Supplementary Online Content

Appendix 1: Detailed methods

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

Protocol

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

Literature Search Strategy

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

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

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

Keywords

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

AND

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

Eligibility Criteria

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

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

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

We included the following efficacy outcomes:

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

We included the following safety outcomes:

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

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

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

Study selection

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

Data abstraction

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

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

Risk of bias assessment

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

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

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

Data Analysis in CADTH report

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

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

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

Data analysis in manuscript

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

Excluded RCT'S

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

Medline Literature Search

Interface: Ovid

Databases:

Embase <1974 to 2015 May 26>

MEDLINE Daily and MEDLINE 1946 to present

MEDLINE In-Process & Other Non-Indexed Citations

Cochrane Central Register of Controlled Trials <April 2015>

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

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

Study Types: Randomized controlled trials

Limits: No date or language limits were used

Human filter was applied

Editorials & letters excluded

Search Strategy:

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1 Retinal Degeneration/

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

3 Macular Degeneration/

4 Wet Macular Degeneration/ [MESH FROM 2010-]

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

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

7 (wAMD or wARMD).tw,kw.

8 Diabetic Retinopathy/

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

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

11 Macular Edema/

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

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

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

15 Retinal Vein Occlusion/

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

17 (BRVO or CRVO).tw,kw.

18 Choroidal Neovascularization/

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

20 CNV.tw,kw.

21 or/2-20 [CONDITIONS – MEDLINE]

22 Vascular Endothelial Growth Factor A/ai

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

24 antiVEGF$1.tw,kw.

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

26 Antibodies, Monoclonal, Humanized/

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

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

29 Angiogenesis Inhibitors/

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

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

32 aflibercept.tw,kw.

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

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

35 aflibercept.rn.

36 Bevacizumab.tw,kw.

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

38 IVB injection$1.tw,kw.

39 Bevacizumab.rn.

40 Pegaptanib.tw,kw.

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

42 Pegaptanib.rn.

43 Ranibizumab.tw,kw.

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

45 IVR injection$1.tw,kw.

46 Ranibizumab.rn.

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

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

49 exp Photochemotherapy/

50 Photosensitizing Agents/

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

52 PDT.tw,kw.

53 or/49-52

54 verteporfin.tw,kw.

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

56 verteporfin.rn.

57 or/54-56

58 53 and 57

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

60 58 or 59 [VISUDYNE PDT – MEDLINE]

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

62 Triamcinolone Acetonide/

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

64 triamcinolone acetonide.rn.

65 Glucocorticoids/

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

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

68 anecortave acetate.rn.

69 Pregnadienediols/

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

71 exp Dexamethasone/

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

73 dexamethasone.rn.

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

75 or/62-74

76 exp Injections/

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

78 or/76-77

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

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

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

82 clinical trials as topic.sh.

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

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

85 trial.ti.

86 or/81-85

87 (48 or 61 or 80) and 86

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

89 87 not 88

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

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

92 89 not (90 or 91)

93 92 use prmz [MEDLINE RCTS]

94 macular degeneration/

95 age related macular degeneration/

96 wet macular degeneration/

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

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

99 (wAMD or wARMD).tw,kw.

100 diabetic retinopathy/

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

102 diabetic macular edema/

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

104 exp macular edema/

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

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

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

108 exp retina vein occlusion/

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

110 (BRVO or CRVO).tw,kw.

111 subretinal neovascularization/

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

113 CNV.tw,kw.

114 or/94-113 [CONDITIONS – EMBASE]

115 vasculotropin inhibitor/

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

117 antiVEGF$1.tw,kw.

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

119 monoclonal antibody/

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

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

122 angiogenesis inhibitor/

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

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

125 aflibercept/

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

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

128 aflibercept.rn.

129 bevacizumab/

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

131 IVB injection$1.tw,kw.

132 Bevacizumab.rn.

133 pegaptanib/

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

135 Pegaptanib.rn.

136 ranibizumab/

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

138 IVR injection$1.tw,kw.

139 Ranibizumab.rn.

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

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

142 photodynamic therapy/

143 photosensitizing agent/

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

145 PDT.tw,kw.

146 or/142-145

147 verteporfin/

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

149 verteporfin.rn.

