Appendix H: GRADE tables and meta-analysis results

H.1 Classification

H.1.1 Classification systems for age-related macular degeneration (AMD)

RQ6: What effective classification tool should be used to inform people with AMD?

Validation outcomes for existing classification systems of AMD

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS 17 (2006)</td>
<td>AREDS 9-step severity scale</td>
<td>Serious¹</td>
<td>Not applicable (N/A)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1225 eyes from the Age Related Eye Disease Study (AREDS)</td>
<td>Complete agreement: 63.4% of eyes, Agreement within 1 step: 86.6%, Agreement within 2 steps in 93.6%, Unweighted κ statistic (SE): 0.58 (0.015), κ weighted to give 75% credit for 1-step disagreement: 0.73(0.013);</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Danis et al (2013)</td>
<td>AREDS 9-step severity scale</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1335 eyes from the AREDS2 study</td>
<td>Contemporaneous regrades, (interobserver agreement) (n=1335) Agreement: 96% Weighted Kappa (SE): 0.76</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
### Studies Classification System Risk of bias Inconsistency Indirectness Imprecision Clinical population (n) Effect Quality

**AREDS 6, (2001) Retrospective cohort**

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS 4-step severity scale</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1230 eyes from the AREDS study</td>
<td>Interobserver contemporaneous reproducability AMD severity level Agreement- 82.8% Agreement within 1 step: 98.7% Kappa, unweighted (SE)- 0.77 (0.01) Kappa, weighted (SE)- 0.88 (0.01)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**Seddon 2006 Retrospective cohort**

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARMS</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>492 eyes recruited for the Progression of Age-Related Macular Degeneration Study</td>
<td>Agreement between Clinical observations and Reading Centre. Agreement: 75% Agreement within 1 step: 89% Kappa, unweighted (95% CI): 0.63 (0.53-0.74) Kappa, weighted (95% CI): 0.78 (0.62-0.93)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamada (2006) Retrospective cohort</td>
<td>The Modified International Classification of ARM</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>164 images of 106 patients taken from consecutive patients referred to the Retinal Research Unit at King's College Hospital.</td>
<td>Agreement between 2 observers assessments of Age-Related Maculopathy. Agreement: 84% Agreement within 1 step: 90% Kappa, unweighted (95% CI): 0.79 (0.47-1.1) Kappa, weighted (95% CI): 0.86 (0.41-1.3)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Leeuwen (2003) Retrospective cohort</td>
<td>The Modified International Classification of ARM</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>91 subjects in the EUREYE study. 131 images of eyes taken to represent the full range of AMD.</td>
<td>On all 8 stages: digital images Agreement: 59.0 Weighted kappa: 0.72 On all 8 stages: 35-mm film Agreement: 65.7% Weighted kappa: 0.78 On the 5 main stages: digital images Agreement: 64.9% Weighted kappa: 0.74</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (2014) Retrospective cohort</td>
<td>Harmonized Three Continent AMD Consortium Severity Scale</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>60 images from participants of the Beaver Dam Eye Study</td>
<td>Interobserver agreement Exact grading agreement of the 60 eyes between centers: 61.0 - 81.4%, Within-one-step agreement was 84.7 - 98.3% between centers. Weighted kappa scores varied from 0.66 to 0.86</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to lack of clarity regarding baseline characteristics of included participants

### Agreement outcomes: Intraobserver Agreement

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danis et al (2013) Retrospective cohort</td>
<td>AREDS 9-step severity scale</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1335 eyes from the AREDS2 study</td>
<td>AREDS2 Temporal Drift Regrade Year 4 Compared to BL, (intraobserver agreement) (n=88) Agreement: 92% Weighted Kappa (SE): 0.73 (0.02)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS 6, (2001) Retrospec</td>
<td>AREDS 4-step severity scale</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1230 eyes from the AREDS study</td>
<td>Intraobserver temporal reproducability AMD severity level</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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## Validation outcomes for existing sub-classification systems of late wet AMD

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interobserver agreement</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Classification: 1) Classic only, 2) predominantly classic, 3) minimally classic, 4) occult without PED (with or without RAP) and 5) vascularised PED (with or without RAP).</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohens 2007</td>
<td>CAMRS</td>
<td>Very serious¹, ³, ⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>207 patients with newly diagnosed exudative AMD</td>
<td>Lesion classification: Kappa: 0.59 Location of lesion: Kappa: 0.52</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

(1) AMD with type 1 CNV; (2) AMD with type 1 + 2 CNV; (3) AMD with type 2 CNV only; (4) Chorioretinal anastomosis (RAP) (5) PCV, (using fundus phot, FA, FA,)

1. Downgraded one level for risk of bias due to lack of clarity regarding baseline characteristics of included participants

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### Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coscas (2014) Prospective cohort</td>
<td>CAMRS</td>
<td>Very Serious(^1,3)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>99 consecutive Japanese eyes and 94 consecutive French eyes with exudative AMD</td>
<td>Crude agreement with final diagnosis: Range, Kyoto patients (n=99) AMD with type 1 CNV: 79.4 - 91.1% AMD with type 1+2 CNV: 33.3- 66.6% AMD with type 2 CNV: 60.0-100% Chorioretinal anastomosis (RAP): 83.3% PCV with type 1 or 2 CNV: 66.6% PCV without type 1 or 2 CNV: 95.6% Other: 100%</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

\(^1\) Very Serious; \(^2\) Serious; \(^3\) Not serious
### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
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<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coscas (2014) Prospective cohort</td>
<td>CAMRS</td>
<td>Very Serious&lt;sup&gt;1, 3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;7&lt;/sup&gt;</td>
<td>99 consecutive Japanese eyes and 94 consecutive French eyes with exudative AMD</td>
<td>Crude agreement with final diagnosis: &lt;br&gt;Range, Kyoto patients (n=99) &lt;br&gt;AMD with type 1 CNV: 79.4 – 82.3% &lt;br&gt;AMD with type 1+2 CNV: 16.6– 66.6% &lt;br&gt;AMD with type 2 CNV: 40– 80% &lt;br&gt;Chorioretinal anastomosis: 66.6– 83.3% &lt;br&gt;PCV with type 1 or 2 CNV: 33.3% &lt;br&gt;PCV without type 1 or 2 CNV: 56.5–91.3% &lt;br&gt;Other: 66.6–88.8% &lt;br&gt;Range, French patients (n=94) &lt;br&gt;AMD with type 1 CNV: 89.5% &lt;br&gt;AMD with type 1+2 CNV: 36.8– 78.9% &lt;br&gt;AMD with type 2 CNV: 60.0– 100%</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

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### Anatomic classification (OCT, photo and FA): 1) type 1 (sub–retinal pigment epithelium [RPE], incl PCV), 2) type 2 (subretinal), 3) type 3 (intraretinal, RAP), or 4) mixed NV.

### MPS criteria and the Digital Angiographic Reading Center (DARC): occult or classic CNV

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jung (2014) Prospective cohort</td>
<td>CARMS</td>
<td>Serious&lt;sup&gt;1, 6&lt;/sup&gt;</td>
<td>N/A</td>
<td>Serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Not serious</td>
<td>374 treatment naïve patients with neovascular AMD in at least 1 eye</td>
<td>Agreement between FA and anatomic classification: Kappa 0.65</td>
<td>LOW</td>
</tr>
<tr>
<td>1) Classic only, 2) occult only, 3) mixed, or 4) unable to determine</td>
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<td></td>
</tr>
<tr>
<td>Friedman (2000) Retrospective cohort</td>
<td>CARMS</td>
<td>Very serious&lt;sup&gt;1, 3, 4, 6&lt;/sup&gt;</td>
<td>N/A</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not serious</td>
<td>6 fluorescein angiograms read by 21 ophthalmologists</td>
<td>Membrane type Mean agreement, % (SD): 72.5 (23.0) Mean kappa (SD): 0.64 (0.30)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1) classic, 2) occult, or 3) mixed with classic component less or equal/greater than 50%</td>
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<tr>
<td>Holz (2003) Prospective cohort</td>
<td>CARMS</td>
<td>Very serious&lt;sup&gt;1, 3, 4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not serious</td>
<td>40 patients with neovascular ARMD, graded by 16 retinal specialists.</td>
<td>Mean kappa agreement (SD): Randomised series A: 0.40 (0.05) Randomised series B: 0.37 (0.05)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Predominantly classic, minimally classic, or occult</td>
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</tr>
<tr>
<td>Olsen (2004)</td>
<td>CAMRS</td>
<td>Very serious&lt;sup&gt;1, 4, 6&lt;/sup&gt;</td>
<td>N/A</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not serious</td>
<td>200 cases of nAMD from 2 centres</td>
<td>kappa agreement: 0.63</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

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### Macular Degeneration

Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
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<th>Clinical population (n)</th>
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<tbody>
<tr>
<td>Retrosp</td>
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<td>tive cohort</td>
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</tbody>
</table>

1) Classic only 2) Occult only 3) Classic and Occult (mixed <50%/>50% classic) 4) Disciform scar 5) cannot determine 6) Serous PED (present/absent)

| Maguire (2008) Retrospective cohort | CAMRS | Serious¹ | N/A | Serious² | Not serious | 282 eyes developed CNV or serous PED in CAPT trial | Agreement: 80-100% Weighted kappa: 0.75-100 | LOW |

**Intraobserver agreement**

classic, occult, or mixed with classic component less or equal/greater than 50%

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
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<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holz (2003) Prospective cohort</td>
<td>CAMRS</td>
<td>Very serious¹, ³, ⁴</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>40 patients with neovascular ARMD, graded by 16 retinal specialists.</td>
<td>Mean kappa agreement (SD): 0.64 (SD 0.11)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to lack of clarity regarding baseline characteristics of included participants
2. Downgraded one level for people with PCV excluded or unclear inclusion
3. Downgraded one level for lack of clear pre-specified criteria for diagnosis or unclear
4. Downgraded one level for some participants received an extra investigation (e.g. ICG angiography) without a clear criteria RE who should receive the extra investigation, possibly inconsistent between graders. Or unclear consistency of investigation.
5. Downgraded one level for agreement between classifications systems with multiple graders, unclear if relevant.
6. Downgraded one level for unclear grading was done without knowledge of other graders decision
7. Downgraded one level for only crude agreement, no adjustment possible

**Validation outcomes for existing sub-classification systems of late dry AMD**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification System</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brader (2011) CAPT classification of late dry AMD</td>
<td>CAMRS</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>Sample of 15 photographic sets, some</td>
<td>Interobserver variability kappa: 0.536</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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### Macular Degeneration

#### Appendix H: Grade tables and meta-analysis results

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<table>
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<th>Studies</th>
<th>Classification System</th>
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<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of which included lesions that met the new criteria but not the previously used criteria. Regraded 6m.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Intraobserver agreement
classic, occult, or mixed with classic component less or equal/greater than 50%

<table>
<thead>
<tr>
<th>Brader (2011) Retrospective cohort</th>
<th>CAMRS</th>
<th>Serious¹</th>
<th>N/A</th>
<th>Serious²</th>
<th>Not serious</th>
<th>Sample of 15 photographic sets, some of which included lesions that met the new criteria but not the previously used criteria. Regraded 6m.</th>
<th>Intraobserver agreement kappa: 0.845</th>
<th>LOW</th>
</tr>
</thead>
</table>

1. Downgraded one level for risk of bias due to lack of clarity regarding baseline characteristics of included participants
2. Downgraded one level for people with PCV excluded or unclear inclusion

### Clinical risk assessment models: risk outcomes

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<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Units</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Risk of developing neovascular AMD
<p>| Simple Severity Score        |                       |              |                |               |             |                                                                                       |       |        |         |
| Perlee et al (2013) Prospective cohort study | Simple severity score | Very serious¹, ², ⁵ | N/A            | Not serious   | Not serious | Participants in the Age-Related Eye Disease Study (n=2415)                               | HR (95% CI) | Hazard Ratios for Progression to neovascular AMD 0) referent 1) 4.76 (2.43-9.34) | LOW   |</p>
<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification system</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Units</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandberg 4-point scale</td>
<td>Sandberg 4-point scale</td>
<td>Very Serious 1, 2, 3</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious7</td>
<td>patients with unilateral neovascular AMD (127)</td>
<td>HR (95% CI)</td>
<td>Hazards ratio for development of choroidal neovascular membrane (95% confidence intervals) 1.76 (1.18-2.73)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Risk of developing geographic atrophy</td>
<td>Simple Severity Score</td>
<td>Very serious 1, 2, 5</td>
<td>N/A</td>
<td>Not serious</td>
<td>Nots serious</td>
<td>Participants in the Age-Related Eye Disease Study (n=2415)</td>
<td>HR (95% CI)</td>
<td>Hazard Ratios for Progression to geographic atrophy 0) referent 1) 6.97 (3.01-16.14) 2) 9.33 (4.13-21.05) 3) 23.29 (10.59-51.22)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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### Risk of developing advanced AMD

#### Simple Severity Score

<table>
<thead>
<tr>
<th>Studies</th>
<th>Classification system</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Clinical population (n)</th>
<th>Units</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein et al (2011) Prospective cohort study</td>
<td>Simple severity score</td>
<td>Very serious 1, 2, 3</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Participants in the Age-Related Eye Disease Study (n=2846)</td>
<td></td>
<td></td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to the study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)

2. Downgraded one level for risk of bias due to the study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)

3. Downgraded one level for risk of bias due to the confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured)

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4. Downgraded one level for imprecision was defined by crossing the minimum important difference defined by NICE for showing an effect (0.80 or 1.25), if the confidence intervals crossed two lines of minimum important difference this was defined as very serious imprecision.

5. Downgraded one level for risk of bias due to adjustment for confounders (confounding measurement and account).
H.2 Risk factors

H.2.1 Risk factors for development or progression of AMD

RQ2: What risk factors increase the likelihood of a person developing AMD or progressing to late AMD?

### Demographic and medical risk factors

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose aspirin</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Christen (2001) Prosp. cohort</td>
<td>22,071</td>
<td>Very serious¹ ² ³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>HR (95% CI)</td>
<td>0.77 (0.54, 1.11)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Low dose aspirin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Christen (2009) Prosp. cohort</td>
<td>39,876</td>
<td>Very serious¹ ² ³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.03 (0.88, 1.21)</td>
<td>LOW</td>
</tr>
<tr>
<td>Ethnicity (risk of non-exudative AMD) – white as reference category</td>
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<td></td>
</tr>
<tr>
<td>van der Beek (2011) Prosp. cohort</td>
<td>1,772,962</td>
<td>Very serious¹ ² ³ ⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td></td>
<td>LOW</td>
</tr>
</tbody>
</table>

© NICE 2018. All rights reserved. See Notice of rights.
Studies | Sample size | Risk of bias | Inconsistency | Indirectness | Imprecision | Effect measure | Effect size | Quality |
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein (2011) Prospective cohort</td>
<td>44,103</td>
<td>Very serious\textsuperscript{1,2,3,4}</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>0.82 (0.76, 0.88)</td>
<td>Asian American - age 60: 1.28 (1.20, 1.36) Asian American - age 80: 0.92 (0.83, 1.02)</td>
</tr>
<tr>
<td>Exercise (km/day)</td>
<td>\textsuperscript{4}</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2009 Prospective cohort</td>
<td>41,708</td>
<td>Very serious\textsuperscript{1,2,3,4}</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>0.90 (0.83, 0.97)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Cardiorespiratory fitness (10-k performance times) (m/s)

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### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams 2009 Prospective cohort</td>
<td>41,708</td>
<td>Very serious&lt;sup&gt;1,2,3,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>0.92 (0.60, 1.39)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Evidence of bias from sample selection
2. Evidence of bias from study attrition
3. Evidence of bias from outcome measurement
4. Evidence of bias from prognostic factor measurement
5. Downgraded one level for non-significant effect

### Diet and nutrition

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (&lt;1 drink/week as reference category)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ajani (1999) Prospective cohort</td>
<td>21,041</td>
<td>Very serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;3&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>1 drink/week: 0.92 (0.65, 1.30) 2-4 drinks/week: 0.70 (0.51, 0.97) 5-6 drinks/week: 1.25 (0.92, 1.71) ≥1 drink/day: 1.23 (0.96, 1.57)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

| Alpha carotene, per standard deviation increase | | | | | | | | |
| Leeuwen (2005) Prospective cohort | 4,170 | Serious<sup>1</sup> | N/A | Not serious | Serious<sup>3</sup> | HR (95% CI) | 0.99 (0.94, 1.06) | LOW |

<p>| Beta carotene, per standard deviation increase | | | | | | | | |
| Leeuwen | 4,170 | Serious&lt;sup&gt;1&lt;/sup&gt; | N/A | Not serious | Serious&lt;sup&gt;3&lt;/sup&gt; | HR (95% CI) | 1.00 (0.94, 1.06) | LOW |</p>
<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leeuwen (2005) Prospective cohort</td>
<td>Participants of the Rotterdam study (2005)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>1.01 (0.92, 1.10)</td>
<td>LOW</td>
</tr>
<tr>
<td>Leeuwen (2005) Prospective cohort</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>1.01 (0.93, 1.09)</td>
<td>LOW</td>
</tr>
<tr>
<td>Leeuwen (2005) Prospective cohort</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>1.01 (0.97, 1.04)</td>
<td>LOW</td>
</tr>
<tr>
<td>Leeuwen (2005) Prospective cohort</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>0.95 (0.86, 1.05)</td>
<td>LOW</td>
</tr>
<tr>
<td>Leeuwen (2005) Prospective cohort</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>1.02 (0.94, 1.10)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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### Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leeuwen (2005) Prospective cohort</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>0.92 (0.84, 1.00)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Trace elements Iron, per standard deviation increase</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>0.95 (0.86, 1.04)</td>
<td>LOW</td>
</tr>
<tr>
<td>Zinc, per standard deviation increase</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>0.91 (0.83, 0.98)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Combined intake of 4 predefined antioxidant nutrients (vitamins C and E, beta carotene, and zinc) – medium intake as reference category</td>
<td>4,170</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Low: 1.20 (0.92, 1.56) High: 0.65 (0.46, 0.92)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to the study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)

2. Downgraded one level for risk of bias due to the outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition) Downgraded one level for non-significant effect

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### Ocular risk factors

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large drusen</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Drusen (&gt;125,\mu\text{m} vs &lt;63,\mu\text{m}) in diameter: 5.5 (3.5, 8.7)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**Soft distinct drusen vs hard distinct drusen**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Soft distinct drusen vs hard distinct drusen: 3.0 (2.2, 4.1)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**Drusen area**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Drusen area (&gt;16877 \mu\text{m}^2 vs \leq2596 \mu\text{m}^2): 5.2 (3.7, 7.5)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)

### Demographic and medical risk factors

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
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</tr>
<tr>
<td>Klein (2008) Prospective</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Female: 2.8 (1.6, 4.9)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increasing education</strong></td>
<td></td>
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</tr>
<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^5)</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Increasing education 0.6 (0.4, 0.8)</td>
<td>LOW</td>
</tr>
<tr>
<td>Obesity (BMI)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Howard (2014) Prospective cohort</td>
<td>2,641</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Female, non-smoker: BMI (per 2.5 kg/m(^2)): 1.10 (1.02, 1.19)</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Male, non-smoker: BMI (per 2.5 kg/m(^2)): 0.90 (0.75, 1.07)</td>
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<tr>
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<td></td>
<td></td>
<td>Female smoker BMI (per 2.5 kg/m(^2)): 1.07 (0.98, 1.17)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Male smoker BMI (per 2.5 kg/m(^2)): 1.00 (0.90, 1.10)</td>
<td></td>
</tr>
<tr>
<td>Long term use of aspirin</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Klein (2012) Prospective cohort</td>
<td>4,926</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^6)</td>
<td>HR (95% CI)</td>
<td>Regular aspirin use: 0.86 (0.71, 1.05)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Klein</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted</td>
<td>Age (by increasing</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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### Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>75-86 vs 43-54 years: 47.3 (15.5, 144.3) 65-74 vs 43-54 years: 22.9 (8.1, 65.3) 55-64 vs 43-54 years: 5.8 (1.9, 17.3)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

### Age

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>75-86 vs 43-54 years: 47.3 (15.5, 144.3) 65-74 vs 43-54 years: 22.9 (8.1, 65.3) 55-64 vs 43-54 years: 5.8 (1.9, 17.3)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

### Smoking

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Past vs never smokers: 1.16 (0.91, 1.48) Current vs never smokers: 1.47 (1.08, 1.99)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Current vs never smoker: 1.9 (1.03, 3.6) Past vs never smoker: 1.4 (0.9, 2.3)</td>
<td>LOW</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Seddon (2013)* Prospective cohort</td>
<td>2,914</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Past: 1.2 (1.1, 1.4) Current: 1.6 (1.3, 2.1)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Seddon (2013)* Prospective cohort</td>
<td>980</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>Past: 1.0 (0.8, 1.4) Current: 2.2 (1.4, 3.3)</td>
<td>LOW</td>
</tr>
<tr>
<td>Diabetes history</td>
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<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>0.1 (0.02, 0.8)</td>
<td>LOW</td>
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<tr>
<td>History of MI</td>
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<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.13 (0.60, 2.14)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>History of stroke</td>
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<td></td>
</tr>
<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.25 (0.46, 3.38)</td>
<td>VERY LOW</td>
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<tr>
<td>History of CVD</td>
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<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>0.79 (0.46, 1.37)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

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### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>History of angina</td>
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</tr>
<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>0.90 (0.48, 1.71)</td>
<td>VERY LOW</td>
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<tr>
<td>Exercise</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Knudtson et al (2006) Prospective cohort</td>
<td>3,684</td>
<td>Very Serious¹²³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Sedentary: reference Active: 0.9 (0.7, 1.1)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
4. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
5. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
6. Downgraded one level for non-significant effect
7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference

*Seddon (2011), Seddon (2013) and Seddon (2015) all report the same participants from the ARED2 study*

### Diet and nutrition

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased wine drinking</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Klein</td>
<td>3,917</td>
<td>Serious¹²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Time-adjusted</td>
<td>Increased wine</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2008) Prospective cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>odds ratios (95% CI)</td>
<td>drinking 0.6 (0.3, 1.1)</td>
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<tr>
<td>Daily Alcohol consumption, g (none as reference category)</td>
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<tr>
<td>Boekhoorn (2008) Prospective cohort</td>
<td>4,229</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td>≤10: 1.00 (0.76, 1.30) &gt;10 to ≤20: 0.98 (0.70, 1.36) &gt;20: 1.10 (0.80, 1.51)</td>
<td>LOW</td>
</tr>
<tr>
<td>Beta-carotene (quartile 1 as reference category)</td>
<td></td>
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</tr>
<tr>
<td>Chiu (2009) Prospective cohort</td>
<td>2,924</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Q2 (1.5–2.2 mg/day): 1.02 (0.85, 1.22) Q3 (2.2–3.2 mg/day): 0.98 (0.80, 1.18) Q4 (&gt;3.2 mg/day): 0.97 (0.77, 1.21)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Docosahexaenoic acid (quartile 1 as reference category)</td>
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<td></td>
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<tr>
<td>Chiu (2009) Prospective cohort</td>
<td>2,924</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td>Q2 (26.0–41.9 mg/day): 1.13 (0.95, 1.34) Q3 (41.9–64.0 mg/day): 0.98 (0.81, 1.18) Q4 (&gt;64.0 mg/day): 1.09 (0.88, 1.35)</td>
<td>LOW</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (quartile 1 as reference category)</td>
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</tr>
<tr>
<td>Chiu (2009)</td>
<td>2,924</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td>Q2 (12.7–24.6 mg/day):</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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### Macular Degeneration
Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Prospective cohort</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1.07 (0.90, 1.28)</td>
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<td>Q3 (24.6–42.3 mg/day):</td>
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<td></td>
<td></td>
<td></td>
<td>1.01 (0.84, 1.21)</td>
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<td></td>
<td></td>
<td>Q4 (&gt;42.3 mg/day):</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1.01 (0.83, 1.23)</td>
<td></td>
</tr>
</tbody>
</table>

**Low Glycaemic Index (>81.5 as reference category)**

| Chiu (2009)      | 2,924       | Serious¹     | N/A           | Not serious  | Serious⁴     | HR (95% CI)      | 78.6–81.5: 1.15 (0.96, 1.38) | LOW     |
|                 |             |              |               |              |             |                 | 75.2–78.6: 1.05 (0.87, 1.28) |         |
|                 |             |              |               |              |             |                 | 75.2: 1.03 (0.83, 1.29)     |         |

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
4. Downgraded one level for non-significant effect

### H.2.1.2 Development of geographic atrophy (GA) in people due to AMD: risk outcomes for developing GA

#### Ocular risk factors

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract surgery</td>
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<td></td>
<td></td>
<td>Right eye: 0.80 (0.61, 1.06)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Chew (2009)</td>
<td>5,841</td>
<td>Very serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>HR (95% CI)</td>
<td>Left eye: 0.95 (0.71, 1.26)</td>
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</tr>
<tr>
<td>Prospective cohort</td>
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<table>
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<th>Studies</th>
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<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Hyperpigmentation (none as reference category)</td>
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<tr>
<td>CAPT (2008) Prospective cohort</td>
<td>1,052</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>&lt;250 um: 2.82 (1.30, 6.12) &gt;=250 um: 10.4 (4.51, 24.0)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td></td>
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</tr>
<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious¹,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Increased pigment present vs absent: 15.8 (7.6, 32.8)</td>
<td>MODERATE</td>
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<tr>
<td>Retinal pigment epithelium depigmentation</td>
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<td></td>
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<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>RPE depigmentation present vs absent: 11.1 (5.0, 24.4)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Retinal pigment epithelium depigmentation</td>
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</tr>
<tr>
<td>CAPT (2008) Prospective cohort</td>
<td>1,052</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>2.64 (1.26, 5.53)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Pigmentary changes</td>
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</tr>
<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious¹,³,⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Pigmentary Changes: 5.75 (2.09, 15.84)</td>
<td>LOW</td>
</tr>
<tr>
<td>Pigmentary abnormalities</td>
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</tr>
<tr>
<td>Klein (2007) Prospective</td>
<td>3,917</td>
<td>Serious¹,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Pigmentary abnormalities present vs absent:</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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### Macular Degeneration
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<tr>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPT (2008) Prospective cohort</td>
<td>1,052</td>
<td>Serious1</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>10-24%: 2.39 (1.44, 3.97)</td>
<td>MODERATE</td>
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<td></td>
<td></td>
<td>&gt;=25%: 5.10 (2.57, 10.1)</td>
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<tr>
<td>% of area covered by drusen (&lt;10 as reference category)</td>
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<td>Drusen area</td>
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</tr>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious1,3</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Drusen area &gt;16877 µm² vs ≤2596 µm²: 24.0 (3.2, 179)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Large drusen</td>
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<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious1,3,4</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Drusen ≥125µm: 11.73 (1.47, 93.81)</td>
<td>LOW</td>
</tr>
<tr>
<td>Large drusen</td>
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<td></td>
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<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious1,3</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Drusen &gt; 125µm vs &lt;63µm in diameter: 14.5 (5.9, 35.7)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Soft distinct drusen vs hard distinct drusen</td>
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<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious1,3</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious6</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.2 (0.3, 5.7)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Soft indistinct vs soft distinct drusen or hard distinct drusen</td>
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### Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>14.6 (6.8, 31.1)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>41.78 (9.43, 185.14)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious¹,³,⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Reticular pseudodrusen: 4.93 (1.06, 22.93)</td>
<td>LOW</td>
</tr>
<tr>
<td>Grunwald (2014) Prospective cohort</td>
<td>1,024</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>20/50–20/80: 1.66 (1.14, 2.44) 20/100–20/160: 1.70 (1.10, 2.62) 20/200–20/320: 2.65 (1.43, 4.93)</td>
<td>LOW</td>
</tr>
<tr>
<td>Grunwald</td>
<td>1,024</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.69 (1.16, 2.47)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

### Baseline visual acuity (20/25-20/40 as reference category)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunwald (2014) Prospective cohort</td>
<td>1,024</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>20/50–20/80: 1.66 (1.14, 2.44) 20/100–20/160: 1.70 (1.10, 2.62) 20/200–20/320: 2.65 (1.43, 4.93)</td>
<td>LOW</td>
</tr>
<tr>
<td>Grunwald</td>
<td>1,024</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.69 (1.16, 2.47)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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Appendix H: Grade tables and meta-analysis results

### Geographic atrophy in fellow eye

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunwald (2014)</td>
<td>1,024</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>2.07 (1.40, 3.08)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
2. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
3. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
4. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
5. Downgraded one level for non-significant effect
6. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference

### Demographic and medical risk factors

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<td></td>
</tr>
<tr>
<td>CAPT (2008)</td>
<td>1,052</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Suspected: 1.01 (0.76, 1.35)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Definite: 1.98 (1.16, 3.39)</td>
<td></td>
</tr>
<tr>
<td>Age (50-59 years as reference category)</td>
<td>1,052</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>60-69 years:</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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### Macular Degeneration

Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.09 (1.72, 21.5)</td>
<td>70-79 years: 4.12 (1.18, 14.4) &gt;79: 6.39 (1.64, 24.9)</td>
<td></td>
</tr>
<tr>
<td>Prospective cohort</td>
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<td>Age</td>
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<td></td>
</tr>
<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 4.2 (2.9, 6.1)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Prospective cohort</td>
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<tr>
<td>Diabetes mellitus</td>
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</tr>
<tr>
<td>Hahn (2013)</td>
<td>6,621</td>
<td>Very Serious&lt;sup&gt;1,3,4,5&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>1.03 (0.97, 1.09)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td></td>
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<tr>
<td>Long term use of aspirin</td>
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</tr>
<tr>
<td>Klein (2012)</td>
<td>4,926</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>Regular aspirin use: 1.65 (0.91, 2.99)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td></td>
<td></td>
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<tr>
<td>Smoking</td>
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</tr>
<tr>
<td>Klein (2008)</td>
<td>2,119</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Past vs never smokers: 0.88 (0.41, 1.88) Current vs never smokers: 0.18 (0.02, 1.40)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td></td>
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</tbody>
</table>

