane or "UNII-Y0PC411K4T").tw,kw.
- 19  
20 164 anecortave.rn.
- 21 165 pregnane derivative/
- 22  
23 166 (dihydroxypregnadiene\* or di-hydroxypregnadiene\* or pregnadienediol\*).tw,kw.
- 24  
25 167 dexamethasone/
- 26 168 dexamethasone isonicotinate/
- 27 169 (Dexamethasone or Decaject\* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex  
28 or Millicorten or Oradexon or Ozurdex).tw,kw.
- 29  
30 170 dexamethasone.rn.
- 31 171 dexamethasone isonicotinate.rn.
- 32  
33 172 (intravitreal adj3 (corticoid\* or corticosteroid\* or steroid\*)).tw,kw.
- 34  
35 173 or/155-172
- 36 174 exp injection/
- 37  
38 175 intravitreal drug administration/
- 39 176 vi.fs. [EMBASE FLOATING SUBJECT HEADING FOR INTRAVITREAL DRUG ADMIN]
- 40  
41 177 (depot or implant\* or infus\* or inject\* or intravitreal\* or intra-vitreal\* or microsphere\* or micro-sphere\* or  
42 suspension\*).tw,kw.
- 43  
44 178 or/174-177
- 45 179 173 and 178 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - EMBASE]
- 46 180 114 and 179 [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - EMBASE]
- 47  
48 181 randomized controlled trial/ or controlled clinical trial/
- 49 182 exp "clinical trial (topic)"/
- 50  
51 183 (randomi#ed or randomly or RCT\$1 or placebo\*).tw.
- 52  
53 184 ((singl\* or doubl\* or trebl\* or tripl\*) adj (mask\* or blind\* or dumm\*)).tw.
- 54  
55 185 trial.ti.
- 56  
57 186 or/181-185

1  
2  
3 187 (141 or 154 or 180) and 186  
4 188 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp  
5 vertebrate/  
6  
7 189 exp humans/ or exp human experimentation/ or exp human experiment/  
8  
9 190 188 not 189  
10  
11 191 187 not 190  
12 192 editorial.pt.  
13 193 letter.pt. not (letter.pt. and randomized controlled trial/)  
14  
15 194 191 not (192 or 193)  
16 195 194 use emczd [EMBASE RCTS]  
17  
18 196 93 or 195 [MEDLINE / EMBASE RCTS]  
19 197 remove duplicates from 196 [TOTAL UNIQUE HITS]  
20  
21 198 197 use prmz [UNIQUE MEDLINE]  
22  
23 199 197 use emczd [UNIQUE EMBASE]  
24

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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)
<b>cn-AMD (n = 12)</b>									
Schauwvlieghe <sup>30</sup>	2016	BRAMD	Netherlands Trial Register: NTR1704	Netherlands	Parallel RCT	Jan 2009 - Dec 2011	Multi	332	12
Berg <sup>31</sup>	2015	LUCAS	NCT01127360	Norway	Parallel RCT	Mar 2009 - Jul 2012	Multi	441	12
Scholler <sup>32</sup>	2014	NR	EK-07-192-1007 / EudraCT Nr. 2007-005157-33	Austria	Parallel RCT	2008 - 2011	Single	55	12
Chakravarthy <sup>33</sup>	2013	IVAN	ISRCTN921665 60	UK	Parallel RCT	Mar 27, 2008 - Oct 15, 2010	Multi	610	24
Kodjikian <sup>34</sup>	2013	GEFAL	NCT01170767	France	Parallel RCT	2009 - 2012	Multi	501	12
Krebs <sup>35</sup>	2013	MANTA	NCT00710229	Austria	Parallel RCT	2008 - 2011	Multi	321	12
Heier <sup>36</sup>	2012	VIEW 1	NCT00509795	US, Canada	Parallel RCT	Aug 2007 - Sep 2010	Multi	1217	12
Heier <sup>36</sup>	2012	VIEW 2	NCT00637377	Argentina , Australia, Austria, Belgium, Brazil, Colombia , Czech Republic, France, Germany ,	Parallel RCT	Apr 2008 - Sep 2010	Multi	1240	12

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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, Netherla nds, Poland, Portugal, Singapor e, Slovakia, Spain, Sweden, Switzerla nd, United Kingdom					
Biswas <sup>37</sup>	2011a	NR	NR	India	Parallel RCT	2007 - 2009	Multi	60	18
Biswas <sup>38</sup>	2011b	NR	NR	India	Parallel RCT	NA	Multi	120	18
Martin <sup>39</sup>	2011	CATT	NCT00593450	US	Parallel RCT	2008 - 2010	Multi	1208	12
Subramanian <sup>40</sup>	2010	NR	ISRCTN73359806	US	Parallel RCT	2007 - 2009	Single	28	12
<b>DME (n = 3)</b>									
Fouda <sup>41</sup>	2017	NR	NR	Egypt	Parallel RCT	NR	Single	42	15
Wells <sup>27</sup>	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)
Ekinci <sup>42</sup>	2014	NR	NR	Turkey	RCT Parallel RCT	- Oct 2014 2011 - 2014	NR	100	12
<b>RVO-ME (n = 2)</b>									
Scott <sup>43</sup>	2017	SCORE2	NCT01969708	US	Parallel RCT	Sep 2014 - Dec 2016	MULTI	362	6
Narayanan <sup>44</sup>	2015	MARVEL	CTRI/2012/01/003120	India	Parallel RCT	Jan 2012 - Feb 2013	Single	75	6
<b>m-CNV (n = 2)</b>									
Iacono <sup>45</sup>	2012	NR	NR	Italy	Parallel RCT	Apr 2006 - Jul 2007	Single	55	18
Gharbiya <sup>46</sup>	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
<b>cn-AMD (n = 12)</b>																		
Schauwvlieghe 2016 <sup>30</sup>	332	78	SD	7	79	7	78	7	NR	NR	NR	NR	56	NR	NR	NR	NR	40 % pseudo phakic
Berg 2015 <sup>31</sup>	NR	NR	SD	NR	78.7	7.6	78	8.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Scholler 2014 <sup>32</sup>	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 <sup>33</sup>	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 <sup>34</sup>	501	NR	NR	NR	79.6	6.9	78.7	7.3	NR	NR	NR	NR	66	NR	NR	NR	57	NR
Krebs 2013 <sup>35</sup>	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 <sup>36</sup>	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 <sup>36</sup>	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 <sup>37</sup>	60	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Biswas 2011b <sup>38</sup>	104	NR	NR	NR	63.5	NR	64.4	NR	NR	NR	NR	NR	52	NR	NR	NR	NR	NR
Martin 2011 <sup>39</sup>	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 <sup>40</sup>	28	78.6	SD	NR	78	NR	80	NR	NR	NR	NR	NR	4.6	NR	NR	NR	NR	NR
<b>DME (n = 3)</b>																		
Fouda 2017 <sup>41</sup>	70	NR	SD	NR	55.1	4.7	56.6	5.8	NA	NA	NA	NA	NR	100	NR	NR	NR	NR
Wells 2015 <sup>27</sup>	660	61	SD	10	60	10	62	10	60	11	NR	NR	47	100	NR	NR	NR	NR
Ekinci 2014 <sup>42</sup>	100	NR	NR	NR	68	9	65	14	NR	NR	NR	NR	68	100	NR	0	NR	NR
<b>RVO-ME (n = 2)</b>																		

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 <sup>43</sup>	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 <sup>44</sup>	75	NR	NR	NR	53	NR	50	NR	NR	NR	NR	NR	45.3	17	NR	NR	50	NR
<b>m-CNV (n = 2)</b>																		
Iacono 2012 <sup>45</sup>	55	NR	SD	NR	65	12	61	11	NR	NR	NR	NR	76.4	NR	NR	NR	NR	NR
Gharbiya 2010 <sup>46</sup>	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
<b>cn-AMD (n = 12)</b>							
Schauwvlieghe 2016 <sup>30</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Berg 2015 <sup>31</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Scholler 2014 <sup>32</sup>	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Chakravarthy 2013 <sup>33</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kodjikian 2013 <sup>34</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Krebs 2013 <sup>35</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Heier 2012 – VIEW 1 <sup>36</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Heier 2012 – VIEW 2 <sup>36</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Biswas 2011a <sup>37</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Biswas 2011b <sup>38</sup>	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Martin 2011 <sup>39</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Subramanian 2010 <sup>40</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
<b>DME (n = 3)</b>							
Fouda 2017 <sup>41</sup>	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Wells 2015 <sup>27</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ekinci 2014 <sup>42</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
<b>RVO-ME (n = 2)</b>							
Scott 2017 <sup>43</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Narayanan 2015 <sup>44</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
<b>m-CNV (n = 2)</b>							
Iacono 2012 <sup>45</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Gharbiya 2010 <sup>46</sup>	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

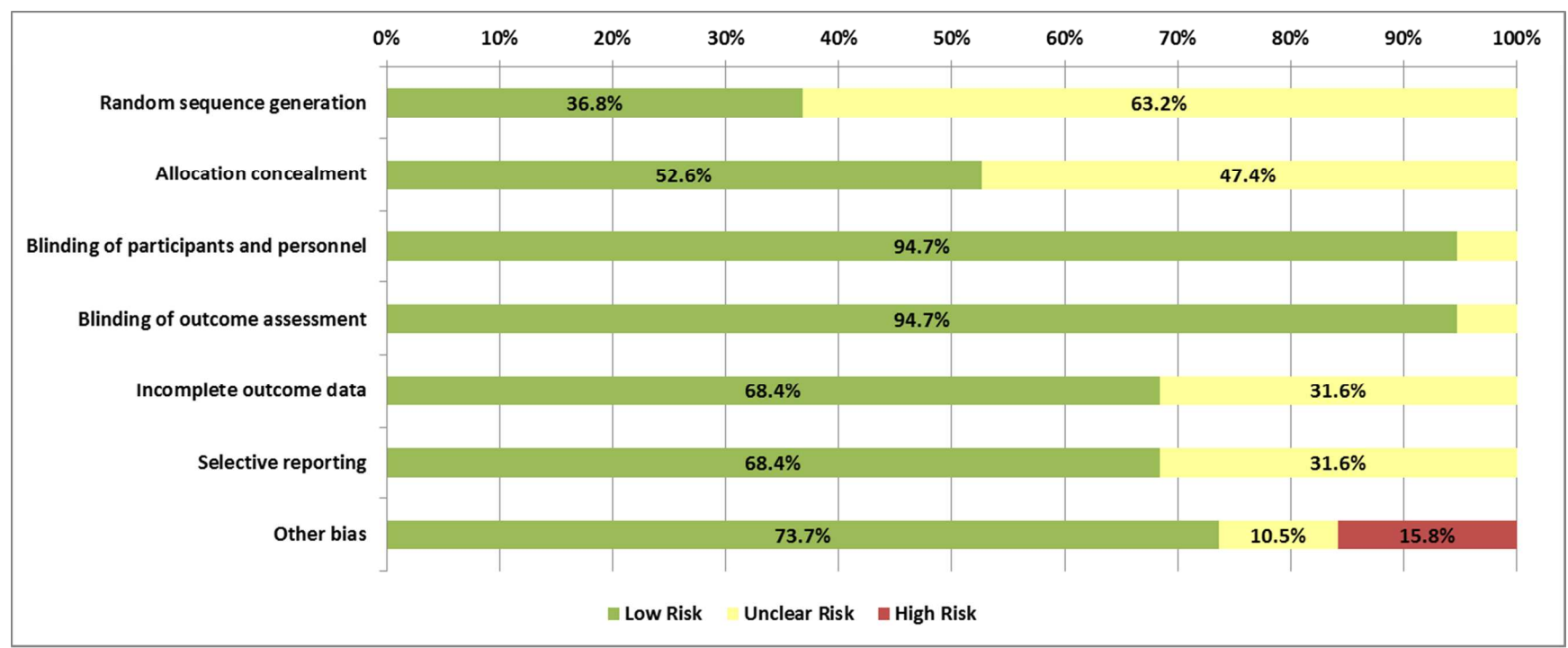
- 1
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- 3 5: Incomplete outcome data
- 4 6: Selective reporting
- 5 7: Other bias
- 6

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

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### Appendix 5: Risk of bias results



## Appendix 6: Treatment effect estimates

Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
<b>Treatment Effects in choroidal neovascular Age-related Macular Degeneration</b>								
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% <sup>b</sup>
	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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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
<b>Treatment Effects in Diabetic Macular Edema</b>								
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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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. Aflibercept	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	Aflibercept							
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	2	512	0	0	NE	NE	NE
	Bevacizumab vs. Ranibizumab	1	436	0.01	0	3.03 (0.12-100)	0.46 (-0.81, 1.72)	NA
	Bevacizumab 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%
	Bevacizumab vs. Ranibizumab	1	436	0.0092	0.0046	2 (0.18-20)	NR	NA
	Bevacizumab vs. Aflibercept	1	436	0.0046	0.0092	0.5 (0.05, 5.47)	-0.46 (-2.01, 1.09)	NA
<b>Treatment Effects in Retinal Vein Occlusion – Macular Edema</b>								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumab vs. Ranibizumab	1	74	0.59	0.59	1 (0.68-1.45)	0 (-22.37, 22.37)	NA
	Bevacizumab 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
	Bevacizumab vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumab 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
	Bevacizumab vs. Ranibizumab	1	77	15.6	18.1	NA	-2.5 (-8.0, 5.0)	NA
	Bevacizumab vs. Aflibercept	1	362	18.6	18.9	NA	-1.5 (-4.2, 1.2)	NA



Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
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
<b>Treatment Effects in Myopic Choroidal Neovascularization</b>								
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

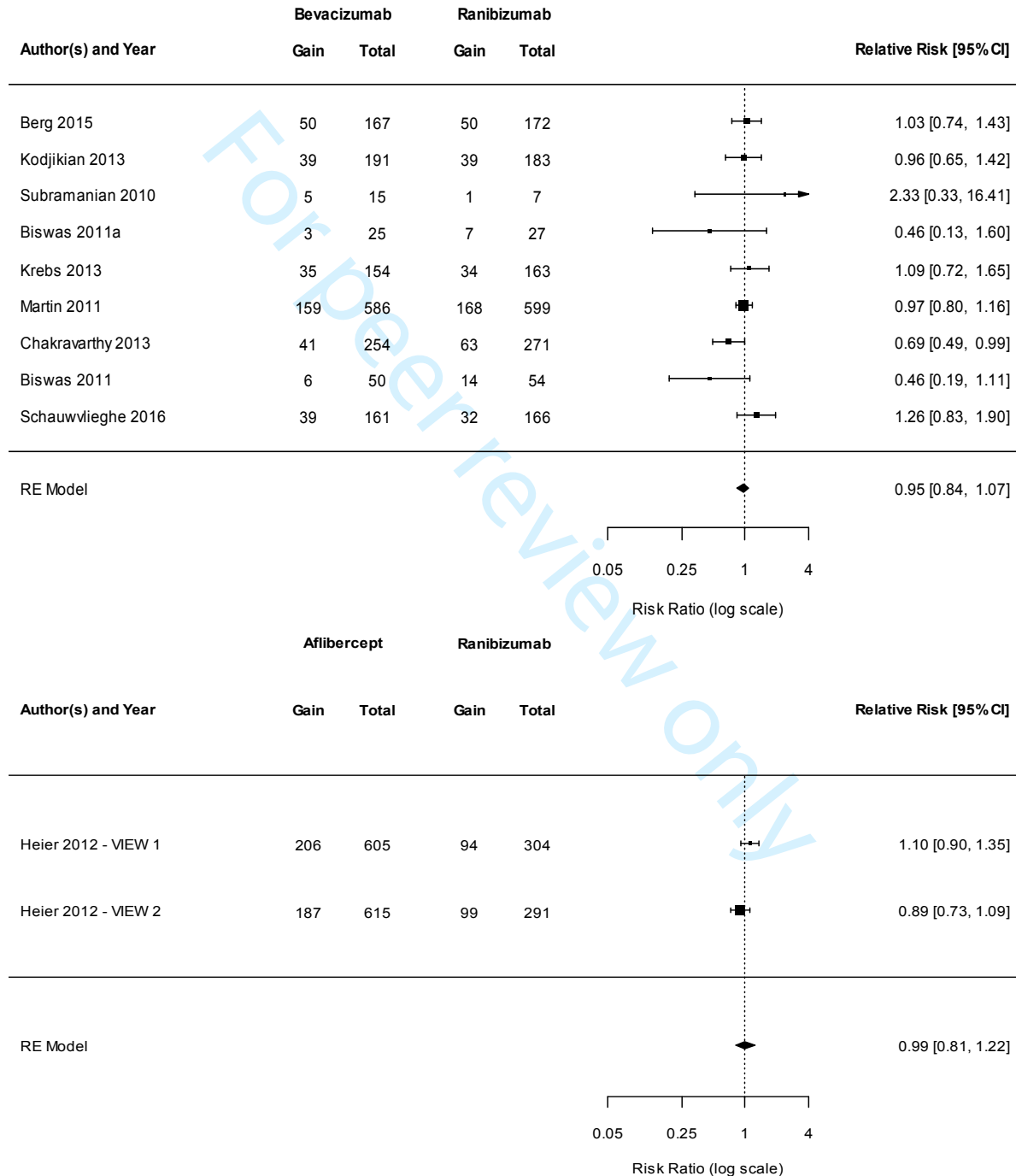
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Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
Mean change in BCVA (MD in # 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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
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
<b>Footnotes:</b>								
<sup>a</sup> 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.								
<sup>b</sup> The summary statistics were derived by taking the mean and range across estimates from included studies.								
<b>Abbreviations:</b> 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								