150 or/147-149

151 146 and 150

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

153 151 or 152 [VISUDYNE PDT – EMBASE]

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

155 triamcinolone/

156 triamcinolone acetonide/

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

158 triamcinolone.rn.

159 triamcinolone acetonide.rn.

160 exp glucocorticoid/

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

162 anecortave/

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

164 anecortave.rn.

165 pregnane derivative/

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

167 dexamethasone/

168 dexamethasone isonicotinate/

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

170 dexamethasone.rn.

171 dexamethasone isonicotinate.rn.

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

173 or/155-172

174 exp injection/

175 intravitreal drug administration/

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

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

178 or/174-177

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

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

181 randomized controlled trial/ or controlled clinical trial/

182 exp "clinical trial (topic)"/

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

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

185 trial.ti.

186 or/181-185

187 (141 or 154 or 180) and 186

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

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

190 188 not 189

191 187 not 190

192 editorial.pt.

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

194 191 not (192 or 193)

195 194 use emczd [EMBASE RCTS]

196 93 or 195 [MEDLINE / EMBASE RCTS]

197 remove duplicates from 196 [TOTAL UNIQUE HITS]

198 197 use prmz [UNIQUE MEDLINE]

199 197 use emczd [UNIQUE EMBASE]

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Appendix 2: Detailed study characteristics

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

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

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

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

Appendix 3: Detailed patient characteristics

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

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

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

Appendix 4: Cochrane risk of bias results for individual studies

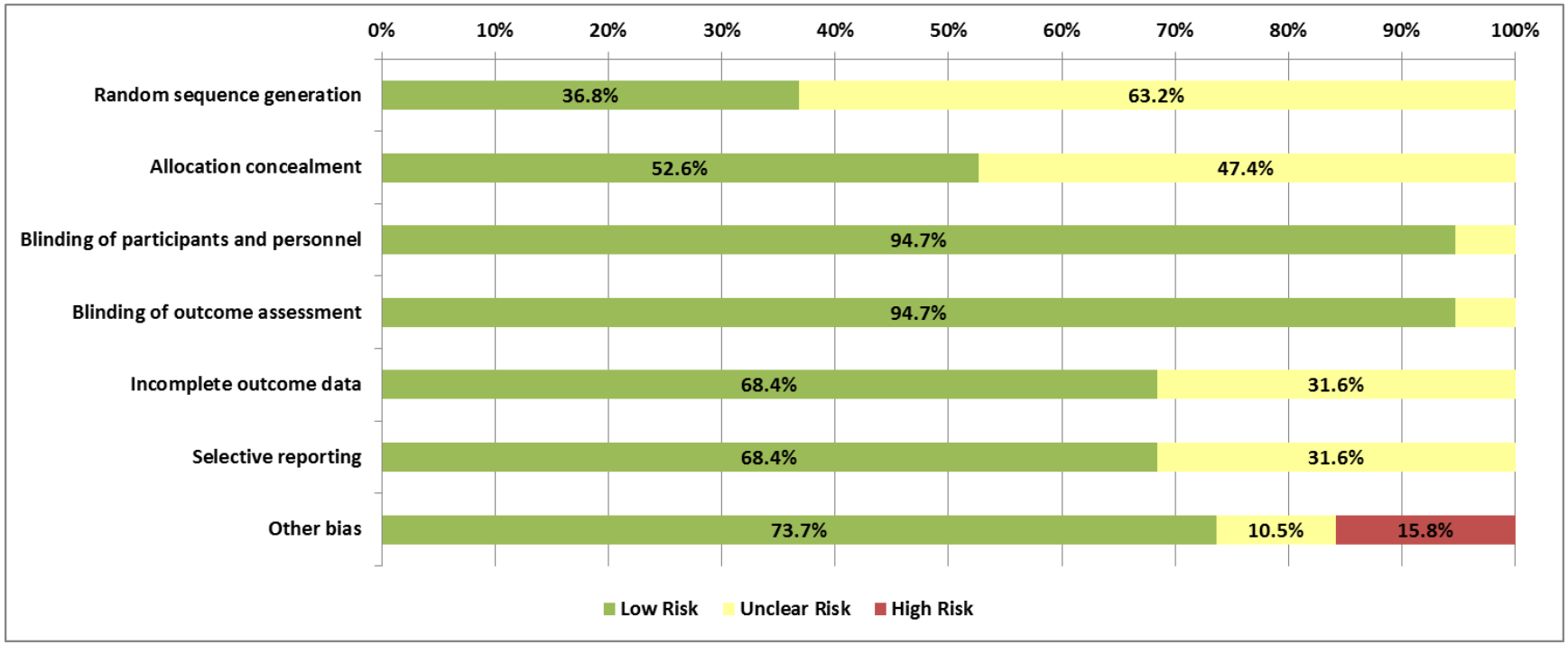
STUDY	Cochrane ROB item						
	1	2	3	4	5	6	7
cn-AMD (n = 12)							
Schauwvlieghe 2016[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Berg 2015[31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Scholler 2014[32]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk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