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## Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of MI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>0.61 (0.07, 5.34)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>History of CVD</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.31 (0.32, 5.27)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>History of angina</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.53 (0.30, 7.85)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Exercise (sedentary as reference group)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Knudtson (2006) Prospective cohort</td>
<td>3,684</td>
<td>Very Serious² ³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Active: 1.1 (0.5, 2.3)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
2. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
3. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
4. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
5. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not...
Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for</td>
<td></td>
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<tr>
<td>6. Downgraded one level for non-significant effect</td>
<td></td>
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<tr>
<td>7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference</td>
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</tr>
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</table>

### Diet and nutrition

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Alcohol consumption, g (0 as reference category)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boekhoo (2008) Prospective cohort</td>
<td>4,229</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td></td>
<td>LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≤10: 1.10 (0.32, 3.80)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;10 to ≤20: 1.38 (0.31, 6.16)</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>&gt;20: 3.27 (0.88, 12.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Fat, g (quintile 1 as reference category)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Quintile 2: 1.14 (0.82, 1.59)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quintile 3: 0.99 (0.70, 1.39)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Quintile 4: 1.54 (1.13, 2.11)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Quintile 5: 1.18 (0.85, 1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Saturated Fat, g (quintile 1 as reference category)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Quintile 2: 1.09 (0.78, 1.51)</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Quintile 3: 1.42 (1.03, 1.95)</td>
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<td></td>
<td>Quintile 4:</td>
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</tbody>
</table>
### Monounsaturated Fat g (quintile 1 as reference category)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.18 (0.85, 1.64)</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Quintile 5: 1.19 (0.87, 1.64)</td>
<td></td>
</tr>
</tbody>
</table>

### Total Polyunsaturated Fatty Acids g (quintile 1 as reference category)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td>0.95 (0.68, 1.33)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quintile 2: 0.95 (0.68, 1.33)</td>
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<td>Quintile 3: 1.22 (0.9, 1.61)</td>
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<td>Quintile 4: 1.38 (0.99, 1.94)</td>
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<td>Quintile 5: 1.47 (1.05, 2.05)</td>
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</tr>
</tbody>
</table>

### Omega-3 fatty acids, Eicosapentaenoic Acid (EPA) - quintile 1 as reference category

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td>0.92 (0.65, 1.30)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quintile 2: 0.92 (0.65, 1.30)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Quintile 3: 1.16 (0.86, 1.58)</td>
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<td></td>
<td>Quintile 4: 1.00 (0.71, 1.39)</td>
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## Studies

<table>
<thead>
<tr>
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<th>Sample size</th>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Omega-3 fatty acids, Docosahexaenoic Acid (DHA) (g) - quintile 1 as reference category</td>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious(^1,2,3)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^4)</td>
<td>HR (95% CI)</td>
<td>Quintile 2: 0.99 (0.73, 1.36) Quintile 3: 1.14 (0.84, 1.53) Quintile 4: 0.93 (0.68, 1.27) Quintile 5: 0.72 (0.52, 1.01)</td>
</tr>
<tr>
<td>Omega-3 fatty acids, DHA + EPA (g) - quintile 1 as reference category</td>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious(^1,2,3)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^4)</td>
<td>HR (95% CI)</td>
<td>Quintile 2: 0.98 (0.70, 1.38) Quintile 3: 1.20 (0.88, 1.64) Quintile 4: 0.91 (0.64, 1.29) Quintile 5: 0.79 (0.55, 1.12)</td>
</tr>
<tr>
<td>Omega-3 fatty acids, Linolenic Acid (g) - quintile 1 as reference category</td>
<td>Reynolds (2013)</td>
<td>4,165</td>
<td>Very serious(^1,2,3)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^4)</td>
<td>HR (95% CI)</td>
<td>Quintile 2: 0.90 (0.64, 1.23) Quintile 3: 1.02 (0.74, 1.42) Quintile 4: 1.06 (0.77, 1.47) Quintile 5:</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Omega-6 Fatty Acids, linoleic acid (g) - quintile 1 as reference category</td>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td>1.08 (0.80, 1.46)</td>
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<td></td>
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<td></td>
<td>Quintile 2: 0.98 (0.70, 1.37)</td>
<td>Quintile 3: 1.04 (0.75, 1.44)</td>
</tr>
<tr>
<td>Omega-6 Fatty Acids, Arachidonic Acid (g) - quintile 1 as reference category</td>
<td>Reynolds (2013) Prospective cohort</td>
<td>4,165</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>HR (95% CI)</td>
<td>1.08 (0.80, 1.46)</td>
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<td></td>
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<td></td>
<td></td>
<td>Quintile 2: 0.92 (0.67, 1.26)</td>
<td>Quintile 3: 0.85 (0.62, 1.17)</td>
</tr>
</tbody>
</table>

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
4. Downgraded one level for non-significant effect

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### Ocular risk factors

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very serious&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>2.1 (1.3, 3.5)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very serious&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.5 (1.0, 2.2)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very serious&lt;sup&gt;1,2,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Large drusen (≥50µm): 2.4 (1.1, 5.1)</td>
<td>LOW</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Very serious&lt;sup&gt;1,2,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Drusen ≥125µm: 1.96 (1.14, 3.36)</td>
<td>LOW</td>
<td></td>
</tr>
</tbody>
</table>
### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large drusen</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Drusen &gt; 125(\mu)m vs &lt;63(\mu)m in diameter: 60.4 (17.7, 206)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**No. of large drusen (quartile 1 as reference category)**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandberg (1998)</td>
<td>127</td>
<td>Very serious(^{1,2,4})</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Quartile 2: 2.09 (0.66, 7.84) Quartile 3: 0.83 (0.20, 3.52) Quartile 4: 3.25 (1.11, 11.75)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

**Drusen area**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Drusen area &gt;16877 (\mu)m(^2) vs (\leq)2596 (\mu)m(^2): 40.4 (5.5, 297)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**Soft distinct drusen vs hard distinct drusen**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Klein et al (2007)</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Soft distinct drusen vs hard distinct drusen: 7.4 (2.4, 22.6)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**Soft indistinct vs soft distinct drusen or hard distinct drusen**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Klein et al (2007)</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Soft indistinct vs soft distinct drusen or hard distinct drusen: 18.3 (8.9, 37.4)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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### Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td><strong>Reticular drusen vs Soft distinct drusen</strong></td>
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<tr>
<td>Klein et al (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>9.89 (2.16, 45.23)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Reticular drusen vs Soft indistinct drusen</strong></td>
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<tr>
<td>Klein et al (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>2.82 (0.66, 12.01)</td>
<td>VERY LOW</td>
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<tr>
<td><strong>Reticular pseudodrusen</strong></td>
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<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious&lt;sup&gt;1,2,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>Reticular pseudodrusen: 1.19 (0.72, 1.94)</td>
<td>VERY LOW</td>
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<tr>
<td><strong>Confluent drusen</strong></td>
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<tr>
<td>Bressler 1990 Prospective cohort</td>
<td>127</td>
<td>Very serious&lt;sup&gt;1,2,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>1.8 (0.8, 3.9)</td>
<td>VERY LOW</td>
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<td><strong>Hyperpigmentation</strong></td>
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<tr>
<td>Macular photocoagulation study group (1997)</td>
<td>670</td>
<td>Very serious&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>2.0 (1.4, 2.9)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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## Macular Degeneration
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td><strong>Hyperpigmentation</strong></td>
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<tr>
<td>Bressler 1990 Prospectve cohort</td>
<td>127</td>
<td>Very serious&lt;sup&gt;1,2,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>2.5 (1.3, 4.9)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Hyperpigmentation (none/questionable as reference category)</strong></td>
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<tr>
<td>CAPT (2008) Prospectve cohort</td>
<td>1,052</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>&lt;250 um: 1.28 (0.94, 1.75) &gt;=250 um: 1.84 (1.22, 2.76)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Hyperpigmentation</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Klein (2007) Prospectve cohort</td>
<td>3,917</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Increased pigment present vs absent: 5.8 (2.9, 11.7)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Retinal pigment epithelium depigmentation</strong></td>
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<td></td>
</tr>
<tr>
<td>Klein et al (2007) Prospectve cohort</td>
<td>3,917</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>RPE depigmentation present vs absent: 7.8 (3.6, 16.6)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Pigmentary changes</strong></td>
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<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious&lt;sup&gt;1,2,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Pigmentary Changes: 2.49 (1.51, 4.10)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Pigmentary abnormalities</strong></td>
<td></td>
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### Macular Degeneration

#### Appendix H: Grade tables and meta-analysis results

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<tr>
<th>Studies</th>
<th>Sample size</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Klein et al (2007)</td>
<td>3,917</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Pigmentary abnormalities present vs absent: 15.2 (7.3, 31.6)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Prospective cohort</td>
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<td></td>
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<tr>
<td>Cataract surgery</td>
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</tr>
<tr>
<td>Chew (2009)</td>
<td>5,841</td>
<td>Very serious(^2,5)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^6)</td>
<td>HR (95% CI)</td>
<td>Right eye 1.20 (0.82, 1.75) Left eye 1.07 (0.72, 1.58)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
4. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
5. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
6. Downgraded one level for non-significant effect
7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference

### Demographic and medical risk factors

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Definite systemic hypertension</td>
<td></td>
<td></td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.7 (1.2, 2.4)</td>
<td>LOW</td>
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<tr>
<td>Macular photocoagulation</td>
<td>670</td>
<td>Very serious(^1,2,3)</td>
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### Studies

<table>
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<tr>
<th>Studies</th>
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<th>Inconsistency</th>
<th>Indirectness</th>
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<th>Effect measure</th>
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<tr>
<td>Prospective cohort</td>
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<td>Hypertension (normal as reference category)</td>
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<tr>
<td>CAPT (2008) Prospective cohort</td>
<td>1,052</td>
<td>Serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>Suspect: 0.69 (0.45, 1.07)</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td>Definite: 1.23 (0.90, 1.68)</td>
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<tr>
<td>Age (50-59 years as reference category)</td>
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<tr>
<td>CAPT (2008) Prospective cohort</td>
<td>1,052</td>
<td>Serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>60-69 years: 2.06 (1.06, 3.97)</td>
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<td>70-79 years: 2.61 (1.39, 4.92)</td>
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<td>&gt;79 years: 2.81 (1.33, 5.94)</td>
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<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 2.9 (2.2, 3.8)</td>
<td>MODERATE</td>
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<tr>
<td>Age</td>
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<tr>
<td>Sandberg (1998) Prospective cohort</td>
<td>127</td>
<td>Very serious¹²⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Age, y, continuous: 1.08 (1.02, 1.14)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

© NICE 2018. All rights reserved. See Notice of rights.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td>Serious²</td>
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<td>Not serious</td>
<td>HR (95% CI)</td>
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<td>MODERATE</td>
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<td>Former: 1.01 (0.76, 1.35) Current: 1.98 (1.16, 3.39)</td>
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</tr>
<tr>
<td>Wilson (2004) Retrospective cohort</td>
<td>326</td>
<td>Serious⁵</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td></td>
<td>MODERATE</td>
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<tr>
<td></td>
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<td>Current smoker: 1.77 (1.06, 2.97)</td>
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<td>Smoking</td>
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<tr>
<td>Klein (2008) Prospective cohort</td>
<td>2,119</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
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<td>VERY LOW</td>
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<td>Past vs never smokers: 1.12 (0.62, 2.01) Current vs never smokers: 0.69 (0.27, 1.76)</td>
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<td>Hahn (2013) Prospective cohort</td>
<td>6,621</td>
<td>Very serious²,³,⁴,⁵</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>1.11 (0.97, 1.27)</td>
<td>VERY LOW</td>
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<tr>
<td>Long term use of aspirin (no regular use as reference category)</td>
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<tr>
<td>Klein (2012) Prospective cohort</td>
<td>4,926</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>Regular aspirin use: 1.07 (0.68, 1.67)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson (2004) Retrospective cohort</td>
<td>326</td>
<td>Serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>0.63 (0.40, 0.98)</td>
<td>MODERATE</td>
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<tr>
<td>History of MI</td>
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</tr>
<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.56 (0.48, 5.08)</td>
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<tr>
<td>History of CVD</td>
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<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.66 (0.65, 4.26)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>History of angina</td>
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<td></td>
</tr>
<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>0.92 (0.27, 3.13)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Exercise</td>
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<tr>
<td>Knudtson (2006) Prospective cohort</td>
<td>3,684</td>
<td>Very Serious&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Sedentary: reference Active: 0.3 (0.1, 0.7)</td>
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<tr>
<td>Ethnicity (white as reference category)</td>
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<tr>
<td>van der Beek (2011)</td>
<td>1,772,962</td>
<td>Very Serious&lt;sup&gt;1,2,3,5&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Black at age 60: Exudative AMD: 0.70 (0.59, 0.83)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td>Prospective cohort</td>
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<td>Blacks at age 80:</td>
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<td>Exudative AMD: 0.45</td>
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<td>(0.37, 0.54)</td>
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<td>Latinos at age 60:</td>
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<td>Exudative AMD: 1.28</td>
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<td>(1.13, 1.45)</td>
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<td>Latinos at age 80:</td>
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<td>Exudative AMD: 0.89</td>
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<td>(0.76, 1.05)</td>
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<td>Asian Americans at</td>
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<td>age 60: Exudative</td>
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<td>AMD: 1.08 (0.89, 1.31)</td>
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<td>Filipino: 1.18 (0.67, 2.09)</td>
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</tr>
</tbody>
</table>
| Steinn (2011)               | 44,103      | Very Serious
1, 2, 3, 5 | N/A           | Not serious   | Very Serious7 | HR (95% CI)   | Vietnamese: 0.70
(0.37, 1.35)            |            |
| Prospective cohort          |             |              |               |              |             |                | Japanese: 0.64 (0.40, 1.04) |            |
|                             |             |              |               |              |             |                | Chinese: 0.95 (0.71, 1.27) |            |
|                             |             |              |               |              |             |                | Filipino: 1.18 (0.67, 2.09) |            |
## Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

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### Diet and nutrition

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol use (&lt;1 drink/week as reference category)</td>
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<tr>
<td>Ajani (1999)</td>
<td>21,041</td>
<td>Very serious(^1,2)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^4)</td>
<td>HR (95% CI)</td>
<td>1 drink/week: 1.12 (0.47, 2.68)</td>
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<td></td>
<td>2-4 drinks/week: 0.88 (0.39, 1.96)</td>
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<td></td>
<td></td>
<td>5-6 drinks/week: 1.20 (0.52, 2.78)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
4. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
5. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
6. Downgraded one level for non-significant effect
7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
### Appendix H: Grade tables and meta-analysis results

#### H.2.1.4 Development of late AMD in people at risk: risk outcomes for developing any late AMD (GA or CNV)

#### Ocular risk factors

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Large drusen</td>
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<td></td>
</tr>
<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Drusen ≥125μm: 2.08 (1.25, 3.49)</td>
<td>LOW</td>
</tr>
<tr>
<td>Large drusen in the fellow eye (&lt;250 μm in diameter in the fellow eye as the reference category)</td>
<td>370</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Drusen ≥250 μm in diameter in the fellow</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

---

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### Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td><strong>Prospective cohort</strong></td>
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<td>Large drusen</td>
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<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious1,2</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Drusen &gt; 125µm vs &lt;63µm in diameter: 29.6 (14.4, 60.7)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Large drusen</strong></td>
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<tr>
<td>Klein (2011)</td>
<td>2,846</td>
<td>Very serious1,2,3</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.79 (1.50, 2.14)</td>
<td>LOW</td>
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<tr>
<td><strong>Largest drusen size in non-advanced eye (&lt;63 µm as reference category)</strong></td>
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<tr>
<td>Seddon (2011)*</td>
<td>2,937</td>
<td>Serious1</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>63-124: 4.1 (1.9, 9.2) 125-249: 7.3 (3.4,15.8) ≥250: 11.7 (5.4, 25.3)</td>
<td>MODERATE</td>
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<tr>
<td><strong>Large drusen in the fellow eye with CNV (&lt;250 µm as reference category)</strong></td>
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<tr>
<td>SST (2009)</td>
<td>370</td>
<td>Serious1,2</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Drusen ≥250 µm in diameter: 1.73 (1.12, 2.66)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Size of drusen for those with no advanced AMD in either eye (&lt;63 µm in both eyes as reference category)</strong></td>
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<tr>
<td>Seddon (2011)*</td>
<td>2,937</td>
<td>Serious1</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>L eye, R eye 63–124, &lt;63: 3.5 (1.9, 6.3) 63–124, 63–124: 7.6 (4.2, 13.5)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tbody>
<tr>
<td><strong>Klein (2011) Prospective cohort</strong></td>
<td>2,846</td>
<td>Very serious(^1,2,3)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Drusen area $&gt;16877 \mu m^2$ vs $\leq 2596 \mu m^2$: 32.3 (7.8, 133)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Seddon (2015) Prospective cohort</strong></td>
<td>2,951</td>
<td>Very Serious(^1,2,4,5)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>63–124: 3.9 (1.7, 8.6) 125–249: 8.4 (3.9, 18.3) $\geq 250$: 13.8 (6.4, 29.5)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Drusen area

**Advanced AMD in one eye: largest drusen size in non-advanced eye, \(\mu m\) (<63 as reference category)**

**No advanced AMD: largest drusen size in each eye, \(\mu m\) (<63 \(\mu m\) in both eyes as reference category)**

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## Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Seddon (2015)* Prospective cohort</td>
<td>2,951</td>
<td>Very Serious(^{1,2,4,5})</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
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<td>LOW</td>
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<td></td>
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<td>L eye, R eye</td>
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<td></td>
<td>63–124, none to &lt;63: 3.0 (1.7, 5.3)</td>
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<td>63–124, 63–124: 7.9 (4.5, 13.8)</td>
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<td>125–249, none to &lt;63: 7.2 (3.9, 13.3)</td>
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<td>125–249, 63–124: 15.2 (9.1, 25.2)</td>
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<td>125–249, 125–249: 29.0 (17.7, 47.5)</td>
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<td>250, ≤124: 31.0 (17.2, 55.9)</td>
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<td>250, 125–249: 50.3 (30.8, 82.2)</td>
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<td>250, ≥250: 72.0 (44.7, 116.2)</td>
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</table>

### Soft distinct drusen vs hard distinct drusen

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<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious(^{1,2})</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Soft distinct drusen vs hard distinct drusen: 3.6 (1.5, 8.6)</td>
<td>MODERATE</td>
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</table>

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### Studies

<table>
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<tr>
<th>Studies</th>
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<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>17.5 (10.3, 29.8)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Reticular drusen vs Soft distinct drusen</strong></td>
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<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>28.29 (9.48, 84.44)</td>
<td>MODERATE</td>
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<tr>
<td><strong>Reticular drusen vs Soft indistinct drusen</strong></td>
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<tr>
<td>Klein (2008) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>N/A</td>
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<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>6.34 (2.28, 17.63)</td>
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<td><strong>Reticular pseudodrusen</strong></td>
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<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>1.20 (0.76, 1.89)</td>
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<td><strong>Pigmentary changes</strong></td>
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<tr>
<td>Finger (2014) Retrospective cohort</td>
<td>200</td>
<td>Very serious¹,²,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>2.55 (1.64, 3.96)</td>
<td>LOW</td>
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<tr>
<td><strong>Pigmentary abnormalities</strong></td>
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<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios</td>
<td>Pigmentary abnormalities present</td>
<td>MODERATE</td>
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</tbody>
</table>

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## Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td><strong>Hyperpigmentation</strong></td>
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<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Increased pigment present vs absent: 10.8 (6.5, 18.0)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Prospective cohort</td>
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<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Increased pigment present vs absent: 9.8 (5.9, 16.3)</td>
<td>MODERATE</td>
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<tr>
<td>Prospective cohort</td>
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<tr>
<td>Virtanen (2008)</td>
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<td>Serious¹,²</td>
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<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Increased pigment present vs absent: 1.7 (1.0, 2.8)</td>
<td>MODERATE</td>
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<tr>
<td>Prospective cohort</td>
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<tr>
<td><strong>Hyperpigmentation in a fellow eye with CNV (no focal hyperpigmentation as reference category)</strong></td>
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<tr>
<td>SST (2009)</td>
<td>370</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Mild/moderate focal hyperpigmentation: 1.43 (0.86, 2.40) Severe focal hyperpigmentation: 2.26 (1.30, 3.94)</td>
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<td>Prospective cohort</td>
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<tr>
<td><strong>Retinal pigment epithelium depigmentation</strong></td>
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<tr>
<td>Klein (2007)</td>
<td>3,917</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>RPE depigmentation present vs absent: 10.5 (5.9, 18.5)</td>
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<td>Prospective cohort</td>
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<td>SST (2009)</td>
<td>370</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.79 (1.14, 2.82)</td>
<td>MODERATE</td>
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<tr>
<td>Prospective cohort</td>
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<tr>
<td><strong>Advanced age related macular degeneration in 1 eye</strong></td>
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<td>Klein (2011)</td>
<td>2,846</td>
<td>Very serious¹,²,³</td>
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<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.21 (1.02, 1.45)</td>
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<td>Prospective cohort</td>
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### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

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<thead>
<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tr>
<td><strong>Advanced AMD in 1 eye</strong></td>
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<tr>
<td>Seddon (2011)*</td>
<td>2,937</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1 eye with geographic atrophy: 7.3 (2.9, 18.4) 1 eye with neovascular disease: 5.1 (2.1, 12.2)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Prospective cohort</td>
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<td>Seddon (2015)*</td>
<td>2,951</td>
<td>Very Serious¹,²,⁴,⁵</td>
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<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Grade 4: 8.3 (3.2, 19.9) Grade 5: 5.8 (2.3, 13.2)</td>
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<td><strong>Geographic atrophy in the fellow eye with CNV</strong></td>
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<td>SST (2009)*</td>
<td>370</td>
<td>Serious¹,²</td>
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<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.82 (1.08, 3.08)</td>
<td>MODERATE</td>
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<td>Prospective cohort</td>
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</tbody>
</table>

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
4. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
5. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
6. Downgraded one level for non-significant effect

*Seddon (2011), Seddon (2013) and Seddon (2015) all report the same participants from the ARED2 study

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### Demographic and medical risk factors

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<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td>Low dose aspirin</td>
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<tr>
<td>Christen (2009)</td>
<td>39,876</td>
<td>Very serious(^1,2,3)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^6)</td>
<td>HR (95% CI)</td>
<td>0.90 (0.53, 1.52)</td>
<td>VERY LOW</td>
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<tr>
<td>Prospective cohort</td>
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<td>Long term use of aspirin</td>
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<tr>
<td>Klein (2012)</td>
<td>4,926</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^6)</td>
<td>HR (95% CI)</td>
<td>Regular aspirin use: 1.21 (0.84, 1.74)</td>
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<tr>
<td>Prospective cohort</td>
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<tr>
<td>Obesity (BMI)</td>
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<td>Howard (2014)</td>
<td>2,641</td>
<td>Serious(^1,2)</td>
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<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Female, non-smoker BMI (per 2.5 kg/m(^2)): 1.31 (1.15, 1.50)</td>
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<td>Prospective cohort</td>
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<td>Male, non-smoker BMI (per 2.5 kg/m(^2)): 0.86 (0.61, 1.20)</td>
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<td>Female smoker BMI (per 2.5 kg/m(^2)): 0.99 (0.81, 1.21)</td>
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<tr>
<td>Obese (≥30)</td>
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<tr>
<td>Obesity (BMI)</td>
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<tr>
<td>Lechanteur (2012)</td>
<td>108</td>
<td>Serious(^1,2)</td>
<td>N/A</td>
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<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Overweight (25–30): 1.3 (0.8, 2.1) Obese (≥30): 2.2 (1.1, 4.1)</td>
<td>MODERATE</td>
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<td>Prospective cohort</td>
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<tr>
<td>Seddon (2003) Prospective cohort</td>
<td>261</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>25-29: 2.32 (1.32, 4.07) ≥30: 2.35 (1.27, 4.34)</td>
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<td>Obesity (BMI) - &lt;25 as reference category</td>
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<tr>
<td>Seddon (2011)* Prospective cohort</td>
<td>2,937</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>25–29: 1.1 (0.9, 1.3) ≥30: 1.3 (1.1, 1.6)</td>
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<td>Obesity (BMI) - &lt;25 as reference category</td>
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<td>Seddon (2013)* Prospective cohort</td>
<td>2,914</td>
<td>Serious¹²</td>
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<td>HR (95% CI)</td>
<td>25–29: 1.1 (0.9, 1.3) ≥30: 1.3 (1.1, 1.6)</td>
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<tr>
<td>Seddon (2015)* Prospective cohort</td>
<td>2,951</td>
<td>Very serious¹²³⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>25–29: 1.1 (0.9, 1.3) ≥30: 1.2 (1.0, 1.5)</td>
<td>LOW</td>
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<tr>
<td>Current smoker</td>
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<tr>
<td>Klein (2011) Prospective cohort</td>
<td>2,846</td>
<td>Very serious¹²⁵</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.78 (1.37, 2.31)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Seddon (2003) Prospective cohort</td>
<td>261</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>Past: 1.32 (0.82, 2.12) Current: 1.99 (0.90, 4.43)</td>
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<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
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<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
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<td><strong>Ve cohort</strong></td>
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<tr>
<td>Smoking (pack years) – 0 to 1 as reference category</td>
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<tr>
<td>Lechanteur (2012) Prospective cohort</td>
<td>108</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1 to 40: 2.4 (1.3, 4.5)</td>
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<td>≥40: 4.4 (1.4, 14.3)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Seddon (2011)* Prospective cohort</td>
<td>2,937</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Past: 1.1 (1.0, 1.3)</td>
<td>MODERATE</td>
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<td>Current: 1.8 (1.4, 2.3)</td>
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<td><strong>Family History of AMD</strong></td>
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<tr>
<td>Klein (2011) Prospective cohort</td>
<td>2,846</td>
<td>Very serious¹,²,⁵</td>
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<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>1.40 (1.16, 1.70)</td>
<td>LOW</td>
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<tr>
<td>Age</td>
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<td></td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 3.5 (2.8, 4.4)</td>
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</tr>
<tr>
<td>Klein (2007) Prospective cohort</td>
<td>3,917</td>
<td>Serious¹,²</td>
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<td>HR (95% CI)</td>
<td>Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 3.5 (2.8, 4.4)</td>
<td>MODERATE</td>
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<tr>
<td>Age (&lt;65 as reference category)</td>
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<tr>
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<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>65 to 70: 1.2 (0.5, 2.7)</td>
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<td>70 to 75: 1.5 (0.7, 3.1)</td>
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<td>75 to 80: 2.6 (1.3, 5.3)</td>
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<td>≥80: 5.0 (2.0, 12.5)</td>
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<tr>
<td>Age (&lt;65 as reference category)</td>
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<tr>
<td>Seddon (2011)* Prospective cohort</td>
<td>2,937</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>65–74: 1.4 (1.1, 1.7)</td>
<td>MODERATE</td>
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<table>
<thead>
<tr>
<th>Studies</th>
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<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tr>
<td>(2011)*</td>
<td>Prospecti ve cohort</td>
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<td>Age (&lt;65 as reference category)</td>
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<tr>
<td>Seddon (2013)*</td>
<td>2,914</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>65-74: 1.4 (1.1, 1.7)</td>
<td>MODERATE</td>
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<tr>
<td></td>
<td>≥75: 2.0 (1.6, 2.5)</td>
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<tr>
<td>Age (≥75 as reference category)</td>
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<tr>
<td>Seddon (2015)*</td>
<td>980</td>
<td>Serious¹,²</td>
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<td>Not serious</td>
<td>HR (95% CI)</td>
<td>65–74: 0.8 (0.6, 0.9)</td>
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<td>55–64: 0.6 (0.5, 0.7)</td>
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<tr>
<td>Klein (2013)</td>
<td>1,700</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.04 (0.36, 3.02)</td>
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<td>History of CVD</td>
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<td>Klein (2013)</td>
<td>1,700</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>1.33 (0.59, 3.01)</td>
<td>VERY LOW</td>
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<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tr>
<td>Klein (2013) Prospective cohort</td>
<td>1,700</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious⁷</td>
<td>Time-adjusted odds ratios (95% CI)</td>
<td>0.89 (0.32, 2.50)</td>
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<td>Cardiovascular disease</td>
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<td>261</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>1.21 (0.73, 2.02)</td>
<td>LOW</td>
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<tr>
<td>Gender (male as reference category)</td>
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<td>Lechanteur (2012) Prospective cohort</td>
<td>108</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Female: 2.6 (1.4, 5.0)</td>
<td>MODERATE</td>
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<td>Gender (female as reference category)</td>
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<tr>
<td>Seddon (2011)* Prospective cohort</td>
<td>2,937</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>Male: 1.0 (0.9, 1.2)</td>
<td>LOW</td>
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<td>Gender (female as reference category)</td>
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<td>Seddon (2013)* Prospective cohort</td>
<td>2,914</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>Male: 1.0 (0.8, 1.1)</td>
<td>LOW</td>
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<td>Gender (female as reference category)</td>
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<tr>
<td>Seddon (2013)* Prospective cohort</td>
<td>980</td>
<td>Serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>HR (95% CI)</td>
<td>Male: 1.0 (0.8, 1.2)</td>
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### Studies: Gender (female as reference category)