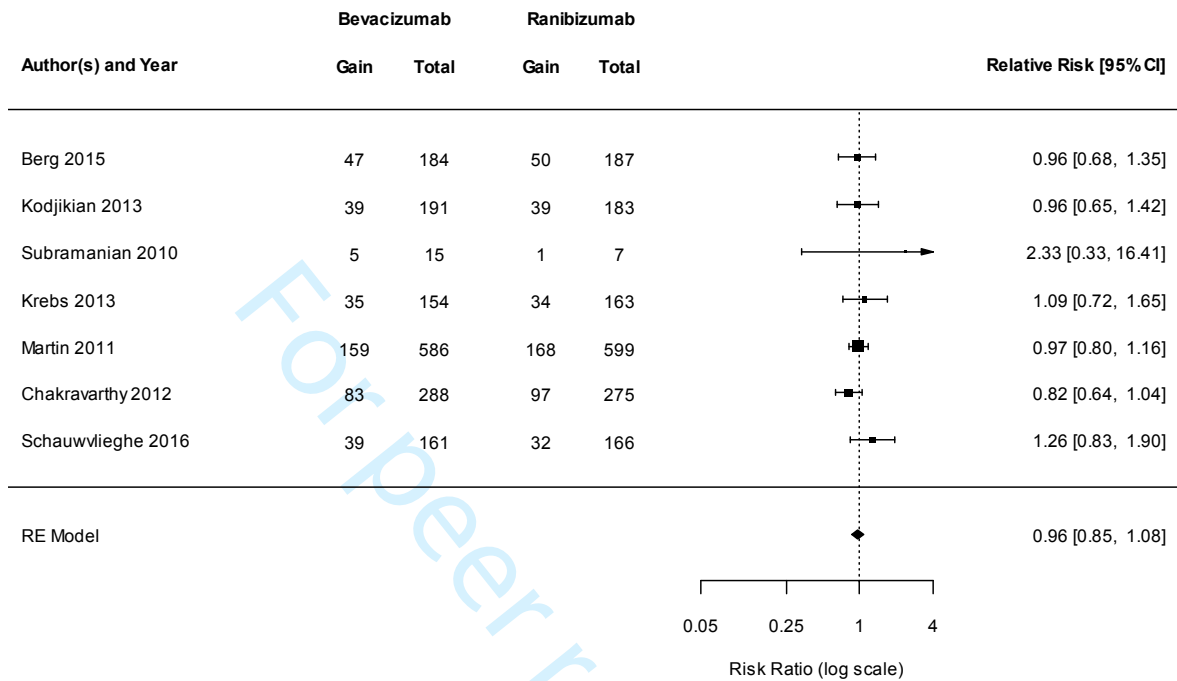
## Appendix 7: Forest plots for primary outcome in choroidal neovascular age related macular degeneration (cn-AMD) population

### A: Vision gain in cn-AMD population

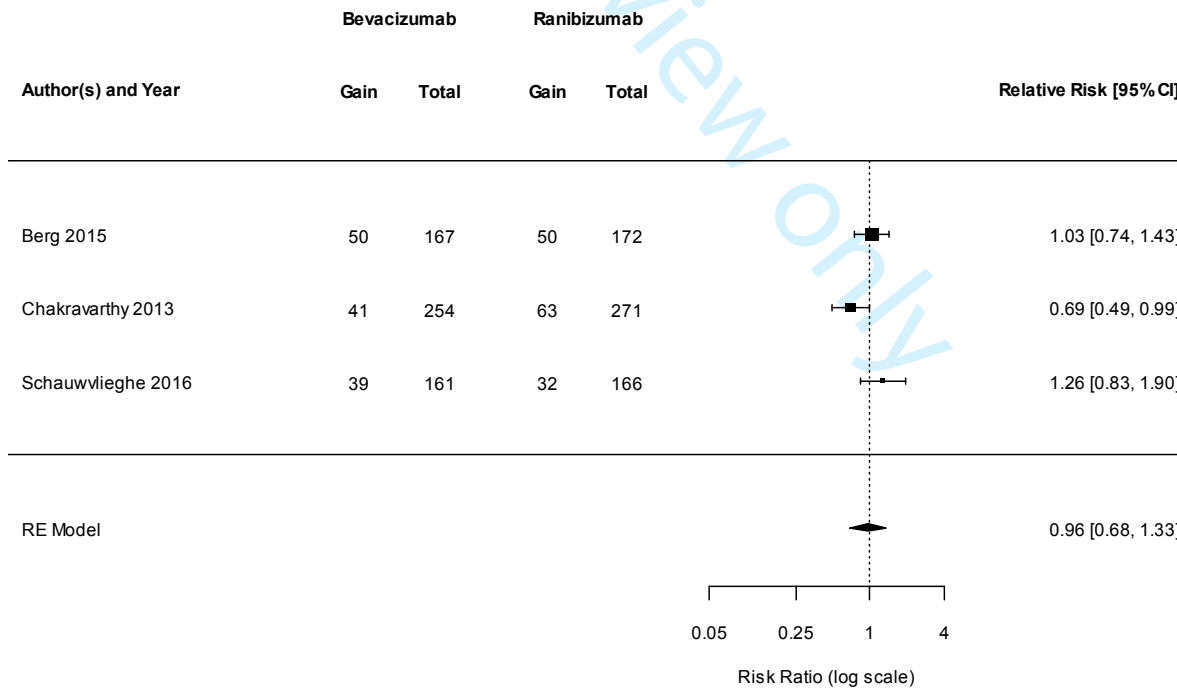


**B: Sensitivity analyses for vision gain in cn-AMD population**

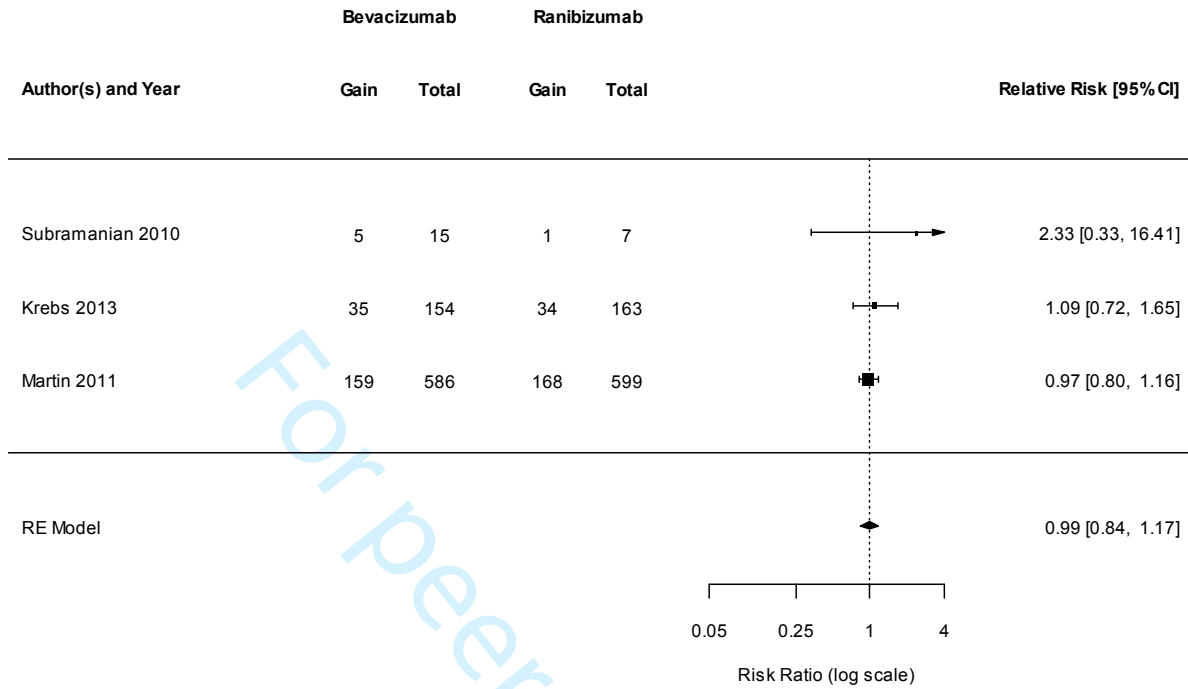
*Sensitivity Analysis: 1 Year Follow-Up*



*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
		<b>cn-AMD</b>							
	# 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)
		<b>DME</b>							
	# of RCTs	1	0	1	0	1	2	0	1
<b>Mean improvement in BCVA letter score (SEM)</b>	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)
		<b>RVO-ME</b>							
	# 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
		<b>m-CNV</b>							
	# 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



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**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

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## Appendix 9: Sensitivity analysis estimates

Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate [Range]	Mean comparator effect estimate <sup>a</sup> [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I <sup>2</sup>
<b>Sensitivity Analyses of Bevacizumab vs. Ranibizumab in choroidal neovascular age-related macular degeneration (cn-AMD)</b>								
<b>Vision gain in BCVA of ≥15 EDTRS letters</b>	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
<b>Vision loss in BCVA of ≥15 EDTRS letters</b>	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
<b>Mean change in BCVA</b>	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%

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Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate[Range ]	Mean comparator effect estimate <sup>a</sup> [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I <sup>2</sup>
	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:**

<sup>a</sup> 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)
<b>cn-AMD (n = 12)</b>				
Schauwvlieghe 2016 <sup>30</sup>	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 <sup>31</sup>	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 <sup>32</sup>	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 $\geq 5$ letters with OCT evidence of fluid in the macula; increase in OCT central retinal thickness of at least 100 $\mu\text{m}$ ; new area of nAMD; new macular haemorrhage; persistent fluid on OCT at least 1 month after the previous intravitreal injection.	No

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Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Chakravarthy 2013 <sup>33</sup>	TX 1: ranibizumab 0.5 mg/0.05 ml	TX 1 & TX 2: 3 monthly injections + monthly injections for 24 months.	Prespecified clinical and OCT criteria for active disease were met.	Yes
	TX 2: bevacizumab 1.25 mg/0.05 ml			
	TX 3: ranibizumab 0.5 mg/0.05 ml	TX 3 & TX 4: 3 monthly injections + repeated 3 monthly injections as needed treatment criteria.		
	TX 4: bevacizumab 1.25 mg/0.05 ml			
Kodjikian 2013 <sup>34</sup>	TX 1: ranibizumab 0.5 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
	TX 2: bevacizumab 1.25 mg/0.05 ml			
Krebs 2013 <sup>35</sup>	TX 1: ranibizumab 0.5 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 µm; new macular haemorrhage; new area of classic CNV; or evidence of persistent fluid on OCT at least 1 month after the previous injection.	Yes
	TX 2: bevacizumab 1.25 mg/0.05 ml			

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Heier 2012 – VIEW 1 <sup>36</sup>	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 <sup>36</sup>	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 <sup>37</sup>	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 <sup>38</sup>	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 <sup>39</sup>	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 <sup>40</sup>	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
<b>DME (n = 3)</b>				
Fouda 2017 <sup>41</sup>	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 <sup>27</sup>	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 <sup>42</sup>	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
<b>RVO-ME (n = 2)</b>				
Scott 2017 <sup>43</sup>	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 <sup>44</sup>	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
<b>m-CNV (n = 2)</b>				
Iacono 2012 <sup>45</sup>	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 <sup>46</sup>	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<sup>a</sup> and Wells 2016<sup>b</sup>)

Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate [Range]	Mean comparator effect estimate <sup>b</sup> [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I <sup>2</sup>
<b>Subgroup Analysis of Anti-VEGF Treatment Effects in Diabetic Macular Edema (DME) According to the DRCR.net RCT</b>								
<b>Aflibercept vs. Ranibizumab</b>								
<b>Vision gain in BCVA of ≥15 EDTRS letters</b>	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	<b>1.30 (1.01, 1.69)</b>	<b>10.1 (1.00, 19.00)</b>	NA
	Participants with baseline BCVA < 69 letters	1	203	0.50	0.67	<b>1.35 (1.06, 1.72)</b>	<b>17.16 (3.79, 30.53)</b>	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
<b>Vision loss in BCVA of ≥15 EDTRS letters</b>	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
<b>Mean change in BCVA (SMD)</b>	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 $\geq$ 69 letters	1	200	8.6 $\pm$ 7.0	7.8 $\pm$ 8.4	NA	-0.7 (-2.9, 1.5)	NA
	Follow-up for 12 months	1	414	11.2 $\pm$ 9.4	13.3 $\pm$ 11.1	NA	<b>2.1 (0.1, 4.2)</b>	NA
	Participants with baseline BCVA < 69 letters	1	203	14.2 $\pm$ 10.6	18.9 $\pm$ 11.5	NA	<b>4.7 (1.4, 8.0)</b>	NA
	Participants with baseline BCVA $\geq$ 69 letters	1	211	8.3 $\pm$ 6.8	8.0 $\pm$ 7.6	NA	-0.4 (-2.3, 1.5)	NA
<b>Bevacizumab vs Aflibercept</b>								
<b>Vision gain in BCVA of <math>\geq</math>15 EDTRS letters</b>	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 $\geq$ 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	<b>0.68 (0.52, 0.89)</b>	<b>-14.0 (-23.00, -4.04)</b>	NA
	Participants with baseline BCVA < 69 letters	1	204	0.41	0.67	<b>0.62 (0.47, 0.81)</b>	<b>-25.49 (-38.72, -12.26)</b>	NA
	Participants with baseline BCVA $\geq$ 69 letters	1	210	0.16	0.18	0.91 (0.5, 1.65)	-1.58 (-11.77, 8.61)	NA
<b>Vision loss in BCVA of <math>\geq</math>15 EDTRS letters</b>	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
<b>Mean change in BCVA (SMD)</b>	Follow-up for 24 months	1	386	10.0 $\pm$ 11.8	12.8 $\pm$ 12.4	NA	<b>-2.7 (-5.2, -0.3)</b>	NA
	Participants with baseline BCVA < 69 letters	1	190	13.3 $\pm$ 13.4	18.1 $\pm$ 13.8	NA	<b>-4.7 (-8.8, -0.5)</b>	NA
	Participants with baseline BCVA $\geq$ 69 letters	1	196	6.8 $\pm$ 8.8	7.8 $\pm$ 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	<b>-3.5 (-1.4, -5.7)</b>	NA
Participants with baseline BCVA < 69 letters	1	204	11.8 ± 12.0	18.9 ± 11.5	NA	<b>-6.5 (-10.1, -2.9)</b>	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

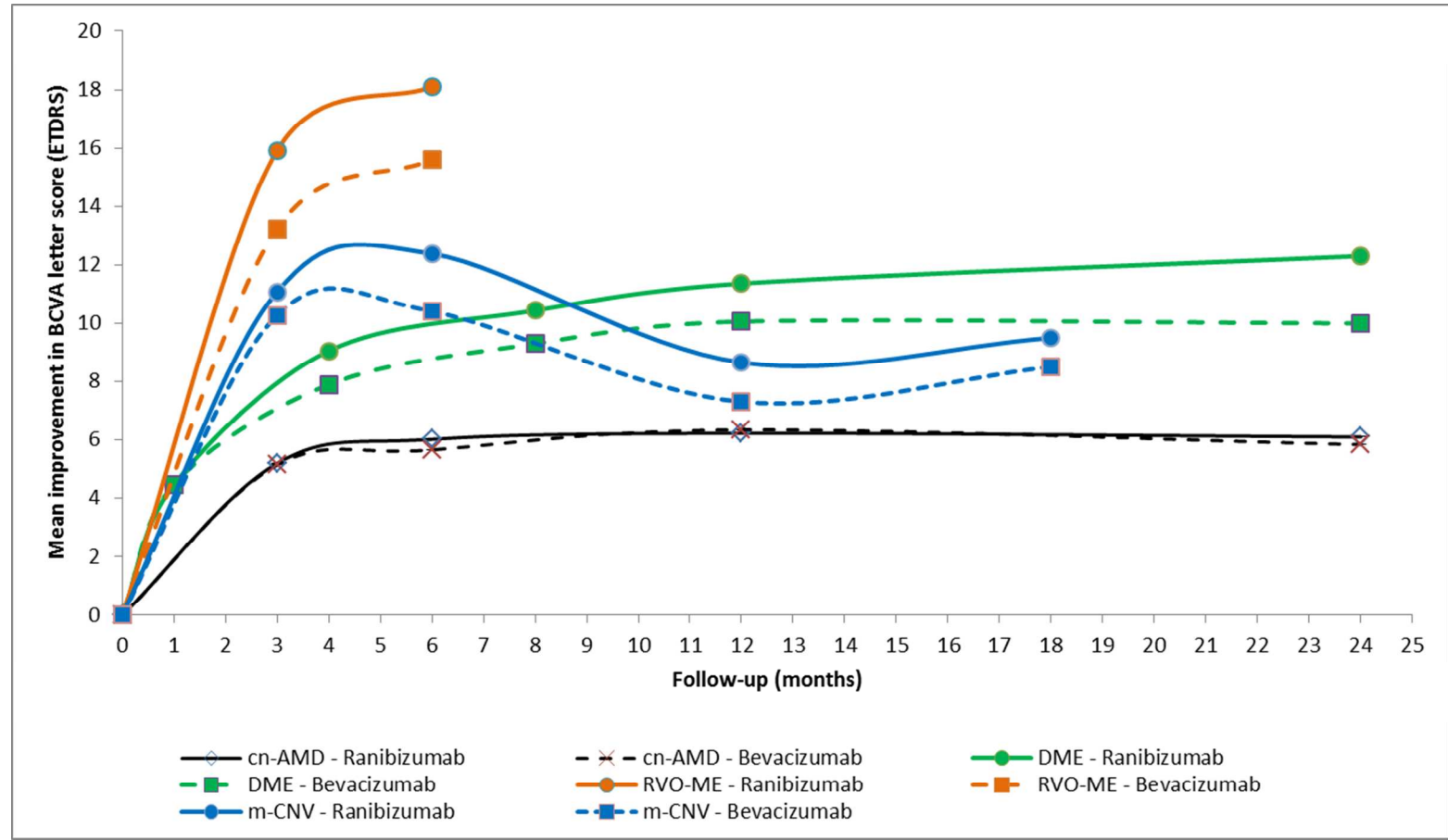
**Footnote:** Bolded estimates indicate statistical significance.