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

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

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

Appendix 5: Risk of bias results



Appendix 6: Treatment effect estimates

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

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

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

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

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

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

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

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

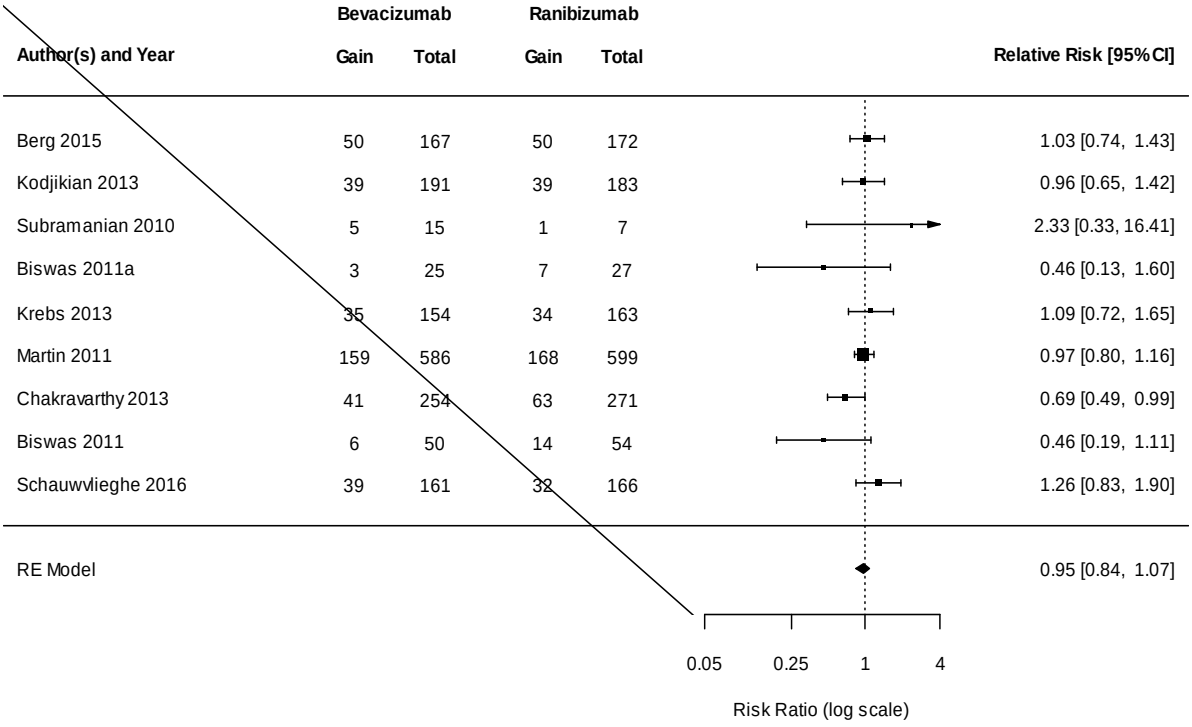
Outcome	Rx vs Ctrl Comparison	No. of RCTs[a]	Total patients	Mean treatment effect estimate[b] [Range]	Mean comparator effect estimate [Range]	Risk Ratio (95% CI)	Risk Difference (95% CI)	I^2
thromboembolic events	Ranibizumab							
	Bevacizumb vs. Ranibizumab	NR	NR	NR	NR	NR	NR	NR
	Bevacizumb vs. Aflibercept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