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<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tr>
<td>Seddon (2015)*</td>
<td>2,951</td>
<td>Very serious&lt;sup&gt;1,2,3,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>Male: 1.1 (0.9, 1.2)</td>
<td>VERY LOW</td>
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### Studies: Education (£ high school as reference category)

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<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<tr>
<td>Lechanteur (2012)</td>
<td>108</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>&gt; high school: 0.6 (0.4, 1.1)</td>
<td>LOW</td>
</tr>
<tr>
<td>Seddon (2011)*</td>
<td>2,937</td>
<td>Serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>&gt; high school: 0.9 (0.8, 1.0)</td>
<td>LOW</td>
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<tr>
<td>Seddon (2013)*</td>
<td>2,914</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>&gt; high school: 0.9 (0.8, 1.0)</td>
<td>LOW</td>
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<tr>
<td>Seddon (2013)*</td>
<td>980</td>
<td>Serious&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>&gt; high school: 0.8 (0.6, 1.0)</td>
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<tr>
<td>Seddon (2015)*</td>
<td>2,951</td>
<td>Very serious&lt;sup&gt;1,2,3,4&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>&gt; high school: 0.9 (0.8, 1.0)</td>
<td>VERY LOW</td>
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Studies | Sample size | Risk of bias | Inconsistency | Indirectness | Imprecision | Effect measure | Effect size | Quality
---|---|---|---|---|---|---|---|---
1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
4. Evidence of bias from the prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
5. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
6. Downgraded one level for non-significant effect
7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
*Seddon (2011), Seddon (2013) and Seddon (2015) all report the same participants from the ARED2 study

### Diet and nutrition

<table>
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<tr>
<th>Studies</th>
<th>Sample size</th>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td>Daily Alcohol consumption, g (0 as reference category)</td>
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<td>Boekhöorn (2008) Prospective cohort</td>
<td>4,229</td>
<td>Serious(^1,2)</td>
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<td>Serious(^3)</td>
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<td>≤10: 1.00 (0.53, 1.89) &gt;10 to ≤20: 0.77 (0.33, 1.80) &gt;20: 1.01 (0.46, 2.21)</td>
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<td>Dietary glycaemic index (quintile 1 as reference category)</td>
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<tr>
<td>Chiu (2007) Prospective cohort</td>
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<td>Serious(^1,2)</td>
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<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Quintile 2: 1.12 (0.90, 1.40) Quintile 3: 1.14 (0.90, 1.44) Quintile 4:</td>
<td>MODERATE</td>
</tr>
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</table>

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## Appendix H: Grade tables and meta-analysis results

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<tr>
<th>Studies</th>
<th>Sample size</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
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<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td>Low dietary glycaemic index (&gt;81.5 as reference category)</td>
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<tr>
<td>Chiu (2009) Prospective cohort</td>
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<td>HR (95% CI)</td>
<td>1.20 (0.94, 1.52)</td>
<td>Quintile 5: 1.39 (1.08, 1.79)</td>
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<td>Beta-carotene (quartile 1 as reference category)</td>
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<tr>
<td>Chiu (2009) Prospective cohort</td>
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<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>Q2 (1.5–2.2 mg/day): 0.97 (0.80, 1.19)</td>
<td>Q3 (2.2–3.2 mg/day): 1.11 (0.90, 1.37)</td>
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<td>Docosahexaenoic acid (quartile 1 as reference category)</td>
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<td>Not serious</td>
<td>HR (95% CI)</td>
<td>Q2 (26.0–41.9 mg/day): 0.97 (0.80, 1.18)</td>
<td>Q3 (41.9–64.0 mg/day): 1.04 (0.85, 1.28)</td>
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<td>Eicosapentaenoic acid (quartile 1 as reference category)</td>
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<td>Chiu</td>
<td>2,924</td>
<td>Serious¹</td>
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<td>Not serious</td>
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<td>HR (95% CI)</td>
<td>Q2 (12.7–24.6)</td>
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### Macular Degeneration

#### Appendix H: Grade tables and meta-analysis results

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<tr>
<th>Studies</th>
<th>Sample size</th>
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<th>Indirectness</th>
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<th>Effect measure</th>
<th>Effect size</th>
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<td>Total fat (quartile 1 as reference category)</td>
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<td>Seddon (2003) Prospective cohort</td>
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<td>Serious¹</td>
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<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
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<td>Seddon (2003) Prospective cohort</td>
<td>261</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
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<td>Vegetable fat (quartile 1 as reference category)</td>
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<td>HR (95% CI)</td>
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### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

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<tr>
<th>Studies</th>
<th>Sample size</th>
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<th>Inconsistency</th>
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<th>Imprecision</th>
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<th>Effect size</th>
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<tr>
<td>Seddon (2003) Prospective cohort</td>
<td>261</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
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<td></td>
<td>2nd quartile: 0.97 (0.49, 1.93)</td>
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<td>4th quartile: 2.09 (0.83, 5.28)</td>
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<td><strong>Monounsaturated fat (quartile 1 as reference category)</strong></td>
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<td>Seddon (2003) Prospective cohort</td>
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<td>Serious¹</td>
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<td>Serious³</td>
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<td>3rd quartile: 2.13 (1.03, 4.43)</td>
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<td>4th quartile: 2.21 (0.90, 5.47)</td>
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<td><strong>Polyunsaturated fat (quartile 1 as reference category)</strong></td>
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<td>HR (95% CI)</td>
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<td>2nd quartile: 1.57 (0.82, 3.02)</td>
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<td>3rd quartile: 1.90 (0.94, 3.84)</td>
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<td>4th quartile: 2.28 (1.04, 4.99)</td>
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<td><strong>Transunsaturated fat (quartile 1 as reference category)</strong></td>
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<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HR (95% CI)</td>
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<td>2nd quartile: 1.67 (0.83, 3.36)</td>
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<td>3rd quartile: 2.39 (1.10, 5.17)</td>
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<th>Studies</th>
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<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
<th>Quality</th>
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<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>1: 1.30 (0.78, 2.16) ≥2: 0.88 (0.49, 1.60)</td>
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<td>High-fat dairy (quartile 1 as reference category)</td>
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<td>Seddon (2003) Prospective cohort</td>
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<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>2nd quartile: 2.08 (1.09, 3.97) 3rd quartile: 1.80 (0.96, 3.38) 4th quartile: 1.91 (0.98, 3.73)</td>
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<td>Meat (quartile 1 as reference category)</td>
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<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>HR (95% CI)</td>
<td>2nd quartile: 1.75 (0.91, 3.34) 3rd quartile: 1.62 (0.81, 3.24) 4th quartile: 2.09 (0.98, 4.47)</td>
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<td>Processed baked goods (quartile 1 as reference category)</td>
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<td>2nd quartile: 1.21 (0.69, 2.26) 3rd quartile: 2.02 (1.06, 3.85) 4th quartile: 2.42 (1.21, 4.84)</td>
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<td>Number of servings of nuts per week (&lt;1 as reference category)</td>
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<td>Seddon</td>
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<td>Serious³</td>
<td>HR (95% CI)</td>
<td>1: 0.69 (0.40, 1.17)</td>
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<table>
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<th>Studies</th>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Effect measure</th>
<th>Effect size</th>
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<td>(2003) Prospective cohort</td>
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<td>≥2: 0.60 (0.32, 1.02)</td>
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<td>Taking antioxidants (clinical trial)</td>
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<td>Serious³</td>
<td>HR (95% CI)</td>
<td>0.9 (0.8, 1.0)</td>
<td>LOW</td>
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<tr>
<td>1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)</td>
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<td>2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)</td>
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<td>3. Downgraded one level for non-significant effect</td>
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*Seddon (2011), Seddon (2013) and Seddon (2015) all report the same participants from the ARED2 study
### H.2.1 Strategies to slow the progression of age-related macular degeneration (AMD)

**RQ7:** What is the effectiveness of strategies to reduce the risk of developing AMD in the unaffected eye or slow the progression of AMD?

The GRADE tables in this section were produced as part of a collaboration between the Cochrane Eyes and Vision group and the NICE Internal Clinical Guidelines Team.

#### Statin for age-related macular degeneration

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<th>Number of studies</th>
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<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
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<tr>
<td>AMD progression</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>114</td>
<td>RR 0.78 (0.50, 1.02)</td>
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<tr>
<td>Adverse outcomes</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>114</td>
<td>RR 0.64 (0.39, 0.92)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for incomplete outcome data, data missing for 30% participants at 3 years follow-up
2. Downgraded one level for confidence interval crossing 1 lines of a defined minimal important difference

#### Omega 3 fatty acids compared to placebo for slowing the progression of age-related macular degeneration

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of 3 or more lines of visual acuity at 24 months</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious¹</td>
<td>236</td>
<td>RR 1.14, (0.53, 2.45)</td>
<td>LOW</td>
</tr>
<tr>
<td>Loss of 3 or more lines of visual acuity at 36 months</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious¹</td>
<td>230</td>
<td>RR 1.25, (0.69, 2.26)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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## Macular Degeneration
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (NAT 2013)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious¹</td>
<td>224</td>
<td>RR 1.06, (0.47,2.40)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Incidence of CNV at 36 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (NAT 2013)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious¹</td>
<td>195</td>
<td>RR 1.12, (0.53 , 2.38)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Progression of AMD over 5 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (ARES and NAT)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>2343</td>
<td>HR 0.96, (0.84 , 1.1)</td>
<td>HIGH</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (ARES and NAT)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>2343</td>
<td>RR 1.01, (0.94 , 1.09)</td>
<td>HIGH</td>
</tr>
<tr>
<td><strong>Visual acuity (ETDRS letters; higher is better)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Ute E K 2015)</td>
<td>RCT</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>79</td>
<td>MD 1.00, (-2.50 , 4.50)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
2. Downgraded one level for risk of bias due to study design (open label)

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## Meta-analysis: Omega 3 fatty acids vs placebo: progression of AMD

**Review**: Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration  
**Comparison**: Omega 3 fatty acids versus control  
**Outcome**: 1 Progression of AMD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log (Hazard Ratio)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Weight</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS2 (O)</td>
<td>-0.0305 (0.009820)</td>
<td>0.97 (0.86, 1.11)</td>
<td>92.5%</td>
<td>92.5%</td>
</tr>
<tr>
<td>N472 (R)</td>
<td>-0.1165 (0.2456)</td>
<td>0.89 (0.55, 1.44)</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.96 (0.84, 1.10)</td>
</tr>
</tbody>
</table>

**Heterogeneity**: CHF = 0.11, df = 1, P = 0.74; P = 0.0%
**Test for overall effect**: I² = 32% (P = 0.59)
**Test for subgroup differences**: Not applicable

1. Progression over 5 years: unit of analysis eye, adjusted for within-person correlation.  
2. Incidence of CNU in fellow eye over 3 years: unit of analysis study eye, one per person; adjusted for age, smoking and stage of maculopathy.
### Laser treatment of drusen to prevent progression of advanced age-related macular degeneration

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of CNV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of geographic atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (CNVPT, laser to Drusen study 1995)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>148 (148 eyes)</td>
<td>RR* 1.27, (0.41, 3.94)</td>
<td>LOW</td>
</tr>
<tr>
<td>Visual loss of 2-3+ lines of visual acuity at 3-year follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Number of studies

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (CNVPT, PTAMD bilateral 2009, PTAMD unilateral 2002)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>Not Serious</td>
<td>570 (944 eyes)</td>
<td>RR* 4.47 (1.64, 12.19)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
2. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
3. Downgraded one level for risk of bias due to visual acuity examiners were masked in less than half of studies
4. Downgraded one level for heterogeneity (i²=89%)

*Converted from odds ratios reported in included Cochrane review
Meta-analysis: Laser treatment of drusen to prevent progression to advanced AMD

### Development of CNV

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Photocoagulation</th>
<th>Control</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral studies (CMT)</td>
<td>41/1008</td>
<td>50/1008</td>
<td>22.6</td>
<td>0.81 (0.53, 1.24)</td>
<td></td>
</tr>
<tr>
<td>DLS</td>
<td>12/103</td>
<td>7/103</td>
<td>7.9</td>
<td>1.82 (0.66, 4.89)</td>
<td></td>
</tr>
<tr>
<td>Figliano 1994</td>
<td>0/31</td>
<td>1/30</td>
<td>0.5</td>
<td>0.32 (0.01, 8.26)</td>
<td></td>
</tr>
<tr>
<td>Linte 1995</td>
<td>3/27</td>
<td>5/27</td>
<td>3.8</td>
<td>0.55 (0.12, 2.58)</td>
<td></td>
</tr>
<tr>
<td>DB 1999</td>
<td>3/31</td>
<td>3/65</td>
<td>3.1</td>
<td>2.21 (0.42, 11.66)</td>
<td></td>
</tr>
<tr>
<td>HTMD Bilateral 2008</td>
<td>24/121</td>
<td>20/225</td>
<td>14.5</td>
<td>1.22 (0.65, 2.30)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1470</td>
<td>1458</td>
<td>53.9</td>
<td>0.89 (0.72, 1.11)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 53 Photocoagulation: 63 Control: 64 Heterogeneity: Test for overall effect: \( I^2 = 0.07 \) \( P = 0.99 \)

<table>
<thead>
<tr>
<th>Bilateral studies</th>
<th>CNVPT</th>
<th>Laser device study 1995</th>
<th>DB 1999</th>
<th>HTMD unilateral 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>12/45</td>
<td>13/47</td>
<td>12/51</td>
<td>13/63</td>
</tr>
</tbody>
</table>

Heterogeneity: Test for overall effect: \( I^2 = 0.72 \) \( P = 0.39 \)

### Development of geographic atrophy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Photocoagulation</th>
<th>Control</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNVPT</td>
<td>5/22</td>
<td>3/24</td>
<td>56.3</td>
<td>1.91 (0.42, 8.76)</td>
<td></td>
</tr>
<tr>
<td>Laser device study 1995</td>
<td>1/41</td>
<td>2/42</td>
<td>43.7</td>
<td>0.51 (0.04, 5.89)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>72</td>
<td>76</td>
<td>100.0</td>
<td>1.20 (0.38, 4.51)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 Photocoagulation: 5 Control: 5 Heterogeneity: Test for overall effect: \( I^2 = 0.45 \) \( P = 0.60 \)

*Meta-analysis were extracted form the Cochrane review, and odds ratios were reported in Cochrane review.*

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### Visual acuity (loss of at least 2 lines)

**Study or subgroup** | InG ODDS Ratio (95% CI) | Oddes Ratio InRandom (95% CI) | Weight | Oddes Ratio InFixed (95% CI) |
--- | --- | --- | --- | --- |
1 Binocular studies | | | | |
CAPP | 0.9661 1.25 (0.174-8.48) | | | |
DLS | 0.5723 0.63 (0.20-1.91) | | | |
Rupni 1998 | 0.3254 2.34 (0.94-73.7) | | | |
PMAC Elsner 2000 | 0.081 0.62 (0.13-3.06) | | | |
**Subtotal (95% CI)** | | | | |
Heterogeneity: T2 = 0.03, df = 3, p = 0.53; I² = 37% | | | | |
Test for overall effect 2.47 (0.47-13.91) | | | | |
2 Binocular studies | | | | |
CAPP | 0.2772 2.89 (0.55-13.06) | | | |
DLS | 0.4966 0.21 (0.40-1.26) | | | |
Lasers vs Drusen Subgroup | 0.71 0.464 (0.27-1.19) | | | |
DK 1999 | 0.23 0.11 (0.00-5.04) | | | |
PMAC unilateral 2000 | 0.31 0.71 (0.00-3.62) | | | |
**Subtotal (95% CI)** | | | | |
Heterogeneity: T2 = 0.02, df = 4, p = 0.68; I² = 0% | | | | |
Test for overall effect 2.75 (0.73-10.53) | | | | |
**Total (95% CI)** | | | | |
Heterogeneity: T2 = 0.02, df = 7,3, p = 0.50; I² = 0% | | | | |
Test for overall effect 2.17 (0.73-6.24) | | | | |

**Drusen reduction**

**Study or subgroup** | Photocoagulation n/N | Control n/N | Oddes Ratio InFixed (95% CI) | Weight | Oddes Ratio InFixed (95% CI) |
--- | --- | --- | --- | --- | --- |
CAPP vs NPT 2009 | 25/31 | 14/31 | 10.0% | 0.07 (0.84, 29.80) |
PMAC unilateral 2002 | 177/377 | 34/74 | 86.5% | 0.94 (0.55, 1.57) |
PMAC unilateral 2002 | 46/131 | 125/125 | 2.5% | 25.38 (7.38, 92.07) |
**Subtotal (95% CI)** | | | | | |
Heterogeneity: T2 = 0.01, df = 1, p = 0.91; I² = 0% | | | | | |
Test for overall effect 1.0 (0.49, 2.19) | | | | | |
Test for subgroup differences: Not applicable | | | | | |
**Total (95% CI)** | | | | | |
Heterogeneity: T2 = 0.01, df = 1, p = 0.91; I² = 0% | | | | | |
Test for overall effect 1.0 (0.49, 2.19) | | | | | |

---

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## Antioxidant vitamin or mineral supplement for slowing the progression of age-related macular degeneration

### Multivitamin supplement

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to Late AMD (wet active or geographic atrophy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (AREDS 2001, CARMA 2013, CARMIS 2011)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>2140</td>
<td>RR* 0.77 (0.67, 0.89)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Progression to Late AMD (wet active)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS 2001)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>1206</td>
<td>RR* 0.67 (0.53, 0.85)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Progression to Late AMD (geographic atrophy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS 2001)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>1206</td>
<td>RR* 0.76 (0.53, 1.10)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Progression to visual loss (loss of 3 or more lines on logMAR chart)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS 2001)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>1807</td>
<td>RR* 0.83 (0.70, 0.97)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Quality of life assessed with change in NEI-VFQ score (higher scores indicate better QoL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (CARMIS 2011)</td>
<td>RCT</td>
<td>Serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>110</td>
<td>MD=12.30 (4.24, 20.36)</td>
<td>LOW</td>
</tr>
<tr>
<td>Visual acuity (logMAR score) (lower values indicate better vision)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (AMDSG 1996, CARMA 2013, Bartlett 2007, Veterans)</td>
<td>RCT</td>
<td>Serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>979</td>
<td>SMD=0.01² (-0.12, 0.13)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

---

² 0.01 logMAR= -0.5 letters, 95%CI -6.5 to 6 letters
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## Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAST study 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downgraded for risk of bias (randomisation and allocation; blinding; incomplete outcome)</td>
<td></td>
</tr>
</tbody>
</table>

*Converted from odds ratios reported in included Cochrane review*
Meta-analysis: Multivitamin antioxidant vitamin or mineral supplement

Progression to late AMD (wet active) or late AMD (geographic atrophy)

| Study or Subgroup | Log(Odds Ratio) | SE | Total | Mean | SD | Total | Mean | SD | Total | Weight | N, Fixed, 95% CI
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AMDOS 1998</td>
<td>-0.3857</td>
<td>0.1041</td>
<td>904</td>
<td>904</td>
<td>65%</td>
<td>903</td>
<td>903</td>
<td>55.7%</td>
<td>0.68</td>
<td>[0.65, 0.83]</td>
<td></td>
</tr>
<tr>
<td>CARMA 2013</td>
<td>-0.2107</td>
<td>0.2564</td>
<td>230</td>
<td>230</td>
<td>13.9%</td>
<td>228</td>
<td>228</td>
<td>12.5%</td>
<td>0.80</td>
<td>[0.64, 1.01]</td>
<td></td>
</tr>
<tr>
<td>CARMA 2011</td>
<td>0.1184</td>
<td>0.00036</td>
<td>103</td>
<td>103</td>
<td>2.5%</td>
<td>103</td>
<td>103</td>
<td>1.6%</td>
<td>1.17</td>
<td>[0.42, 3.44]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1237</td>
<td>1173</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.63, df = 2 (P = 0.30), I² = 0%
Test for overall effect: Z = 3.81 (P = 0.00003)

Footnotes:
(1) Retrieved (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up
(2) Follow-up: 2 years
(3) Follow-up: 24 months

Mean visual acuity

| Study or Subgroup | Multivitamin | Mean | SD | Total | Placebo | Mean | SD | Total | Weight | N, Fixed, 95% CI
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AMDOS 1998</td>
<td>0.33</td>
<td>0.41</td>
<td>35</td>
<td>0.29</td>
<td>0.24</td>
<td>24</td>
<td>5.5%</td>
<td>6.11</td>
<td>[0.41, 0.83]</td>
<td></td>
</tr>
<tr>
<td>CARMA 2013</td>
<td>0.79</td>
<td>0.89</td>
<td>243</td>
<td>0.43</td>
<td>0.24</td>
<td>265</td>
<td>50.7%</td>
<td>-0.67</td>
<td>[0.25, 0.10]</td>
<td></td>
</tr>
<tr>
<td>Karter 1999</td>
<td>-0.61</td>
<td>0.2</td>
<td>9</td>
<td>-0.8</td>
<td>0.22</td>
<td>11</td>
<td>0.6%</td>
<td>-0.22</td>
<td>[0.12, 0.37]</td>
<td></td>
</tr>
<tr>
<td>subtotal (95%) CI</td>
<td>278</td>
<td>274</td>
<td>56.0%</td>
<td>0.06</td>
<td>[0.25, 0.11]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Chi² = 4.45, df = 1 (P = 0.03), I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)

5.2.2 Change in visual acuity

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | N, Fixed, 95% CI
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartlett 2007</td>
<td>0.01</td>
<td>0.07</td>
<td>20</td>
<td>-0.02</td>
<td>0.07</td>
<td>16</td>
<td>2.7%</td>
<td>0.42</td>
</tr>
<tr>
<td>CARMA 2013</td>
<td>0.37</td>
<td>0.7</td>
<td>712</td>
<td>0.6</td>
<td>0.7</td>
<td>712</td>
<td>35.6%</td>
<td>6.02</td>
</tr>
<tr>
<td>Velazquez LAST study 2004</td>
<td>-0.05</td>
<td>0.24</td>
<td>25</td>
<td>-0.14</td>
<td>0.44</td>
<td>27</td>
<td>5.1%</td>
<td>0.30</td>
</tr>
<tr>
<td>subtotal (95%) CI</td>
<td>217</td>
<td>210</td>
<td>43.9%</td>
<td>0.08</td>
<td>[0.11, 0.15]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Chi² = 1.61, df = 1 (P = 0.45), I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)

Total (95%) CI: 0.00 [0.00, 0.00]

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%
Test for subgroup differences: Chi² = 1.17, df = 1 (P = 0.28), I² = 14.4%

Footnotes:
(1) Right eye: LogMAR score (converted from Snellen decimal acuity) at 16 months
(2) Number of letters read at 4m at 12 months
(3) Study eye: Snellen acuity (expressed as decimal) at 16 months.
(4) Study eye: Change in LogMAR score (EDITAS chart) event months
(5) Right eye: Change in LogMAR score (converted from Snellen decimal acuity) at 12 months

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## Lutein/zeaxanthin

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression to Late AMD (wet active or geographic atrophy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS2 2013)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>6891</td>
<td>RR 0.94 (0.87, 1.01)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Progression to Late AMD (wet active)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS2 2013)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>6891</td>
<td>RR 0.92 (0.84, 1.02)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Progression to Late AMD (geographic atrophy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS2 2013)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>6891</td>
<td>RR 0.92 (0.80, 1.05)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Quality of life assessed with change in NEI-VFQ score (higher scores better)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Huang 2015)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>108</td>
<td>MD 1.48 (-5.53, 8.49)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Visual acuity (logMAR score) (lower values better)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (CLEAR 2013, Huang 2015)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not Serious</td>
<td>180</td>
<td>MD -0.01³ (-0.06, 0.04)</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

1. Downgraded one level for indirectness as everyone in trial took AREDS formula which may have affected the estimate of effect
2. Downgraded one levels for confidence interval crossing 1 line of a defined minimal important difference

³ -0.01 logMAR= + 0.5 letters, 95%CI -2 to 3 letters
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Meta-analysis: Lutein and zeaxanthin

Distance visual acuity mean (logMAR)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lutein/zeaxanthin Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5.1 Mean visual acuity at end of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLEARD 2012 (1)</td>
<td>0.09</td>
<td>0.14</td>
<td>38</td>
<td>0.06</td>
<td>0.13</td>
<td>38</td>
<td>0.43</td>
</tr>
<tr>
<td>Huang 2015 (2)</td>
<td>0.27</td>
<td>0.1859</td>
<td>60</td>
<td>0.3</td>
<td>0.26</td>
<td>28</td>
<td>0.29</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>Heterogeneity: Ch^2 = 0.24, df = 1 (P = 0.62); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.31 (P = 0.75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.5.2 Change in visual acuity |
| Na 2012 (3) | -0.02 | 0.1017 | 80 | 0 | 0.2276 | 27 | 0.00 | -0.02 [-0.11, 0.07] |
| Subtotal (95% CI) | | | | | | | 0 | Not estimable |
| Heterogeneity: Not applicable |
| Test for overall effect: Not applicable |

Total (95% CI) | 116 | 64 | 100.0% | 0.01 [-0.06, 0.04] |
| Heterogeneity: Ch^2 = 0.24, df = 1 (P = 0.62); I^2 = 0% |
| Test for overall effect: Z = 0.31 (P = 0.75) |
| Test for subgroup differences: Not applicable |

Footnotes:
(1) 12 months
(2) 24 months
(3) 12 months

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### Zinc supplement

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression to Late AMD (wet active or geographic atrophy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (AREDS 2001, Holz 1993, Stur 1996)</td>
<td>RCT</td>
<td>Not serious(^1)</td>
<td>Not serious</td>
<td>Not Serious</td>
<td>Serious(^2)</td>
<td>3776</td>
<td>RR* 0.87 (0.77, 0.98)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Progression to Late AMD (wet active)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS 2001)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>3640</td>
<td>RR* 0.80 (0.67, 0.94)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Progression to Late AMD (geographic atrophy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (AREDS 2001)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>3640</td>
<td>RR* 0.85 (0.66, 1.09)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Distance visual acuity (logMAR) (lower values better)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (Stur 1996, Newsome 1998)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Serious(^3)</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>155</td>
<td>MD -0.09(^4) (-0.57, 0.39)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Although there were risk of bias due to incomplete outcome data and selective reporting in Holz 1993 and Stur 1996, AREDS contributed to 98% of weight in pooled results, so not downgraded.
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.
3. Downgraded one level for heterogeneity ($i^2>50\%$)
4. Converting from odds ratios reported in included Cochrane review

\(^{-0.09}\text{logMAR}=+4.5\text{ letters, 95\%CI: -11.5 to 20.5}\)
Meta-analysis: Zinc supplements

Progression to late AMD (wet active) or late AMD (geographic atrophy)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS 2001 (1)</td>
<td>-0.1905</td>
<td>0.043</td>
<td>1702</td>
<td>1849</td>
<td>99.9% 0.82 (0.70, 0.97)</td>
</tr>
<tr>
<td>Hotz 1993 (2)</td>
<td>-0.6921</td>
<td>1.1533</td>
<td>28</td>
<td>30</td>
<td>0.99% 0.50 (0.36, 0.71)</td>
</tr>
<tr>
<td>Star 1996 (3)</td>
<td>0.6391</td>
<td>0.7073</td>
<td>37</td>
<td>41</td>
<td>1.4% 2.21 (0.90, 4.67)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>1829</td>
<td>1889</td>
<td>100.0% 0.83 (0.71, 0.98)</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.12, df = 1 (P = 0.15), I² = 3%
Test for overall effect: Z = 2.20 (P = 0.03)

Visual acuity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5.1 Mean visual acuity at end of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Star 1996 (1)</td>
<td>0.05</td>
<td>0.12</td>
<td>37</td>
<td>0.03</td>
<td>0.14</td>
<td>41</td>
<td>0.83 [0.29, 0.60]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>37</td>
<td>41</td>
<td>50.3%</td>
<td>0.15 [0.29, 0.60]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.67 (P = 0.51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5.2 Change in visual acuity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newsome 1996 (2)</td>
<td>0.1</td>
<td>0.21</td>
<td>40</td>
<td>0.1</td>
<td>0.19</td>
<td>37</td>
<td>-0.34 [-0.79, 0.11]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>40</td>
<td>37</td>
<td>49.7%</td>
<td>-0.34 [-0.79, 0.11]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.47 (P = 0.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>77</td>
<td>78</td>
<td>100.0%</td>
<td>-0.09 [-0.57, 0.39]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.07, Chi² = 2.29, df = 1 (P = 0.13), I² = 59%
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.49), I² = 17%

Footnotes:
(1) Study eye: LogMAR score (Bailey-Lovie chart) at 24 months
(2) Study eye: Change in number of correct letters (ETDRS chart) 18 to 24 months

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## H.3 Diagnosis

### H.3.1 Signs and symptoms of AMD

**RQ1:** What signs and symptoms should prompt a healthcare professional to suspect AMD in people presenting to healthcare services?