<sup>a</sup> 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.

<sup>b</sup> 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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## PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			

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

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43 38 **Word count:** 300/300 (Abstract), 3955/4000 (Main text), 1 figure, 4 tables, 2 supplementary

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4 **40 ABSTRACT**

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7 **41 Objectives:** To evaluate the comparative effectiveness and safety of intravitreal bevacizumab,  
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10 **42** ranibizumab, and aflibercept for patients with choroidal neovascular age-related macular  
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12 **43** degeneration (cn-AMD), diabetic macular edema (DME), macular edema due to retinal vein  
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14 **44** occlusion (RVO-ME) and myopic choroidal neovascularization (m-CNV).

15  
16  
17 **45 Design:** Systematic review and random-effects meta-analysis.

18  
19 **46 Methods:** Multiple databases were searched from inception to August 17th, 2017. Eligible head-  
20  
21 **47** to-head randomized controlled trials (RCTs) comparing the anti-VEGF drugs in adult patients  
22  
23 **48** aged  $\geq 18$  years with the retinal conditions of interest. Two reviewers independently screened  
24  
25 **49** studies, extracted data and assessed risk of bias.

26  
27  
28 **50 Results:** Nineteen RCTs involving 7459 patients with cn-AMD (n=12), DME (n=3), RVO-ME  
29  
30 **51** (n=2), and m-CNV (n=2) were included. Vision gain was not significantly different in patients  
31  
32 **52** with cn-AMD, DME, RVO-ME, and m-CNV treated with bevacizumab versus ranibizumab.  
33  
34 **53** Similarly, vision gain was not significantly different between cn-AMD patients treated with  
35  
36 **54** aflibercept versus ranibizumab. Patients with DME treated with aflibercept experienced  
37  
38 **55** significantly higher vision gain at 12 months than patients receiving ranibizumab or  
39  
40 **56** bevacizumab, however this difference was not significant at 24 months. Rates of systemic  
41  
42 **57** serious harms were similar across anti-VEGF agents. Post-hoc analyses revealed that an as-  
43  
44 **58** needed treatment regimen (6-9 injections per year) was associated with a mortality increase of  
45  
46 **59** 1.8% (RR: 2.0, [1.2, 3.5], 2 RCTs, 1795 patients) compared to monthly treatment in cn-AMD  
47  
48 **60** patients.



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3 61 **Conclusions:** Intravitreal bevacizumab was a reasonable alternative to ranibizumab and  
4  
5 62 aflibercept in patients with cn-AMD, DME, RVO-ME and m-CNV. The only exception was for  
6  
7 63 patients with DME and low visual acuity (<69 ETDRS letters), where treatment with aflibercept  
8  
9 64 was associated with significantly higher vision gain ( $\geq 15$  ETDRS letters) than bevacizumab or  
10  
11 65 ranibizumab at 12 months; but the significant effects were not maintained at 24 months. The  
12  
13 66 choice of anti-VEGF drugs may depend on the specific retinal condition, baseline visual acuity,  
14  
15 67 and treatment regimen.  
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17  
18

19 68 **Trial registration:** PROSPERO CRD 42015022041  
20  
21  
22 69

23  
24 70 **Keywords:** ranibizumab, bevacizumab, aflibercept, anti-vascular endothelial growth factor, age-  
25  
26 71 related macular degeneration, diabetic macular edema, retinal vein occlusion, myopic choroidal  
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28 72 neovascularization  
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4 73 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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8 74 • We consolidated the evidence for treatment choice of all common retinal conditions,  
9  
10 75 allowing the interpretation of the strength of the evidence of benefits and harms of the anti-  
11  
12 76 VEGF drugs across conditions.  
13  
14 77 • We summarized information regarding treatment regimens (e.g., 3 initial monthly intravitreal  
15  
16 78 injections and as-needed monthly retreatment, treat and extend), as-needed retreatment  
17  
18 79 criteria, and the reconstitution of bevacizumab, and examined the influence of the choice of  
19  
20 80 treatment regimens on the benefits and harms of the anti-VEGF drugs for specific retinal  
21  
22 81 conditions.  
23  
24 82 • We limited our review to English studies, and found that very few RCTs evaluated the anti-  
25  
26 83 VEGF drugs in patients with RVO-ME and m-CNV.  
27  
28 84 • Our sensitivity and subgroup analyses were not specified *a-priori* and should be interpreted  
29  
30 85 with caution.  
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## 86 BACKGROUND

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

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

## 103 METHODS

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

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3 107 recommendations.<sup>16, 17</sup> The report included a meta-analysis of pairwise comparisons of the anti-  
4  
5 108 VEGF drugs for individual retinal conditions, as well as a network meta-analysis to evaluate the  
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7  
8 109 anti-VEGF drugs in cn-AMD patients. This paper summarizes results of the meta-analysis; a  
9  
10 110 separate paper is underway for the network meta-analysis results.

11 111 The current review was conducted using the Cochrane Handbook for Systematic Reviews and  
12  
13 112 reported using the PRISMA statement<sup>18</sup> (Additional file 1). The methods are outlined briefly  
14  
15 113 below, as they are described in greater detail in Additional file 2: Appendix 1 and a related  
16  
17 114 therapeutic review report.<sup>17</sup>

### 115 ***Data Sources and Searches:***

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

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

### 125 ***Study Selection and Outcome Definitions:***

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

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3 128 cn-AMD, DME, RVO-ME or m-CNV. We excluded RCTs comparing anti-VEGF drugs with  
4  
5 129 other comparators, such as photodynamic therapy, intravitreal corticosteroids, and grid laser  
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7  
8 130 photocoagulation (Appendix 1). Due to time and resource constraints, we only included studies  
9  
10 131 published in English.

11  
12  
13 132 Eligible RCTs reported one of the following benefits and harms outcomes: vision gain, defined  
14  
15 133 as a gain in Best-Corrected Visual Acuity (BCVA) letter score of  $\geq 15$  on the Early Treatment  
16  
17 134 Diabetic Retinopathy Study (ETDRS) chart;<sup>21</sup> vision loss, defined as a loss in BCVA letter score  
18  
19 135 of  $\geq 15$ ; mean change in BCVA from baseline; legal blindness (BCVA of 20/200 or worse  
20  
21 136 measured on a standard Snellen chart, or worse than 20/100 visual acuity measured on ETDRS  
22  
23 137 chart); vision-related function according to the 25-item National Eye Institute Visual Function  
24  
25 138 Questionnaire (NEI-VFQ-25);<sup>22</sup> serious adverse events; all-cause mortality; arterial  
26  
27 139 thromboembolic events (TEs); venous TEs; bacterial endophthalmitis; and retinal detachment.  
28  
29  
30 140 All titles/abstracts and potentially relevant full-text articles were screened by two reviewers,  
31  
32 141 independently. Discrepancies were discussed and if necessary, resolved with input from a third  
33  
34 142 reviewer. When multiple reports of the same trial were identified, the main report was included,  
35  
36 143 and the others were treated as companion reports.<sup>23</sup>

#### 144 ***Data Extraction and Quality Assessment:***

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

#### 149 ***Patient and Public Involvement***

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2  
3 150 There was no patient or public involvement in the conduct of this study.  
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6 151 ***Synthesis of study results***  
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9 152 Study results were synthesized with respect to benefits and harms of treatment, treatment  
10  
11 153 regimen (e.g., monthly and as-needed regimens), and trends in BCVA improvement over time.  
12  
13 154 With respect to visual acuity improvement, meta-analyses were conducted with studies reporting  
14  
15 155 BCVA letter score as measured on the ETDRS chart. For studies reporting visual acuity in  
16  
17 156 logMAR and decimal values, the values were converted to approximate ETDRS letter scores,<sup>25</sup>  
18  
19 157 with approximate standard deviations.<sup>26</sup> Pairwise comparisons of drugs were assessed at the  
20  
21 158 longest treatment duration, allowing for the inclusion of trials in the meta-analysis that reported  
22  
23 159 outcome data at different time points. Subgroup analyses were conducted at 12 months and 24  
24  
25 160 months, as these were the most frequently reported time points. A post hoc analysis was  
26  
27 161 conducted to compare different treatment regimens across the drugs. For DME patients,  
28  
29 162 treatment effect estimates were obtained for all patients as well as subgroups based upon baseline  
30  
31 163 BCVA, which were pre-specified in the DRCR.net trial.<sup>27</sup> The meta-analysis was conducted  
32  
33 164 using a random-effects model, as we assumed treatment effects varied across trials. A sensitivity  
34  
35 165 analysis was conducted by restricting results to trials determined to be at low risk of selection  
36  
37 166 bias. Between-study heterogeneity was assessed using the  $I^2$  statistic, with values above 75%  
38  
39 167 indicating substantial heterogeneity.<sup>28</sup>  
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47 168 **RESULTS**  
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50 169 ***Literature search***  
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53 170 After screening 3176 titles/abstracts and 440 full-text articles, 19 head-to-head RCTs of the anti-  
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3 171 VEGF drugs were included, with 7459 patients, including 12 RCTs for cn-AMD, 3 RCTs for  
4  
5 172 DME, 2 RCTs for RVO-ME, and 2 RCTs for m-CNV (Figure 1, Additional file 2: Appendix  
6  
7 173 1).<sup>27, 29-42</sup> Given our inclusion criteria, we excluded RCTs that compared anti-VEGF drugs with  
8  
9 174 placebo or laser photocoagulation.<sup>43-49</sup>

### 13 175 ***Study and patient characteristics***

16 176 Studies were completed between 2010 and 2017 with an average sample size of 393 patients per  
17  
18 177 trial (range: 28, 1240) (Table 1, Additional file 2: Appendix 2-3). The mean age ranged from  
19  
20 178 approximately 60 to 80 years, and females accounted for 5% to 76% of the patients. The average  
21  
22 179 follow-up duration was 13 months (range: 6-24 months). RCTs were conducted in Europe (n=8),  
23  
24 180 North America (n=5), Asia (n=4), Africa (n=1) and across multiple continents (n=1); most were  
25  
26 181 multi-centre RCTs (n=13), in addition to 6 single-centre RCTs.

### 31 182 ***Risk of bias assessment***

34 183 Random sequence generation and allocation concealment were unclear for 12/19 (63.2%) and  
35  
36 184 9/19 (47.4%) of the included RCTs, respectively, suggesting the potential for selection bias  
37  
38 185 (Additional file 2: Appendix 4-5). The RCTs were at low risk with respect to blinding of  
39  
40 186 participants and trial personnel 18/19 (94.7%), blinding of outcome assessment 18/19 (94.7%),  
41  
42 187 incomplete outcome data 13/19 (68.4%), and selective reporting 13/19 (68.4%). Two of the 19  
43  
44 188 RCTs (10.5%) were industry-funded.<sup>38</sup>

### 48 189 ***Patients with cn-AMD***

52 190 *Comparative effectiveness of bevacizumab and ranibizumab*

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3 191 Results from 10 RCTs (3302 patients) showed that approximately 22% of patients attained vision  
4  
5 192 gain of  $\geq 15$  BCVA letter scores with treatment, and patients treated with bevacizumab were as  
6  
7 193 likely to attain vision gain as those treated with ranibizumab (Risk Ratio (RR): 1.05; [95%  
8  
9 194 confidence interval (CI), 0.93, 1.19], Table 2, Additional file 2: Appendix 6-7). Over an average  
10  
11 195 treatment duration of 16 months, approximately 94% of patients maintained their vision, with no  
12  
13 196 statistical difference between patients treated with bevacizumab or ranibizumab (RR of vision  
14  
15 197 loss: 0.91 [95% CI, 0.70, 1.19]). Patients treated with bevacizumab or ranibizumab gained an  
16  
17 198 average of 7 letters in terms of mean BCVA with no statistical difference between the drugs  
18  
19 199 (mean difference [MD] 0.03 letters [95% CI, -1.02, 1.08]). Approximately 2-4% patients treated  
20  
21 200 with bevacizumab or ranibizumab became legally blind (RR: 2.04 [95% CI, 0.32 to 12.50], 3  
22  
23 201 trials, 1823 patients). Overall, the results were consistent across the 10 trials and did not change  
24  
25 202 with the sensitivity analyses restricted to trials determined to be at low risk of selection bias and  
26  
27 203 with different follow-up lengths (Additional file 2: Appendix 6, 8-9).