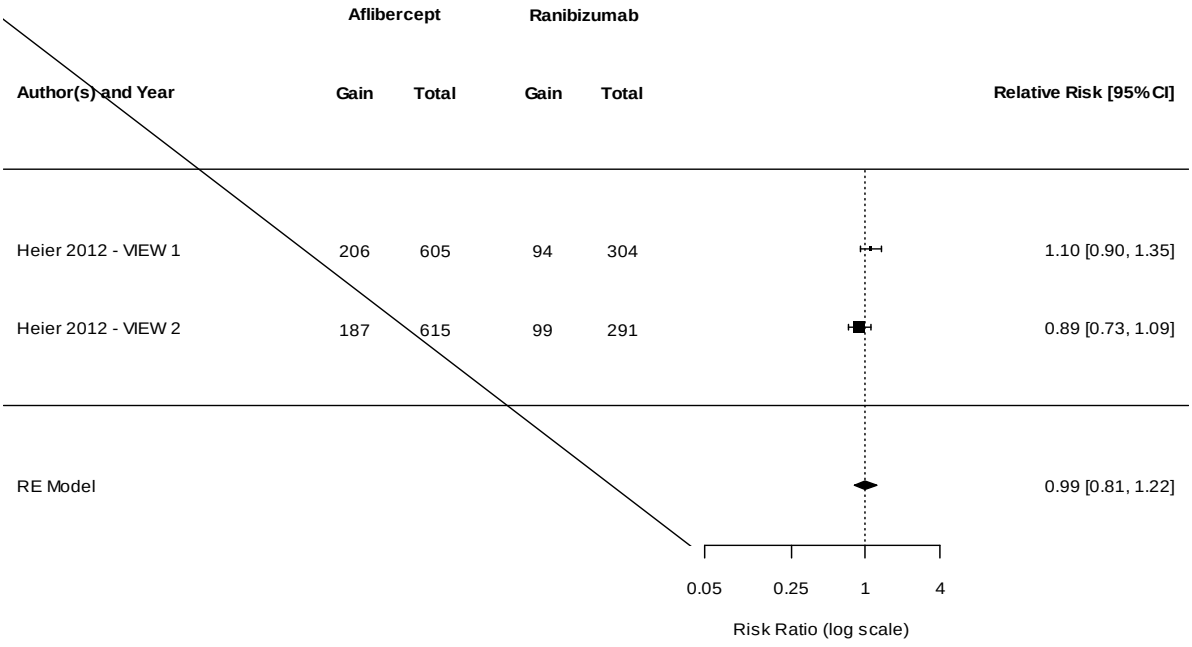
Footnotes:
[a] Meta-analysis was not conducted for comparisons with 1 RCT; the point estimate and 95% confidence interval were calculated using data from a single trial.
[b] The summary statistics were derived by taking the mean and range across estimates from included studies.