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blurred vision</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Hesselund)</td>
<td>Prospective cohort</td>
<td>1,683</td>
<td>83% (80, 86%)</td>
<td>26% (24, 29%)</td>
<td>LR+</td>
<td>1.12 (1.07, 1.18)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-</td>
<td>0.65 (0.53, 0.80)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Central dark spot</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Hesselund)</td>
<td>Prospective cohort</td>
<td>1,683</td>
<td>46% (42, 50%)</td>
<td>68% (65, 71%)</td>
<td>LR+</td>
<td>1.45 (1.28, 1.64)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-</td>
<td>0.79 (0.72, 0.86)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Metamorphosia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Hesselund)</td>
<td>Prospective cohort</td>
<td>1,683</td>
<td>51% (47, 55%)</td>
<td>60% (57, 63%)</td>
<td>LR+</td>
<td>1.27 (1.13, 1.41)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-</td>
<td>0.80 (0.75, 0.91)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Micropsia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Hesselund)</td>
<td>Prospective cohort</td>
<td>1,683</td>
<td>10% (8, 113%)</td>
<td>89% (87, 91%)</td>
<td>LR+</td>
<td>0.88 (0.65, 1.20)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-</td>
<td>1.01 (0.98, 1.05)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

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### Dyschromatopsia

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Hesselund)</td>
<td>Prospective cohort</td>
<td>1,683</td>
<td>18% (15, 22%)</td>
<td>89% (87, 90%)</td>
<td>LR+ 1.62 (1.27, 2.05)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious³</td>
<td>VERY LOW</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.92 (0.88, 0.96)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
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</table>

### Sudden onset

<table>
<thead>
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<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Hesselund)</td>
<td>Prospective cohort</td>
<td>1,683</td>
<td>36% (32, 40%)</td>
<td>73% (70, 75%)</td>
<td>LR+ 1.31 (1.13, 1.51)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
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<tr>
<td></td>
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<td></td>
<td>LR- 0.88 (0.82, 0.95)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

### Worsening of symptoms

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Hesselund)</td>
<td>Prospective cohort</td>
<td>1,683</td>
<td>62% (58, 66%)</td>
<td>46% (43, 49%)</td>
<td>LR+ 1.15 (1.05, 1.25)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
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<td></td>
<td>LR- 0.83 (0.73, 0.94)</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded two levels for risk of bias due to patient selection, lack of blinding to other test results and flow and timing of study
2. Downgraded one level for population not fully as specified in review protocol (only includes people with ‘treatable’ neovascular AMD)
3. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference

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### H.3.2 Tools for triage, diagnosis and informed treatment

#### Review question

RQ4: What tools are useful for triage, diagnosis, informing treatment and determining management in people with suspected AMD?

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LR+</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tools for use in detecting drusen</td>
<td>Fundus photograph (grading criteria) to detect drusen</td>
<td></td>
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<tr>
<td>1</td>
<td>Prospective case series</td>
<td>33 eyes (17 people)</td>
<td>50.0% (9.4, 90.6)</td>
<td>98.4% (79.4, 99.9)</td>
<td>LR+</td>
<td>32.00 (1.64, 626.10)</td>
<td>Very serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>LR-</td>
<td>0.51 (0.16, 1.58)</td>
<td>Very serious¹,²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

| Diagnostic tools for use in detecting age-related macular degeneration |
| Optical coherence tomography vs Fundus photograph to detect age-related macular degeneration(the presence of ≥10 small (≤63μm) hard druse and pigmentary changes or at least intermediate or large drusen inside the 6mm ETDRS grid) |
| 1 | Retrospective case-control | 120 eyes (66 people) | 89.3% (81.5, 95.2) | 75.6% (62.2, 86.8) | LR+ | 3.65 (2.17, 6.14) | Very serious⁴ | N/A | Not serious | Not serious | LOW |
| | | | | | LR- | 0.14 (0.07, 0.28) | Very serious⁴ | N/A | Not serious | Not serious | LOW |

| Fluorescein angiography vs Fundus photograph to detect age-related macular degeneration(the presence of ≥10 small (≤63μm) hard druse and pigment changes or at least intermediate or large drusen inside the 6mm ETDRS grid) |
| 1 | Retrospective case-control | 120 eyes (66 people) | 92.0% (84.9, 97.0) | 82.2% (69.9, 91.8) | LR+ | 5.18 (2.75, 9.73) | Very serious⁴ | N/A | Serious⁵ | Not serious | VERY LOW |
| | | | | | LR- | 0.10 | Very | N/A | Serious⁵ | Not serious | VERY LOW |

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<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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<tr>
<td>1 (Pirbhai 2004)</td>
<td>Prospective case series</td>
<td>223 eyes (118 people)</td>
<td>66.0% (51.5, 78.0)</td>
<td>86.9% (81.1, 91.2)</td>
<td>LR+ 5.05 (3.27, 7.78)</td>
<td>Serious</td>
<td>N/A</td>
<td>Serious5</td>
<td>Not serious</td>
<td>LOW</td>
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<tr>
<td>1 (Pirbhai 2004)</td>
<td>Prospective case series</td>
<td>223 eyes (118 people)</td>
<td>40.0% (21.44, 61.6)</td>
<td>94.1% (90.5, 96.9)</td>
<td>LR+ 6.77 (3.14, 14.58)</td>
<td>Serious</td>
<td>N/A</td>
<td>Serious5</td>
<td>Not serious</td>
<td>LOW</td>
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<tr>
<td>1 (Lim 2002)</td>
<td>Prospective cross sectional</td>
<td>33 eyes(17 people)</td>
<td>50.0% (18.5, 81.5)</td>
<td>98.2% (77.0, 99.9)</td>
<td>LR+ 28.00 (1.63, 481.68)</td>
<td>Very serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious3</td>
<td>VERY LOW</td>
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<tr>
<td>4 (Talks 2007; Wilde 2015)</td>
<td>Retrospective</td>
<td>30/128/476/130/120 eyes (759)</td>
<td>93.5% (72.2, 98.8)</td>
<td>89.2% (74.8, 95.8)</td>
<td>LR+ 6.72 (3.19, 14.14)</td>
<td>Serious</td>
<td>Serious6</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
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</table>

### Diagnostic tools for use in detecting dry age-related macular degeneration

**Fundus photography vs clinical assessment to detect geographic atrophy**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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</table>

### Diagnostic tools for use in detecting pigment epithelial detachment (PED)

**Fundus photography vs clinical assessment to detect pigment epithelial detachment (PED)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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### Fundus photograph (grading criteria) to detect pigment epithelial detachment (PED)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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</table>

### Diagnostic tools for use in detecting neovascular age-related macular degeneration/choroidal neovascularization

**Optical coherence tomography vs fluorescein angiography to detect choroidal neovascularisation**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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</table>
## Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mathew 2014; Mokwa 2013</strong></td>
<td>3 (Do 2012; Padnick 2012; Sandhu 2005)</td>
<td>295 eyes: 87/77/1 31 eyes (282 people)</td>
<td>84.4% (49.0, 96.8)</td>
<td>75.0% (48.6, 90.5)</td>
<td>LR+ 3.27 (1.27, 8.43)</td>
<td>Serious⁷</td>
<td>Serious⁶</td>
<td>Not serious</td>
<td>Serious³</td>
<td>VERY LOW</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>LR- 0.21 (0.05, 0.96)</td>
<td>Serious⁷</td>
<td>Serious⁶</td>
<td>Not serious</td>
<td>Serious³</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

### Optical coherence tomography angiography vs fluorescein angiography to detect choroidal neovascularisation

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 (De Carlo 2015)</strong></td>
<td>Retrospective</td>
<td>30 eyes (24 people)</td>
<td>50.0% (20, 80%)</td>
<td>90.9% (70, 97.9%)</td>
<td>LR+ 5.50 (1.24, 24.5)</td>
<td>Serious⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>LOW</td>
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<tr>
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<td></td>
<td></td>
<td>LR- 0.55 (0.27, 1.11)</td>
<td>Serious⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>LOW</td>
</tr>
</tbody>
</table>

### Optical coherence tomography angiography vs fluorescein angiography to detect neovascular AMD

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 (Gong 2016)</strong></td>
<td>Retrospective</td>
<td>86 eyes (53 people)</td>
<td>86.5% (76.1-94.3%)</td>
<td>79.4% (64.5-91.0%)</td>
<td>LR+ 4.20 (2.15,8.20)</td>
<td>Serious⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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<td></td>
<td></td>
<td>LR- 0.17 (0.08, 0.35)</td>
<td>Serious⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

### Fluorescein angiography vs Indocyanine green angiography to detect wet age-related macular degeneration (predominantly classic, minimally classic, serous pigment epithelial detachment, disciform scar, branch retinal vein occlusion, retinal macroaneurysm, occult CNV, late leak, vascularised PED)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 (Talks 2007)</strong></td>
<td>Retrospective audit</td>
<td>111 people</td>
<td>93.5% (87.9, 97.4)</td>
<td>96.2% (81.5,100.0)</td>
<td>LR+ 24.31 (1.60, 368.47)</td>
<td>Very serious⁴,⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.07 (0.03, 0.14)</td>
<td>Very serious⁴,⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fundus photography vs Fluorescein angiography to detect neovascular age-related macular degeneration – cohort study</strong></td>
<td>1 (Maberley 2005)</td>
<td>Prospective cross sectional</td>
<td>74 eyes (40 people)</td>
<td>97.0% (89.1, 99.9)</td>
<td>86.6% (74.8, 95.1)</td>
<td>LR+ 7.23 (3.31, 15.77)</td>
<td>Serious⁹ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>LR- 0.03 (0.01, 0.24)</td>
<td>Serious⁹ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
<td></td>
</tr>
<tr>
<td><strong>Fundus photography vs Fluorescein angiography to detect neovascular age-related macular degeneration – case-control study</strong></td>
<td>1 (Mokwa 2013)</td>
<td>Retrospective case control</td>
<td>120 eyes (66 people)</td>
<td>77.9% (67.4, 86.9)</td>
<td>98.1% (93.0, 100)</td>
<td>LR+ 40.53 (5.79, 283.49)</td>
<td>Very serious⁴ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>LR- 0.22 (0.14, 0.35)</td>
<td>Very serious⁴ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
<td></td>
</tr>
<tr>
<td><strong>Fundus photography + clinical information vs Fluorescein angiography to detect neovascular age-related macular degeneration</strong></td>
<td>1 (Maberley 2005)</td>
<td>Prospective cross sectional</td>
<td>74 eyes (40 people)</td>
<td>98.5% (92.7, 100)</td>
<td>76.2% (62.4, 87.6)</td>
<td>LR+ 4.14 (2.41, 7.12)</td>
<td>Serious⁹ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.02 (0.00, 0.30)</td>
<td>Serious⁹ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
<td></td>
</tr>
<tr>
<td><strong>Fundus photography vs clinical assessment to detect neovascular age-related macular degeneration</strong></td>
<td>1 (Pirbhai 2004)</td>
<td>Prospective case series</td>
<td>223 eyes (118 people)</td>
<td>82.1% (43.3, 89.5)</td>
<td>79.1% (72.0, 85.5)</td>
<td>LR+ 3.94 (2.81, 5.53)</td>
<td>Serious⁴ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.23 (0.14, 0.36)</td>
<td>Serious⁴ N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
<td></td>
</tr>
<tr>
<td><strong>Fundus photograph (grading criteria) to detect CNV</strong></td>
<td>1 (Lim 2002)</td>
<td>Prospective cross sectional</td>
<td>33 eyes (17 people)</td>
<td>64.0% (44.7, 81.2)</td>
<td>87.5% (59.0, 99.6)</td>
<td>LR+ 5.12 (0.80, 32.78)</td>
<td>Very serious¹,² N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>VERY LOW</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.41</td>
<td>Very N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>VERY LOW</td>
<td></td>
</tr>
</tbody>
</table>

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### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

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<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fundus autofluorescence vs fluorescein angiography to detect CNV</strong></td>
<td></td>
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<tr>
<td>1 (Cachulo 2011)</td>
<td>Prospective cohort</td>
<td>58 eyes (52 people)</td>
<td>88.2% (63.2, 97.0)</td>
<td>94.3% (79.8, 98.6)</td>
<td>LR+</td>
<td>15.44 (3.98, 59,97)</td>
<td>Very serious1,2</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-</td>
<td>0.12 (0.03, 0.46)</td>
<td>Very serious1,2</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
</tr>
</tbody>
</table>

| **Indocyanine green angiography vs fluorescein angiography to detect choroidal neovascularisation (see figure 2, meta analysis)** | | | | | | | | | | | |
| 2 (Cachulo 2011; Sallet 1996) | Prospective cohort; retrospective cross sectional | 52/58 eyes (104 people) | 58.4% (46.2, 69.7) | 82.8% (70.0, 90.8) | LR+ | 3.25 (1.64, 6.45) | Very serious4,8 | Not serious | Not serious | Serious3 | VERY LOW |
| | | | | | LR- | 0.49 (0.36, 0.66) | Very serious4,8 | Not serious | Not serious | Serious3 | VERY LOW |

| **Diagnostic tools for use in detecting polypoidal choroidal vasculopathy (PCV)** | | | | | | | | | | | |
| **Optical coherence tomography vs Indocyanine green angiography to detect polypoidal choroidal vasculopathy (PCV)** | | | | | | | | | | | |
| 1 (De Salvo 2014) | Retrospective case-control | 51 eyes (44 people) | 94.6% (85.5, 99.3) | 92.9% (75.3, 99.8) | LR+ | 13.24 (2.00, 87.68) | Very serious4 | N/A | Not serious | Not serious | LOW |
| | | | | | LR- | 0.06 (0.02, 0.23) | Very serious4 | N/A | Not serious | Not serious | LOW |

| **Optical coherence tomography angiography (OCT-A) vs Indocyanine green angiography to detect polypoidal choroidal vasculopathy (PCV)** | | | | | | | | | | | |
| 1 (Cheung 2016) | Prospective cross section | 86 eyes | 40.5% (26.3, 55.5) | 81.4% (68.6, 91.4) | LR+ | 2.18 (1.05, 4.49) | Serious1 | N/A | Not serious | Serious | LOW |
| | | | | | LR- | 0.73 (0.55, 0.98) | Serious1 | N/A | Not serious | Not serious | MODERATE |

**Flash fundus camera-based indocyanine green angiography vs confocal scanning laser ophthalmoscope-based indocyanine green angiography**

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## (grading criteria) to detect polypoidal choroidal vasculopathy (PCV)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Cheung et al. 2015)</td>
<td>Retrospective comparative</td>
<td>241 eyes (230 people)</td>
<td>78.6% (71.2, 85.2)</td>
<td>87.3% (80.5, 92.8)</td>
<td>LR+ 6.18 (3.76, 10.16)</td>
<td>LR- 0.24 (0.18, 0.34)</td>
<td>N/A</td>
<td>Very serious 4,2</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
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</tbody>
</table>

### Fundus photography vs clinical assessment to detect choroidal neovascular membrane

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Pirbhai 2004)</td>
<td>Prospective case series</td>
<td>223 eyes (118 people)</td>
<td>89.2% (81.9, 93.8)</td>
<td>85.7% (77.9, 91.1)</td>
<td>LR+ 6.24 (3.95, 9.87)</td>
<td>LR- 0.13 (0.07, 0.22)</td>
<td>N/A</td>
<td>Serious 4</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

1. Downgraded one level for inadequate or unclear blinding between index test and reference standard;
2. Downgraded one level for exclusion criteria not reported;
3. Downgraded one level for confidence interval cross 1 line of defined minimal important difference;
4. Downgraded two levels for case-control study design; downgraded one level for case series, retrospective study;
5. Downgraded one level for reference test was not consistent with protocol reference test (OCT);
6. Downgraded one level for heterogeneity (I²>50%);
7. Downgraded one level for time interval between index test and reference standard unclear;
8. Downgraded one level for selection bias (pre-defined study population or patients being treated with anti-VGF);
9. Downgraded one level for risk of bias due to multiple imaging readers;
Figure 1: Optical coherence tomography vs fluorescein angiography to detect CNV

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005 Sandhu</td>
<td>81</td>
<td>3</td>
<td>16</td>
<td>31</td>
<td>0.96 (0.92, 0.99)</td>
<td>0.66 (0.52, 0.79)</td>
</tr>
<tr>
<td>2012 Do</td>
<td>5</td>
<td>6</td>
<td>33</td>
<td>40</td>
<td>0.95 (0.95, 0.95)</td>
<td>0.66 (0.44, 0.47)</td>
</tr>
<tr>
<td>2012 Pudich-Silver</td>
<td>12</td>
<td>3</td>
<td>4</td>
<td>56</td>
<td>0.80 (0.57, 0.95)</td>
<td>0.94 (0.68, 0.98)</td>
</tr>
<tr>
<td>RE meta-analysis</td>
<td>0.84 (0.65, 0.93)</td>
<td>0.75 (0.49, 0.90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity—sensitivity: Tau=1.98, Chi²=13.58, df=2 (p=0.001); I²=69.3%</td>
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<tr>
<td>Heterogeneity—specificity: Tau=0.91, Chi²=15.67, df=2 (p=0.001); I²=69.3%</td>
<td></td>
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<tr>
<td>Retrospective</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2007 Takah</td>
<td>93</td>
<td>0</td>
<td>12</td>
<td>23</td>
<td>0.95 (0.97, 1.00)</td>
<td>0.95 (0.94, 0.98)</td>
</tr>
<tr>
<td>2013 Malv</td>
<td>64</td>
<td>4</td>
<td>1</td>
<td>50</td>
<td>0.94 (0.87, 0.99)</td>
<td>0.95 (0.93, 0.99)</td>
</tr>
<tr>
<td>2014 Mathew</td>
<td>17</td>
<td>5</td>
<td>4</td>
<td>100</td>
<td>0.70 (0.67, 0.91)</td>
<td>1.00 (1.00, 1.00)</td>
</tr>
<tr>
<td>2016 Wilke</td>
<td>231</td>
<td>0</td>
<td>47</td>
<td>108</td>
<td>1.00 (0.99, 1.00)</td>
<td>0.81 (0.74, 0.88)</td>
</tr>
<tr>
<td>RE meta-analysis</td>
<td>0.97 (0.82, 1.00)</td>
<td>0.89 (0.71, 0.95)</td>
<td></td>
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<tr>
<td>Heterogeneity—sensitivity: Tau=1.79, Chi²=17.94, df=3 (p=0.001); I²=82.2%</td>
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<tr>
<td>Heterogeneity—specificity: Tau=1.11, Chi²=19.02, df=3 (p=0.001); I²=84.3%</td>
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</table>

Figure 2: Indocyanine green angiography vs fluorescein angiography to detect CNV

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
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<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
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<tbody>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cachios 2011</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>28</td>
<td>0.53 (0.30, 0.75)</td>
<td>0.90 (0.65, 0.99)</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sallat 1996</td>
<td>25</td>
<td>19</td>
<td>2</td>
<td>17</td>
<td>0.66 (0.46, 0.74)</td>
<td>0.89 (0.71, 0.95)</td>
</tr>
<tr>
<td>RE meta-analysis</td>
<td>0.39 (0.45, 0.70)</td>
<td>0.83 (0.74, 0.91)</td>
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<tr>
<td>Overall heterogeneity—sensitivity: Tau=0.50, Chi²=25.81, df=6 (p&lt;0.001); I²=85.8%</td>
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<tr>
<td>Overall heterogeneity—specificity: Tau=0.45, Chi²=25.81, df=6 (p&lt;0.001); I²=85.8%</td>
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</tr>
<tr>
<td>Between-stratum heterogeneity—sensitivity: Chi²=2.52, df=3 (p=0.12); I²=28.9%</td>
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<tr>
<td>Between-stratum heterogeneity—specificity: Chi²=0.33, df=1 (p=0.001); I²=20.3%</td>
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H.4 Referral

H.4.1 Organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow-up of people with suspected and confirmed age-related macular degeneration

RQ5: How do different organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow-up influence outcomes for people with suspected AMD (for example correct diagnosis, errors in diagnosis, delays in diagnosis, process outcomes)?

RQ16: How do different organisational models for ongoing treatment and follow-up influence outcomes for people with diagnosed neovascular AMD (for example disease progression, time to treatment, non-attendance)?

RQ24: How soon should people with neovascular AMD be diagnosed and treated after becoming symptomatic?

<table>
<thead>
<tr>
<th>Models of care</th>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis agreement between optometrist and ophthalmologist</td>
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<td></td>
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</tr>
<tr>
<td>Rapid access referral form (history finding (reduction in vision, distortion, central scotoma))</td>
<td>1 (Muen 2011)</td>
<td>Prospective cohort</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>54 (referrals)</td>
<td>57.4% (n=31) (44.2 to 70.6%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Rapid access referral form (accuracy in detecting Exudative AMD)</td>
<td>1 (Muen 2011)</td>
<td>Prospective cohort</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>54 (referrals)</td>
<td>37.0% (n=20) (24.1 to 50.0%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Vignette (no. of correctly classified nAMD)</td>
<td>1 (Reeves 2016)</td>
<td>RCT</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>2016 images</td>
<td>RR 1.01 (0.99 to 1.04)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Vignette (no. of correctly classified as reactivated)</td>
<td>1 (Reeves 2016)</td>
<td>RCT</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>994 images</td>
<td>RR 0.93</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
### Number of studies

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vignette (no. of error occurred that classified as reactivated)</td>
<td>1 (Reeves 2016)</td>
<td>RCT</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious⁴</td>
<td>994 images</td>
<td>RR 1.09 (0.77 to 1.54)</td>
</tr>
<tr>
<td>Vignette (no. of correctly classified as quiescent/suspicious)</td>
<td>1 (Reeves 2016)</td>
<td>RCT</td>
<td>Serious³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1022 images</td>
<td>RR 1.09 (1.06 to 1.11)</td>
</tr>
<tr>
<td>Number of patients referred</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Routine eye examination (patients with no symptoms being referred for AMD)</td>
<td>1 (Dobbelsteyn 2015)</td>
<td>Retrospective cohort</td>
<td>Serious⁷</td>
<td>N/A</td>
<td>Serious⁸</td>
<td>Not serious</td>
<td>1084</td>
<td>2.7% (n=30) (1.7 to 3.7%)</td>
</tr>
<tr>
<td>Routine eye examination (patients with symptoms being referred for AMD)</td>
<td>1 (Dobbelsteyn 2015)</td>
<td>Retrospective cohort</td>
<td>Serious⁷</td>
<td>N/A</td>
<td>Serious⁸</td>
<td>Not serious</td>
<td>2992</td>
<td>5.1% (n=153) (4.3 to 6.0%)</td>
</tr>
<tr>
<td>Routine eye examination (number of patients without symptoms vs no. of patients with symptoms being referred for AMD</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (Dobbelsteyn 2015)</td>
<td>Retrospective cohort</td>
<td>Serious⁷</td>
<td>N/A</td>
<td>Serious⁸</td>
<td>Not serious</td>
<td>4,076</td>
<td>RR 0.54 (0.37 to 0.80)</td>
</tr>
<tr>
<td>Teleretinal screening</td>
<td>1 (Chasan 2014)</td>
<td>Retrospective cohort</td>
<td>Serious⁷</td>
<td>N/A</td>
<td>Serious⁸</td>
<td>Not serious</td>
<td>1935</td>
<td>24.0% (n=465) (22.1 to 25.9%)</td>
</tr>
<tr>
<td>Electronically referrals resulting in a hospital appointment (with vs without attached images)</td>
<td>1 (Goudie 2014)</td>
<td>Retrospective cohort</td>
<td>Serious⁷</td>
<td>N/A</td>
<td>Serious⁸</td>
<td>Not serious</td>
<td>1152 (referrals)</td>
<td>RR 0.73 (0.73 to 0.79)</td>
</tr>
</tbody>
</table>

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### Anti-VEGF injection administration

**% of injection cycles were uninterrupted injection (by retinal specialist)**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Engman 2011)</td>
<td>Chart review</td>
<td>Serious⁷</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>175 injection cycles</td>
<td>76.5% (70.2 to 82.8%)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

### Visual acuity

**Community vs hospital follow-up**

**% of people had a gain of 15 ETDRS letters**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Tschuor 2013)</td>
<td>Prospective cohort</td>
<td>Serious⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>62 people (72 eyes)</td>
<td>RR 9.00 (1.17 to 68.92)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**% of eyes had a loss of 15 letters**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Tschuor 2013)</td>
<td>Prospective cohort</td>
<td>Serious⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious⁴</td>
<td>62 people (72 eyes)</td>
<td>RR 0.43 (0.12 to 1.59)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Visual change over 6 visits, ETDRS letters (higher values better)**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Tschuor 2013)</td>
<td>Prospective cohort</td>
<td>Serious⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>62 people (72 eyes)</td>
<td>MD 1.20 (-4.00 to 6.40)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Improvement in service provision (after vs before)**

**% of patients had a gain of 15 letter or more**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Ghazala 2013)</td>
<td>Audit study</td>
<td>Serious⁷,⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>113</td>
<td>RR 3.53 (1.05 to 11.85)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**% patients maintained vision**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Ghazala 2013)</td>
<td>Audit study</td>
<td>Serious⁷,⁸</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>113</td>
<td>RR 1.11 (0.94 to 1.45)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Chronic model of care vs usual care**

**VA at the end of follow-up (12 months) (ETDRS letters; higher scores indicate better vision)**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Markun)</td>
<td>RCT</td>
<td>Serious¹⁰</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>169</td>
<td>MD -4.80 letters</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(-11.31 to 1.71)</td>
<td></td>
</tr>
</tbody>
</table>

#### Teleconsultation network vs usual care

**VA after treatment (logMAR; lower scores indicate better vision)**

<table>
<thead>
<tr>
<th>Azzolini 2013</th>
<th>Prospective cohort</th>
<th>Serious⁸</th>
<th>n/a</th>
<th>Not serious</th>
<th>Very serious¹¹</th>
<th>360</th>
<th>MD -0.05 (n/a)</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

#### Time interval (diagnosis interval, treatment interval)

**Improvement in service provision (after vs before)**

<table>
<thead>
<tr>
<th>% of patients being referred to 1st assessment within 1 week</th>
<th>1 (Ghazala 2013) Audit study</th>
<th>Serious⁷</th>
<th>n/a</th>
<th>Not serious</th>
<th>Not serious</th>
<th>120</th>
<th>RR 2.14 (1.33 to 3.45)</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

**Teleophthalmology vs routine**

**Time from referral to diagnosis (diagnostic image), days**

<table>
<thead>
<tr>
<th>Li 2015</th>
<th>RCT</th>
<th>Serious¹²</th>
<th>N/A</th>
<th>Not serious</th>
<th>Serious¹³</th>
<th>106</th>
<th>MD 4.5 (-2.80 to 11.80)</th>
<th>LOW</th>
</tr>
</thead>
</table>

**Time from referral to treatment, days**

<table>
<thead>
<tr>
<th>Li 2015</th>
<th>RCT</th>
<th>Serious¹²</th>
<th>N/A</th>
<th>Not serious</th>
<th>Serious¹³</th>
<th>106</th>
<th>MD 8.7 (-5.29 to 22.69)</th>
<th>LOW</th>
</tr>
</thead>
</table>

**Time to recurrence, days**

<table>
<thead>
<tr>
<th>Li 2015</th>
<th>RCT</th>
<th>Serious¹²</th>
<th>N/A</th>
<th>Not serious</th>
<th>Serious¹³</th>
<th>63</th>
<th>MD -4.2 (-47.77 to 39.15)</th>
<th>LOW</th>
</tr>
</thead>
</table>

**Recurrence to treatment, days**

<table>
<thead>
<tr>
<th>Li 2015</th>
<th>RCT</th>
<th>Serious¹²</th>
<th>N/A</th>
<th>Not serious</th>
<th>Not serious</th>
<th>63</th>
<th>MD 13.5 (9.0 to 18.2)</th>
<th>MODERATE</th>
</tr>
</thead>
</table>

**Teleconsultation network vs usual care (time from first visit to treatment), days**

<table>
<thead>
<tr>
<th>Azzolini 2013</th>
<th>Prospective</th>
<th>Serious⁸</th>
<th>N/A</th>
<th>Not serious</th>
<th>Not serious</th>
<th>360</th>
<th>MD=-23.20 (n/a)</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

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## Evidence on association between diagnosis/treatment time and visual acuity

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time interval and visual acuity</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Visual acuity score change (longest vs shortest time to treatment)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Arias 2009)</td>
<td>Retrospective cohort</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>100</td>
<td>Correlation r 0.3534</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(p=0.0004)</td>
<td></td>
</tr>
<tr>
<td><strong>Visual acuity change treatment and baseline, BCVA decimal (higher values better)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Rauch)</td>
<td>Case series</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>22</td>
<td>MD 0.09</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for study population (a selection of patients being referred through eye causality, GPs, or other ophthalmologists’ clinics, and some patients may be seen by other ophthalmologists).
2. Downgraded one level for wide 95%CI
3. Downgraded one level for selection and assessment bias (different experience and training in using vignettes)
4. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
5. Downgraded one level for confidence interval crossing 1 lines of a defined minimal important difference
6. Downgraded one level for conditions included in the study not AMD specific
7. Downgraded one level for retrospective study design
8. Downgraded one level for study design (audit study; before-after)
9. Downgraded one level for Injection by nurse practitioners, no head-to-head comparison
10. Downgraded one level for risk of bias due to open label study
11. Downgraded two levels for 95%CI of the effect cannot be estimated
12. Downgraded one level for risk of bias due to masking of study participants being unclear
13. Downgraded one level for non-significant effect estimate (mean difference crosses 0)
### Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2012</strong> &lt;br&gt;(symptoms duration &lt;1m)<strong>&lt;br&gt;1 (Rauch 2012)</strong>&lt;br&gt;(symptoms duration 1-6m)<strong>&lt;br&gt;1 (Rauch 2012)</strong>&lt;br&gt;(symptoms duration &gt;6m)</td>
<td>Case series</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>17</td>
<td>MD 0.07 &lt;br&gt;(-0.04 to 0.18)</td>
<td>VERY LOW</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MD 0.06 &lt;br&gt;(-0.05 to 0.19)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**VA change between diagnosis and treatment (longer vs shorter treatment waiting time) (ETDRS letters; higher scores indicate better vision)**

<table>
<thead>
<tr>
<th></th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 (Real 2013)</strong></td>
<td>Case series</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious³</td>
<td>78</td>
<td>MD -7.55⁵ &lt;br&gt;(-12.94 to -2.16)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1 (Rasmussen 2015)</strong></td>
<td>Case series</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious³</td>
<td>1185</td>
<td>MD -4.24⁶ &lt;br&gt;(-5.93 to -2.55)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**% of people had a gain of more than 2 lines (10 letters)**

**Longer (>21 w) vs shorter (<7 w) delay from symptom to treatment**

<table>
<thead>
<tr>
<th></th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 (Lim 2012)</strong></td>
<td>Case series</td>
<td>Serious⁴</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious³</td>
<td>109</td>
<td>RR 0.53 &lt;br&gt;(0.29 to 1.00)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Longer (>3w) vs shorter (<1w) delay from diagnosis to treatment**

<table>
<thead>
<tr>
<th></th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 (Lim 2012)</strong></td>
<td>Case series</td>
<td>Serious⁴</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious⁵</td>
<td>134</td>
<td>RR 0.77 &lt;br&gt;(0.41 to 1.43)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**% of people had a loss of more than 2 lines (10 letters)**

⁵ Time difference=long waiting time (average 153.80)–short waiting time (average 36.06)=117.74 days, so about 1 letter loss in 15 days more waiting to treatment.