#### 204 *Comparative effectiveness of aflibercept and ranibizumab*

205 Results from 2 RCTs (1815 patients; Table 2, and Additional file 2: Appendix 6) showed that  
206 approximately 32% of patients attained vision gain with treatment, and patients treated with  
207 aflibercept were as likely to attain vision gain as patients treated with ranibizumab (RR: 0.99  
208 [95% CI, 0.81 to 1.22]). Over an average assessment and treatment duration of 12 months,  
209 approximately 95% of patients maintained their vision, and aflibercept patients were as likely to  
210 maintain vision as ranibizumab patients (RR of vision loss: 0.90 [95% CI, 0.60 to 1.35]). With  
211 respect to mean BCVA, patients gained on average 9 letters (MD: -0.05 [95% CI, -2.5, 2.4]).  
212 Compared to baseline, patients gained some visual-related function, with an average of 5 points



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3 213 on the NEI-VFQ-25 questionnaire (MD: 2.2 [95% CI, -0.6, 5.1]).  
4  
5

6 214 *Comparative effectiveness of bevacizumab and aflibercept*  
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9  
10 215 There were no RCTs that directly compared bevacizumab and aflibercept (Table 2, and

11  
12 216 Additional file 2: Appendix 6). Regarding BCVA change, the *mean difference between*

13  
14 217 *bevacizumab and ranibizumab was -0.03 (95% CI: -1.08, 1.02) whereas the mean difference*

15  
16 218 *between aflibercept and ranibizumab was -0.05 (95% CI: -2.5, 2.4), suggesting a mean*

17  
18 219 *difference between bevacizumab and aflibercept of 0.02 (95% CI: -2.60, 2.64)*<sup>50</sup>. For vision gain,

19  
20 220 the corresponding risk ratio estimate was 0.95 (95% CI: 0.84, 1.07) for bevacizumab versus

21  
22 221 ranibizumab and 0.99 (95% CI: 0.81, 1.22) for bevacizumab versus ranibizumab, suggesting a

23  
24 222 risk ratio estimate of 0.96 (95% CI: 0.75, 1.22) between bevacizumab and aflibercept.  
25  
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27

28  
29 223 *Treatment regimens*  
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32 224 Additional file 2: Appendix 10 provides detailed information regarding the treatment regimens in

33  
34 225 the included trials, the as-needed re-treatment criteria and the reconstitution of bevacizumab for

35  
36 226 intravitreal injections. The treatment regimens varied widely, and are summarized in Table 3

37  
38 227 along with the mean number of injections per year for each treatment regimen. The number of

39  
40 228 reported treatment regimens varied by condition (cn-AMD (n=6), DME (n=3), RVO-ME (n=2),

41  
42 229 and m-CNV (n=1)). In cn-AMD patients, the two most commonly reported regimens for

43  
44 230 bevacizumab and ranibizumab included monthly injections (~11 injections/year) and 3 monthly

45  
46 231 injections followed by as-needed treatment (~6 injections/year). Aflibercept was most commonly

47  
48 232 administered using a monthly regimen (~11 injections/year).  
49  
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51  
52 233 Results of our posthoc analysis comparing as-needed versus monthly treatment in cn-AMD  
53  
54

1  
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3 234 patients are summarized in Table 4. The as-needed treatment regimen with ranibizumab or  
4  
5 235 bevacizumab was less effective than the monthly regimen in improving mean BCVA (MD: -1.9  
6  
7 236 letters [95% CI, -3.3 to -0.5 letters], 2 RCTs, 1622 patients) and vision gain (RR: 0.73 [95% CI,  
8  
9 237 0.55 to 0.95]). When the regimens were assessed for non-inferiority at 1 year with an inferiority  
10  
11 238 margin of 5 points, monthly bevacizumab was equivalent to monthly ranibizumab (MD: -0.5  
12  
13 239 [95% CI, -3.9, 2.9]), as-needed bevacizumab was equivalent to as-needed ranibizumab (MD: -0.8  
14  
15 240 [95% CI, -4.1, 2.5]), as-needed ranibizumab was equivalent to monthly ranibizumab (MD: -1.7  
16  
17 241 [95% CI, -4.7, 1.3]) but monthly bevacizumab was not equivalent to as-needed bevacizumab  
18  
19 242 (MD: -2.1 [95% CI, -5.7, 1.6]).<sup>51</sup> Compared to the monthly regimen, the as-needed regimen was  
20  
21 243 associated with a significant increase in mortality of 1.8% (95% CI, 0.1% to 3.4%, meta-analysis  
22  
23 244 of mortality data reported in 2 RCTs, 1795 patients) [RR, 2.0; 95% CI, 1.2 to 3.5].<sup>35, 51</sup>

### 245 *Harms*

246 Over an average of 14 months (range: 12-24 months), mortality was reported in 4% and 3% of  
247 patients treated with bevacizumab or ranibizumab, respectively (RR: 1.14 [95% CI, 0.72 to  
248 1.79], 6 RCTs, 2941 patients, Additional file 2: Appendix 6). Serious adverse events were  
249 reported in 19% and 18% of patients treated with bevacizumab or ranibizumab, respectively  
250 (RR: 1.09 [95% CI, 0.93 to 1.27], 5 RCTs, 3026 patients). Arterial thromboembolic events were  
251 reported in 4% and 3% of patients treated with bevacizumab or ranibizumab, respectively (RR:  
252 0.86 [95% CI, 0.51, 1.47], 4 RCTs, 2033 patients). Venous thromboembolic events, bacterial  
253 endophthalmitis and retinal detachment were reported in <1% of patients treated with either  
254 drug. In the trials evaluating aflibercept and ranibizumab, arterial thromboembolic events were  
255 reported in 2% of patients treated with aflibercept or ranibizumab (RR: 0.96 [95% CI, 0.45,

256 2.04], 2 RCTs, 1818 patients), and venous thromboembolic events were reported in <1% of  
257 patients treated with either drug. Data on other harms were not available.

### 258 ***Patients with DME***

#### 259 *Comparative effectiveness of ranibizumab, bevacizumab and aflibercept*

260 Results from the trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net trial,  
261 620 patients) showed that over 2 years of treatment, patients were as likely to attain vision gain  
262 with ranibizumab (37%), bevacizumab (35%), or aflibercept (39%) - bevacizumab versus  
263 ranibizumab: RR: 0.94 [95% CI, 0.72, 1.23]; aflibercept versus bevacizumab: RR: 1.06 [95% CI,  
264 0.80, 1.38]; and aflibercept versus ranibizumab: RR: 1.06 [95% CI, 0.82, 1.37]; Table 2). Over 2  
265 years of treatment, approximately 98% of patients maintained their vision with all 3 drugs.  
266 Besides the DRCR.net RCT, two small single-centered RCTs reported BCVA data, one  
267 comparing aflibercept with ranibizumab<sup>14</sup>, and another comparing bevacizumab and  
268 ranibizumab<sup>31</sup>. Patients' mean BCVA improved by approximately 13 letters with aflibercept, 10  
269 letters with bevacizumab and 12 letters with ranibizumab (aflibercept versus ranibizumab: MD,  
270 1.4 [95% CI, -1.6, 4.3]; bevacizumab versus aflibercept: MD, -2.7 [95% CI, -5.2 to -0.3]; and  
271 bevacizumab versus ranibizumab: MD, -2.0 [95% CI, -3.9 to -0.1], Table 2).

272 The DRCR.net trial reported results stratified by baseline visual acuity at 12 and 24 months  
273 (Appendix 11). In patients with high baseline visual acuity (BCVA  $\geq$  69 letters), approximately  
274 16% of patients treated with bevacizumab, 15% of patients treated with ranibizumab and 18% of  
275 patients treated with aflibercept attained vision gain at 12 months (RR of bevacizumab versus  
276 aflibercept: 0.91 [95% CI: 0.50, 1.65]; RR of aflibercept versus ranibizumab: 1.18 [95% CI:

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2  
3 277 0.64, 2.17]). Vision gain at 24 months was 17% with bevacizumab, 19% with ranibizumab and  
4  
5 278 20% with aflibercept (RR of bevacizumab versus aflibercept: 0.84 [95% CI: 0.47, 1.52]; RR of  
6  
7 279 aflibercept versus ranibizumab: 1.10 [95% CI: 0.63, 1.92]). In patients with low baseline visual  
8  
9 280 acuity (BCVA < 69 letters), approximately 41% of patients treated with bevacizumab, 50% of  
10  
11 281 patients treated with ranibizumab and 67% of patients treated with aflibercept attained vision  
12  
13 282 gain at 12 months (RR of bevacizumab versus aflibercept: 0.62 [95% CI: 0.47, 0.81]; RR of  
14  
15 283 aflibercept versus ranibizumab: 1.35 [95% CI: 1.06, 1.72]). At 24 months, vision gain was 52%  
16  
17 284 with bevacizumab, 55% with ranibizumab and 58% with aflibercept (RR of bevacizumab versus  
18  
19 285 aflibercept: 0.90 [95% CI: 0.69, 1.16]; RR of aflibercept versus ranibizumab: 1.05 [95% CI:  
20  
21 286 0.82, 1.35]).  
22  
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26

### 27 *Treatment regimen*

28  
29  
30 288 With respect to treatment regimen, the DRCR.net trial treated patients initially with monthly  
31  
32 289 injections until stable visual acuity within 6 months, followed by as-needed treatment  
33  
34 290 (Additional file 2: Appendix 10).<sup>52</sup> The median number of injections administered over a one-  
35  
36 291 year period was 10 in the bevacizumab group, 9 in the aflibercept group, and 10 in the  
37  
38 292 ranibizumab group (Table 3).<sup>52</sup> In the second year, the median number of injections was: 6, 5,  
39  
40 293 and 6 in the bevacizumab, aflibercept, and ranibizumab groups, respectively.<sup>53</sup> Two smaller trials  
41  
42 294 both started treatment with 3 monthly intravitreal injections, followed by monthly re-treatment  
43  
44 295 with persistence of macular edema, thickening of central macular or worsening of visual acuity  
45  
46 296 (Table 3 and Appendix 10 – Summary of treatment protocols).<sup>14, 31</sup>  
47  
48  
49  
50  
51

### 52 *Harms*

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3 298 After 24 months of treatment in the DRCR.net trial,<sup>27</sup> mortality was reported in approximately  
4  
5 299 6% of bevacizumab patients, 2% of aflibercept patients and 5% of ranibizumab patients  
6  
7  
8 300 (Additional file 2: Appendix 6). Serious adverse events were reported in 21% of bevacizumab  
9  
10 301 patients, 27% of aflibercept patients, and 25% of ranibizumab patients. Arterial thromboembolic  
11  
12 302 events were reported in 4%, 3%, and 5%, of patients treated with bevacizumab, aflibercept, and  
13  
14 303 ranibizumab, respectively. Bacterial endophthalmitis and retinal detachments were reported in  
15  
16  
17 304 <1% of patients treated with any of the drugs.  
18  
19

### 20 305 *Patients with RVO-ME*

#### 21 22 23 306 *Comparative effectiveness of ranibizumab, bevacizumab, and aflibercept*

24  
25  
26  
27 307 Results from one randomized, double-blind, controlled and non-inferiority trial conducted in  
28  
29 308 India (including 77 patients with ME due to branch RVO) showed that approximately 59% of  
30  
31 309 patients attained vision gain with bevacizumab and ranibizumab treatment, and no statistical  
32  
33 310 difference was observed between the drugs (RR: 1.0 [95% CI, 0.68 to 1.45]; Table 2 and  
34  
35  
36 311 Additional file 2: Appendix 8).<sup>32</sup> With respect to mean BCVA, patients treated with either drug  
37  
38 312 gained an average of 16 letters (MD -2.5 [95% CI, -8.0 to 5.0]).  
39  
40  
41 313 Results from the SCORE2 randomized non-inferiority trial conducted in 66 centers in the United  
42  
43 314 States (348 patients with ME due to central RVO) showed that approximately 61% of patients  
44  
45 315 treated with bevacizumab or aflibercept attained vision gain, with no statistical difference  
46  
47  
48 316 between the drugs (RR: 1.06 [95% CI, 0.91 to 1.25]; Table 2).<sup>13</sup> With respect to mean BCVA,  
49  
50 317 patients treated with either drug gained an average of 19 letters (MD 1.52 [95% CI, -1.2 to 4.2]).  
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#### 53 318 *Treatment regimens*

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3 319 In the SCORE2 trial, patients were treated with monthly intravitreal injections for 6 months, with  
4  
5 320 a mean number of 5.8 injections in patients treated with bevacizumab or aflibercept (Table 3 and  
6  
7 321 Additional file 2: Appendix 11).<sup>13</sup> In the other trial, patients were treated with one initial  
8  
9 322 intravitreal injection and then as-needed monthly re-treatment over 6 months, with a mean  
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11 323 number of 3 injections in patients treated with bevacizumab or ranibizumab.<sup>13, 32</sup>  
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#### 15 324 *Harms*

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18 325 Serious adverse events were reported in 3% of bevacizumab patients and 5% of ranibizumab  
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20 326 patients (RR: 0.5 [95% CI, 0.05 to 5.26], 1 RCT, 74 patients; Additional file 2: Appendix 8).<sup>32</sup>  
21  
22 327 Serious adverse events were reported in 8% of the patients treated with bevacizumab or  
23  
24 328 aflibercept over 6 months (RR: 0.99 [95% CI, 0.49 to 2.00], 1 RCT, 362 patients).<sup>13</sup>  
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#### 29 329 *Patients with m-CNV*

##### 30 31 32 330 *Comparative effectiveness of ranibizumab and bevacizumab*

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35 331 Two small RCTs both conducted in Italy evaluated ranibizumab and bevacizumab for patients  
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37 332 with m-CNV. Results from one RCT (32 patients) showed that 62% of patients treated with  
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39 333 bevacizumab and 56% of patients treated with ranibizumab attained vision gain (RR: 1.11 [95%  
40  
41 334 CI, 0.63, 1.96], 1 RCT; Table 2 and Additional file 2: Appendix 11).<sup>30</sup> The other RCT (55  
42  
43 335 patients) only report BCVA results.<sup>29</sup> With respect to mean BCVA, patients treated with  
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45 336 bevacizumab gained 12 letters and patients treated with ranibizumab gained 13 letters (MD: -1.3  
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47 337 [95% CI, -6.5 to 4.0], 2 RCTs, 80 patients).<sup>29, 30</sup> The included trials did not report data on harms.  
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#### 52 53 338 *Treatment regimens*

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3 339 Both trials evaluated ranibizumab and bevacizumab with patients receiving one monthly  
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5 340 intravitreal injection and as-needed monthly re-treatment for 18 and 6 months, respectively, with  
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8 341 a mean number of 3.1 injections per year in patients treated with bevacizumab and 2.4 injections  
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10 342 in patients treated with ranibizumab (Table 3 and Additional file 2: Appendix 6).<sup>29, 30</sup>  
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### 13 343 **DISCUSSION**

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16 344 This systematic review synthesized results from 19 RCTs to evaluate the comparative  
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18 345 effectiveness and safety of intravitreal bevacizumab, ranibizumab, and aflibercept for patients  
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20 346 with cn-AMD, DME, RVO-ME and m-CNV. Intravitreal bevacizumab was as effective as  
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22 347 ranibizumab in patients with cn-AMD, DME, RVO-ME, and m-CNV for the outcomes we  
23  
24 348 examined. Ranibizumab was as effective as aflibercept in patients with cn-AMD.  
25  
26 349 In patients with DME that were treated for 2 years, vision gain was equally likely to be attained  
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28 350 with aflibercept, ranibizumab or aflibercept. In the first year of treatment, however, patients  
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30 351 treated with aflibercept were more likely to attain vision gain than patients treated with  
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32 352 ranibizumab or bevacizumab - differential effects that were observed mainly in patients with  
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34 353 initial BCVA < 69 letter scores (equivalent to 20/50 or worse) but not observed in patients with  
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36 354 initial BCVA  $\geq$  69 letter scores (equivalent to 20/40 or better) based on the results from the sub-  
37  
38 355 group analyses. Rates of systemic serious harms were similarly low among the anti-VEGF drugs,  
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40 356 across the retinal conditions. None of the included RCTs were designed with sufficient statistical  
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42 357 power to detect significant differences between the treatments with respect to the incidence of  
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44 358 harms. In our post-hoc analysis, cn-AMD patients and compared to monthly treatment, an as-  
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46 359 needed treatment regimen (i.e., 6 to 9 monthly injections per year) was significantly associated  
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48 360 with a small loss in visual acuity, but a significant increase in mortality risk of 1.8% (RR: 2.0  
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3 361 [95% CI, 1.2, 3.5]).  
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6 362 Results from the CATT and IVAN trials showed that relative to monthly treatment, patients with  
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8 363 cn-AMD receiving as-needed treatment experienced a significant increase in risk of mortality.  
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10 364 Whether there are any biological explanations for the increased risk of mortality associated with  
11  
12 365 fewer monthly injections is unclear and this finding may have been attributable to chance. As  
13  
14 366 such, further research should be conducted to verify this result. In DME, RVO-ME and m-CNV  
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16 367 trials, patients tended to receive fewer monthly injections per year (Table 3). None of the trials in  
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18 368 DME, RVO-ME and m-CNV patients evaluated a monthly treatment regimen, and therefore the  
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20 369 safety risk between as-needed and monthly regimens could not be evaluated. This requires  
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22 370 further study.  
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28 371 Additional file 2: Appendix 12 displays the mean change in BCVA over time in patients treated  
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30 372 with bevacizumab or ranibizumab. For all of the retinal conditions, patients showed  
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32 373 improvement in mean BCVA by 3-6 months with initial monthly injections, and maintained a  
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34 374 plateau to 24 months in the treatment of cn-AMD patients (average improvement of 6 letters),  
35  
36 375 DME patients (8 letters), RVO-ME patients (16 letters), and m-CNV patients (11 letters).  
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38 376 Comparative outcomes beyond 6 months in patients with RVO-ME and m-CNV were lacking  
39  
40 377 and as such, long-term comparative data of anti-VEGF drugs in these patients are needed.  
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42 378 Our findings are consistent with findings from previous systematic reviews. A meta-analysis of 6  
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44 379 head-to-head trials concluded that bevacizumab and ranibizumab had equivalent efficacy with  
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46 380 respect to visual acuity in cn-AMD patients.<sup>11</sup> A meta-analysis of five RCTs suggested no  
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48 381 differences in effectiveness between ranibizumab and bevacizumab in DME patients.<sup>54</sup> Other  
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50 382 reviews in patients with RVO-ME and m-CNV came to similar conclusions.<sup>9, 10, 55, 56</sup> Although  
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3 383 findings were consistent with those in these recent reviews, our review serves as an update (with  
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5 384 the inclusion of data up to 2017) while also examining the additional factor of treatment regimen.  
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7 385 There are several limitations worth noting. First, none of our sensitivity and subgroup analyses  
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9 386 were specified *a-priori* and as such, these results should be interpreted with caution. This also  
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11 387 pertains to our post-hoc analysis on treatment regimen. Secondly, we limited our review to  
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13 388 English studies due to time and resources constraints. We believe, however, that the impact of  
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15 389 the restrictions is small since our findings are consistent with previous systematic reviews that  
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17 390 included RCTs reported in all languages, evaluating the same anti-VEGF drugs for specific  
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19 391 retinal conditions,<sup>11, 54, 57</sup> and results were consistent across studies, so the impact of including  
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21 392 additional studies reported in other languages, if any, would be insignificant. We only identified  
22  
23 393 a few RCTs evaluating the anti-VEGF drugs in patients with DME, RVO-ME and m-CNV. We  
24  
25 394 did not include ziv-aflibercept (a low-cost anti-VEGF alternative to aflibercept and  
26  
27 395 bevacizumab<sup>58</sup>), the old anti-VEGF pegaptanib, or the newest anti-VEGF brolucizumab.  
28  
29 396 Although the rates of reported adverse events were similar across the anti-VEGF drugs, the  
30  
31 397 assessment of harms using comparative trial data is limited. We excluded RCTs which  
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33 398 randomized eyes (instead of patients) since the reported analyses failed to adjust for the  
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35 399 correlation between the outcomes of eyes from the same individuals.<sup>59</sup> Similarly, we also  
36  
37 400 excluded one quasi-randomized trial,<sup>60</sup> because we focused on randomized studies.  
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## 401 **CONCLUSIONS**