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

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

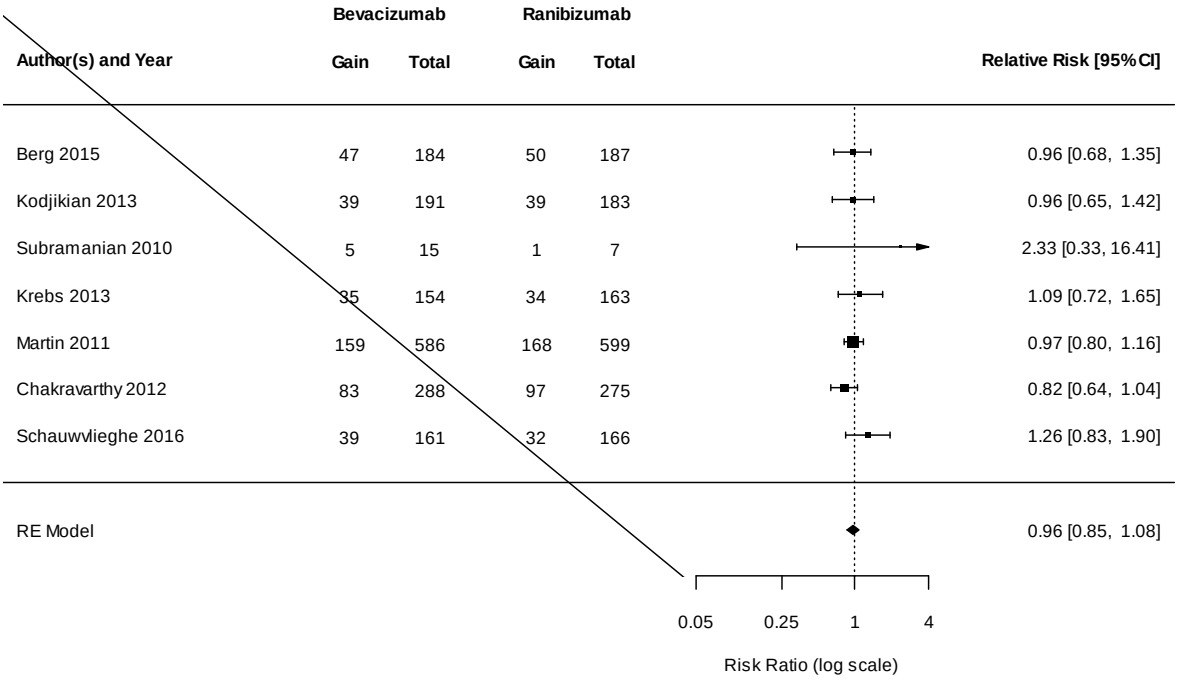
A: Vision gain in cn-AMD population



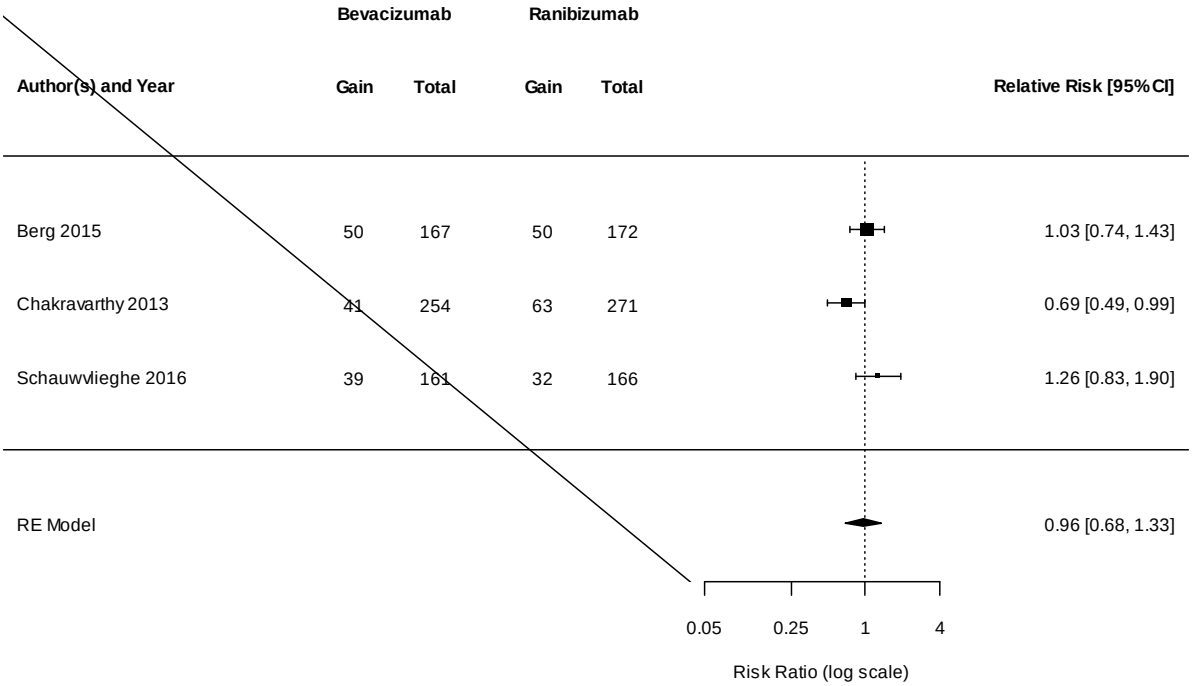


B: Sensitivity analyses for vision gain in cn-AMD population

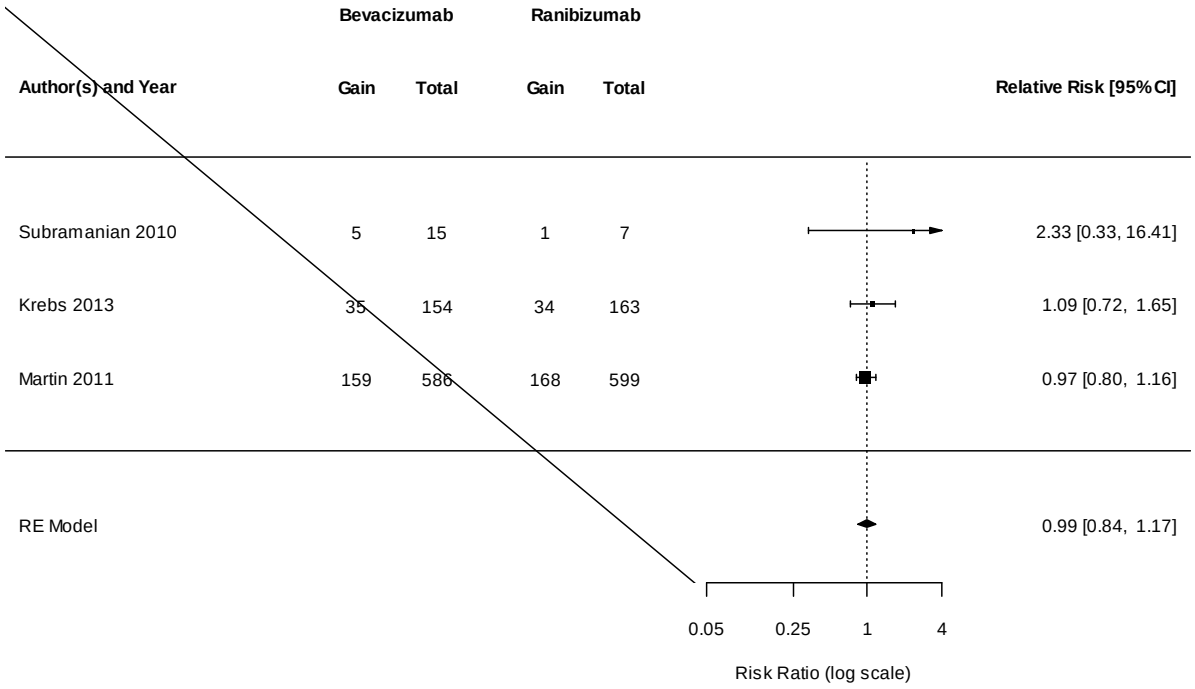
Sensitivity Analysis: 1 Year Follow-Up



Sensitivity Analysis: Low Risk of Selection Bias



Sensitivity Analysis: De Novo Patients



Appendix 8: Summary data used in risk of bias results

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

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

Appendix 9: Sensitivity analysis estimates

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