⁶ Time difference=long time to treatment (average 13.5) – short time to treatment (average 1.5)=12 days, so about 1 letter loss in 3 days more to treatment.

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### Number of studies, Design, Risk of bias, Inconsistency, Indirectness, Imprecision, Sample size, Effect (95%CI), Quality

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longer (&gt;21w) vs shorter (7w) delay from symptom to treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Lim 2012)</td>
<td>Case series</td>
<td>Serious⁴</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious⁵</td>
<td>109</td>
<td>RR 1.19 (0.43 to 3.31)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Longer (&gt;3w) vs shorter (&lt;1w) delay from diagnosis to treatment</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (Lim 2012)</td>
<td>Case series</td>
<td>Serious⁴</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious⁵</td>
<td>134</td>
<td>RR 0.84 (0.34 to 2.10)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Vision loss during latency (ETDRS letters; higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Muether 2013)</td>
<td>Non-randomised trial</td>
<td>Serious⁶</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>83</td>
<td>MD -1.79 (-3.71 to 0.13)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Vision loss with time delay (between initial referral and assessment and treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Oliver-Fermandez 2005)</td>
<td>Case series</td>
<td>Serious⁸</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>38</td>
<td>Coefficient -0.00674 (a decrease of 0.00674 logMAR with every one day delay) (-0.010 to -0.003)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Time delay in first treatment, days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>People with visual loss vs no visual loss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Muether 2011)</td>
<td>Non-randomised trial</td>
<td>Serious ⁶</td>
<td>N/A</td>
<td>Serious²</td>
<td>Not serious</td>
<td>69</td>
<td>MD 7.6 (1.07 to 14.13)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>People had a loss of more than 1 line vs no visual loss more than 1 line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Muether 2011)</td>
<td>Non-randomised trial</td>
<td>Serious ⁶</td>
<td>N/A</td>
<td>Serious²</td>
<td>Serious⁷</td>
<td>69</td>
<td>MD 11.0 (-0.27 to 22.27)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Time days in recurrent treatment, days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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## Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>People with visual loss vs no visual loss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Muether 2011)</td>
<td>Non-randomised trial</td>
<td>Serious 6</td>
<td>N/A</td>
<td>Serious2</td>
<td>Serious7</td>
<td>21</td>
<td>MD 5.4 (-3.54 to 14.34)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>People had a loss of more than 1 line vs no visual loss more than 1 line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Muether 2011)</td>
<td>Non-randomised trial</td>
<td>Serious 6</td>
<td>N/A</td>
<td>Serious2</td>
<td>Not serious</td>
<td>21</td>
<td>MD 32.0 (10.05 to 53.93)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for retrospective study design
2. Downgraded one level for no head-to-head comparisons and outcomes differed from primary interest-for instance.
3. Downgraded one level for confidence interval crossing 1 lines of a defined minimal important difference
4. Downgraded one level for self-reported time delay (questionnaire collected information)
5. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
6. Downgraded one level for study design (interventional case series/non-randomised trial)
7. Downgraded one level for non-significant effect estimate (mean difference crosses 0)
8. Downgraded one level for study population (selected from a review of letters from referring doctors)

### Vision related quality of life (NEI VFQ25)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vision-related quality of life (NEI-VFQ-25) (higher values better)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic model of care vs usual care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markun 2015</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>169</td>
<td>MD 2.10 (-0.96 to 5.16)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for open label study
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.
## H.5 Non-pharmacological management

### H.5.1 Psychological therapies

**RQ8: What is the effectiveness of psychological therapies for AMD?**

#### Problem solving treatment vs usual care (delayed treatment)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression at 6 months (better indicated by lower values)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>206</td>
<td>RR 0.74 (0.44, 1.24)</td>
<td>LOW</td>
</tr>
<tr>
<td>Mean difference in Hamilton Depression Rating Score (6 months) (better indicated by lower values)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>206</td>
<td>MD 0.01 (-1.14, 1.16)</td>
<td>LOW</td>
</tr>
<tr>
<td>No. of lost activities at 6 months (better indicated by lower values)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>206</td>
<td>RR 0.66 (0.45, 0.98)</td>
<td>LOW</td>
</tr>
<tr>
<td>Mean difference in NEI VFQ-17 score at 6 months (better indicated by higher values)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>206</td>
<td>MD 1.48 (-1.05, 4.01)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeted Vision Function at 6 months (better indicated by lower values)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 0.03 (-0.21, 0.27)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Activities Inventory at 6 months (better indicated by lower values)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 0.01 (-0.29, 0.31)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>NEI-VFQ total score at 6 months (better indicated by higher values)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious³</td>
<td>141</td>
<td>MD 1.60 (-2.71, 5.91)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>NEI-VFQ QoL Social Functioning at 6 months (better indicated by higher values)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 2.53 (-4.19, 9.25)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>NEI-VFQ QoL Mental Health (better indicated by higher values)</strong></td>
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</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 5.50 (-1.14, 12.14)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>NEI-VFQ QoL Role Functioning at 6 months (better indicated by higher values)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD -0.70 (-6.17, 4.77)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>NEI-VFQ QoL Dependency at 6 months (better indicated by higher values)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 6.10 (-1.55, 13.75)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Control strategies: selective primary control at 6 months (better indicated by higher values)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>141</td>
<td>MD -1.00 (-1.79, -0.21)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Control strategies: compensatory primary control at 6 months (better indicated by higher values)</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Rovner 2013)</td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 0.20</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>
### Control strategies: selective secondary control at 6 months (better indicated by higher values)

1 (Rovner 2013)  
<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 0.10 (-1.30, 1.50)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for single masked; unclear if important differences in those included and those lost to follow up
2. Downgraded one level for non-significant result
3. Downgraded one level for confidence interval crossing 2 lines of a defined minimal important difference

### Control strategies: compensatory secondary control at 6 months (better indicated by higher values)

1 (Rovner 2013)  
<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCT</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 1.20 (-0.02, 2.42)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

### Psychosocial intervention programme vs usual care

#### Mean difference Positive affect (PANAS) score at 7-9 weeks follow up (better indicated by lower values)

1 (Birk 2004)  
<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-randomised trial</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>22</td>
<td>MD -0.12 (-0.58, 0.34)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

#### Mean difference negative affect (PANAS) score at 7-9 weeks (better indicated by higher values)

1 (Birk 2004)  
<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-randomised trial</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>22</td>
<td>MD 0.53 (0.13, 0.93)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Mean difference geriatric depression scale (GDS) score at 7-9 weeks (better indicated by higher values)

1 (Birk 2004)  
<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-randomised trial</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>22</td>
<td>MD 1.45 (0.31, 2.59)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Mean difference activities of daily living score at 7-9 weeks (better indicated by higher values)

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## Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Birk 2004)</td>
<td>Non-randomised trial</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>22</td>
<td>MD 6.10 (1.18, 11.02)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

**Mean difference perceived autonomy at 7-9 weeks (better indicated by lower values)**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Birk 2004)</td>
<td>Non-randomised trial</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>20</td>
<td>MD -1.80 (-3.62, 0.02)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Mean difference active problem orientation score at 7-9 weeks (better indicated by lower values)**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Birk 2004)</td>
<td>Non-randomised trial</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>20</td>
<td>MD -3.50 (-7.22, 0.22)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for no randomisation performed; allocation sequence not adequately generated; unmasked; large proportional of drop outs; unclear if comparison group received any other psychosocial therapy during course of the study
2. Downgraded one level for non-significant result

### Self-management vs waiting list for age-related macular degeneration

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Mean difference total profile of mood states (POMS) score at 6 months (better indicated by lower values)
1 (Brody 2002)     | RCT    | Serious¹     | N/A           | Not serious  | Serious²    | 214         | MD -11.78 (-18.43, -5.13) | LOW     |

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Mean difference NEI-VFQ-25 total score at 6 months (better indicated by higher values)
1 (Brody 2002)     | RCT    | Serious¹     | N/A           | Not serious  | Serious²    | 213         | MD 2.63 (0.23, 5.03)   | LOW     |

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Mean difference AMD self-efficacy scale total score at 6 months (better indicated by higher values)
1 (Brody 2002)     | RCT    | Serious¹     | N/A           | Not serious  | Not serious | 213         | MD 5.64 (2.11, 9.17)   | MODERATE |

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<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference in POMS total score at 6 months among those with depression at baseline (better indicated by lower values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>51</td>
<td>MD -26.24 (-42.40, -10.08)</td>
</tr>
<tr>
<td>Mean difference in total NEI-VFQ-25 at 6 months among those with depression at baseline (better indicated by higher values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>50</td>
<td>MD 6.12 (0.12, 12.12)</td>
</tr>
<tr>
<td>Mean difference in POMS total score at 6 months among those without depression at baseline (better indicated by lower values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>162</td>
<td>MD 2.67 (-3.76, 9.10)</td>
</tr>
<tr>
<td>Mean difference in total NEI-VFQ-25 at 6 months among those without depression at baseline (better indicated by higher values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>161</td>
<td>MD -0.83 (-3.29, 1.63)</td>
</tr>
<tr>
<td>Mean difference in AMD self-efficacy score at 6 months amongst those with depression at baseline (better indicated by higher values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>66</td>
<td>MD 9.87 (2.31, 17.43)</td>
</tr>
<tr>
<td>Mean difference in AMD self-efficacy score at 6 months amongst those without depression at baseline (better indicated by higher values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>161</td>
<td>MD 1.42 (-2.22, 5.06)</td>
</tr>
<tr>
<td>Mean difference in geriatric depression scale total score at 6-months amongst those with a diagnosis of depression at baseline (better indicated by lower values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>32</td>
<td>MD -1.82 (-4.40, 0.56)</td>
</tr>
<tr>
<td>Mean difference Duke Social Support Index-11 score at 6 months among those with depression at baseline (better indicated by higher values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>32</td>
<td>MD 5.72 (-3.37, 14.81)</td>
</tr>
<tr>
<td>Mean difference life orientation test at 6-months amongst those with depression at baseline (better indicated by higher values)</td>
<td>1 (Brody 2002)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>32</td>
<td>MD -0.87</td>
</tr>
<tr>
<td>Number of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Sample size</td>
<td>Effect size (95% CI)</td>
<td>Quality</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------</td>
<td>--------------</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(-3.72, 1.98)</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downgraded one level for single masked; unclear if important differences in those included and those lost to follow up</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downgraded one level for non-significant result</td>
<td></td>
</tr>
</tbody>
</table>

**Behavioural activation and low vision rehabilitation (LVR) vs supportive therapy and LVR**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Rovner 2014)</td>
<td>RCT</td>
<td>Very serious(^1)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>188</td>
<td>RR 0.59 (0.29, 1.17)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downgraded two levels for single masked; differences in baseline characteristics between those who did and did not complete follow-up</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference</td>
<td></td>
</tr>
</tbody>
</table>

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H.5.2 The effectiveness of support strategies for people with impairment and age-related macular degeneration (AMD)

RQ9: What is the effectiveness of support strategies for people with visual impairment and AMD (for example reablement services and strategies for optimising existing visual performance)?

Activities of daily living

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL step scale 0-9, rate “0” as least dependence, 28 months follow-up (health education programme vs individual programme)</td>
<td>1 (Eklund 2008)</td>
<td>RCT</td>
<td>Very serious(^{1,6})</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^{2})</td>
<td>131</td>
<td>RR 1.78 (1.03, 3.08)</td>
</tr>
</tbody>
</table>

Self rated restriction in everyday activities because of vision impairment, Manchester Low Vision Questionnaire, 12 months follow-up (enhanced low vision rehabilitation vs conventional low vision rehabilitation)

Self rated restriction score (enhanced low vision rehabilitation by a rehabilitation officer vs conventional low vision rehabilitation)

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Reeves 2004)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious(^{4})</td>
<td>124</td>
<td>MD 0.04 (-0.02, 0.11)</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

Self rated restriction score, enhanced low vision rehabilitation by community care worker vs conventional low vision rehabilitation

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Reeves 2004)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^{3})</td>
<td>130</td>
<td>MD -0.00 (-0.06, 0.06)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

Melbourne low vision activities of daily living index, at 3 months follow-up (prism spectacle vs placebo)

Melbourne low vision activities of daily living, part 1 (performance of ADL dependent on vision), custom prisms vs placebo (higher values better)

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Smith 2005)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^{3})</td>
<td>150</td>
<td>MD -0.72 (-2.30, 0.87)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

Melbourne low vision activities of daily living, part 1 (performance of ADL dependent on vision), standard prisms vs placebo (higher values better)

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Smith 2005)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^{3})</td>
<td>155</td>
<td>MD 0.45 (-1.11, 2.01)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

Melbourne low vision activities of daily living, part 2 (self assessment of ADL performance), custom prisms vs placebo (higher values better)

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### Melbourne low vision activities of daily living, part 2 (self assessment of ADL performance), standard prisms vs placebo (higher values better)

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Smith 2005)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>150</td>
<td>MD -0.14 (-0.67, 0.39)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

#### Melbourne low vision activities of daily living index (part 2), 8 weeks (eccentric viewing vs control) (higher values better)

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Vukicevic 2009)</td>
<td>RCT</td>
<td>Serious⁵</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>48</td>
<td>MD 6.25 (3.72, 8.78)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded one level for masking of study participants not reported.
2. Downgraded one level for confidence interval cross 1 line of a defined minimal important difference.
3. Downgraded one level for non-significant effect.
4. Non-significant result but confidence interval sufficiently narrow as to be confident there is no clinically meaningful effect.
5. Downgrade one level for risk of bias due to allocation and randomisation were unclear in the study.
6. Downgraded one level for high dropout rate (75%).

### Perceived security in the performance of daily activities

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Eklund 2004)</td>
<td>RCTs</td>
<td>Very serious¹³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>131</td>
<td>MD² 0.42 (0.19, 0.65)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for non-significant effect
2. Difference in relative positons between two groups (based on 15 activities that two groups had significant differences in perceived security)
3. Downgraded one level for high dropout rate (75%)
### Visual acuity

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual acuity, percentage of people with VA 0.1 (20/200), measure the distance visual acuity at a test distance of 5m, 28 months follow-up (health promotion vs individual programme)</strong>&lt;br&gt;1 (Eklund 2008)</td>
<td>RCT</td>
<td>Very serious¹,³</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>131</td>
<td>RR 0.97 (0.52, 1.83)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Visual acuity logMAR at 1 year (prisms correction vs control) (lower values indicate better vision)</strong> 1 (Parodi 2004)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>28</td>
<td>MD -0.40 (-0.52, -0.28)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Visual acuity at 3 month (prism spectacle vs placebo)</strong>&lt;br&gt;Visual acuity logMAR at 3 month (custom prism spectacle vs placebo) (lower values indicate better vision)&lt;br&gt;1 (Smith 2005)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>150</td>
<td>MD -0.02 (-0.07, 0.02)</td>
<td>HIGH</td>
</tr>
<tr>
<td>Visual acuity logMAR at 3 month (standard prism spectacle vs placebo) (lower values indicate better vision)&lt;br&gt;1 (Smith 2005)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>155</td>
<td>MD -0.02 (-0.06, 0.03)</td>
<td>HIGH</td>
</tr>
<tr>
<td><strong>Visual acuity logMAR at 8-week follow up (eccentric viewing vs control) (lower values indicate better vision)</strong>&lt;br&gt;1 (Vukicevic 2009)</td>
<td>RCT</td>
<td>Serious⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>48</td>
<td>MD -0.38 (-0.47, -0.29)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded one level for masking of study participants not reported;
2. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference;
3. Downgraded one level for high dropout rate (75%)
4. Downgrade one level for allocation and randomisation were unclear in the study
### Quality of life

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision-specific QoL, 12 months follow-up (enhanced low vision rehabilitation by rehabilitation officer or community worker vs conventional low vision rehabilitation)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>124</td>
<td>MD 0.06 (-0.17, 0.30)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Vision specific quality of life score (enhanced low vision rehabilitation vs conventional low vision rehabilitation) (higher scores indicate poorer QoL)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>130</td>
<td>MD -0.05 (-0.29, 0.18)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>NEI-VFQ-25 at 3 months</td>
<td>NEI-VFQ-25, custom prisms vs placebo (higher scores indicate better QoL)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>150</td>
<td>MD 1.25 (-1.98, 4.47)</td>
</tr>
<tr>
<td>NEI-VFQ-25, standard prisms vs placebo (higher scores indicate better QoL)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>155</td>
<td>MD 0.29 (-2.90, 3.49)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded one level for non-significant effect
2. Downgraded one level of confidence interval crossing 1 line of a defined minimal important difference

### General health

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36, percentage of people reporting “excellent” health 28 month follow-up (health promotion programme vs individual programme)</td>
<td>1 (Eklund 2008)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>131</td>
<td>RR 6.68 (0.83, 53.93)</td>
</tr>
<tr>
<td>SF-36, percentage of people reporting “bad” health 28 month follow-up (health education programme vs individual programme)</td>
<td>1 (Eklund 2008)</td>
<td>RCT</td>
<td>Vert serious¹ ¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>131</td>
<td>RR 0.56 (0.31, 0.98)</td>
</tr>
<tr>
<td>SF-36, physical health (enhanced low vision rehabilitation by rehabilitation officer or community worker vs conventional low vision rehabilitation), 12 months follow-up</td>
<td>1 (Reeves 2004)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>124</td>
<td>MD -6.05 (-10.2, -1.91)</td>
</tr>
<tr>
<td>SF-36, mental health (enhanced low vision rehabilitation by rehabilitation officer vs conventional low vision rehabilitation) (higher values indicate better HRQoL)</td>
<td>1 (Reeves 2004)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>130</td>
<td>MD -2.27 (-6.29, 1.76)</td>
</tr>
<tr>
<td>SF-36, physical (enhanced low vision rehabilitation by community worker vs conventional low vision rehabilitation) (higher values indicate better HRQoL)</td>
<td>1 (Reeves 2004)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>124</td>
<td>MD -4.04 (-7.44, -0.65)</td>
</tr>
<tr>
<td>SF-36, physical (enhanced low vision rehabilitation by community worker vs conventional low vision rehabilitation) (higher values indicate better HRQoL)</td>
<td>1 (Reeves 2004)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>130</td>
<td>MD -1.48 (-4.69, 1.73)</td>
</tr>
</tbody>
</table>

¹ Downgraded one level for masking of study populations not reported in the study

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### Macular Degeneration

Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
- Downgraded one level for non-significant effect
- Downgraded one level for high dropout rate (75%)

### Reading performance

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading rate, at 3-months (prism spectacle vs control) (higher scores indicate better reading)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Smith 2005)</td>
<td>RCTs</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>250</td>
<td>MD 6.50 (-7.84, 20.84)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

- Downgraded one level for non-significant effect

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H.6 Pharmacological management

H.6.1 Anti-angiogenic therapies and frequency of administration

RQ12: What is the effectiveness of different anti-angiogenic therapies (including photodynamic therapy) for the treatment of late age-related macular degeneration (wet active)?

RQ18: What is the effectiveness of different frequencies of administration of antiangiogenic therapies for the treatment of late age-related macular degeneration (wet active)?

The GRADE tables for pairwise meta-analyses in this section were produced by the Cochrane Eyes and Vision group, as part of a collaboration with the NICE Internal Clinical Guidelines Team.

H.6.1.1 Photodynamic therapy versus placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect</th>
<th>No of Participants</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corresponding risk</td>
<td>Assumed risk</td>
<td>(95% CI)</td>
<td>(studies)</td>
</tr>
<tr>
<td></td>
<td>Intervention (photodynamic therapy with verteporfin)</td>
<td>Control (photodynamic therapy with 5% dextrose in water)</td>
<td>RR 0.8, 0.73 to 0.89</td>
<td>1381 (4 studies)</td>
</tr>
<tr>
<td>Loss of 3 or more lines (15 or more letter) visual acuity ETDRS at 24 months</td>
<td>487 per 1000 (445 to 536)</td>
<td>609 per 1000</td>
<td>1381 (4 studies)</td>
<td>⊕⊕⊕⊕ Moderate</td>
</tr>
<tr>
<td>Loss of 6 or more lines (30 or more letter) visual acuity ETDRS at 24 months</td>
<td>220 per 1000 (176 to 276)</td>
<td>333 per 1000</td>
<td>1381 (4 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
</tbody>
</table>
| Gain of 3 or more lines (15 or more) | 80 per 1000 | 36 per 1000 | 941 | ⊕⊕⊕⊕
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Macular Degeneration</th>
<th>ETDRS at 24 months</th>
<th>1.33 to 5.06</th>
<th>(3 studies)</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse effects:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute severe visual acuity decrease (follow-up: 7 days)</td>
<td>11 per 1000 (3 to 48)</td>
<td>3 per 1000</td>
<td>RR 3.75 (0.87 to 16.12)</td>
<td>1075 (3 studies)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>270 per 1000</td>
<td>170 per 1000</td>
<td>RR 1.56 (1.21 to 2.01)</td>
<td>1075 (3 studies)</td>
</tr>
<tr>
<td>Injection site</td>
<td>120 per 1000</td>
<td>60 per 1000</td>
<td>RR 1.36 (0.50 to 3.71)</td>
<td>1075 (3 studies)</td>
</tr>
<tr>
<td>Infusion-related back pain</td>
<td>20 per 1000 (6 to 70)</td>
<td>2 per 1000</td>
<td>RR 9.93 (2.82 to 35.02)</td>
<td>1439 (4 studies)</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>17 per 1000</td>
<td>19 per 1000</td>
<td>RR 0.94 (0.35 to 2.51)</td>
<td>948 (2 studies)</td>
</tr>
<tr>
<td>Photosensitivity reactions</td>
<td>24 per 1000</td>
<td>3 per 1000</td>
<td>RR 2.73 (0.08 to 97.96)</td>
<td>948 (2 studies)</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)
1. Downgrade one level of imprecision: 95% CI of the estimated effect across 1 line of defined minimal important difference
2. Downgrade one level of heterogeneity (I² >= 50%), and downgrade two levels of imprecision (wide confidence interval)
3. Not downgraded for imprecision: confidence interval wide however do not include 1 (no effect)
4. Downgrade two levels of serious imprecision.
Visual acuity

One year

Visual acuity (loss of 3 or more lines ETDRS)

<table>
<thead>
<tr>
<th>Study/Subgroup</th>
<th>PDT</th>
<th>Placebo</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>156</td>
<td>402</td>
<td>558</td>
<td>111</td>
<td>0.72 [0.61, 0.86]</td>
</tr>
<tr>
<td>YIM 2005</td>
<td>16</td>
<td>36</td>
<td>52</td>
<td>11</td>
<td>0.59 [0.31, 1.00]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>144</td>
<td>225</td>
<td>369</td>
<td>114</td>
<td>0.93 [0.75, 1.15]</td>
</tr>
<tr>
<td>VIO 2007</td>
<td>91</td>
<td>244</td>
<td>335</td>
<td>120</td>
<td>0.83 [0.64, 1.07]</td>
</tr>
</tbody>
</table>

Total (95% CI): 0.79 [0.71, 0.89]

Total events: 371

Visual acuity (loss of 6 or more lines ETDRS)

<table>
<thead>
<tr>
<th>Study/Subgroup</th>
<th>PDT</th>
<th>Placebo</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>69</td>
<td>202</td>
<td>271</td>
<td>49</td>
<td>0.62 [0.44, 0.87]</td>
</tr>
<tr>
<td>YIM 2005</td>
<td>3</td>
<td>36</td>
<td>39</td>
<td>6</td>
<td>0.53 [0.14, 1.95]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>37</td>
<td>106</td>
<td>143</td>
<td>30</td>
<td>0.68 [0.45, 1.03]</td>
</tr>
<tr>
<td>VIO 2007</td>
<td>39</td>
<td>244</td>
<td>283</td>
<td>20</td>
<td>0.96 [0.59, 1.57]</td>
</tr>
</tbody>
</table>

Total (95% CI): 0.70 [0.56, 0.88]

Total events: 138

Visual acuity (gain of 3 or more line (15 or more letters) of visual acuity)

<table>
<thead>
<tr>
<th>Study/Subgroup</th>
<th>PDT</th>
<th>Placebo</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>24</td>
<td>402</td>
<td>426</td>
<td>5</td>
<td>88.3% 2.47 [0.95, 6.30]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>4</td>
<td>36</td>
<td>40</td>
<td>2</td>
<td>86.8% 1.39 [0.27, 7.00]</td>
</tr>
<tr>
<td>VIM 2005</td>
<td>1</td>
<td>38</td>
<td>39</td>
<td>0</td>
<td>9.8%  3.16 [0.13, 75.20]</td>
</tr>
</tbody>
</table>

Total (95% CI): 2.22 [1.01, 4.88]

Total events: 30

Heterogeneity: Chi² = 0.42, df = 2 (P = 0.81), I² = 0%
Two years

Visual acuity (loss of 3 or more line ETDRS)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>189</td>
<td>129</td>
</tr>
<tr>
<td>VIM 2005</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>VOP 2007</td>
<td>114</td>
<td>63</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>903</td>
<td>478</td>
</tr>
<tr>
<td>Total events</td>
<td>441</td>
<td>291</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.94, df = 3 (P = 0.85), I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.34 (P &lt; 0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Visual acuity (loss of 6 or more lines ETDRS)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>73</td>
<td>62</td>
</tr>
<tr>
<td>VIM 2005</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>VOP 2007</td>
<td>67</td>
<td>54</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>903</td>
<td>478</td>
</tr>
<tr>
<td>Total events</td>
<td>199</td>
<td>159</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 4.35, df = 3 (P = 0.23), I² = 31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.64 (P &lt; 0.00001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Visual acuity (gain of 3 or more lines ETDRS)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>VIM 2005</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>VOP 2007</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>604</td>
<td>337</td>
</tr>
<tr>
<td>Total events</td>
<td>47</td>
<td>10</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83), I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.80 (P = 0.005)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adverse effects

Acute severe visual acuity decrease

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VM 2005</td>
<td>1</td>
<td>97</td>
<td>1</td>
<td>40</td>
<td>50.9%</td>
<td>0.46 [0.03, 7.17]</td>
<td></td>
</tr>
<tr>
<td>TAP 1999</td>
<td>3</td>
<td>402</td>
<td>0</td>
<td>207</td>
<td>24.5%</td>
<td>3.61 [0.19, 69.61]</td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>10</td>
<td>225</td>
<td>0</td>
<td>114</td>
<td>24.6%</td>
<td>10.69 [0.63, 180.74]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>714</strong></td>
<td><strong>391</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>381</strong></td>
<td><strong>3.75 [0.87, 16.12]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>14</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Chisq = 2.77, df = 2 (P = 0.28); I^2 = 26%
Test for overall effect: Z = 1.78 (P = 0.08)

Infusion-related back pain

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>10</td>
<td>402</td>
<td>0</td>
<td>207</td>
<td>19.6%</td>
<td>10.84 [0.64, 184.05]</td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>5</td>
<td>225</td>
<td>0</td>
<td>114</td>
<td>19.7%</td>
<td>5.68 [0.31, 100.35]</td>
<td></td>
</tr>
<tr>
<td>VM 2005</td>
<td>9</td>
<td>37</td>
<td>1</td>
<td>40</td>
<td>40.8%</td>
<td>4.14 [0.54, 31.56]</td>
<td></td>
</tr>
<tr>
<td>VIO 2007</td>
<td>25</td>
<td>244</td>
<td>0</td>
<td>120</td>
<td>19.9%</td>
<td>25.19 [1.55, 410.73]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>950</strong></td>
<td><strong>491</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>409</strong></td>
<td><strong>0.63 [3.82, 35.02]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>49</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Chisq = 1.30, df = 3 (P = 0.73); I^2 = 0%
Test for overall effect: Z = 3.57 (P = 0.0014)

Visual disturbance

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>88</td>
<td>402</td>
<td>32</td>
<td>207</td>
<td>51.4%</td>
<td>1.43 [0.99, 2.07]</td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>94</td>
<td>225</td>
<td>26</td>
<td>114</td>
<td>42.0%</td>
<td>1.82 [1.26, 2.66]</td>
<td></td>
</tr>
<tr>
<td>VM 2005</td>
<td>7</td>
<td>87</td>
<td>4</td>
<td>40</td>
<td>6.7%</td>
<td>0.80 [0.25, 2.59]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>714</strong></td>
<td><strong>361</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>324</strong></td>
<td><strong>1.56 [1.21, 2.01]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>190</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Chisq = 2.16, df = 2 (P = 0.34); I^2 = 7%
Test for overall effect: Z = 3.42 (P = 0.0006)

Injection site

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>64</td>
<td>402</td>
<td>12</td>
<td>267</td>
<td>41.2%</td>
<td>2.76 [1.52, 4.97]</td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>10</td>
<td>225</td>
<td>6</td>
<td>114</td>
<td>34.5%</td>
<td>1.52 [0.82, 3.72]</td>
<td></td>
</tr>
<tr>
<td>VM 2005</td>
<td>3</td>
<td>87</td>
<td>4</td>
<td>40</td>
<td>24.1%</td>
<td>0.34 [0.08, 1.47]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>714</strong></td>
<td><strong>361</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>322</strong></td>
<td><strong>1.36 [0.50, 3.71]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>85</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Tau^2 = 0.55; Chisq = 7.07, df = 2 (P = 0.03); I^2 = 72%
Test for overall effect: Z = 0.59 (P = 0.55)
**Allergic reactions**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>0</td>
<td>402</td>
<td>3</td>
</tr>
<tr>
<td>YIF 2001</td>
<td>3</td>
<td>225</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>627</strong></td>
<td><strong>321</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 11

Heterogeneity: Chi² = 3.90, df = 1 (P = 0.049); I² = 0%

Test for overall effect: Z = 0.13 (P = 0.90)

**Photosensitivity reactions**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PDT</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>14</td>
<td>402</td>
<td>0</td>
</tr>
<tr>
<td>YIF 2001</td>
<td>1</td>
<td>225</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>627</strong></td>
<td><strong>321</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 15

Heterogeneity: Tau² = 4.65; Chi² = 3.30, df = 1 (P = 0.07); I² = 70%

Test for overall effect: Z = 0.55 (P = 0.58)
### H.6.1.2 Bevacizumab vs control

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain of 15 letters or more visual acuity at one year</td>
<td>Bevacizumab 293 per 1000 (92 to 937)</td>
<td>RR 8.43 (2.65 to 26.80)</td>
<td>159 (2 studies)</td>
<td>⊕⊕⊕⊝</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 38 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Loss of fewer than 15 letters visual acuity at one year</td>
<td>Bevacizumab 896 per 1000 (763 to 1000)</td>
<td>RR 1.32 (1.13 to 1.54)</td>
<td>159 (2 studies)</td>
<td>⊕⊕□□ Low²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 700 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in visual acuity at one year (number of letters)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean change from baseline in visual acuity was 7.0 letters in the bevacizumab group and -9.4 letters in the control group in one study. The second study reported participants in the bevacizumab group gained 8 letters on average and participants in the control group lost 3 letters.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate at 1 year</th>
<th>Rate in Control</th>
<th>RRR (95% CI)</th>
<th>N of Studies</th>
<th>Bias</th>
<th>Imprecision</th>
<th>Overall Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious systemic adverse events at one year</td>
<td>31 per 1000</td>
<td>15 per 1000</td>
<td>RR 2.03 (0.19 to 21.85)</td>
<td>131 (1 study)</td>
<td>⊙⊙⊙⊙</td>
<td>⊙⊙⊙⊙</td>
<td>Low^3</td>
</tr>
<tr>
<td>Serious ocular adverse events at one year</td>
<td>169 per 1000</td>
<td>91 per 1000</td>
<td>RR 1.86 (0.73 to 4.74)</td>
<td>131 (1 study)</td>
<td>⊙⊙⊙⊙</td>
<td>⊙⊙⊙⊙</td>
<td>Low^3</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)
1. Downgrade one level due to one study (Sacu 2009) being an open label study.
2. Downgrade one level for risk of bias due to open label study design and one level for imprecision due to 95% CI of estimated effect crossing 1 line of defined minimal important difference
3. Downgrade two levels of serious imprecision
Visual acuity (gain of 15 letters or more visual acuity at one year)

<table>
<thead>
<tr>
<th>Study/Subgroup</th>
<th>Bevacizumab</th>
<th>Control</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC 2010 (1)</td>
<td>21</td>
<td>65</td>
<td>21</td>
<td>10.66 [2.60, 43.64]</td>
</tr>
<tr>
<td>Sacu 2009 (2)</td>
<td>4</td>
<td>14</td>
<td>14</td>
<td>6.65 [0.61, 31.46]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>25</td>
<td>79</td>
<td>100.0%</td>
<td>8.43 [2.65, 26.00]</td>
</tr>
</tbody>
</table>

Footnotes:
1. Control group in the ABC study received standard therapy including pegaptanib injections, verteporfin PDT, or sham injection.
2. Control group in the Sacu 2009 study received verteporfin photodynamic therapy plus same day 4 mg intravitreal triamcinolone...