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

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3 405 associated with significantly higher vision gain ( $\geq 15$  ETDRS letters) than bevacizumab or  
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5 406 ranibizumab at 12 months; but the significant effects were not maintained at 24 months. The  
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7 407 choice of anti-VEGF drug may depend on specific retinal conditions, baseline visual acuity, and  
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9 408 treatment regimen.  
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For peer review only

## 409 LIST OF ABBREVIATIONS

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

## 416 ACKNOWLEDGEMENTS

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

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6 428 BP screened titles, abstracts, and full-text articles; abstracted and cleaned data, conducted quality  
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10 430 drafted the protocol; screened titles, abstracts, and full-text articles; abstracted and cleaned data;  
11  
12 431 conducted quality assessment; and helped draft and revise the manuscript. TL screened titles,  
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14 432 abstracts, and full-text articles; abstracted and cleaned data; conducted quality assessment;  
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16 433 helped conduct meta-analysis; and reviewed the manuscript. EL screened titles, abstracts, and  
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18 434 full-text articles; abstracted and cleaned data; conducted quality assessment; and reviewed the  
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22 436 TR helped with conceptualizing the research design, drafting and revising the protocol,  
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24 437 interpretation of data; and reviewed the manuscript. GJ helped draft and revise the protocol;  
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26 438 screened titles, abstracts, and full-text articles; abstracted data; conducted quality assessment;  
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3 449 ACT conceptualized the research and design; drafted the protocol; obtained funding; assisted  
4  
5 450 with data acquisition and interpretation; and drafted and revised the manuscript. Authors ACT  
6  
7 451 and BP had full access to all the data in the study and takes responsibility for the integrity of the  
8  
9 452 data and the accuracy of the data analysis.  
10  
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### 13 453 **FUNDING**

14  
15  
16 454 This work was supported by the Canadian Institutes of Health Research/Drug Safety and  
17  
18 455 Effectiveness Network (CIHR/DSEN). SES is funded by a Tier 1 Canada Research Chair in  
19  
20 456 Knowledge Translation. ACT is funded by a Tier 2 Canada Research Chair in Knowledge  
21  
22 457 Synthesis. The therapeutic review was commissioned by the Canadian Agency for Drugs and  
23  
24 458 Technology in Health (CADTH) and funded by a grant from the Canadian Institutes of Health  
25  
26 459 Research Drug Safety and Effectiveness Network. The funders had no role in design and conduct  
27  
28 460 of the study; collection, management, analysis, and interpretation of the data; preparation,  
29  
30 461 review, or approval of the manuscript; and decision to submit the manuscript for publication.  
31  
32  
33  
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### 36 462 **COMPETING INTERESTS**

37  
38  
39 463 All authors declare no competing interests.  
40  
41

### 42 464 **PROVENANCE AND PEER REVIEW**

43  
44  
45 465 Not commissioned; externally peer reviewed.  
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3 466 **DATA SHARING STATEMENT**  
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6 467 All datasets generated and/or analysed during the current study are available from the  
7  
8 468 corresponding author on reasonable request.  
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12 469 **MEETING PRESENTATION**  
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14  
15 470 The data from the original therapeutic review was presented by ACT and SMT to the Canadian  
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17 471 Drug Expert Committee in Ottawa, Ontario, on Nov 17<sup>th</sup>, 2015.  
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3 680 **FIGURE LEGENDS**  
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6 681 *Figure 1. Study Flow*  
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TABLE 1. SUMMARY STUDY CHARACTERISTICS

Study Characteristic	Total No. of trials included (n=19) <sup>a</sup> (%)	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) (%)
<b>Year of publication</b>					
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)
<b>Geographic region</b>					
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)
<b>Setting</b>					
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)
<b>Follow-up duration</b>					
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:**

<sup>a</sup> 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 <sup>a</sup>	# of RCTs (# of patients)	Baseline ETDRS letters <sup>b</sup> ~Snellen equivalent	Treatment Effect Mean (Range) <sup>b</sup>	Comparator effect Mean (Range) <sup>b</sup>	Risk Ratio or Mean Difference Estimate (95% CI)	I <sup>2c</sup>
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:**

<sup>a</sup> In terms of outcomes, vision gain was defined as a gain in BCVA of  $\geq 15$  EDTRS letters, vision loss of  $\geq 15$  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.

<sup>b</sup> Mean (range) were derived across control groups of the included RCTs.

<sup>c</sup>  $I^2 < 75$  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) <sup>a</sup>
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 <sup>b</sup>
	3 initial monthly treatment and as-needed treatment (every 2 months) with aflibercept	2	6.9 <sup>b</sup>
	DME	3 initial monthly treatments + as-needed treatment (every month) with ranibizumab	1
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 <sup>c</sup>
As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment		1	10 <sup>c</sup>



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	(every month) with bevacizumab		
	As-needed treatment till stable visual acuity (up to 6 months) + as-needed treatment (every month) with aflibercept	1	9 <sup>c</sup>
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:**

<sup>a</sup>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.  
<sup>b</sup>Value was reported once for both trials in Heier et al. 2012.  
<sup>c</sup>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 <sup>a</sup> , # of patients	Baseline ETDRS letters <sup>b</sup> and Snellen equivalent	As-needed regimen Mean (Range) <sup>b</sup>	Monthly Regimen Mean (Range) <sup>b</sup>	Risk Ratio or <i>Mean Difference</i> Estimate (95% CI)	I <sup>2c</sup>
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:**

<sup>a</sup> CATT and IVAN trials. (Martin, 2011; Chakravarthy 2013)

<sup>b</sup> Mean (range) were derived across control groups of the included RCTs.

<sup>c</sup> I<sup>2</sup> <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.

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4 **682 ADDITIONAL FILES**

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7 **683 Additional File 1: PRISMA Checklist**

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9 **684 Additional File 2: Supplementary Online Content**

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11 **685 Appendix 1: Detailed methods**

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13 **686 Appendix 2: Detailed study characteristics**

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15 **687 Appendix 3: Detailed patient characteristics**

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19 **689 Appendix 5: Risk of bias results**

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23 **691 Appendix 7: Forest plots for primary outcome in choroidal neovascular age related macular**  
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28 **692 degeneration (cn-AMD) population**

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30 **693 Appendix 8: Summary data used in risk of bias results**

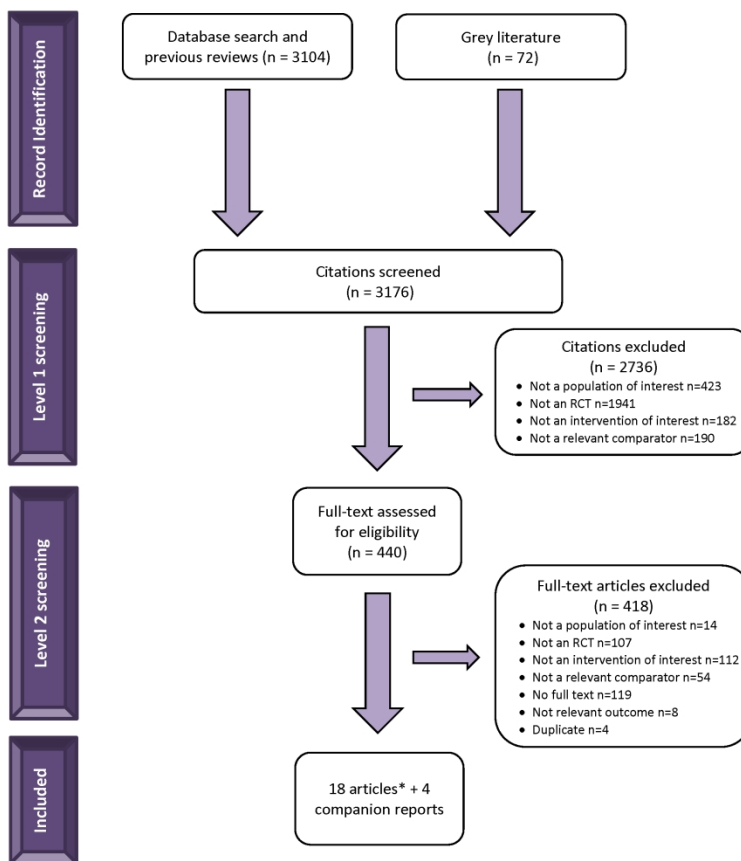
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32 **694 Appendix 9: Sensitivity analysis estimates**

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34 **695 Appendix 10: Summary of anti-VEGF treatment protocols**

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36 **696 Appendix 11: Summary of results from the DRCR.net trial (Wells 2015<sup>a</sup> and Wells 2016<sup>b</sup>)**

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38 **697 Appendix 12: Mean change in best-corrected visual acuity letter scores over time in patients**  
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42 **698 treated with bevacizumab or ranibizumab**

FIGURE 1: STUDY FLOW



\*18 articles describing 19 randomized controlled trials

Figure 1. Study Flow

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## PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			

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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
<b>FUNDING</b>			
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

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## 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.<sup>1</sup> 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.<sup>2</sup>

### *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 17<sup>th</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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-vitreous 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).<sup>5</sup>

- Populations: patients  $\geq 18$  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  $\geq 15$  letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart,
2. Vision loss, defined as a loss in BCVA of  $\geq 15$  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.<sup>6</sup> The Snellen chart is the current standard for measurement of visual acuity in clinical practice.<sup>6-8</sup> The ETDRS chart is the 'gold standard' for measuring visual acuity in clinical trials.<sup>6</sup> 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  $\pm 5$  to 16.5 letters in normal patients.<sup>9 10</sup> The test-retest variability of the ETDRS charts ranges from  $\pm 3.5$  to 10 letters.<sup>11</sup> A change of at least 10 letters (or two lines) is required to capture a true clinical

1  
2  
3 change in visual acuity.<sup>6 12</sup> With respect to vision-related function, we abstracted data from the 25-item National  
4 Eye Institute Visual Function Questionnaire (NEI VFQ-25), which is a self-reported survey questionnaire that  
5 assesses the influence of visual impairment on health-related quality of life.<sup>13</sup> Changes in the NEI VFQ overall  
6 scores of 10 points or more are associated with clinically relevant changes in vision.<sup>14</sup>  
7

### 8 ***Study selection***

9  
10 Citations from the literature search were imported into an online systematic review software.<sup>15</sup> Also imported were  
11 the inclusion criteria, which were used for level-1 screening of citations (titles/abstracts) and level-2 screening of  
12 potentially relevant full-text articles. The 14 members of the review team underwent two training exercises; each  
13 involved a random sample of 50 citations, which were screened independently by all team members. Level-1  
14 screening proceeded after 80% agreement had been achieved among the reviewers on the second training exercise.<sup>16</sup>  
15 <sup>17</sup> Paired reviewers conducted the level-1 screening of each citation, independently. The estimated frequency of  
16 disagreement was 8%, which was resolved by a third reviewer. We retrieved the full-text articles of potentially  
17 relevant citations identified by at least one reviewer for level-2 screening. The team underwent a training exercise  
18 using a random sample of 20 full-text articles, which resulted in 70% agreement. Paired reviewers independently  
19 screened each full-text article. The estimated frequency of disagreement was 14%, which was resolved by a third  
20 reviewer. This reviewer also verified all eligible studies.  
21  
22

### 23 ***Data abstraction***

24  
25 We developed a data abstraction form with inputs from two physicians. We piloted and refined the form two times,  
26 each time using five randomly selected studies. Subsequently, paired reviewers conducted the abstraction,  
27 independently. Numerical data available only in figures were extracted using WebPlotDigitizer.<sup>18</sup> A third reviewer  
28 conducted a quality check on all data, and resolved any remaining discrepancies.  
29

30 We abstracted data pertaining to study characteristics, patient populations, interventions, and outcomes. Multiple  
31 reports of the same trial (hereafter companion reports) were identified using the trial registration identifier, trial  
32 name, or a juxtaposition of the author names, treatment comparisons, sample sizes and outcomes, if necessary.<sup>19</sup> We  
33 abstracted data from all companion reports, identified differences, and reconciled the differences through discussion.  
34 For each set of companion reports, we considered one as the major publication and others as companion reports. We  
35 abstracted outcome data from all trial reports and used the data corresponding to the longest duration of follow-up in  
36 the meta-analysis.<sup>5</sup>  
37  
38

### 39 ***Risk of bias assessment***

40  
41 The risk of bias in the included trials was appraised using the Cochrane risk-of-bias tool, including selection bias,  
42 performance bias, detection bias, attrition bias, reporting bias, and other biases such as funding sources.<sup>20</sup> For  
43 selection bias, we assessed the reporting of random sequence generation and allocation concealment. For  
44 performance bias, we assessed the reporting of blinding of patients and trial personnel, and for detection bias, the  
45 reporting of the blinding of outcome assessors. In the assessment of performance and detection biases, we  
46 considered the objectivity of the primary outcome of individual trials in assessing performance and detection biases.  
47

48 For RCTs that had been registered, the primary outcome was identified from the trial protocol, which was vision  
49 gain or change in mean BCVA in the majority of the included RCTs. Otherwise, we identified the primary outcome  
50 using an *a-priori* defined algorithm.<sup>21 22</sup> In brief, we selected from the trial report the outcome that was listed in the  
51 title or objectives, the most serious clinical outcome among all the trial outcomes, or the first reported outcome in  
52 the results section.  
53

54 Paired reviewers conducted the risk of bias assessment, independently. Discrepancies were resolved by discussion or  
55 the involvement of a third reviewer.  
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### ***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.<sup>5</sup> 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.<sup>23</sup> 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.<sup>5</sup> Pooled treatment effect estimates and 95% confidence intervals (CIs) were derived using the meta-analytical random effects model.<sup>23</sup> The meta-analyses were conducted using the "metafor" package in R (version 3.1.1).<sup>24</sup>

### ***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,<sup>25</sup> with approximate standard deviations.<sup>26</sup> 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.<sup>27</sup> 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.<sup>5</sup>

### ***Excluded RCT'S***

The RCT by Rajagopal et al. 2015<sup>28</sup> (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<sup>29</sup> 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>

1  
2  
3 MEDLINE Daily and MEDLINE 1946 to present

4 MEDLINE In-Process & Other Non-Indexed Citations

5  
6 Cochrane Central Register of Controlled Trials <April 2015>

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

9  
10 Date of Search: May 27, 2015 (Updated November 13, 2015)