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

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

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

Appendix 10: Summary of anti-VEGF treatment protocols

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

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

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

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

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

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

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

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

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

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

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

Footnote: Bolded estimates indicate statistical significance.
[a] Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193-1203.
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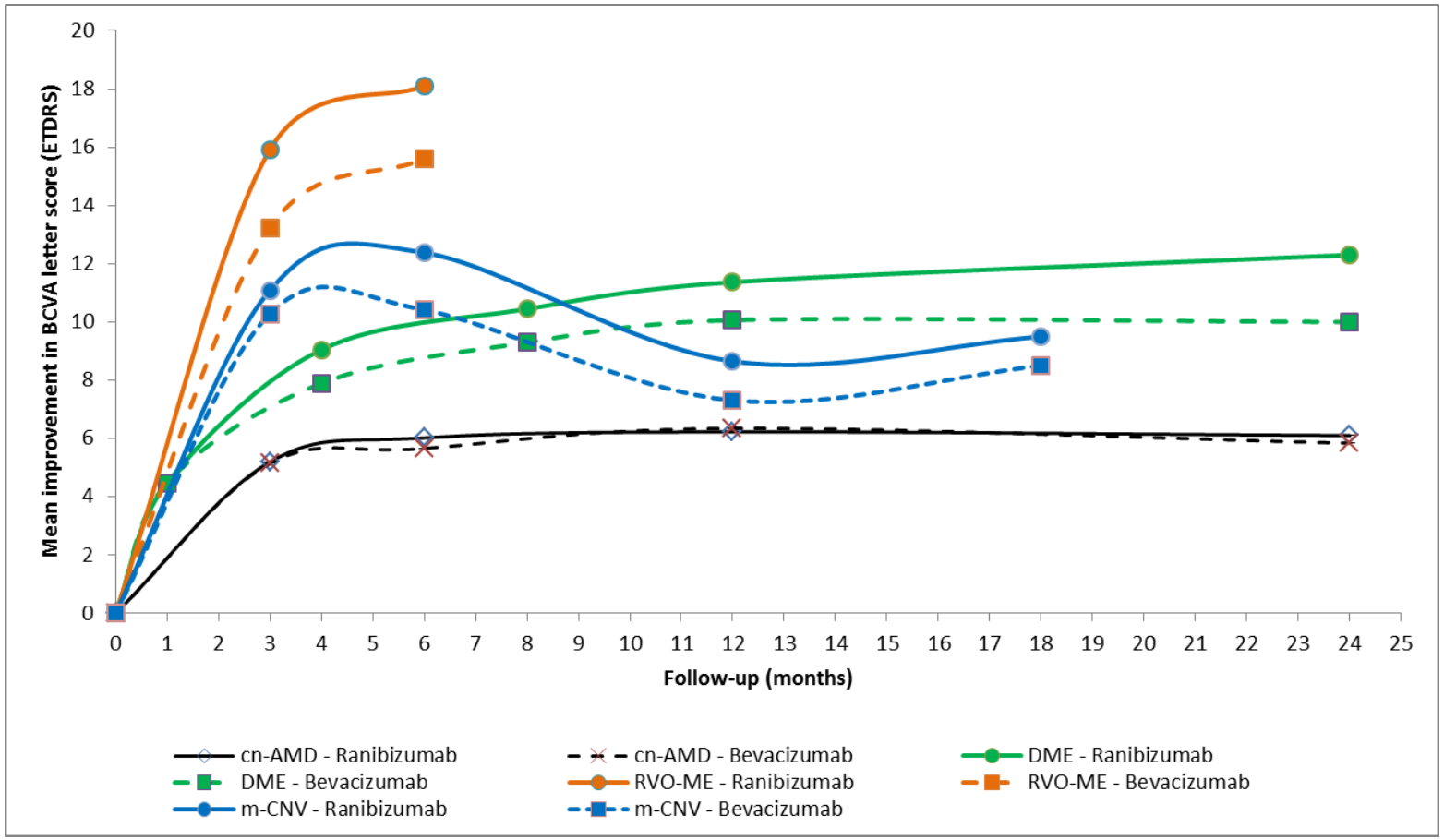
Abbreviations: BCVA - best-corrected visual acuity; CI - confidence interval; ETDRS - Early Treatment Diabetic Retinopathy Study; NA - not applicable; RCT - randomized controlled trials; Rx - treatment; SA - sensitivity analysis; SMD - standardized mean difference

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



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

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