Visual acuity (loss of fewer than 15 letters visual acuity at one year)

<table>
<thead>
<tr>
<th>Study/Subgroup</th>
<th>Bevacizumab</th>
<th>Control</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC 2010 (1)</td>
<td>69</td>
<td>65</td>
<td>69</td>
<td>1.26 [1.13, 1.64]</td>
</tr>
<tr>
<td>Sacu 2009 (2)</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>1.16 [0.91, 1.49]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>73</td>
<td>80</td>
<td>100.0%</td>
<td>1.32 [1.13, 1.54]</td>
</tr>
</tbody>
</table>

Footnotes:
1. Control group in the ABC study received standard therapy including pegaptanib injections, verteporfin PDT, or sham injection.
2. Control group in the Sacu 2009 study received verteporfin photodynamic therapy plus same day 4 mg intravitreal triamcinolone...
### H.6.1.3 Ranibizumab vs control (sham injection or PDT)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect</th>
<th>No of Participants</th>
<th>Quality of the evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corresponding risk</td>
<td>Assumed risk</td>
<td>(95% CI)</td>
<td>(studies)</td>
<td>(GRADE)</td>
<td></td>
</tr>
<tr>
<td>Gain of 15 letters or more visual acuity at one year</td>
<td>230 per 1000 (93 to 566)</td>
<td>RR 3.25</td>
<td>1415 (4 studies)</td>
<td>⊕⊕⊕ Moderate¹</td>
<td></td>
</tr>
<tr>
<td>Loss of fewer than 15 letters visual acuity at one year</td>
<td>934 per 1000 (861 to 1000)</td>
<td>RR 1.51</td>
<td>1415 (4 studies)</td>
<td>⊕⊕⊕⊕ High</td>
<td></td>
</tr>
<tr>
<td>Mean change in visual acuity at one year (number of letters)</td>
<td>The mean change in visual acuity in the ranibizumab groups was on average 17.80 more letters gained (95% CI 15.95 to 19.65 letters)</td>
<td>MD 17.81 (15.94 to 19.67)</td>
<td>1322 (3 studies)</td>
<td>⊕⊕⊕⊕ High</td>
<td></td>
</tr>
<tr>
<td>Mean change in vision-related quality of life</td>
<td>The mean change in vision related quality of life in the ranibizumab groups ranged from 5 to 7 points</td>
<td>MD 6.69 (3.38 to 9.99)</td>
<td>1134 (2 studies)</td>
<td>⊕⊕⊕⊕ High</td>
<td></td>
</tr>
<tr>
<td>Serious systemic adverse events at one year</td>
<td>Range of 0 to 55 per 1000</td>
<td>Range of RR 0.17 (0.01 to 4.24) to 2.08 (0.23 to 18.45)</td>
<td>603 (2 studies)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 per 1000</td>
<td>RR 2.08 (0.23, 18.45)</td>
<td>603 (2 studies)</td>
<td>⊕⊕⊕⊕ Low²</td>
<td></td>
</tr>
</tbody>
</table>
Macular Degeneration
Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate 1 per 1000</th>
<th>Rate 2 per 1000</th>
<th>RR (95% CI)</th>
<th>Studies</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or cerebral infarction</td>
<td>&lt; 10 per 1000</td>
<td>&lt; 10 per 1000</td>
<td>1.04 (0.09, 11.38)</td>
<td>603 (2 studies)</td>
<td>⊕⊕⊕⊝ Low&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treatment-emergent hypertension</td>
<td>60 per 1000</td>
<td>80 per 1000</td>
<td>0.67 (0.36, 1.24)</td>
<td>603 (2 studies)</td>
<td>⊕⊕⊕ Moderate&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-ocular hemorrhage</td>
<td>60 per 1000</td>
<td>30 per 1000</td>
<td>1.90 (0.78, 4.62)</td>
<td>603 (2 studies)</td>
<td>⊕⊕⊕ Low&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serious ocular adverse events at one year</td>
<td>Range of 3 to 118 per 1000</td>
<td>Range of 0 to 68 per 1000 for various systematic adverse events</td>
<td>Range of RR 0.52 (0.03 to 8.25) to 2.71 (1.36 to 5.42)</td>
<td>603 (2 studies)</td>
<td></td>
</tr>
<tr>
<td>Ocular inflammation</td>
<td>120 per 1000</td>
<td>40 per 1000</td>
<td>2.71 (1.36 to 5.42)</td>
<td>603 (2 studies)</td>
<td>⊕⊕⊕ High</td>
</tr>
<tr>
<td>Elevated intraocular pressure (30 mmHg or more increase)</td>
<td>80 per 1000</td>
<td>30 per 1000</td>
<td>2.22 (0.99, 4.98)</td>
<td>603 (2 studies)</td>
<td>⊕⊕⊕ Moderate&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cataract</td>
<td>100 per 1000</td>
<td>70 per 1000</td>
<td>1.48 (0.83, 2.66)</td>
<td></td>
<td>⊕⊕⊕ Moderate&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
1. Downgrade one level for inconsistency due to heterogeneity (i²>=50%).
2. Downgrade two levels for serious imprecision.
3. Downgrade one level for imprecision.
Macular Degeneration
Appendix H: Grade tables and meta-analysis results

One year

Visual acuity (loss of fewer than 15 letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>ANCHOR 2008 (1)</td>
<td>256</td>
<td>279</td>
<td>92</td>
</tr>
<tr>
<td>LAPTOP 2013</td>
<td>43</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td>MARINA 2006 (2)</td>
<td>452</td>
<td>478</td>
<td>149</td>
</tr>
<tr>
<td>PIER 2008 (3)</td>
<td>105</td>
<td>121</td>
<td>31</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>924</td>
<td>941</td>
<td>491</td>
</tr>
<tr>
<td>Total events</td>
<td>896</td>
<td>905</td>
<td>305</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Chi^2 = 4.04$, df = 3 ($P = 0.26$); $I^2 = 26%$
Test for overall effect: $Z = 9.00$ ($P < 0.00001$)

Footnotes:
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
(3) Control group in the PIER study received sham injections

Visual acuity (loss of fewer than 30 letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>ANCHOR 2008 (1)</td>
<td>279</td>
<td>279</td>
<td>124</td>
</tr>
<tr>
<td>LAPTOP 2013</td>
<td>46</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>MARINA 2006 (2)</td>
<td>473</td>
<td>478</td>
<td>204</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>993</td>
<td>1020</td>
<td>428</td>
</tr>
<tr>
<td>Total events</td>
<td>798</td>
<td>817</td>
<td>373</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Chi^2 = 0.33$, df = 2 ($P = 0.84$); $I^2 = 68%$
Test for overall effect: $Z = 3.43$ ($P = 0.0005$)

Footnotes:
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections

Mean change in visual acuity (number of letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean, SD</td>
<td>Total</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>MARINA 2008 (2)</td>
<td>6.8515, 13.5765</td>
<td>478</td>
<td>17.25 [14.77, 19.73]</td>
</tr>
<tr>
<td>PIER 2008 (3)</td>
<td>-0.8947, 14.8086</td>
<td>121</td>
<td>15.41 [8.35, 21.48]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>878</td>
<td>444</td>
<td>17.31 [15.79, 19.87]</td>
</tr>
</tbody>
</table>

Heterogeneity: $Chi^2 = 1.75$, df = 2 ($P = 0.42$); $I^2 = 0%$
Test for overall effect: $Z = 18.74$ ($P < 0.00001$)

Footnotes:
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
(3) Control group in the PIER study received sham injections
Appendix H: Grade tables and meta-analysis results

### Quality of life score

<table>
<thead>
<tr>
<th>Rankitnorm</th>
<th>Ramsey (n = 12)</th>
<th>Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Total Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.15.1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.008</td>
<td>15.256</td>
<td>276</td>
<td>2.2</td>
<td>15.086</td>
<td>142</td>
<td>44.6%</td>
<td>4.01 (9.74, 7.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.400</td>
<td>13.326</td>
<td>275</td>
<td>-2.8</td>
<td>14.055</td>
<td>230</td>
<td>65.4%</td>
<td>5.22 (5.45, 10.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.069</td>
<td>22.729</td>
<td>276</td>
<td>3.7</td>
<td>10.063</td>
<td>142</td>
<td>44.6%</td>
<td>4.10 (0.19, 0.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.901</td>
<td>10.293</td>
<td>275</td>
<td>-2.6</td>
<td>10.011</td>
<td>230</td>
<td>65.4%</td>
<td>12.00 (0.03, 16.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.069</td>
<td>22.729</td>
<td>276</td>
<td>3.7</td>
<td>10.063</td>
<td>142</td>
<td>44.6%</td>
<td>4.10 (0.19, 0.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.901</td>
<td>10.293</td>
<td>275</td>
<td>-2.6</td>
<td>10.011</td>
<td>230</td>
<td>65.4%</td>
<td>12.00 (0.03, 16.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.069</td>
<td>22.729</td>
<td>276</td>
<td>3.7</td>
<td>10.063</td>
<td>142</td>
<td>44.6%</td>
<td>4.10 (0.19, 0.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.901</td>
<td>10.293</td>
<td>275</td>
<td>-2.6</td>
<td>10.011</td>
<td>230</td>
<td>65.4%</td>
<td>12.00 (0.03, 16.02)</td>
</tr>
</tbody>
</table>
Two years

Visual acuity (gain of 15 letters or more ETDRS)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>ANCHOR 2006 (1)</td>
<td>105</td>
<td>279</td>
<td>9</td>
<td>143</td>
</tr>
<tr>
<td>MARINA 2006 (2)</td>
<td>142</td>
<td>476</td>
<td>9</td>
<td>238</td>
</tr>
<tr>
<td>PIER 2008 (3)</td>
<td>14</td>
<td>121</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>261</td>
<td>678</td>
<td>444</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Chi^2 = 3.84, df = 2 (P = 0.24); I^2 = 30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 8.39 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnotes:
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
(3) Control group in the PIER study received sham injections

Visual acuity (loss of fewer than 15 letters or more ETDRS)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>ANCHOR 2006 (1)</td>
<td>251</td>
<td>279</td>
<td>94</td>
<td>143</td>
</tr>
<tr>
<td>MARINA 2006 (2)</td>
<td>426</td>
<td>478</td>
<td>128</td>
<td>239</td>
</tr>
<tr>
<td>PIER 2008 (3)</td>
<td>97</td>
<td>121</td>
<td>26</td>
<td>63</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>753</td>
<td>670</td>
<td>444</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.02; Chi^2 = 9.02, df = 2 (P = 0.01); I^2 = 78%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.19 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnotes:
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
(3) Control group in the PIER study received sham injections

Visual acuity (loss of fewer than 30 letters or more ETDRS)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>ANCHOR 2006 (1)</td>
<td>277</td>
<td>279</td>
<td>120</td>
<td>143</td>
</tr>
<tr>
<td>MARINA 2006 (2)</td>
<td>464</td>
<td>478</td>
<td>194</td>
<td>239</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>741</td>
<td>757</td>
<td>301</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Chi^2 = 1.28, df = 1 (P = 0.24); I^2 = 28%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.78 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnotes:
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
### Mean change in visual acuity (number of letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab Mean</th>
<th>SD Total</th>
<th>Control Mean</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCHOR 2006 (1)</td>
<td>9.395</td>
<td>16.372</td>
<td>379</td>
<td>-9.8</td>
<td>17.6</td>
<td>143</td>
<td>19.20 [15.73, 22.66]</td>
</tr>
<tr>
<td>MARINA 2008 (2)</td>
<td>6.092</td>
<td>15.866</td>
<td>478</td>
<td>-14.9</td>
<td>18.7</td>
<td>238</td>
<td>54.00 [38.13, 73.67]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>878</strong></td>
<td><strong>444</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>20.11</strong></td>
<td><strong>18.08, 22.15</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\hat{\chi}^2 = 0.68$, df = 2 ($P = 0.71$); $I^2 = 0$

Test for overall effect $Z = 18.37$ ($P < 0.00001$)

**Footnotes**
- (1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
- (2) Control group in the MARINA study received sham injections
- (3) Control group in the PIER study received sham injections

### Quality of life score
Macular Degeneration

Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Rank检验</th>
<th>Mean Rank</th>
<th>P value</th>
<th>Mean Difference (95% CI)</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCHOR 2006 (1)</td>
<td>-4.074</td>
<td>34.02</td>
<td>0.47</td>
<td>0.05 (-0.36, 0.46)</td>
<td>0.05 (-0.36, 0.46)</td>
</tr>
<tr>
<td>BIONICA 2007 (2)</td>
<td>4.488</td>
<td>35.92</td>
<td>0.14</td>
<td>0.09 (-0.34, 0.52)</td>
<td>0.09 (-0.34, 0.52)</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Test for overall effect Z = 2.10, P = 0.042</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- (1) Control group in the ANCHOR study received subcutaneous injections plus active vitaminphospholipid therapy
- (2) Control group in the BIONICA study received sham injections
### H.6.1.4 Bevacizumab vs ranibizumab

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corresponding risk</strong></td>
<td><strong>Assumed risk</strong></td>
<td><strong>(95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain of 15 letters or more visual acuity at one year</td>
<td>238 per 1000 (202 to 279)</td>
<td>258 per 1000</td>
<td>RR 0.96 (0.85 to 1.08)</td>
<td>3101 (8 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
<tr>
<td>Loss of fewer than 15 letters visual acuity at one year</td>
<td>942 per 1000 (923 to 960)</td>
<td>942 per 1000</td>
<td>RR 1.00 (0.98 to 1.02)</td>
<td>2817 (7 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
<tr>
<td>Mean change in visual acuity at one year (number of letters)</td>
<td>The mean change in visual acuity in the bevacizumab groups was on average 0.48 fewer letters gained (95% CI 1.47 fewer letters to 0.51 more letters)</td>
<td>The mean change across ranibizumab groups ranged from gains of 3 to 8 letters</td>
<td>MD -0.48 (-1.47 to 0.51)</td>
<td>3101 (8 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
<tr>
<td>Serious systemic adverse events at one year</td>
<td>148 per 1000 (150 to 206)</td>
<td>175 per 1000 with at least one serious systemic adverse event</td>
<td>RR 1.18 (1.01 to 1.39)</td>
<td>3038 (5 studies)</td>
<td>⊕⊕⊕ Moderate¹</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 per 1000</td>
<td>20 per 1000</td>
<td>RR 1.85 (1.01, 3.40)</td>
<td>3038 (5 studies)</td>
<td>⊕⊕⊕ Moderate¹</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>&lt;10 per 1000</td>
<td>&lt;10 per 1000</td>
<td>RR 0.51 (0.22 to 1.19)</td>
<td>3038 (5 studies)</td>
<td>⊕⊕⊕ Low²</td>
</tr>
<tr>
<td>Stroke or cerebral infarction</td>
<td>&lt;10 per 1000</td>
<td>&lt;10 per 1000</td>
<td>RR 0.65 (0.25 to 1.67)</td>
<td>3038 (5 studies)</td>
<td>⊕⊕⊕ Low²</td>
</tr>
<tr>
<td>Venous thrombotic event</td>
<td>&lt;10 per 10000</td>
<td>&lt;10 per 1000</td>
<td>RR 2.04 (0.61 to 6.75)</td>
<td>2721 (4 studies)</td>
<td>⊕⊕⊕ Low²</td>
</tr>
</tbody>
</table>
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Serious ocular adverse events at one year</th>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 5 per 1000</td>
<td>&lt;5 per 1000</td>
<td>Range of RRs</td>
<td>Range 1670 to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.51 (0.05 to</td>
<td>2280 (2 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.62) to 7.05</td>
<td>studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.36 to 136.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Studies reported different ocular adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0</td>
<td>&lt;10 per 1000</td>
<td>RR 7.05 (0.36</td>
<td>1670 (2 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to 136.28)</td>
<td></td>
<td>⊕⊕⊕⊕ L Low²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe uveitis</td>
<td>&lt; 10 per 1000</td>
<td>&lt;10 per 1000</td>
<td>RR 4.14 (0.46</td>
<td>1795 (2 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to 36.97)</td>
<td></td>
<td>⊕⊕⊕⊕ L Low²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>&lt;10 per 1000</td>
<td>&lt;10 per 1000</td>
<td>RR 1.68 (0.40</td>
<td>2111 (3 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to 7.00)</td>
<td></td>
<td>⊕⊕⊕⊕ L Low²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal pigment epithelial tear</td>
<td>&lt;10 per 1000</td>
<td>&lt;10 per 1000</td>
<td>RR 1.37 (0.31</td>
<td>2236 (3 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to 6.12)</td>
<td></td>
<td>⊕⊕⊕⊕ L Low²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>&lt;10 per 1000</td>
<td>&lt;10 per 1000</td>
<td>RR 0.51 (0.05</td>
<td>2280 (3 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to 5.62)</td>
<td></td>
<td>⊕⊕⊕⊕ L Low²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)

1. Adverse event outcome downgrade to moderate quality as not all eligible trials reported these outcomes and numbers of some adverse events were small (<1%), and 95%CI of estimated effect under the possibility of significant and non-significant values
2. Downgrade two levels for serious imprecision

### Number of injections

<table>
<thead>
<tr>
<th>Number of injections</th>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab vs ranibizumab</td>
<td>5 studies (CATT 2011, Biswas 2011, GEFAL 2013, LUCAS 2015, MANTA 2013)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1660</td>
<td>MD=0.60 (0.33, 0.87)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

¹Downgrade for masking of participants and incomplete outcome data.
## Bevacizumab vs ranibizumab

### One year

**Visual acuity (gain of 15 letters or more at one year)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivone 2011 (1)</td>
<td>6</td>
<td>50</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>BRANO study 2016</td>
<td>39</td>
<td>161</td>
<td>32</td>
<td>186</td>
</tr>
<tr>
<td>CATT 2011</td>
<td>159</td>
<td>536</td>
<td>168</td>
<td>569</td>
</tr>
<tr>
<td>DEDAL 2013</td>
<td>39</td>
<td>161</td>
<td>38</td>
<td>183</td>
</tr>
<tr>
<td>IAN 2013</td>
<td>40</td>
<td>251</td>
<td>64</td>
<td>273</td>
</tr>
<tr>
<td>LUCAS 2015</td>
<td>47</td>
<td>164</td>
<td>50</td>
<td>187</td>
</tr>
<tr>
<td>MANTRA 2013</td>
<td>36</td>
<td>164</td>
<td>35</td>
<td>183</td>
</tr>
<tr>
<td>Subramaniam 2010</td>
<td>5</td>
<td>15</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

Total (95% CI): 1542 / 1602; 100.0%; 0.96 (0.85, 1.08)

Total events: 371 / 402
Heterogeneity: Chi² = 0.31, df = 7 (P = 0.92; P = 25%
Test for overall effect: Z = 0.71 (P = 0.48)

**Footnotes**

(1) follow-up was 18 months

---

**Visual acuity (loss of fewer than 15 letters at one year)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivone 2011 (1)</td>
<td>50</td>
<td>50</td>
<td>54</td>
<td>3.8%</td>
</tr>
<tr>
<td>CATT 2011</td>
<td>147</td>
<td>191</td>
<td>103</td>
<td>127.7%</td>
</tr>
<tr>
<td>DEDAL 2013</td>
<td>174</td>
<td>191</td>
<td>103</td>
<td>127.7%</td>
</tr>
<tr>
<td>IAN 2013</td>
<td>240</td>
<td>251</td>
<td>200</td>
<td>273</td>
</tr>
<tr>
<td>LUCAS 2015</td>
<td>177</td>
<td>184</td>
<td>179</td>
<td>197</td>
</tr>
<tr>
<td>MANTRA 2013</td>
<td>146</td>
<td>154</td>
<td>153</td>
<td>103</td>
</tr>
<tr>
<td>Subramaniam 2010</td>
<td>15</td>
<td>15</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Total (95% CI): 1381 / 1436; 100.0%; 1.00 (0.98, 1.02)

Total events: 1299 / 1355
Heterogeneity: Chi² = 4.86, df = 6 (P = 0.56; P = 9%
Test for overall effect: Z = 0.27 (P = 0.79)

**Footnotes**

(1) follow-up was 18 months

---

**Visual acuity (mean change in number of letters)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab Mean</th>
<th>SD</th>
<th>Total</th>
<th>Ranibizumab Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivone 2011</td>
<td>0.52</td>
<td>0.57</td>
<td>100</td>
<td>0.52</td>
<td>0.57</td>
<td>100</td>
<td>54</td>
<td>1.9%</td>
<td>-2.70 (-4.88, 0.48)</td>
<td>-4.30 (-7.48, 1.20)</td>
</tr>
<tr>
<td>BRANO study 2016</td>
<td>8.08</td>
<td>12.67</td>
<td>142</td>
<td>6.93</td>
<td>12.67</td>
<td>142</td>
<td>12.83</td>
<td>142</td>
<td>0.56 (0.31, 0.82)</td>
<td>-0.76 (-1.02, 0.20)</td>
</tr>
<tr>
<td>CATT 2011</td>
<td>0.92</td>
<td>1.80</td>
<td>191</td>
<td>2.93</td>
<td>1.91</td>
<td>191</td>
<td>15.08</td>
<td>183</td>
<td>10.7% (1.15, 4.83)</td>
<td>3.05 (1.55, 4.54)</td>
</tr>
<tr>
<td>DEDAL 2013</td>
<td>3.7</td>
<td>3.84</td>
<td>184</td>
<td>3.78</td>
<td>3.84</td>
<td>184</td>
<td>12.6</td>
<td>187</td>
<td>14.2% (2.94, 2.34)</td>
<td>-0.30 (-2.94, 2.34)</td>
</tr>
<tr>
<td>IAN 2013</td>
<td>4.9</td>
<td>10.27</td>
<td>154</td>
<td>4.1</td>
<td>10.36</td>
<td>154</td>
<td>15.33</td>
<td>163</td>
<td>8.7% (0.00, 16.76)</td>
<td>6.90 (4.94, 8.86)</td>
</tr>
<tr>
<td>LUCAS 2015</td>
<td>4.9</td>
<td>10.27</td>
<td>154</td>
<td>4.1</td>
<td>10.36</td>
<td>154</td>
<td>15.33</td>
<td>163</td>
<td>8.7% (0.00, 16.76)</td>
<td>6.90 (4.94, 8.86)</td>
</tr>
<tr>
<td>MANTRA 2013</td>
<td>7.5</td>
<td>1.54</td>
<td>15</td>
<td>8.3</td>
<td>1.54</td>
<td>15</td>
<td>13.7</td>
<td>7</td>
<td>0.3% (11.60, 14.00)</td>
<td>13.7 (11.60, 14.00)</td>
</tr>
<tr>
<td>Subramaniam 2010</td>
<td>7.5</td>
<td>1.54</td>
<td>15</td>
<td>8.3</td>
<td>1.54</td>
<td>15</td>
<td>13.7</td>
<td>7</td>
<td>0.3% (11.60, 14.00)</td>
<td>13.7 (11.60, 14.00)</td>
</tr>
</tbody>
</table>

Total (95% CI): 1523 / 1678; 100.0%; 0.94 (1.47, 0.51)

Heterogeneity: Chi² = 4.67, df = 7 (P = 0.76; P = 9%
Test for overall effect: Z = 0.95 (P = 0.34)
Quality of life (no problem in quality of life)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>4.1.1 Mobility</td>
<td>156</td>
<td>262</td>
<td>173</td>
<td>286</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1.2 Self-care</td>
<td>217</td>
<td>262</td>
<td>246</td>
<td>286</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1.3 Usual activities</td>
<td>178</td>
<td>262</td>
<td>199</td>
<td>286</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1.4 Pain/discomfort</td>
<td>158</td>
<td>262</td>
<td>168</td>
<td>285</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1.5 Anxiety/depression</td>
<td>158</td>
<td>262</td>
<td>214</td>
<td>286</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of injections

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Slovak 2011</td>
<td>7.7</td>
<td>3.6</td>
<td>310</td>
<td>6.8</td>
</tr>
<tr>
<td>CATT 2011</td>
<td>6.8</td>
<td>2.7</td>
<td>191</td>
<td>6.5</td>
</tr>
<tr>
<td>GEFAL 2013</td>
<td>6.9</td>
<td>2.8</td>
<td>184</td>
<td>6.2</td>
</tr>
<tr>
<td>LUCAS 2015</td>
<td>6.1</td>
<td>2.9</td>
<td>154</td>
<td>5.8</td>
</tr>
<tr>
<td>MANTA 2013</td>
<td>6.1</td>
<td>2.9</td>
<td>154</td>
<td>5.8</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.829</td>
<td></td>
<td>0.811</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 4.43 (P = 0.0000)

Two years

Visual acuity (gain of 15 letters or more)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>4.2.1 Participants in groups as randomized at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CATT 2011</td>
<td>144</td>
<td>502</td>
<td>162</td>
<td>526</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>41</td>
<td>249</td>
<td>53</td>
<td>286</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>185</td>
<td>751</td>
<td>215</td>
<td>786</td>
</tr>
<tr>
<td>Total events</td>
<td>189</td>
<td>775</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.98 (P = 0.05)

4.2.2 Participants remaining in same groups after re-randomization

| CATT 2011         | 112         | 390         | 125        | 396        | 66.6% [0.70, 1.14] |
| IVAN 2013         | 41          | 249         | 83          | 266        | 33.3% [0.09, 0.50] |
| Subtotal (95% CI) | 153         | 629         |             |            | 66.0% [0.72, 1.03] |
| Total events      | 153         | 666         |             |            |                   |

Test for overall effect: Z = 1.83 (P = 0.05)
Macular Degeneration
Appendix H: Grade tables and meta-analysis results