11 Study Types: Randomized controlled trials

12 Limits: No date or language limits were used

13 Human filter was applied

14 Editorials & letters excluded

15  
16  
17 Search Strategy:  
18  
19  
20  
21

- 22 -----
- 23 1 Retinal Degeneration/
  - 24 2 limit 1 to yr="1973-2009" [EARLIER MESH FOR WET MACULAR DEGENERATION]
  - 25 3 Macular Degeneration/
  - 26 4 Wet Macular Degeneration/ [MESH FROM 2010-]
  - 27 5 ((exudative or neovascular or wet) adj3 ((macula\* adj2 degeneration) or (macula\* adj2 deterioration) or  
28 maculopath\* or (macula\* adj2 dystroph\*))).tw,kw.
  - 29 6 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.
  - 30 7 (wAMD or wARMD).tw,kw.
  - 31 8 Diabetic Retinopathy/
  - 32 9 ((diabet\* or DM) adj3 retinopath\*).tw,kw.
  - 33 10 (PDR or DME or DMO).tw,kw.
  - 34 11 Macular Edema/
  - 35 12 ((macula\* or retina\*) adj3 (edema\$1 or oedema\$1)).tw,kw.
  - 36 13 (Irvine-Gass adj3 (edema\$1 or oedema\$1 or syndrome\$1)).tw,kw.
  - 37 14 (cystoid macula\* adj dystroph\*).tw,kw.
  - 38 15 Retinal Vein Occlusion/
  - 39 16 (retinal vein adj3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or embolism\*)).tw,kw.
  - 40 17 (BRVO or CRVO).tw,kw.
  - 41 18 Choroidal Neovascularization/
  - 42 19 ((choroid\* or subretinal or sub-retinal) adj1 neovasculari#ation\*).tw,kw.
  - 43 20 CNV.tw,kw.
  - 44 21 or/2-20 [CONDITIONS – MEDLINE]
  - 45 22 Vascular Endothelial Growth Factor A/ai

- 1  
2  
3 23 (anti adj2 VEGF\$1).tw,kw.  
4  
5 24 antiVEGF\$1.tw,kw.  
6  
7 25 (antivascular endothelial growth factor\$1 or anti-vascular endothelial growth factor\$1).tw,kw.  
8  
9 26 Antibodies, Monoclonal, Humanized/  
10  
11 27 (monoclonal antibod\* and humani#ed).tw,kw.  
12  
13 28 (antibod\* adj2 humani#ed).tw,kw.  
14  
15 29 Angiogenesis Inhibitors/  
16  
17 30 (angiogen\* adj3 (inhibitor\* or antagonist\*)).tw,kw.  
18  
19 31 (anti-angiogen\* or antiangiogen\*).tw,kw.  
20  
21 32 aflibercept.tw,kw.  
22  
23 33 ("AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or Eylea or "UNII-  
24  
25 15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.  
26  
27 34 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap\*).tw,kw.  
28  
29 35 aflibercept.rn.  
30  
31 36 Bevacizumab.tw,kw.  
32  
33 37 (Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-2S9ZZM9Q9V").tw,kw.  
34  
35 38 IVB injection\$1.tw,kw.  
36  
37 39 Bevacizumab.rn.  
38  
39 40 Pegaptanib.tw,kw.  
40  
41 41 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-3HP012Q0FH").tw,kw.  
42  
43 42 Pegaptanib.rn.  
44  
45 43 Ranibizumab.tw,kw.  
46  
47 44 (Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.  
48  
49 45 IVR injection\$1.tw,kw.  
50  
51 46 Ranibizumab.rn.  
52  
53 47 or/22-46 [ANTI-VEGF AGENTS – MEDLINE]  
54  
55 48 21 and 47 [ANTI-VEGF AGENTS & CONDITIONS – MEDLINE]  
56  
57 49 exp Photochemotherapy/  
58  
59 50 Photosensitizing Agents/  
60  
61 51 (photochemo\* or photo-chemo\* or photodynamic\* or photo-dynamic\* or photosensiti\* or photo-  
62  
63 sensiti\*).tw,kw.  
64  
65 52 PDT.tw,kw.  
66  
67 53 or/49-52  
68  
69 54 verteporfin.tw,kw.  
70  
71 55 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.  
72  
73 56 verteporfin.rn.

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2  
3 57 or/54-56  
4  
5 58 53 and 57  
6 59 (PDTV or "PDT-V" or VPDT or "V-PDT").tw,kw.  
7  
8 60 58 or 59 [VISUDYNE PDT – MEDLINE]  
9  
10 61 21 and 60 [VISUDYNE PDT & CONDITIONS – MEDLINE]  
11  
12 62 Triamcinolone Acetonide/  
13 ((Triamcinol\* adj acet\*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS  
14 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog\* or Kenlog or "NSC 21916" or  
15 Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort\* or Triesense or Tristoject or "UNII-  
16 F446C597KA" or Volon).tw,kw.  
17 64 triamcinolone acetonide.rn.  
18  
19 65 Glucocorticoids/  
20 66 (glucocorticoid\* or glucorticoid\*).tw,kw.  
21  
22 67 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or Retaane  
23 or "UNII-Y0PC411K4T").tw,kw.  
24 68 anecortave acetate.rn.  
25  
26 69 Pregnadienediols/  
27 70 (dihydroxypregnadiene\* or di-hydroxypregnadiene\* or pregnadienediol\*).tw,kw.  
28  
29 71 exp Dexamethasone/  
30 72 (Dexamethasone or Decaject\* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex  
31 or Millicorten or Oradexon or Ozurdex).tw,kw.  
32  
33 73 dexamethasone.rn.  
34 74 (intravitreal adj3 (corticoid\* or corticosteroid\* or steroid\*)).tw,kw.  
35  
36 75 or/62-74  
37  
38 76 exp Injections/  
39 77 (depot or implant\* or infus\* or inject\* or intravitreal\* or intra-vitre\* or microsphere\* or micro-sphere\* or  
40 suspension\*).tw,kw.  
41  
42 78 or/76-77  
43 79 75 and 78 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - MEDLINE]  
44  
45 80 21 and 79 (3513) [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - MEDLINE]  
46 81 (controlled clinical trial or randomized controlled trial).pt.  
47  
48 82 clinical trials as topic.sh.  
49 83 (randomi#ed or randomly or RCT\$1 or placebo\*).tw.  
50  
51 84 ((singl\* or doubl\* or trebl\* or tripl\*) adj (mask\* or blind\* or dumm\*)).tw.  
52  
53 85 trial.ti.  
54  
55 86 or/81-85  
56  
57 87 (48 or 61 or 80) and 86



- 1  
2  
3 88 exp Animals/ not (exp Animals/ and Humans/)  
4  
5 89 87 not 88  
6  
7 90 (comment or editorial or interview or news).pt.  
8  
9 91 (letter not (letter and randomized controlled trial)).pt.  
10  
11 92 89 not (90 or 91)  
12  
13 93 92 use prmz [MEDLINE RCTS]  
14  
15 94 macular degeneration/  
16  
17 95 age related macular degeneration/  
18  
19 96 wet macular degeneration/  
20  
21 97 ((exudative or neovascular or wet) adj3 ((macula\* adj2 degeneration) or (macula\* adj2 deterioration) or  
22 maculopath\* or (macula\* adj2 dystroph\*))).tw,kw.  
23  
24 98 ((exudative or neovascular or wet) adj2 (AMD or ARMD)).tw,kw.  
25  
26 99 (wAMD or wARMD).tw,kw.  
27  
28 100 diabetic retinopathy/  
29  
30 101 ((diabet\* or DM) adj3 retinopath\*).tw,kw.  
31  
32 102 diabetic macular edema/  
33  
34 103 (PDR or DME or DMO).tw,kw.  
35  
36 104 exp macular edema/  
37  
38 105 ((macula\* or retina\*) adj3 (edema\$1 or oedema\$1)).tw,kw.  
39  
40 106 (Irvine-Gass adj3 (edema\$1 or oedema\$1 or syndrome\$1)).tw,kw.  
41  
42 107 (cystoid macula\* adj dystroph\*).tw,kw.  
43  
44 108 exp retina vein occlusion/  
45  
46 109 (retinal vein adj3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or embolism\*)).tw,kw.  
47  
48 110 (BRVO or CRVO).tw,kw.  
49  
50 111 subretinal neovascularization/  
51  
52 112 ((choroid\* or subretinal or sub-retinal) adj1 neovasculari#ation\*).tw,kw.  
53  
54 113 CNV.tw,kw.  
55  
56 114 or/94-113 [CONDITIONS – EMBASE]  
57  
58 115 vasculotropin inhibitor/  
59  
60 116 (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/



- 1  
2  
3 123 (angiogen\* adj3 (inhibitor\* or antagonist\*)).tw,kw.  
4  
5 124 (anti-angiogen\* or antiangiogen\*).tw,kw.  
6  
7 125 aflibercept/  
8  
9 126 (aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005 or "Bay 86-5321" or "Bay86-5321" or  
10 Eylea or "UNII-15C2VL427D" or Zaltrap or ZIV-aflibercept).tw,kw.  
11  
12 127 ((vasculotropin or vascular endothelial growth factor or VEGF) adj trap\*).tw,kw.  
13  
14 128 aflibercept.rn.  
15  
16 129 bevacizumab/  
17  
18 130 (bevacizumab or Altuzan or Avastin or "nsc 704865" or nsc704865 or "rhuMAb-VEGF" or "UNII-  
19 2S9ZZM9Q9V").tw,kw.  
20  
21 131 IVB injection\$.tw,kw.  
22  
23 132 Bevacizumab.rn.  
24  
25 133 pegaptanib/  
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27 134 (Pegaptanib or "EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838 or "UNII-  
28 3HP012Q0FH").tw,kw.  
29  
30 135 Pegaptanib.rn.  
31  
32 136 ranibizumab/  
33  
34 137 (Ranibizumab or Lucentis or "rhuFab V2" or "UNII-ZL1R02VT79").tw,kw.  
35  
36 138 IVR injection\$.tw,kw.  
37  
38 139 Ranibizumab.rn.  
39  
40 140 or/115-139 [ANTI-VEGF AGENTS – EMBASE]  
41  
42 141 114 and 140 [ANTI-VEGF AGENTS & CONDITIONS – EMBASE]  
43  
44 142 photodynamic therapy/  
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46 143 photosensitizing agent/  
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48 144 (photochemo\* or photo-chemo\* or photodynamic\* or photo-dynamic\* or photosensiti\* or photo-  
49 sensiti\*).tw,kw.  
50  
51 145 PDT.tw,kw.  
52  
53 146 or/142-145  
54  
55 147 verteporfin/  
56  
57 148 (verteporphin or "BPD-MA" or "CL 318,952" or "CL 318952" or "UNII-0X9PA28K43" or Visudyne).tw,kw.  
58  
59 149 verteporfin.rn.  
60  
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/

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3 156 triamcinolone acetone/
- 4  
5 157 ((Triamcinol\* adj acet\*) or Aristocort or Aristospan or Asmacort or Azmacort or "BRN 0060069" or "CCRIS  
6 5231" or Cinonide or Clinacort or "EINECS 200-948-7" or Kenacort or Kenalog\* or Kenlog or "NSC 21916" or  
7 Triamcot or Triam-Forte or Triam-Injekt or Triamonide or Tricort\* or Triesense or Tristoject or "UNII-  
8 F446C597KA" or Volon).tw,kw.
- 9  
10 158 triamcinolone.rn.
- 11 159 triamcinolone acetone.rn.
- 12  
13 160 exp glucocorticoid/
- 14 161 (glucocorticoid\* or glucorticoid\*).tw,kw.
- 15  
16 162 anecortave/
- 17 163 (anecortave or "AL 3789" or "AL-3789" or "EINECS 231-812-5" or "NSC 15475" or "NSC 24345" or  
18 Retaane or "UNII-Y0PC411K4T").tw,kw.
- 19  
20 164 anecortave.rn.
- 21 165 pregnane derivative/
- 22  
23 166 (dihydroxypregnadiene\* or di-hydroxypregnadiene\* or pregnadienediol\*).tw,kw.
- 24  
25 167 dexamethasone/
- 26 168 dexamethasone isonicotinate/
- 27 169 (Dexamethasone or Decaject\* or Decameth or Dexasone or Dexpak or Hexadecadrol or Hexadrol or Maxidex  
28 or Millicorten or Oradexon or Ozurdex).tw,kw.
- 29  
30 170 dexamethasone.rn.
- 31 171 dexamethasone isonicotinate.rn.
- 32  
33 172 (intravitreal adj3 (corticoid\* or corticosteroid\* or steroid\*)).tw,kw.
- 34  
35 173 or/155-172
- 36 174 exp injection/
- 37  
38 175 intravitreal drug administration/
- 39 176 vi.fs. [EMBASE FLOATING SUBJECT HEADING FOR INTRAVITREAL DRUG ADMIN]
- 40  
41 177 (depot or implant\* or infus\* or inject\* or intravitreal\* or intra-vitreal\* or microsphere\* or micro-sphere\* or  
42 suspension\*).tw,kw.
- 43  
44 178 or/174-177
- 45 179 173 and 178 [CORTICOSTEROID/INTRAVITREAL INJECTIONS - EMBASE]
- 46 180 114 and 179 [CORTICOSTEROID/INTRAVITREAL INJECTIONS & CONDITIONS - EMBASE]
- 47  
48 181 randomized controlled trial/ or controlled clinical trial/
- 49 182 exp "clinical trial (topic)"/
- 50  
51 183 (randomi#ed or randomly or RCT\$1 or placebo\*).tw.
- 52  
53 184 ((singl\* or doubl\* or trebl\* or tripl\*) adj (mask\* or blind\* or dumm\*)).tw.
- 54  
55 185 trial.ti.
- 56  
57 186 or/181-185

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- 3 187 (141 or 154 or 180) and 186
- 4 188 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp
- 5 vertebrate/
- 6
- 7 189 exp humans/ or exp human experimentation/ or exp human experiment/
- 8
- 9 190 188 not 189
- 10 191 187 not 190
- 11
- 12 192 editorial.pt.
- 13 193 letter.pt. not (letter.pt. and randomized controlled trial/)
- 14
- 15 194 191 not (192 or 193)
- 16 195 194 use emczd [EMBASE RCTS]
- 17 196 93 or 195 [MEDLINE / EMBASE RCTS]
- 18 197 remove duplicates from 196 [TOTAL UNIQUE HITS]
- 19 198 197 use prmz [UNIQUE MEDLINE]
- 20 199 197 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)
<b>cn-AMD (n = 12)</b>									
Schauwvlieghe <sup>30</sup>	2016	BRAMD	Netherlands Trial Register: NTR1704	Netherlands	Parallel RCT	Jan 2009 - Dec 2011	Multi	332	12
Berg <sup>31</sup>	2015	LUCAS	NCT01127360	Norway	Parallel RCT	Mar 2009 - Jul 2012	Multi	441	12
Scholler <sup>32</sup>	2014	NR	EK-07-192-1007 / EudraCT Nr. 2007-005157-33	Austria	Parallel RCT	2008 - 2011	Single	55	12
Chakravarthy <sup>33</sup>	2013	IVAN	ISRCTN921665 60	UK	Parallel RCT	Mar 27, 2008 - Oct 15, 2010	Multi	610	24
Kodjikian <sup>34</sup>	2013	GEFAL	NCT01170767	France	Parallel RCT	2009 - 2012	Multi	501	12
Krebs <sup>35</sup>	2013	MANTA	NCT00710229	Austria	Parallel RCT	2008 - 2011	Multi	321	12
Heier <sup>36</sup>	2012	VIEW 1	NCT00509795	US, Canada	Parallel RCT	Aug 2007 - Sep 2010	Multi	1217	12
Heier <sup>36</sup>	2012	VIEW 2	NCT00637377	Argentina , Australia, Austria, Belgium, Brazil, Colombia , Czech Republic, France, Germany ,	Parallel RCT	Apr 2008 - Sep 2010	Multi	1240	12

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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 <sup>37</sup>	2011a	NR	NR	India	Parallel RCT	2007 - 2009	Multi	60	18
Biswas <sup>38</sup>	2011b	NR	NR	India	Parallel RCT	NA	Multi	120	18
Martin <sup>39</sup>	2011	CATT	NCT00593450	US	Parallel RCT	2008 - 2010	Multi	1208	12
Subramanian <sup>40</sup>	2010	NR	ISRCTN73359806	US	Parallel RCT	2007 - 2009	Single	28	12
<b>DME (n = 3)</b>									
Fouda <sup>41</sup>	2017	NR	NR	Egypt	Parallel RCT	NR	Single	42	15
Wells <sup>27</sup>	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)
Ekinci <sup>42</sup>	2014	NR	NR	Turkey	RCT Parallel RCT	- Oct 2014 2011 - 2014	NR	100	12
<b>RVO-ME (n = 2)</b>									
Scott <sup>43</sup>	2017	SCORE2	NCT01969708	US	Parallel RCT	Sep 2014 - Dec 2016	MULTI	362	6
Narayanan <sup>44</sup>	2015	MARVEL	CTRI/2012/01/003120	India	Parallel RCT	Jan 2012 - Feb 2013	Single	75	6
<b>m-CNV (n = 2)</b>									
Iacono <sup>45</sup>	2012	NR	NR	Italy	Parallel RCT	Apr 2006 - Jul 2007	Single	55	18
Gharbiya <sup>46</sup>	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
<b>cn-AMD (n = 12)</b>																		
Schauwvlieghe 2016 <sup>30</sup>	332	78	SD	7	79	7	78	7	NR	NR	NR	NR	56	NR	NR	NR	NR	40 % pseudo phakic
Berg 2015 <sup>31</sup>	NR	NR	SD	NR	78.7	7.6	78	8.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Scholler 2014 <sup>32</sup>	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 <sup>33</sup>	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 <sup>34</sup>	501	NR	NR	NR	79.6	6.9	78.7	7.3	NR	NR	NR	NR	66	NR	NR	NR	57	NR
Krebs 2013 <sup>35</sup>	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 <sup>36</sup>	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 <sup>36</sup>	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 <sup>37</sup>	60	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Biswas 2011b <sup>38</sup>	104	NR	NR	NR	63.5	NR	64.4	NR	NR	NR	NR	NR	52	NR	NR	NR	NR	NR
Martin 2011 <sup>39</sup>	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 <sup>40</sup>	28	78.6	SD	NR	78	NR	80	NR	NR	NR	NR	NR	4.6	NR	NR	NR	NR	NR
<b>DME (n = 3)</b>																		
Fouda 2017 <sup>41</sup>	70	NR	SD	NR	55.1	4.7	56.6	5.8	NA	NA	NA	NA	NR	100	NR	NR	NR	NR
Wells 2015 <sup>27</sup>	660	61	SD	10	60	10	62	10	60	11	NR	NR	47	100	NR	NR	NR	NR
Ekinci 2014 <sup>42</sup>	100	NR	NR	NR	68	9	65	14	NR	NR	NR	NR	68	100	NR	0	NR	NR
<b>RVO-ME (n = 2)</b>																		