Visual acuity (loss of fewer than 15 letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.4.1 Participants in groups as randomized at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CATT 2011</td>
<td>447</td>
<td>502</td>
<td>489</td>
<td>526</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>226</td>
<td>249</td>
<td>245</td>
<td>266</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>773</td>
<td>733</td>
<td>706</td>
<td>103.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>673</td>
<td>733</td>
<td>706</td>
<td>103.0%</td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.78, df = 1 (P = 0.38), P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.16 (P = 0.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.4.2 Participants remaining in same groups after re-randomization

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATT 2011</td>
<td>341</td>
<td>399</td>
<td>370</td>
<td>398</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>226</td>
<td>249</td>
<td>245</td>
<td>266</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>629</td>
<td>666</td>
<td>666</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>557</td>
<td>515</td>
<td>666</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.63, df = 1 (P = 0.43), P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.10 (P = 0.13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Visual acuity (mean change in number of letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab Mean</th>
<th>SD</th>
<th>Total</th>
<th>Ranibizumab Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATT 2011</td>
<td>6.90 (5.38)</td>
<td>310</td>
<td>398</td>
<td>6.48 (5.06)</td>
<td>388</td>
<td>398</td>
<td>-0.45 (0.77)</td>
<td>-0.45 (0.77)</td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>4.1 (1.6)</td>
<td>48</td>
<td>4.8</td>
<td>1.3 (1.6)</td>
<td>15</td>
<td>288</td>
<td>-2.62 (0.31)</td>
<td>-2.62 (0.31)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>629</td>
<td>100</td>
<td>100</td>
<td>-1.51 (0.54)</td>
<td>100</td>
<td>100</td>
<td>-1.51 (0.54)</td>
<td>-1.51 (0.54)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.15, df = 1 (P = 0.70), P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.66 (P = 0.095)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quality of life (no problem in quality of life)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bevacizumab Events</th>
<th>Total</th>
<th>Ranibizumab Events</th>
<th>Total</th>
<th>Risk Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.12.1 Mobility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>171</td>
<td>247</td>
<td>172</td>
<td>260</td>
<td>1.05</td>
<td>[0.93, 1.18]</td>
</tr>
<tr>
<td><strong>4.12.2 Self care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>218</td>
<td>247</td>
<td>217</td>
<td>267</td>
<td>0.95</td>
<td>[0.90, 1.01]</td>
</tr>
<tr>
<td><strong>4.12.3 Usual activities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>179</td>
<td>247</td>
<td>177</td>
<td>267</td>
<td>0.98</td>
<td>[0.88, 1.09]</td>
</tr>
<tr>
<td><strong>4.12.4 Pain/discomfort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>145</td>
<td>247</td>
<td>145</td>
<td>267</td>
<td>1.02</td>
<td>[0.88, 1.18]</td>
</tr>
<tr>
<td><strong>4.12.5 Anxiety/depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAN 2013</td>
<td>203</td>
<td>247</td>
<td>203</td>
<td>267</td>
<td>1.00</td>
<td>[0.92, 1.08]</td>
</tr>
</tbody>
</table>
Appendix H: Grade tables and meta-analysis results
## H.6.1.5 Aflibercept vs ranibizumab

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect</th>
<th>No of Participants</th>
<th>Quality of the evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean change in BCVA in ETDRS letters at 1 year</strong></td>
<td>Mean change in visual acuity in aflibercept groups was on average 0.15 fewer letters gained (95% CI 1.47 fewer letters to 1.17 more letters)</td>
<td>Mean change in visual acuity across ranibizumab groups ranged from gains of 8.57 letters to 8.71 letters</td>
<td>MD -0.15 (-1.47 to 1.17)</td>
<td>2412 (2 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
<tr>
<td><strong>Gain of 15 of BCVA at one year</strong></td>
<td>314 per 1000 (275 to 360)</td>
<td>324 per 1000</td>
<td>RR 0.97 (0.85 to 1.11)</td>
<td>2412 (2 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
<tr>
<td><strong>Quality of life measures at 1 year (national eye institute-visual function questionnaire)</strong></td>
<td>Mean improvement in composite NEI-VQF score in intervention groups was on average 0.39 points lower (95% CI 1.71 points lower to 0.93 points higher)</td>
<td>Mean improvement in composite NEI-VQF score ranged across control groups from 4.9 to 6.3 points</td>
<td>MD -0.39 (-1.71 to 0.93)</td>
<td>2412 (2 studies)</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
<tr>
<td><strong>Adverse events (serious systemic events at 1 year)</strong></td>
<td>138 per 1000 (110 to 174)</td>
<td>139 per 1000</td>
<td>RR 0.99 (0.79 to 1.25)</td>
<td>2419 (2 studies)</td>
<td>⊕⊕⊕⊕ Moderate¹</td>
</tr>
<tr>
<td><strong>Adverse events (serious ocular events at 1 year)</strong></td>
<td>20 per 1000 (12 to 34)</td>
<td>32 per 1000</td>
<td>RR 0.62 (0.36 to 1.07)</td>
<td>2419 (2 studies)</td>
<td>⊕⊕⊕⊕ Moderate¹</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

1. Adverse event outcome downgrade to moderate quality as the numbers of events were small (wide confidence intervals), and 95%CI of estimated effect under the possibility of significant and non-significant values.
The data presented in the GRADE table below were identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

**Aflibercept vs ranibizumab: NEI-VFQ 25**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of people gaining more than 5 ETDRS letters and having clinical improvement (more than 6-points) in the NEI-VFQ25 at 52-weeks follow–up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (VIEW 1, VIEW2)</td>
<td>Not serious</td>
<td>Serious(^1)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1193</td>
<td>RR 0.97 (0.86, 1.10)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>NEI-VFQ-25 subscale score changes from baseline to week 52 (higher scores indicate better QoL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General vision</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1193</td>
<td>MD 0.06 (-2.00, 2.13)</td>
<td>HIGH</td>
</tr>
<tr>
<td>Near activities</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1193</td>
<td>MD -0.62 (-3.09, 1.86)</td>
<td>HIGH</td>
</tr>
<tr>
<td>Distance activities</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>1193</td>
<td>MD 0.08 (-2.43, 2.58)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Mental health</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>1193</td>
<td>MD 0.14 (-2.41, 2.70)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Role difficulties</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>1193</td>
<td>MD 1.09 (-2.04, 4.23)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Dependency</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>1193</td>
<td>MD -1.29 (-4.00, 1.43)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Social functioning</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>1193</td>
<td>MD 0.18 (-2.35, 2.70)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Driving</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>1193</td>
<td>MD 1.51 (-1.15, 4.17)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Colour vision</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1193</td>
<td>MD -2.04 (-4.33, 0.26)</td>
<td>HIGH</td>
</tr>
<tr>
<td>Number of studies</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Sample size</td>
<td>Effect (95%CI)</td>
<td>Quality</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1193</td>
<td>MD -0.94 (-3.21, 1.32)</td>
<td>HIGH</td>
</tr>
<tr>
<td>Peripheral vision</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1193</td>
<td>MD 0.86 (-3.73, 2.00)</td>
<td>HIGH</td>
</tr>
<tr>
<td>General health</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1193</td>
<td>MD -0.23 (-2.56, 2.10)</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

1. Downgraded one level for inconsistency due to heterogeneity ($i^2>50\%$)
2. Downgraded one level for imprecision due to 95% CI of estimated effect crossing 1 line of a defined minimal important difference (2.3 point)
Aflibercept vs ranibizumab (one year)

Gain of ≥ 15 letters of BCVA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>M.H. Fixed, 95% CI</td>
<td>M.H. Fixed, 95% CI</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>281</td>
<td>908</td>
<td>94</td>
<td>304</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>290</td>
<td>911</td>
<td>99</td>
<td>291</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>571</td>
<td>1817</td>
<td>595</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.28, df = 1 (P = 0.13), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.47 (P = 0.64)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Loss of ≥ 15 letters of BCVA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>M.H. Fixed, 95% CI</td>
<td>M.H. Fixed, 95% CI</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>47</td>
<td>908</td>
<td>19</td>
<td>304</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>45</td>
<td>911</td>
<td>15</td>
<td>291</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>92</td>
<td>1817</td>
<td>595</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.61 (P = 0.54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean change in BCVA in ETDRS letters

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Total Weight</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>6.57 ± 4.13</td>
<td>14.19 ± 8.08</td>
<td>908</td>
<td>81 ± 15.3</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>8.71 ± 4.13</td>
<td>13.72 ± 8.11</td>
<td>911</td>
<td>94 ± 13.5</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1617</td>
<td>595</td>
<td>100.0%</td>
<td>0.15 [-1.47, 1.17]</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.23 (P = 0.82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Arterial thrombotic events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept Events</th>
<th>Total</th>
<th>Ramikizumab</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.8.1 Any Antiplatedlet Thrombosis</strong></td>
<td><strong>Total</strong></td>
<td><strong>Total</strong></td>
<td><strong>Weight</strong></td>
<td><strong>M.H. Fixed, 95% CI</strong></td>
<td><strong>Risk Ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>15</td>
<td>911</td>
<td>5</td>
<td>304</td>
<td>49.7%</td>
<td>1.00 [0.37, 2.73]</td>
<td>1.00 [0.37, 2.73]</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>17</td>
<td>913</td>
<td>5</td>
<td>301</td>
<td>49.3%</td>
<td>1.00 [0.40, 2.91]</td>
<td>1.00 [0.40, 2.91]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>32</td>
<td>1824</td>
<td>10</td>
<td>595</td>
<td>100.0%</td>
<td>1.04 [0.32, 2.11]</td>
<td>1.04 [0.32, 2.11]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>10</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Ch² = 0.01, df = 1 (P = 0.91), I² = 0%</strong></td>
<td><strong>Test for overall effect: Z = 0.12 (P = 0.91)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1.8.2 Vascular death**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept Events</th>
<th>Total</th>
<th>Ramikizumab</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIEW 1</td>
<td>5</td>
<td>911</td>
<td>1</td>
<td>304</td>
<td>49.7%</td>
<td>1.87 [0.30, 14.23]</td>
<td>1.87 [0.30, 14.23]</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>4</td>
<td>913</td>
<td>1</td>
<td>291</td>
<td>50.3%</td>
<td>1.27 [0.44, 4.08]</td>
<td>1.27 [0.44, 4.08]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1824</td>
<td>595</td>
<td>100.0%</td>
<td>1.47 [0.32, 6.79]</td>
<td>1.47 [0.32, 6.79]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Ch² = 0.03, df = 1 (P = 0.86), I² = 0%</strong></td>
<td><strong>Test for overall effect: Z = 0.48 (P = 0.62)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**1.8.3 Non-fatal myocardial infarction**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept Events</th>
<th>Total</th>
<th>Ramikizumab</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIEW 1</td>
<td>6</td>
<td>911</td>
<td>4</td>
<td>304</td>
<td>66.4%</td>
<td>0.50 [0.14, 4.17]</td>
<td>0.50 [0.14, 4.17]</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>3</td>
<td>913</td>
<td>2</td>
<td>291</td>
<td>53.7%</td>
<td>1.43 [0.31, 6.66]</td>
<td>1.43 [0.31, 6.66]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1824</td>
<td>595</td>
<td>100.0%</td>
<td>0.81 [0.32, 2.09]</td>
<td>0.81 [0.32, 2.09]</td>
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<td></td>
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<tr>
<td><strong>Total events</strong></td>
<td>15</td>
<td>6</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Ch² = 1.10, df = 1 (P = 0.29), I² = 9%</strong></td>
<td><strong>Test for overall effect: Z = 0.43 (P = 0.67)</strong></td>
<td></td>
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</tr>
</tbody>
</table>

**1.8.4 Non-fatal stroke**

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Aflibercept Events</th>
<th>Total</th>
<th>Ramikizumab</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIEW 1</td>
<td>4</td>
<td>911</td>
<td>0</td>
<td>304</td>
<td>19.8%</td>
<td>3.01 [0.16, 56.74]</td>
<td>3.01 [0.16, 56.74]</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>4</td>
<td>913</td>
<td>2</td>
<td>291</td>
<td>52.2%</td>
<td>0.54 [0.12, 2.44]</td>
<td>0.54 [0.12, 2.44]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1824</td>
<td>595</td>
<td>100.0%</td>
<td>1.11 [0.27, 4.50]</td>
<td>1.11 [0.27, 4.50]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Ch² = 0.06, df = 1 (P = 0.35), I² = 0%</strong></td>
<td><strong>Test for overall effect: Z = 0.14 (P = 0.89)</strong></td>
<td></td>
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</tr>
</tbody>
</table>

Test for subaraneous differences: Ch² = 0.46, df = 3 (P = 0.63), I² = 0%

### Serious systemic events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept Events</th>
<th>Total</th>
<th>Ramikizumab</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.9.1 Any severe systemic adverse event</strong></td>
<td><strong>Total</strong></td>
<td><strong>Total</strong></td>
<td><strong>Weight</strong></td>
<td><strong>M.H. Fixed, 95% CI</strong></td>
<td><strong>Risk Ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>141</td>
<td>911</td>
<td>57</td>
<td>304</td>
<td>66.4%</td>
<td>0.89 [0.62, 1.24]</td>
<td>0.89 [0.62, 1.24]</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>111</td>
<td>913</td>
<td>26</td>
<td>281</td>
<td>51.6%</td>
<td>1.36 [0.51, 4.04]</td>
<td>1.36 [0.51, 4.04]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>252</td>
<td>1824</td>
<td>83</td>
<td>595</td>
<td>100.0%</td>
<td>0.98 [0.79, 1.23]</td>
<td>0.98 [0.79, 1.23]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>252</td>
<td>83</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Ch² = 4.00, df = 1 (P = 0.05), I² = 75%</strong></td>
<td><strong>Test for overall effect: Z = 0.05 (P = 0.96)</strong></td>
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**1.9.2 Congestive heart failure event**

<table>
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<th>Study or Subgroup</th>
<th>Aflibercept Events</th>
<th>Total</th>
<th>Ramikizumab</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIEW 1</td>
<td>8</td>
<td>911</td>
<td>2</td>
<td>304</td>
<td>66.4%</td>
<td>1.00 [0.20, 4.99]</td>
<td>1.00 [0.20, 4.99]</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>1</td>
<td>913</td>
<td>1</td>
<td>291</td>
<td>53.7%</td>
<td>0.33 [0.02, 5.08]</td>
<td>0.33 [0.02, 5.08]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1824</td>
<td>595</td>
<td>100.0%</td>
<td>0.77 [0.26, 2.97]</td>
<td>0.77 [0.26, 2.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>7</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Ch² = 0.44, df = 1 (P = 0.46), I² = 0%</strong></td>
<td><strong>Test for overall effect: Z = 0.55 (P = 0.58)</strong></td>
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<td></td>
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**1.9.3 Non-ocular hemorrhagic event**

<table>
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<th>Aflibercept Events</th>
<th>Total</th>
<th>Ramikizumab</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIEW 1</td>
<td>7</td>
<td>911</td>
<td>1</td>
<td>304</td>
<td>66.4%</td>
<td>2.34 [0.28, 18.91]</td>
<td>2.34 [0.28, 18.91]</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>3</td>
<td>913</td>
<td>0</td>
<td>291</td>
<td>53.6%</td>
<td>2.26 [0.12, 43.17]</td>
<td>2.26 [0.12, 43.17]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1824</td>
<td>595</td>
<td>100.0%</td>
<td>2.30 [0.42, 12.70]</td>
<td>2.30 [0.42, 12.70]</td>
<td></td>
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</tr>
<tr>
<td><strong>Total events</strong></td>
<td>10</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Ch² = 0.00, df = 1 (P = 0.96), I² = 0%</strong></td>
<td><strong>Test for overall effect: Z = 0.96 (P = 0.34)</strong></td>
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</table>

Test for subaraneous differences: Ch² = 1.66, df = 2 (P = 0.49), I² = 0%
### Serious ocular events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M.H, Fixed, 95% CI</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>16</td>
<td>911</td>
<td>10</td>
<td>304</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>20</td>
<td>913</td>
<td>9</td>
<td>291</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1024</td>
<td>595</td>
<td>100.0%</td>
<td>0.62 [0.36, 1.07]</td>
</tr>
<tr>
<td>Total events</td>
<td>35</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.25, df = 1 (P = 0.61); I² = 0%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.72 (P = 0.08)</td>
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</tbody>
</table>

#### 1.10.2 Visual acuity reduced

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M.H, Fixed, 95% CI</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>3</td>
<td>911</td>
<td>2</td>
<td>304</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>7</td>
<td>913</td>
<td>1</td>
<td>291</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1024</td>
<td>595</td>
<td>100.0%</td>
<td>1.06 [0.30, 3.93]</td>
</tr>
<tr>
<td>Total events</td>
<td>10</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 1.18, df = 1 (P = 0.26); I² = 15%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.12 (P = 0.91)</td>
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</table>

#### 1.10.3 Retinal hemorrhage

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M.H, Fixed, 95% CI</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>2</td>
<td>911</td>
<td>2</td>
<td>304</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>4</td>
<td>913</td>
<td>1</td>
<td>291</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1024</td>
<td>595</td>
<td>100.0%</td>
<td>0.95 [0.18, 5.00]</td>
</tr>
<tr>
<td>Total events</td>
<td>8</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.01, df = 1 (P = 0.97); I² = 0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.61 (P = 0.54)</td>
<td></td>
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</tr>
</tbody>
</table>

Test for subgroup differences: Ch² = 0.62, df = 2 (P = 0.73), I² = 0%

### Proportion of people had gain more than 5 ETDRS letters and had clinical improvement in NEI-VFQ composite score (more than 6-point)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M.H, Random, 95% CI</td>
</tr>
<tr>
<td>VIEW 1</td>
<td>192</td>
<td>293</td>
<td>192</td>
<td>393</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>182</td>
<td>308</td>
<td>180</td>
<td>291</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>374</td>
<td>594</td>
<td>100.0%</td>
<td>0.97 [0.86, 1.10]</td>
</tr>
<tr>
<td>Total events</td>
<td>374</td>
<td>362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Ch² = 2.08, df = 1 (P = 0.15); I² = 52%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.46 (P = 0.65)</td>
<td></td>
<td></td>
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</table>
Mean change in NEI-VFQ subscale score
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Alliscept</th>
<th>Ranibizumab</th>
<th>Mean Difference</th>
<th>Mean Difference 46% fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.3 General vision</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VIEW 1</td>
<td>11.1</td>
<td>19</td>
<td>233</td>
<td>9.5</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>11.1</td>
<td>17</td>
<td>306</td>
<td>9.6</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.09 [-1.26, 2.33]</td>
</tr>
<tr>
<td><strong>1.1.2 Near activities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>8.1</td>
<td>22.2</td>
<td>233</td>
<td>7.2</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>7.1</td>
<td>21.03</td>
<td>306</td>
<td>7.2</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.09 [-2.45, 2.55]</td>
</tr>
<tr>
<td><strong>1.1.3 Distance activities</strong></td>
<td></td>
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<td>VIEW 1</td>
<td>4.2</td>
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<td>2.5</td>
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<tr>
<td>VIEW 2</td>
<td>4.2</td>
<td>21.8</td>
<td>306</td>
<td>7.6</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.08 [-2.45, 2.55]</td>
</tr>
<tr>
<td><strong>1.1.4 Mental health</strong></td>
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<td></td>
</tr>
<tr>
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<td>24.1</td>
<td>233</td>
<td>9.0</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>11.4</td>
<td>22.2</td>
<td>306</td>
<td>10.4</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.14 [-2.41, 2.70]</td>
</tr>
<tr>
<td><strong>1.1.5 Role difficulties</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>27.9</td>
<td>233</td>
<td>5.0</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>1.8</td>
<td>24.1</td>
<td>306</td>
<td>6.9</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>1.09 [-2.84, 4.23]</td>
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<td><strong>1.1.6 Dependency</strong></td>
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<td>22.9</td>
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<td>VIEW 2</td>
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<td>25.2</td>
<td>306</td>
<td>4.5</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>1.29 [-4.08, 6.63]</td>
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<tr>
<td><strong>1.1.7 Social functioning</strong></td>
<td></td>
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<tr>
<td>VIEW 1</td>
<td>2.6</td>
<td>22.1</td>
<td>233</td>
<td>3.0</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>1.4</td>
<td>24.0</td>
<td>306</td>
<td>0.1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.48 [-2.36, 2.70]</td>
</tr>
<tr>
<td><strong>1.1.8 DMEg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>2.2</td>
<td>28.4</td>
<td>233</td>
<td>0.1</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>1.1</td>
<td>24.0</td>
<td>306</td>
<td>0.1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>1.51 [-1.45, 4.47]</td>
</tr>
<tr>
<td><strong>1.1.9 Colour vision</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>1.6</td>
<td>22.3</td>
<td>233</td>
<td>1.8</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>6.4</td>
<td>21.2</td>
<td>306</td>
<td>3.1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>2.39 [-4.33, 3.06]</td>
</tr>
<tr>
<td><strong>1.1.10 Ocular pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>1.2</td>
<td>20.2</td>
<td>233</td>
<td>1.3</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>1.1</td>
<td>19.4</td>
<td>306</td>
<td>5.1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.39 [-1.27, 1.95]</td>
</tr>
<tr>
<td><strong>1.1.11 Peripheral vision</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>4.4</td>
<td>23.9</td>
<td>233</td>
<td>5.5</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>2.5</td>
<td>25.7</td>
<td>306</td>
<td>3.1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.06 [-1.37, 1.49]</td>
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<tr>
<td><strong>1.1.12 General health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIEW 1</td>
<td>-4.9</td>
<td>22.1</td>
<td>233</td>
<td>-3.6</td>
</tr>
<tr>
<td>VIEW 2</td>
<td>1.5</td>
<td>19.5</td>
<td>306</td>
<td>0.5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>599</td>
<td>594</td>
<td>100.0%</td>
<td>0.30 [-2.52, 3.12]</td>
</tr>
</tbody>
</table>
### Treatment frequency: PRN vs routine injection

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRN vs routine injections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain of ≥15 letters at one year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 studies (CATT 2011, HARBOUR 2013, EI-Mollayess 2012, IVAN 2012, Chan 2015, RABIMO 2017)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>serious³</td>
<td>2928</td>
<td>RR 0.89 (0.79, 0.99)</td>
<td>LOW</td>
</tr>
<tr>
<td>Loss of &lt;15 letters at one year</td>
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</tr>
<tr>
<td>4 studies (CATT 2011, IVAN 2012, HARBOUR 2013, RABIMO 2017)</td>
<td>Serious¹,²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>2795</td>
<td>RR 0.99 (0.97, 1.01)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Mean change in BCVA in ETDRS letters at one year (higher values indicate better vision)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 studies (CATT 2011, HARBOUR 2013, , EI-Mollayess 2012, IVAN 2012)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>2874</td>
<td>MD -1.45 (-2.45, -0.45)</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Mean number of injections at one year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies (CATT 2011, , HARBOUR 2013)</td>
<td>Serious¹</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>Not serious</td>
<td>2202</td>
<td>MD -4.22 (-4.72, -3.73)</td>
<td>LOW</td>
</tr>
<tr>
<td>Adverse events (serious systemic events at one year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies (CATT 2011, HARBOUR 2013,)</td>
<td>Serious¹</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>2280</td>
<td>RR 1.07 (0.70, 1.63)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Adverse events (serious ocular events at one year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies (CATT 2011, HARBOUR 2013,)</td>
<td>Serious¹</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>not serious</td>
<td>2280</td>
<td>RR 0.31 (0.13, 0.78)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to masking of participants (either not reported in the study or participants were not blinded in the study)
2. Downgraded one level for risk of bias due to incomplete data (IVAN)
3. Downgraded one level for imprecision due to 95%CI of estimated effect crossing 1 line of a defined minimal important difference
Macular Degeneration
Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.</td>
<td>Downgraded for inconsistency due to heterogeneity ($i^2&gt;50%$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Downgrade one level for imprecision due to 95%CI of the effect cannot be estimated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
### PRN vs routine injections

#### Gain of 15 or more letters ETDRS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN Events</th>
<th>Routine Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1 Bevacizumab monthly</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CATT 2011</td>
<td>76</td>
<td>271</td>
<td>83</td>
<td>265</td>
<td>18.3%</td>
</tr>
<tr>
<td>El-Mollayess 2012</td>
<td>24</td>
<td>60</td>
<td>21</td>
<td>60</td>
<td>4.6%</td>
</tr>
<tr>
<td>GMAN 2015</td>
<td>22</td>
<td>166</td>
<td>40</td>
<td>165</td>
<td>Not estimable</td>
</tr>
<tr>
<td>IVAN 2012</td>
<td>25</td>
<td>136</td>
<td>19</td>
<td>134</td>
<td>4.2%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>467</td>
<td>459</td>
<td>27.0%</td>
<td></td>
<td>1.00 [0.81, 1.23]</td>
</tr>
<tr>
<td>Total events</td>
<td>125</td>
<td>123</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 1.87, df = 2 (P = 0.39); I² = 0%</td>
<td>Test for overall effect: Z = 0.01 (P = 0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.2 Ranibizumab monthly</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CATT 2011</td>
<td>71</td>
<td>285</td>
<td>97</td>
<td>284</td>
<td>21.1%</td>
</tr>
<tr>
<td>Chan 2015</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>0.9%</td>
</tr>
<tr>
<td>HARBOR 2013</td>
<td>90</td>
<td>273</td>
<td>99</td>
<td>274</td>
<td>21.5%</td>
</tr>
<tr>
<td>HARBOR 2013</td>
<td>83</td>
<td>275</td>
<td>95</td>
<td>275</td>
<td>20.7%</td>
</tr>
<tr>
<td>IVAN 2012</td>
<td>29</td>
<td>143</td>
<td>36</td>
<td>140</td>
<td>7.9%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>983</td>
<td>979</td>
<td>71.7%</td>
<td></td>
<td>0.84 [0.73, 0.95]</td>
</tr>
<tr>
<td>Total events</td>
<td>276</td>
<td>329</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 2.17, df = 4 (P = 0.70); I² = 0%</td>
<td>Test for overall effect: Z = 2.64 (P = 0.008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.3 Ranibizumab 2-monthly</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RABIMO 2017</td>
<td>8</td>
<td>20</td>
<td>6</td>
<td>20</td>
<td>1.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>20</td>
<td>20</td>
<td>1.3%</td>
<td></td>
<td>1.33 [0.57, 3.14]</td>
</tr>
<tr>
<td>Total events</td>
<td>8</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td>Test for overall effect: Z = 0.66 (P = 0.51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1470</td>
<td>1458</td>
<td>100.0%</td>
<td>0.89 [0.79, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>409</td>
<td>408</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 6.70, df = 8 (P = 0.57); I² = 0%</td>
<td>Test for overall effect: Z = 2.12 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 2.86, df = 2 (P = 0.24), I² = 30.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.2 0.5 1 2 5
Favors routine injections Favors PRN injections

---

*Macular Degeneration*

Appendix H: Grade tables and meta-analysis results
### Loss of fewer than 15 letters ETDRS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Routine</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.8.1 Bevacizumab monthly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAN 2012</td>
<td>131</td>
<td>136</td>
<td>127</td>
<td>134</td>
</tr>
<tr>
<td>GMAN 2015</td>
<td>139</td>
<td>166</td>
<td>152</td>
<td>165</td>
</tr>
<tr>
<td>CATT 2011</td>
<td>248</td>
<td>271</td>
<td>249</td>
<td>265</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>407</td>
<td>399</td>
<td>28.6%</td>
<td>0.99 [0.95, 1.02]</td>
</tr>
<tr>
<td>Total events</td>
<td>379</td>
<td>367</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.50, df = 1 (P = 0.22); I² = 33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.65 (P = 0.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.8.2 Ranibizumab monthly |        |        |        |        |        |        |        |
| IVAN 2012 | 137 | 143 | 134 | 140 | 10.2% | 1.00 [0.95, 1.05] |        |
| HARBOR 2013 | 260 | 275 | 269 | 275 | 20.3% | 0.97 [0.93, 1.00] |        |
| HARBOR 2013 | 259 | 273 | 256 | 274 | 19.3% | 1.02 [0.97, 1.06] |        |
| CATT 2011 | 262 | 285 | 268 | 284 | 20.2% | 0.97 [0.93, 1.02] |        |
| Subtotal (95% CI) | 976 | 973 | 79.0% | 0.99 [0.97, 1.01] |        |
| Total events | 918 | 927 |        |        |        |        |        |
| Heterogeneity: Chi² = 3.93, df = 3 (P = 0.27); I² = 24% |
| Test for overall effect: Z = 1.20 (P = 0.23) |

| 1.8.3 Ranibizumab 2-monthly |        |        |        |        |        |        |        |
| RABIMO 2017 | 19 | 20 | 18 | 20 | 1.4% | 1.06 [0.88, 1.26] |        |
| Subtotal (95% CI) | 20 | 20 | 1.4% | 1.06 [0.88, 1.26] |        |
| Total events | 19 | 18 |        |        |        |        |        |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.60 (P = 0.55) |