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 <sup>43</sup>	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 <sup>44</sup>	75	NR	NR	NR	53	NR	50	NR	NR	NR	NR	NR	45.3	17	NR	NR	50	NR
<b>m-CNV (n = 2)</b>																		
Iacono 2012 <sup>45</sup>	55	NR	SD	NR	65	12	61	11	NR	NR	NR	NR	76.4	NR	NR	NR	NR	NR
Gharbiya 2010 <sup>46</sup>	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
<b>cn-AMD (n = 12)</b>							
Schauwvlieghe 2016 <sup>30</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Berg 2015 <sup>31</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Scholler 2014 <sup>32</sup>	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Chakravarthy 2013 <sup>33</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kodjikian 2013 <sup>34</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Krebs 2013 <sup>35</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Heier 2012 – VIEW 1 <sup>36</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Heier 2012 – VIEW 2 <sup>36</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Biswas 2011a <sup>37</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Biswas 2011b <sup>38</sup>	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Martin 2011 <sup>39</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Subramanian 2010 <sup>40</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
<b>DME (n = 3)</b>							
Fouda 2017 <sup>41</sup>	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Wells 2015 <sup>27</sup>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ekinci 2014 <sup>42</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
<b>RVO-ME (n = 2)</b>							
Scott 2017 <sup>43</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Narayanan 2015 <sup>44</sup>	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
<b>m-CNV (n = 2)</b>							
Iacono 2012 <sup>45</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Gharbiya 2010 <sup>46</sup>	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

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- 3 5: Incomplete outcome data
- 4 6: Selective reporting
- 5 7: Other bias
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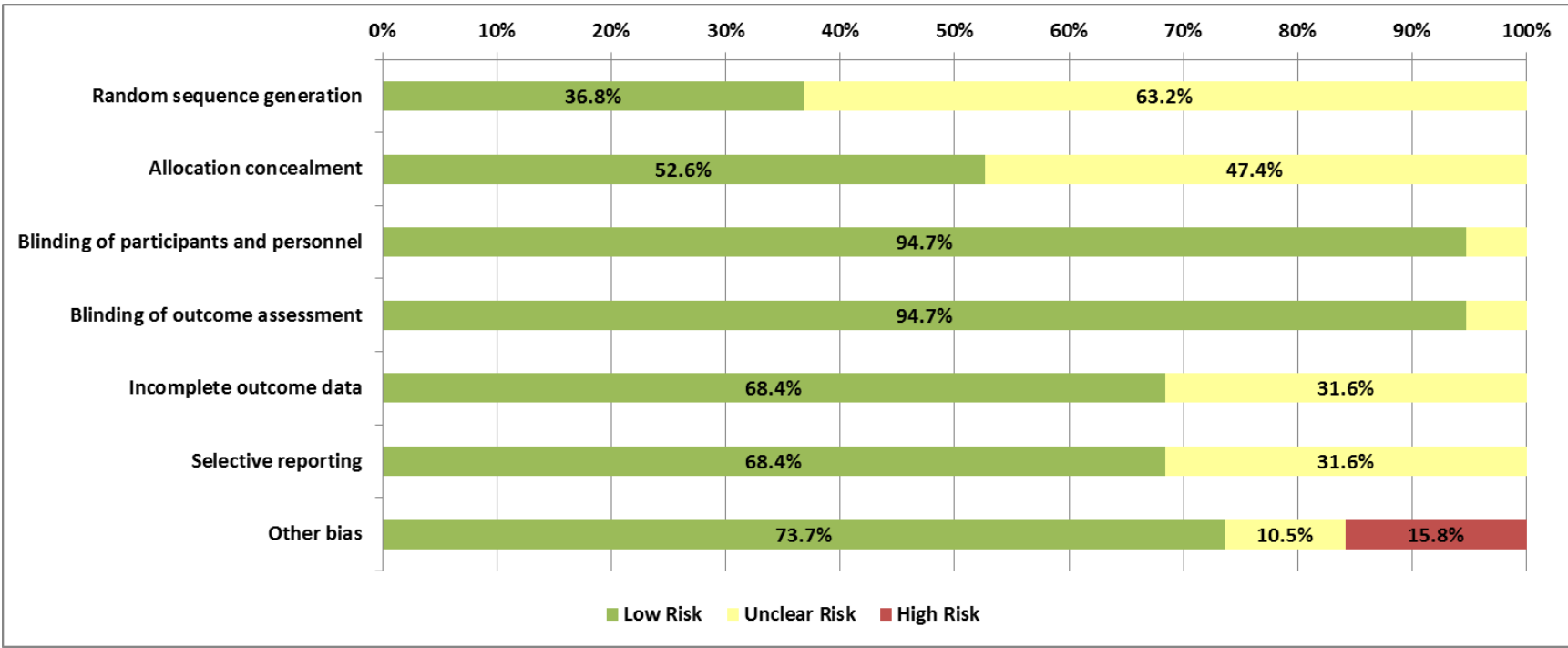
7 **Abbreviations:** cn-AMD – choroidal neovascular age-related macular degeneration; DME – diabetic  
8 macular oedema; m-CNV – myopic choroidal neovascularization; RVO-ME – macular edema due to  
9 retinal vein occlusion

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### Appendix 5: Risk of bias results



## Appendix 6: Treatment effect estimates

Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
<b>Treatment Effects in choroidal neovascular Age-related Macular Degeneration</b>								
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% <sup>b</sup>
	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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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
<b>Treatment Effects in Diabetic Macular Edema</b>								
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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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. Aflibercept	NR	NR	NR	NR	NR	NR	NR

Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	Aflibercept							
Bacterial endophthalmitis	Aflibercept vs. Ranibizumab	2	512	0	0	NE	NE	NE
	Bevacizumab vs. Ranibizumab	1	436	0.01	0	3.03 (0.12-100)	0.46 (-0.81, 1.72)	NA
	Bevacizumab 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%
	Bevacizumab vs. Ranibizumab	1	436	0.0092	0.0046	2 (0.18-20)	NR	NA
	Bevacizumab vs. Aflibercept	1	436	0.0046	0.0092	0.5 (0.05, 5.47)	-0.46 (-2.01, 1.09)	NA
<b>Treatment Effects in Retinal Vein Occlusion – Macular Edema</b>								
Vision gain in BCVA of ≥15 EDTRS letters	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumab vs. Ranibizumab	1	74	0.59	0.59	1 (0.68-1.45)	0 (-22.37, 22.37)	NA
	Bevacizumab 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
	Bevacizumab vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumab 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
	Bevacizumab vs. Ranibizumab	1	77	15.6	18.1	NA	-2.5 (-8.0, 5.0)	NA
	Bevacizumab vs. Aflibercept	1	362	18.6	18.9	NA	-1.5 (-4.2, 1.2)	NA



Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
	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

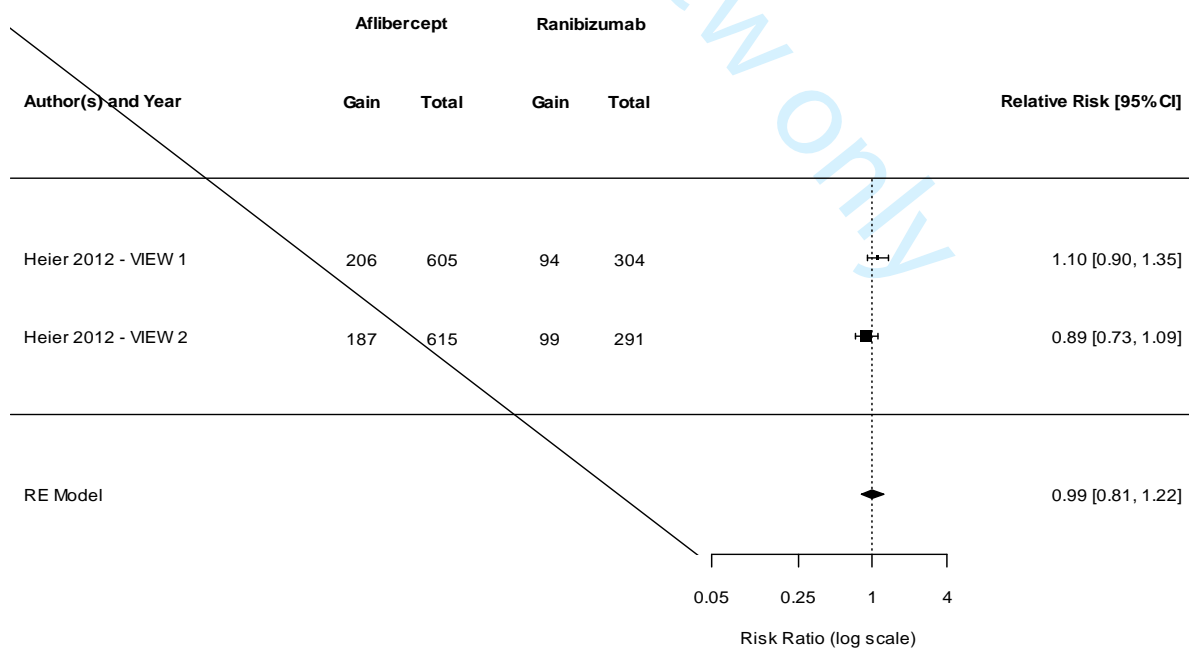
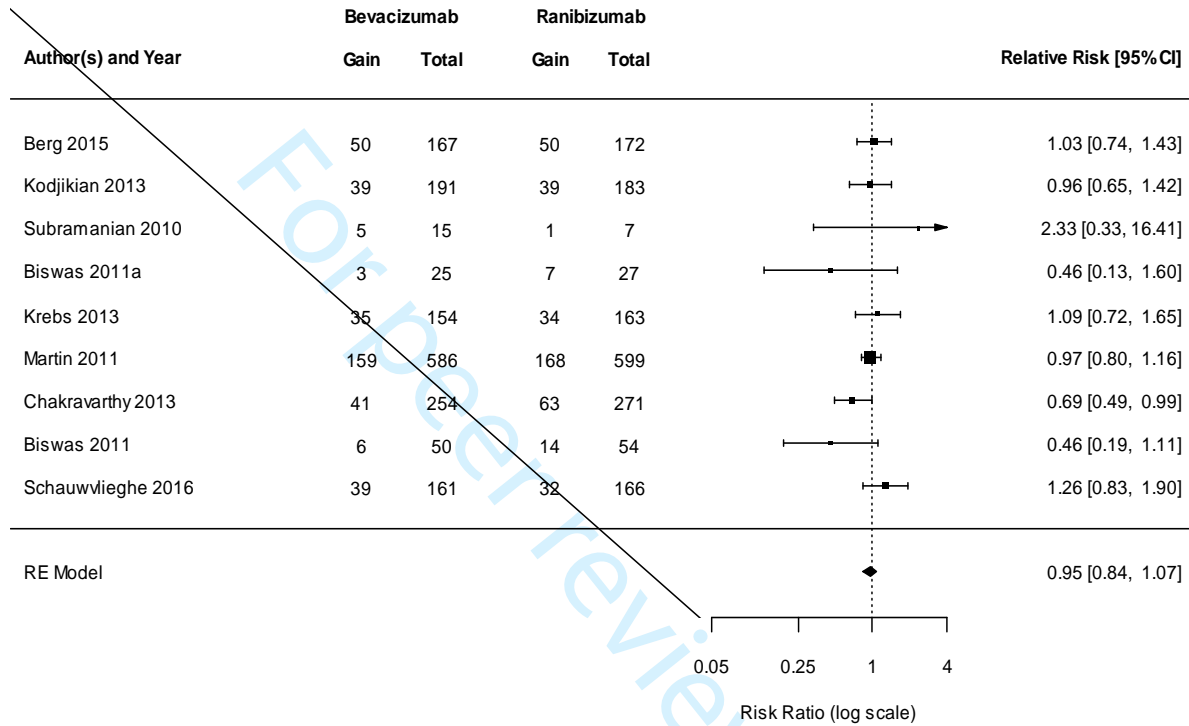
Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
Venous thromboembolic events	Aflibercept vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	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
<b>Treatment Effects in Myopic Choroidal Neovascularization</b>								
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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
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 <sup>a</sup>	Total patients	Mean treatment effect estimate <sup>b</sup> [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I <sup>2</sup>
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
<p><b>Footnotes:</b></p> <p><sup>a</sup> 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.</p> <p><sup>b</sup> The summary statistics were derived by taking the mean and range across estimates from included studies.</p> <p><b>Abbreviations:</b> 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</p>								

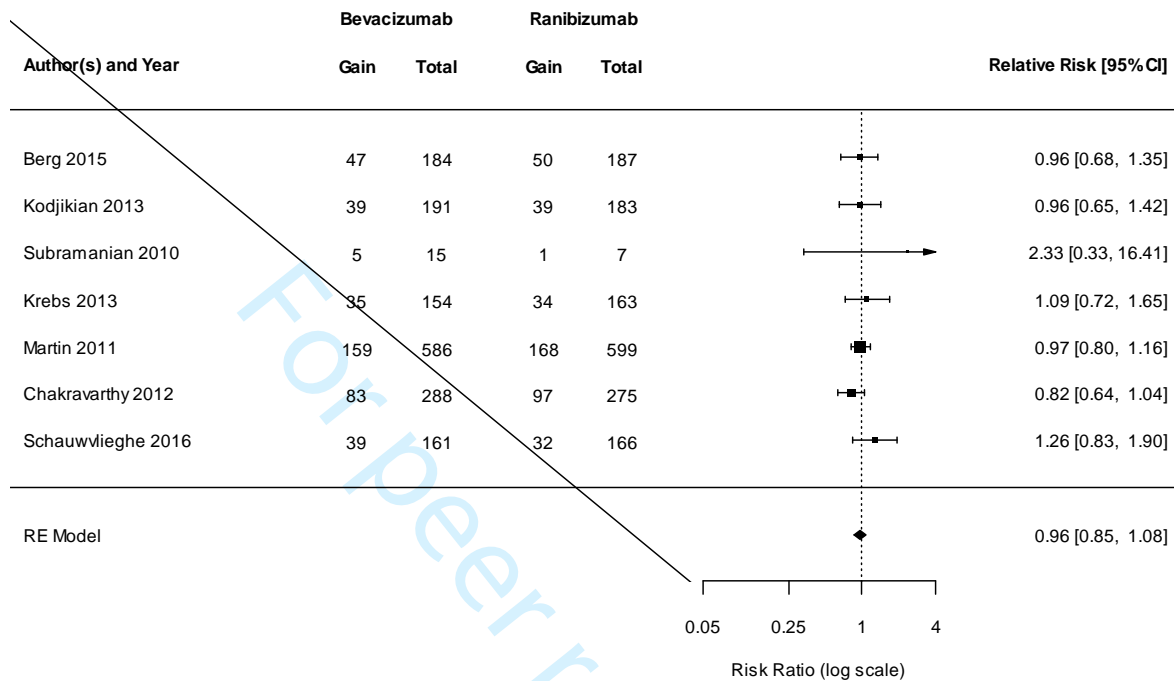
## Appendix 7: Forest plots for primary outcome in choroidal neovascular age related macular degeneration (cn-AMD) population

### A: Vision gain in cn-AMD population

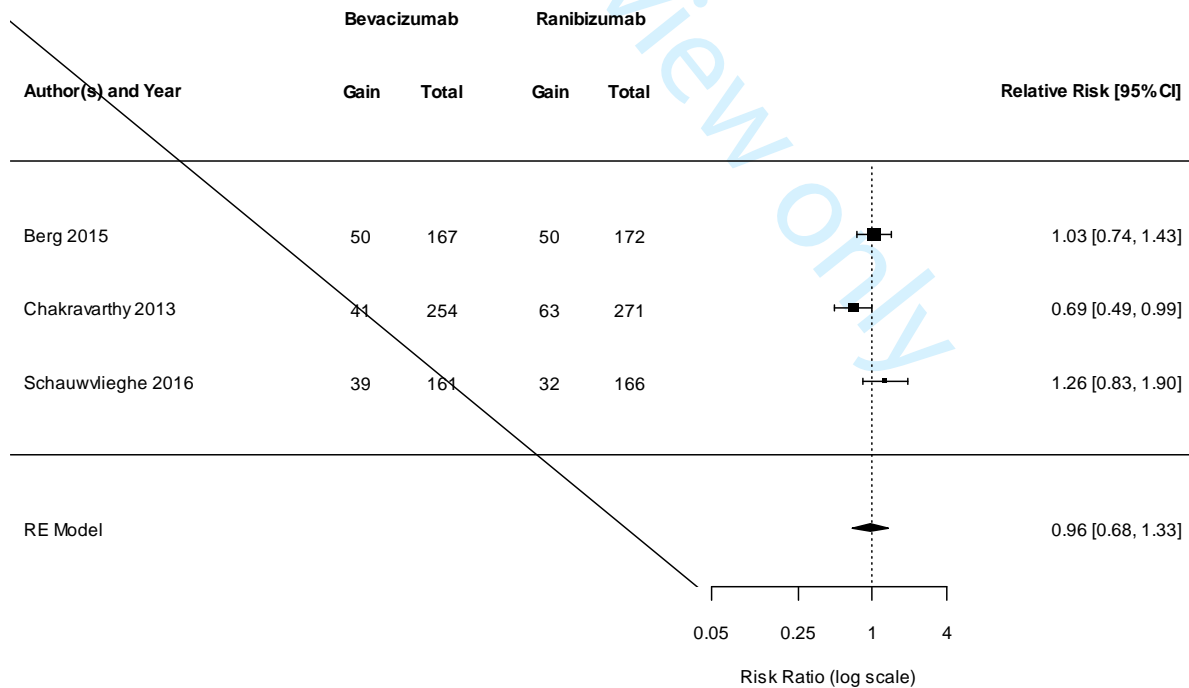


**B: Sensitivity analyses for vision gain in cn-AMD population**

*Sensitivity Analysis: 1 Year Follow-Up*

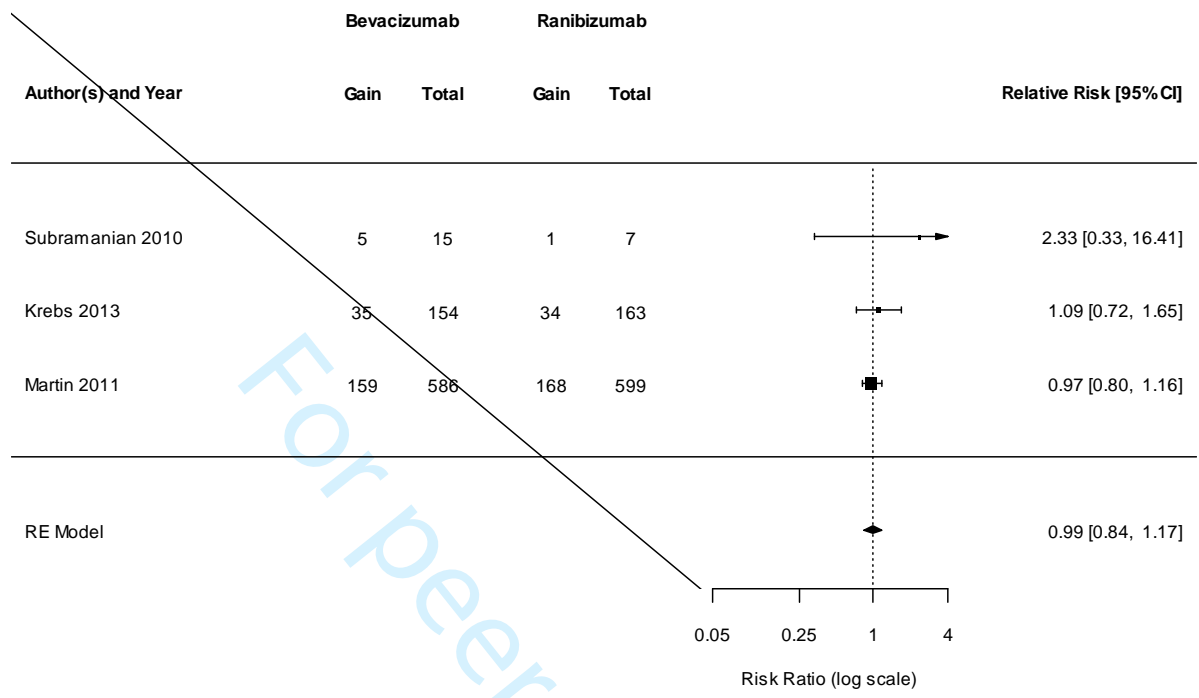


*Sensitivity Analysis: Low Risk of Selection Bias*



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Sensitivity Analysis: De Novo Patients



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## Appendix 8: Summary data used in risk of bias results

		Length of follow-up (months)							
		1	3	4	6	8	12	18	24
		<b>cn-AMD</b>							
	# 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)
		<b>DME</b>							
	# of RCTs	1	0	1	0	1	2	0	1
<b>Mean improvement in BCVA letter score (SEM)</b>	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)
		<b>RVO-ME</b>							
	# 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
		<b>m-CNV</b>							
	# 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



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**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

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## Appendix 9: Sensitivity analysis estimates

Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate [Range]	Mean comparator effect estimate <sup>a</sup> [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I <sup>2</sup>
<b>Sensitivity Analyses of Bevacizumab vs. Ranibizumab in choroidal neovascular age-related macular degeneration (cn-AMD)</b>								
<b>Vision gain in BCVA of ≥15 EDTRS letters</b>	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
<b>Vision loss in BCVA of ≥15 EDTRS letters</b>	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
<b>Mean change in BCVA</b>	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%

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Outcome	Analysis	No. of RCTs	Total patients	Mean treatment effect estimate[Range ]	Mean comparator effect estimate <sup>a</sup> [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I <sup>2</sup>
	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:**

<sup>a</sup> 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)
<b>cn-AMD (n = 12)</b>				
Schauwvlieghe 2016 <sup>30</sup>	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 <sup>31</sup>	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 <sup>32</sup>	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 $\geq 5$ letters with OCT evidence of fluid in the macula; increase in OCT central retinal thickness of at least 100 $\mu\text{m}$ ; new area of nAMD; new macular haemorrhage; persistent fluid on OCT at least 1 month after the previous intravitreal injection.	No

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Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Chakravarthy 2013 <sup>33</sup>	TX 1: ranibizumab 0.5 mg/0.05 ml	TX 1 & TX 2: 3 monthly injections + monthly injections for 24 months.	Prespecified clinical and OCT criteria for active disease were met.	Yes
	TX 2: bevacizumab 1.25 mg/0.05 ml			
	TX 3: ranibizumab 0.5 mg/0.05 ml	TX 3 & TX 4: 3 monthly injections + repeated 3 monthly injections as needed treatment criteria.		
	TX 4: bevacizumab 1.25 mg/0.05 ml			
Kodjikian 2013 <sup>34</sup>	TX 1: ranibizumab 0.5 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
	TX 2: bevacizumab 1.25 mg/0.05 ml			
Krebs 2013 <sup>35</sup>	TX 1: ranibizumab 0.5 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 µm; new macular haemorrhage; new area of classic CNV; or evidence of persistent fluid on OCT at least 1 month after the previous injection.	Yes
	TX 2: bevacizumab 1.25 mg/0.05 ml			

Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Heier 2012 – VIEW 1 <sup>36</sup>	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 <sup>36</sup>	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 <sup>37</sup>	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 <sup>38</sup>	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

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Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Martin 2011 <sup>39</sup>	TX 1: ranibizumab 0.5 mg/0.05 ml	TX 1 & TX 2: monthly injections for 12 months.	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
	TX 2: bevacizumab 1.25 mg/0.05 ml			
	TX 3: ranibizumab 0.5 mg/0.05 ml	TX 3 & TX 4: monthly injections as needed treatment criteria.		
	TX 4: bevacizumab 1.25 mg/0.05 ml			
Subramanian 2010 <sup>40</sup>	TX 1: ranibizumab 0.5 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
	TX 2: bevacizumab 1.25 mg/0.05 ml			
<b>DME (n = 3)</b>				
Fouda 2017 <sup>41</sup>	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 <sup>27</sup>	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 <sup>42</sup>	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
<b>RVO-ME (n = 2)</b>				
Scott 2017 <sup>43</sup>	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



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Author, year	Treatment arms	Treatment protocol	As needed treatment criteria	Reconstitution of bevacizumab for intravitreal injection reported (Yes/No)
Narayanan 2015 <sup>44</sup>	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
<b>m-CNV (n = 2)</b>				
Iacono 2012 <sup>45</sup>	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 <sup>46</sup>	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<sup>a</sup> and Wells 2016<sup>b</sup>)**

Outcome	Rx vs Ctrl Comparison	No. of RCTs <sup>a</sup>	Total patients	Mean treatment effect estimate [Range]	Mean comparator effect estimate <sup>b</sup> [Range]	Risk Ratio (95% CI)	Proportion Difference (%) / Mean Difference (95% CI)	I <sup>2</sup>
<b>Subgroup Analysis of Anti-VEGF Treatment Effects in Diabetic Macular Edema (DME) According to the DRCR.net RCT</b>								
<b>Aflibercept vs. Ranibizumab</b>								
<b>Vision gain in BCVA of ≥15 EDTRS letters</b>	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	<b>1.30 (1.01, 1.69)</b>	<b>10.1 (1.00, 19.00)</b>	NA
	Participants with baseline BCVA < 69 letters	1	203	0.50	0.67	<b>1.35 (1.06, 1.72)</b>	<b>17.16 (3.79, 30.53)</b>	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
<b>Vision loss in BCVA of ≥15 EDTRS letters</b>	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
<b>Mean change in BCVA (SMD)</b>	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 $\geq$ 69 letters	1	200	8.6 $\pm$ 7.0	7.8 $\pm$ 8.4	NA	-0.7 (-2.9, 1.5)	NA
	Follow-up for 12 months	1	414	11.2 $\pm$ 9.4	13.3 $\pm$ 11.1	NA	<b>2.1 (0.1, 4.2)</b>	NA
	Participants with baseline BCVA < 69 letters	1	203	14.2 $\pm$ 10.6	18.9 $\pm$ 11.5	NA	<b>4.7 (1.4, 8.0)</b>	NA
	Participants with baseline BCVA $\geq$ 69 letters	1	211	8.3 $\pm$ 6.8	8.0 $\pm$ 7.6	NA	-0.4 (-2.3, 1.5)	NA
<b>Bevacizumab vs Aflibercept</b>								
<b>Vision gain in BCVA of <math>\geq</math>15 EDTRS letters</b>	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 $\geq$ 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	<b>0.68 (0.52, 0.89)</b>	<b>-14.0 (-23.00, -4.04)</b>	NA
	Participants with baseline BCVA < 69 letters	1	204	0.41	0.67	<b>0.62 (0.47, 0.81)</b>	<b>-25.49 (-38.72, -12.26)</b>	NA
	Participants with baseline BCVA $\geq$ 69 letters	1	210	0.16	0.18	0.91 (0.5, 1.65)	-1.58 (-11.77, 8.61)	NA
<b>Vision loss in BCVA of <math>\geq</math>15 EDTRS letters</b>	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
<b>Mean change in BCVA (SMD)</b>	Follow-up for 24 months	1	386	10.0 $\pm$ 11.8	12.8 $\pm$ 12.4	NA	<b>-2.7 (-5.2, -0.3)</b>	NA
	Participants with baseline BCVA < 69 letters	1	190	13.3 $\pm$ 13.4	18.1 $\pm$ 13.8	NA	<b>-4.7 (-8.8, -0.5)</b>	NA
	Participants with baseline BCVA $\geq$ 69 letters	1	196	6.8 $\pm$ 8.8	7.8 $\pm$ 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	<b>-3.5 (-1.4, -5.7)</b>	NA
Participants with baseline BCVA < 69 letters	1	204	11.8 ± 12.0	18.9 ± 11.5	NA	<b>-6.5 (-10.1, -2.9)</b>	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

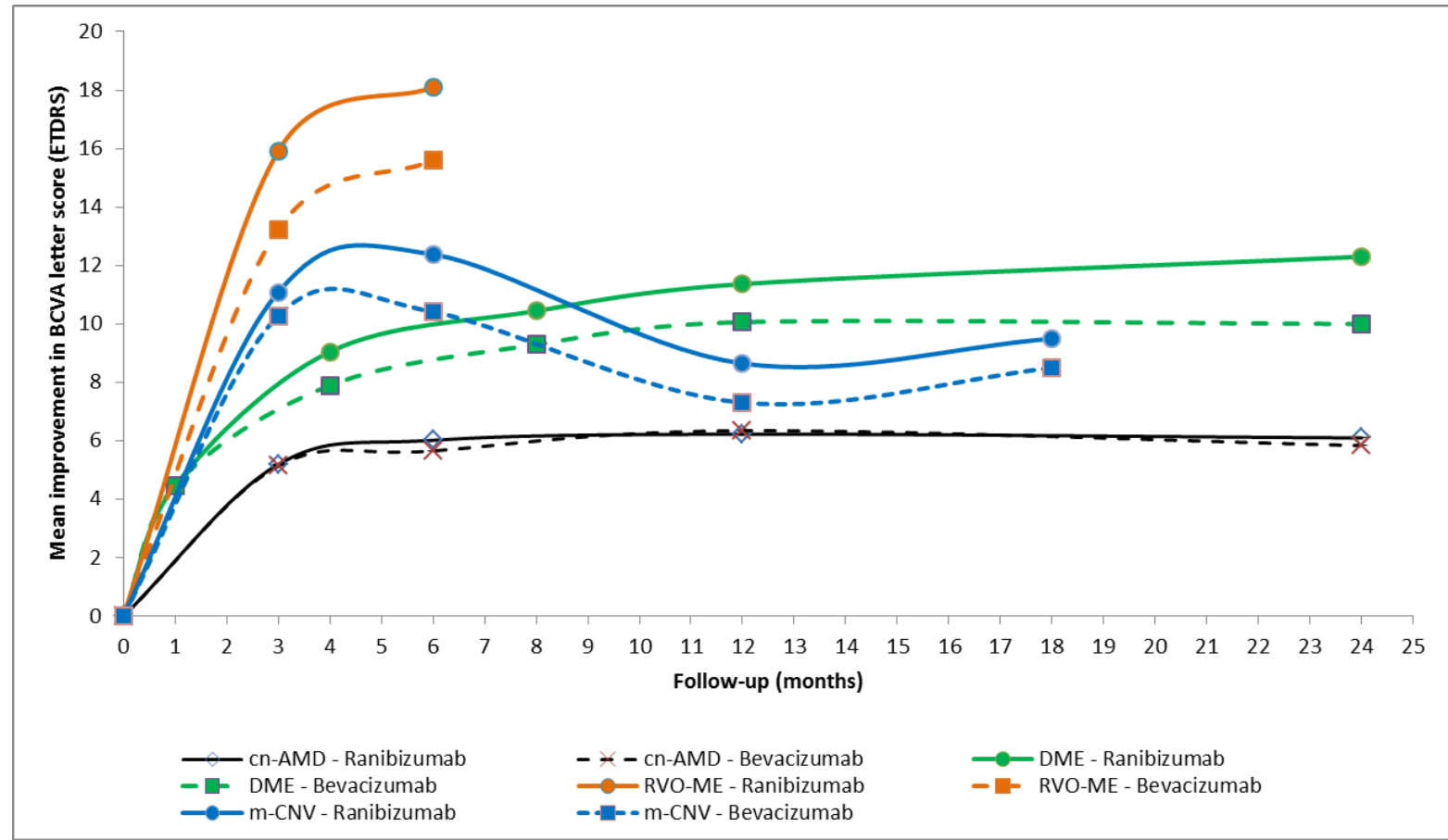
**Footnote:** Bolded estimates indicate statistical significance.

<sup>a</sup> 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.

<sup>b</sup> 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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