### Mean change in BCVA of ETDRS letters

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Routine</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Monthly</td>
<td>Mean</td>
</tr>
<tr>
<td>1.1.1 Ranibizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CATT 2011</td>
<td>6.8</td>
<td>13.1</td>
<td>287</td>
<td>8.5</td>
</tr>
<tr>
<td>HARBOR 2013</td>
<td>8.2</td>
<td>13.3</td>
<td>273</td>
<td>10.1</td>
</tr>
<tr>
<td>HARBOR 2013</td>
<td>8.6</td>
<td>13.8</td>
<td>273</td>
<td>9.2</td>
</tr>
<tr>
<td>IVAN 2012</td>
<td>2.1</td>
<td>10.4</td>
<td>143</td>
<td>7.8</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>976</td>
<td>973</td>
<td>69.7%</td>
<td>-1.65 [-2.85, -0.45]</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.92, df = 6 (P = 0.66); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.26 (P = 0.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 0.54, df = 2 (P = 0.76); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.1.2 Bevacizumab |        |        |        |        |        |        |        |        |        |
| CATT 2011         | 5.6   | 15.7  | 271   | 8.5  | 15.8 | 265   | 14.0% | -2.10 [-4.77, 0.57] |        |
| GMAN 2015         | 5.2   | 16.4  | 58    | 0.0  | 14.7 | 265   | 60.0% | -1.60 [5.20, 2.78] |        |
| CATT 2011         | 6.1   | 11.4  | 136   | 4.4  | 13.2 | 134   | 11.5% | 0.70 [2.24, 3.94] |        |
| Subtotal (95% CI) | 459   | 30.3% | -0.99 [-2.80, 0.82] |        |
| Heterogeneity: Chi² = 2.05, df = 2 (P = 0.36); I² = 3% |
| Test for overall effect: Z = 1.07 (P = 0.29) |
| Test for subgroup differences: Chi² = 0.71, df = 6 (P = 0.72); I² = 0% |
| Test for overall effect: Z = 2.04 (P = 0.04) |
| Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.55); I² = 0% |
### Serious systemic events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.7.1 Ranibizumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CATT 2011</td>
<td>29</td>
<td>268</td>
<td>21</td>
<td>301</td>
<td>23.3%</td>
<td>1.23 (0.81, 1.90)</td>
</tr>
<tr>
<td>HARBOUR 2013</td>
<td>31</td>
<td>272</td>
<td>28</td>
<td>274</td>
<td>25.1%</td>
<td>1.12 (0.69, 1.81)</td>
</tr>
<tr>
<td>HARBOUR 2013</td>
<td>20</td>
<td>275</td>
<td>16</td>
<td>274</td>
<td>23.9%</td>
<td>0.55 (0.33, 0.93)</td>
</tr>
<tr>
<td>IVAN 2012</td>
<td>24</td>
<td>302</td>
<td>10</td>
<td>300</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>845</td>
<td>849</td>
<td>72.3%</td>
<td>0.95</td>
<td>(0.58, 1.62)</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>90</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tau² = 0.16; Chi² = 6.52, df = 2 (P = 0.04); P = 68%</td>
<td></td>
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</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td>Z = 0.10 (P = 0.92)</td>
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<tr>
<td><strong>1.7.2 Bevacizumab</strong></td>
<td></td>
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</tr>
<tr>
<td>CATT 2011</td>
<td>50</td>
<td>300</td>
<td>33</td>
<td>296</td>
<td>27.7%</td>
<td>1.44 (0.86, 2.41)</td>
</tr>
<tr>
<td>GOIMP 2015</td>
<td>29</td>
<td>166</td>
<td>20</td>
<td>165</td>
<td>Not estimable</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>300</td>
<td>296</td>
<td>27.7%</td>
<td>1.44</td>
<td>(0.86, 2.41)</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>50</td>
<td>33</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Not applicable; Test for overall effect: Z = 1.76 (P = 0.08)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1145</td>
<td>1135</td>
<td>100.0%</td>
<td>1.07</td>
<td>(0.70, 1.63)</td>
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<tr>
<td><strong>Total events</strong></td>
<td>130</td>
<td>118</td>
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<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tau² = 0.12; Chi² = 9.15, df = 3 (P = 0.03); P = 67%</td>
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<tr>
<td><strong>Test for overall effect</strong></td>
<td>Z = 3.30 (P = 0.00)</td>
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<tr>
<td><strong>Test for subgroup differences</strong></td>
<td>Chi² = 1.48, df = 1 (P = 0.22); P = 32.4%</td>
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### Serious ocular events
Macular Degeneration
Appendix H: Grade tables and meta-analysis results

### 1.8.1 Bevacizumab

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Monthly Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H</th>
<th>Fixed</th>
<th>95% CI</th>
<th>Risk Ratio M-H</th>
<th>Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CATT 2011</strong></td>
<td></td>
<td>0</td>
<td>300</td>
<td>4</td>
<td>286</td>
<td>24.1%</td>
<td>0.11</td>
<td>[0.01, 1.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OAKAN 2015</strong></td>
<td></td>
<td>44</td>
<td>166</td>
<td>35</td>
<td>165</td>
<td>0.8%</td>
<td>1.25</td>
<td>[0.85, 1.84]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>300</td>
<td>286</td>
<td>4</td>
<td>286</td>
<td>24.1%</td>
<td>0.11</td>
<td>[0.01, 1.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.51 (P = 0.13)</td>
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1.8.2 Ranibizumab

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Monthly Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H</th>
<th>Fixed</th>
<th>95% CI</th>
<th>Risk Ratio M-H</th>
<th>Fixed</th>
<th>95% CI</th>
</tr>
</thead>
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<tr>
<td><strong>CATT 2011</strong></td>
<td></td>
<td>0</td>
<td>298</td>
<td>2</td>
<td>301</td>
<td>13.8%</td>
<td>0.26</td>
<td>[0.01, 4.16]</td>
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<td></td>
</tr>
<tr>
<td><strong>HARBOR 2013</strong></td>
<td></td>
<td>4</td>
<td>273</td>
<td>5</td>
<td>278</td>
<td>26.3%</td>
<td>0.60</td>
<td>[0.22, 2.04]</td>
<td></td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>845</td>
<td>840</td>
<td>14</td>
<td>75.0%</td>
<td>0.38</td>
<td>[0.14, 1.01]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td>5</td>
<td>14</td>
<td>0</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.24, df = 2 (P = 0.33), P = 11%</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.94 (P = 0.05)</td>
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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Monthly Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H</th>
<th>Fixed</th>
<th>95% CI</th>
<th>Risk Ratio M-H</th>
<th>Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td>1145</td>
<td>1135</td>
<td>100</td>
<td>100</td>
<td>0.31</td>
<td>[0.13, 0.70]</td>
<td></td>
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</table>

Total events: 5, 18

Heterogeneity: Chi² = 3.11, df = 3 (P = 0.37), P = 4%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for successful differences: Chi² = 0.68, df = 1 (P = 0.42), P = 0%

### Number of injections

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Monthly Mean</th>
<th>SD Total</th>
<th>Mean</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<tbody>
<tr>
<td><strong>15.1 Ranibizumab</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>CATT 2011</strong></td>
<td></td>
<td>8.0</td>
<td>3</td>
<td>285</td>
<td>11.7</td>
<td>1.6</td>
<td>284</td>
<td>25.2%</td>
<td>-4.96 [5.59, -4.41]</td>
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</tr>
<tr>
<td><strong>HARBOR 2013</strong></td>
<td></td>
<td>7.7</td>
<td>2.7</td>
<td>273</td>
<td>11.3</td>
<td>1.8</td>
<td>276</td>
<td>25.3%</td>
<td>-3.60 [3.08, -3.22]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>8.23</td>
<td>3.43</td>
<td>833</td>
<td>75.3%</td>
<td>4.23</td>
<td>4.94[3.36, -3.56]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.32, Chi² = 18.72, df = 2 (P &lt; 0.0001), P = 98%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 12.24 (P &lt; 0.00001)</td>
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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Monthly Mean</th>
<th>SD Total</th>
<th>Mean</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<tbody>
<tr>
<td><strong>15.2 Bevacizumab</strong></td>
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</tr>
<tr>
<td><strong>CATT 2011</strong></td>
<td></td>
<td>7.7</td>
<td>3.5</td>
<td>271</td>
<td>11.8</td>
<td>1.2</td>
<td>265</td>
<td>24.1%</td>
<td>-4.20 [4.64, 3.76]</td>
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<tr>
<td><strong>Ei-Kollagen 2012</strong></td>
<td></td>
<td>3.0</td>
<td>0</td>
<td>80</td>
<td>9.5</td>
<td>0</td>
<td>80</td>
<td>Not estimable</td>
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</tr>
<tr>
<td><strong>OAKAN 2015</strong></td>
<td></td>
<td>9.1</td>
<td>0.6</td>
<td>108</td>
<td>10.6</td>
<td>0</td>
<td>108</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>8.31</td>
<td>3.31</td>
<td>331</td>
<td>24.1%</td>
<td>4.20</td>
<td>[4.84, -3.75]</td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 10.66 (P &lt; 0.00001)</td>
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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRN</th>
<th>Monthly Mean</th>
<th>SD Total</th>
<th>Mean</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
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<td>1164</td>
<td>1150</td>
<td>100</td>
<td>100</td>
<td>0.31</td>
<td>[0.13, 0.70]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.21, Chi² = 18.73, df = 2 (P &lt; 0.0003), P = 94%</td>
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<tr>
<td>Test for overall effect: Z = 16.99 (P &lt; 0.00001)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for successful differences: Chi² = 0.01, df = 1 (P = 0.94), P = 6%</td>
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Favors PRN injections - Favors monthly injections
### Treatment frequency: ≤6 weeks vs >6 weeks treatment intervals

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gain of ≥15 letters at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRN vs (6 and/or 12 weeks) interval injections</td>
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</tr>
<tr>
<td>1 study (GMAN 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>231</td>
<td>RR 0.55 (0.34 to 0.88)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Loss of &lt;15 letters at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (GMAN 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>231</td>
<td>RR 0.91 (0.84 to 0.99)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Mean change in BCVA in ETDRS letters at one year (higher values indicate better vision)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 study (GMAN 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>231</td>
<td>MD -4.40 (-8.39 to -0.41)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Adverse events (serious systemic events at one year)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (GMAN 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>231</td>
<td>RR 1.39 (0.82 to 2.37)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Adverse events (serious ocular events at one year)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (GMAN 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>231</td>
<td>RR 1.25 (0.85 to 1.84)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Routine injections (interval 6 weeks or less vs more than 6 weeks)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Gain of ≥15 letters at one year</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 studies (Lushchyk 2013, NATTB 2012, VIEW 2012, EXCITE)</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>1276</td>
<td>RR 1.28 (1.08, 1.52)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Loss of &lt;15 letters at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 studies (Lushchyk 2013, NATTB 2012, EXCITE)</td>
<td>Serious³</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>not serious</td>
<td>671</td>
<td>RR 0.99 (0.92, 1.06)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)
Macular Degeneration

Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 studies (Lushchyk 2013, NATTB 2012, VIEW 2012, EXCITE 2010)</td>
<td>Serious³</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1276</td>
<td>MD 1.87 (0.36, 3.39)</td>
<td>LOW</td>
</tr>
<tr>
<td>Adverse events (serious systemic events at one year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies (Lushchyk 2013, VIEW 2012)</td>
<td>Serious⁵</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>798</td>
<td>RR 0.77 (0.53, 1.11)</td>
<td>LOW</td>
</tr>
<tr>
<td>Adverse events (serious ocular events at one year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 studies (Lushchyk 2013, NATTB 2012, VIEW 2012)</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>983</td>
<td>RR 1.52 (0.86, 2.69)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to masking of participants (patients, treating clinicians, and other staff involved in the study were not masked)
2. Downgraded one level for imprecision due to 95%CI of estimated effect crossing of 1 line of defined minimal important difference
3. Downgrade one level for risk of bias due to open label study design (Lushchyk 2013 and NATTB 2012) and selection bias (randomisation sequence were unclear in EXCITE and VIEW study)
4. Downgraded one level for inconsistency due to heterogeneity (i²>50%)
5. Downgraded one level for risk of bias due to open label study design (Lushchyk 2013)
# Macular Degeneration

## Appendix H: Grade tables and meta-analysis results

### Treatment frequency: ≤6 weeks vs >6 weeks treatment intervals

#### Gain of 15 or more letters of visual acuity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>6 weeks or less</th>
<th>More than 6 weeks</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutshhirk 2013</td>
<td>14</td>
<td>103</td>
<td>74</td>
<td>1.95 (0.65, 2.44)</td>
</tr>
<tr>
<td>EXCITE 2013</td>
<td>33</td>
<td>115</td>
<td>59</td>
<td>1.80 (0.91, 2.77)</td>
</tr>
<tr>
<td>NATTB 2012</td>
<td>75</td>
<td>79</td>
<td>54</td>
<td>1.00 (0.77, 1.35)</td>
</tr>
<tr>
<td>VIEW 2012</td>
<td>114</td>
<td>304</td>
<td>361</td>
<td>1.23 (0.90, 1.68)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>601</td>
<td>675</td>
<td>1.20 (1.08, 1.52)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>196</td>
<td>170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 3.65, df = 3 (p = 0.60), P = 16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.88 (P = 0.004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Loss of fewer than 15 letters of visual acuity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>6 weeks or less</th>
<th>More than 6 weeks</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCITE 2013</td>
<td>103</td>
<td>220</td>
<td>238</td>
<td>1.02 (0.97, 1.08)</td>
</tr>
<tr>
<td>Lutshhirk 2013</td>
<td>94</td>
<td>64</td>
<td>54</td>
<td>0.92 (0.86, 0.98)</td>
</tr>
<tr>
<td>NATTB 2012</td>
<td>76</td>
<td>8</td>
<td>82</td>
<td>1.02 (0.96, 1.10)</td>
</tr>
<tr>
<td>VIEW 2012</td>
<td>75</td>
<td>54</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>297</td>
<td>374</td>
<td>0.99 (0.92, 1.06)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>279</td>
<td>351</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Ch² = 7.71, df = 2 ( P = 0.02), P = 74%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.32 (P = 0.0006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Mean visual change in BCVA (EDTRS letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>6 weeks or less</th>
<th>More than 6 weeks</th>
<th>Mean Difference (M-H, Random, 95% CI)</th>
<th>Mean Difference (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCITE 2010</td>
<td>0.17</td>
<td>0.34</td>
<td>0.17</td>
<td>0.16 (0.05, 0.28)</td>
</tr>
<tr>
<td>Lutshhirk 2013</td>
<td>1.63</td>
<td>11.25</td>
<td>1.63</td>
<td>1.63 (0.50, 2.75)</td>
</tr>
<tr>
<td>NATTB 2012</td>
<td>10.9</td>
<td>13.8</td>
<td>10.9</td>
<td>10.9 (0.70, 2.00)</td>
</tr>
<tr>
<td>VIEW 2012</td>
<td>49.4</td>
<td>21.6</td>
<td>49.4</td>
<td>49.4 (21.6, 77.2)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>601</td>
<td>675</td>
<td>4.87 (2.36, 3.39)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 17.72, df = 3 (P = 0.0009), P = 93%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.43 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Serious systemic events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>6 weeks or less</th>
<th>More than 6 weeks</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutshhirk 2013</td>
<td>5</td>
<td>127</td>
<td>64</td>
<td>0.53 (0.10, 2.27)</td>
</tr>
<tr>
<td>VIEW 2012</td>
<td>40</td>
<td>304</td>
<td>363</td>
<td>0.76 (0.33, 1.85)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>431</td>
<td>367</td>
<td>0.77 (0.53, 1.11)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>45</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.10, df = 1 (P = 0.75), P = 90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.42 (P = 0.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Serious ocular events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>6 weeks or less Events</th>
<th>Total Events</th>
<th>More than 6 weeks Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCITE 2010</td>
<td>62</td>
<td>115</td>
<td>91</td>
<td>238</td>
<td>77.2%</td>
<td>1.41 [1.12, 1.78]</td>
</tr>
<tr>
<td>Lustikov 2013</td>
<td>3</td>
<td>127</td>
<td>5</td>
<td>64</td>
<td>8.7%</td>
<td>0.91 [0.77, 1.07]</td>
</tr>
<tr>
<td>HALTIS 2012</td>
<td>17</td>
<td>91</td>
<td>0</td>
<td>94</td>
<td>11.5%</td>
<td>1.96 [0.92, 4.16]</td>
</tr>
<tr>
<td>VIEW 2012</td>
<td>4</td>
<td>304</td>
<td>2</td>
<td>306</td>
<td>2.8%</td>
<td>1.90 [0.97, 3.81]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>637</strong></td>
<td><strong>689</strong></td>
<td><strong>108.0%</strong></td>
<td></td>
<td></td>
<td><strong>1.44 [1.15, 1.79]</strong></td>
</tr>
</tbody>
</table>

Total events: 91

Heterogeneity: Ch² = 1.51, df = 3 (P = 0.65); I² = 0%

Test for overall effect: Z = 3.17 (P = 0.0019)
### Treatment frequency: PRN loading

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gain of ≥15 letters at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (Barikian 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>60</td>
<td>RR 0.83 (0.43, 1.63)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Gain of ≥10 letters at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (BeMoc 2013)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>99</td>
<td>RR 0.93 (0.38, 2.25)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies (Barikian 2015, BeMoc 2013)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious³</td>
<td>189</td>
<td>MD 1.20 (-2.51, 4.91)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Mean number of injections at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies (Barikian 2015, BeMoc 2013)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious³</td>
<td>189</td>
<td>MD -0.30 (-1.92, 1.32)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Quality of life measures at one year (VFQ-25) (higher values indicate better QoL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (BeMoc 2013)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>99</td>
<td>MD -0.06</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>PRN with 4 week vs 12 weeks loading phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gain of ≥15 letters at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (CLEART-IT 2011)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>126</td>
<td>RR 0.94 (0.51, 1.72)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Loss of &lt;15 letter at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (CLEART-IT 2011)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>126</td>
<td>RR 1.05 (0.94, 1.18)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
### Mean change in BCVA (ETDRS letters)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study (CLEART-IT 2011)</td>
<td>Serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>126</td>
<td>MD 3.41 (-0.16, 6.98)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded for risk of bias due to randomisation, allocation concealment, masking of participants, and selective report were unclear
2. Downgrade two levels for imprecision due to 95%CI of the effect crossing 2 lines of a defined minimal important difference
3. Downgraded one level for imprecision as one of studies (BeMoc 2013) had no SD reported to estimate effect
4. Downgraded one level for imprecision due to SD was not reported with mean quality of life score
5. Downgraded one level for imprecision due to 95%CI of the effect crossing 1 line of a defined minimal important difference.
### Visual acuity (mean change in visual acuity BCVA of ETDRS letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>No Loading PRN</th>
<th>Loading PRN</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banikam 2016</td>
<td>8.3 ± 6.7</td>
<td>8 ± 10.4</td>
<td>50</td>
<td>0.39 [4.13, 4.73]</td>
</tr>
<tr>
<td>SEMO 2013</td>
<td>0.06 ± 0.49</td>
<td>2.08</td>
<td>69</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>79</strong></td>
<td><strong>80</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.30 [4.13, 4.73]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)
### Treatment frequency: treat-and-extend vs routine month injection

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gain of ≥15 letters at one year</strong></td>
<td>2 studies (TREX-AMD 2015; TREND 2017)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>646</td>
<td>RR 1.02 (0.78, 1.33)</td>
</tr>
<tr>
<td><strong>Mean change in BCVA in ETDRS letters at one year</strong> (higher scores indicate better vision)</td>
<td>2 studies (TREX-AMD 2015; TREND 2017)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious³</td>
<td>703</td>
<td>MD -1.46 (-3.26, 0.34)</td>
</tr>
<tr>
<td><strong>Mean number of injections at one year</strong></td>
<td>1 study (TREND 2017)</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>643</td>
<td>MD -2.40 (-2.80, -2.00)</td>
</tr>
<tr>
<td><strong>Adverse events (serious systemic events at one year)</strong></td>
<td>2 studies (TREX-AMD 2015; TREND 2017)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>709</td>
<td>RR 1.04 (0.68, 1.58)</td>
</tr>
<tr>
<td><strong>Adverse events (serious ocular events at one year)</strong></td>
<td>2 studies (TREX-AMD 2015; TREND 2017)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>709</td>
<td>RR 1.61 (0.61, 4.22)</td>
</tr>
<tr>
<td><strong>Gain of ≥15 letters at two years</strong></td>
<td>1 study (TREX-AMD 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>60</td>
<td>RR 1.50 (0.55, 4.06)</td>
</tr>
<tr>
<td><strong>Mean change in BCVA in ETDRS letters at two years</strong> (higher scores indicate better vision)</td>
<td>1 study (TREX-AMD 2015)</td>
<td>Very serious¹.⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>41</td>
<td>MD -1.80 (-10.48, 6.88)</td>
</tr>
<tr>
<td><strong>Adverse events (serious systemic events at two years)</strong></td>
<td>1 study (TREX-AMD 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>60</td>
<td>RR 9.50 (1.37, 65.97)</td>
</tr>
<tr>
<td><strong>Adverse events (serious ocular events at two years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Macular Degeneration
Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study (TREX-AMD 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>60</td>
<td>RR 5.63 (0.33, 97.10)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to masking of participants (method of random sequence generation was not reported) in TREX-AMD.
2. Downgraded two levels of serious imprecision due to 95% confidence interval of estimated effect crossing 2 lines of a defined minimal important difference
3. 95% confidence interval of estimated effect within bounds of a defined minimal important difference
4. Substantial, asymmetric, unexplained attrition between year 1 and year 2

Gain of ≥15 letters at one year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TREX</th>
<th>Monthly</th>
<th>Weight</th>
<th>Risk Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREND 2017</td>
<td>75</td>
<td>291</td>
<td>295</td>
<td>95.0% 0.98 [0.75, 1.30]</td>
</tr>
<tr>
<td>TREX-AMD 2015</td>
<td>10</td>
<td>40</td>
<td>20</td>
<td>5.0% 1.67 [0.52, 5.38]</td>
</tr>
</tbody>
</table>

Total (95% CI) 331 315 100.0% 1.02 [0.78, 1.33]

Total events 85 30

Heterogeneity: Χ² = 0.73, df = 1 (P = 0.39), I² = 0%
Test for overall effect Z = 0.15 (P = 0.88)

Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TREX</th>
<th>Monthly</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREND 2017</td>
<td>6.2</td>
<td>12.22</td>
<td>320</td>
<td>81.125005 -1.90 [-3.94, 0.04]</td>
</tr>
<tr>
<td>TREX-AMD 2015</td>
<td>10.5</td>
<td>12.96934</td>
<td>40</td>
<td>9.2 8.20099 13.7% 1.30 [-3.57, 6.17]</td>
</tr>
</tbody>
</table>

Total (95% CI) 360 343 100.0% -1.46 [-3.26, 0.34]

Heterogeneity: Χ² = 1.43, df = 1 (P = 0.23), I² = 30%
Test for overall effect Z = 1.59 (P = 0.11)

Adverse events (serious systemic events at one year)
### Adverse events (serious ocular events at one year)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TREX Events Total</th>
<th>Monthly Events Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREND 2017</td>
<td>4 323</td>
<td>4 328</td>
<td>59.9%</td>
<td>1.01 [0.25, 4.03]</td>
<td></td>
</tr>
<tr>
<td>TREX-AMD 2015</td>
<td>10 40</td>
<td>2 20</td>
<td>40.1%</td>
<td>2.50 [0.36, 19.34]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>363</strong></td>
<td><strong>346</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.61 [0.01, 4.22]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>14</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)

### Treatment frequency: PRN-and-extend vs PRN

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain of ≥15 letters at one year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (Elden 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>67</td>
<td>RR 1.48 (0.72, 3.05)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

| Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision) |
| 1 study (Elden 2015) | Serious¹ | N/A | Not serious | Serious³ | 67 | MD 4.50 (-3.78, 12.78) | LOW |
## Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean number of injections at one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 study (Eldem 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>67</td>
<td>MD 1.1</td>
<td>LOW</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events (serious systemic events at one year)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study (Eldem 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>67</td>
<td>RR 1.71 (0.44, 6.66)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events (ocular events at one year)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study (Eldem 2015)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious²</td>
<td>67</td>
<td>RR 0.99 (0.70, 1.38)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to open label study design
2. Downgraded two levels of serious imprecision due to 95% confidence interval of estimated effect crossing 2 lines of a defined minimal important difference
3. Downgraded one level for imprecision due to 95% confidence interval of estimated effect crossing 1 line of defined minimal important difference
4. Downgraded one level for imprecision due to SD cannot be estimated to estimate confidence interval of the effect

---

**Network meta-analysis on anti-angiogenic therapies and treatment frequency** (network meta-analysis results are provided in Appendix G)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in BCVA at 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>RCT</td>
<td>10,925</td>
<td>Anti-VEGF agents vs placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Head-to-head anti-VEGF agents</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy compared with placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Sample size</td>
<td>Comparison</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Quality</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
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<td>--------------</td>
<td>--------------</td>
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<td>---------</td>
</tr>
<tr>
<td>12</td>
<td>RCT</td>
<td>7,623</td>
<td>Anti-VEGF agents vs placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Head-to-head anti-VEGF agents</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy compared with placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy compared with anti-VEGF</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – PRN compared with monthly</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – PRN with and without</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
## Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>loading phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF frequency – treat-and-extend compared with routine or PRN</td>
<td>Serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>LOW</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Categorical change in BCVA⁷ (change in ETDRS letters) at 12months

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>RCT</td>
<td>9,950</td>
<td>Anti-VEGF agents vs placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Head-to-head anti-VEGF agents</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy compared with placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy compared with anti-VEGF</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – PRN compared with routine treatment</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – PRN with and without loading phase</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – different frequencies of routine treatment</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – treat-and-extend compared with routine or PRN</td>
<td>Serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – PRN-and-extend compared with routine or PRN</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>LOW</td>
</tr>
</tbody>
</table>

⁷ The estimated effects=\( z \text{ score} \times 13.7 \) (standard deviation) at 12 months; and \( z \text{ score} \times 15.1 \) (standard deviation) at 24 months
## Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>RCT</td>
<td>7,041</td>
<td>Anti-VEGF agents vs placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Head-to-head anti-VEGF agents</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy compared with placebo</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious³</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photodynamic therapy compared with anti-VEGF</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>HIGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – PRN compared with monthly</td>
<td>Not serious</td>
<td>Serious⁶</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-VEGF frequency – PRN with and without loading phase</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

1. Downgraded one level due to confidence/credible intervals of estimated effects of comparison crossing 1 line of defined minimal important difference.
2. Downgraded one level for individual studies at risk of bias (treatment frequency/schedule were not masked to patients).
3. Downgraded one level for individual studies at risk of bias (randomisation, allocation concealment, and selective outcome reporting were unclear).
4. Downgraded one level of individual studies at risk of bias (study design, randomisation of the study).
5. Downgraded one level of individual studies at risk bias (treatment frequency/schedule were not masked to patients, study design or incomplete data).
6. Downgraded one level due to substantial inconsistency between study heterogeneity ($I^2>50%$)
### H.6.2 Treatment in people presenting with visual acuity better than 6/12 or people presenting with visual acuity worse than 6/96

RQ10: What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity better than 6/12?

RQ25: What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity worse than 6/96?

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual acuity at 1 year (visual acuity ≥ 6/12 vs VA&lt;6/12 to VA&gt;6/96) (ETDRS letters; higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (Writing committee for the UK AMD EMR user group 2014, Ying 2013)</td>
<td>Cohort study</td>
<td>Serious¹</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>11,914</td>
<td>MD 16.52 (13.41, 19.64)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Visual acuity at 1 year (visual acuity ≤6/96 vs VA&lt;6/12 to VA&gt;6/96) (ETDRS letters; higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Writing committee for the UK AMD EMR user group 2014)</td>
<td>Cohort study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>8,888</td>
<td>MD -17.23 (-22.36, -12.10)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Change in visual acuity at 1 year (visual acuity ≥ 6/12 vs VA&lt;6/12 to VA&gt;6/96) (ETDRS letters; higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (Writing committee for the UK AMD EMR user group 2014, William 2011, Ying 2013)</td>
<td>Cohort study</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>12,529</td>
<td>MD -6.34 (-7.33, -5.36)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Change in visual acuity at 1 year (visual acuity &lt;6/96 vs VA&lt;6/12 letters to VA≥6/96) (ETDRS letters; higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Writing committee for the UK AMD EMR user group 2014)</td>
<td>Cohort study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>8888</td>
<td>MD 13.99</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Number of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Sample size</td>
<td>Effect</td>
<td>Quality</td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------</td>
</tr>
<tr>
<td>committee for the UK AMD EMR user group 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(10.39, 17.59)</td>
<td></td>
</tr>
<tr>
<td><strong>Change in visual acuity at 6 months (visual acuity &lt;6/96 vs VA≥6/96) (Fang 2013, vision threshold up to≥60 letters) (ETDRS letters; higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (Fang 2013, Writing committee for the UK AMD EMR user group 2014)</td>
<td>Cohort study</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>9032</td>
<td>MD 7.77 (5.44, 10.10)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Change in visual acuity at 5 years (visual acuity ≥ 6/12 vs VA &lt;6/12 to VA≥6/60) (ETDRS letters; higher scores indicate better vision)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Zhu 2015)</td>
<td>Case series</td>
<td>Very serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>186</td>
<td>MD -11.75 (-18.98, -4.52)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Percentage of people who lost 15 letters or more at 1 year (visual acuity ≥6/12 vs VA &lt;6/12 to VA &gt;6/100 (23 letter)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (Buckle 2014, El-Mollagyess 2013)</td>
<td>Prospective cohorts</td>
<td>Serious¹</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Very serious⁴</td>
<td>1389</td>
<td>RR 0.41 (0.04, 3.94)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Percentage of people who lost less than 15 letters at 1 year (visual acuity ≥6/12 vs VA &lt;6/12 to VA ≥6/196)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (William 2011)</td>
<td>Prospective cohort</td>
<td>Very serious²</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>615</td>
<td>RR 10.01 (0.95, 1.08)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Percentage of people who gained 15 letters or more at 1 year (visual acuity≥6/12 vs VA&lt;6/12 )</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (El-Mollagyess 2013, Regillo 2015, William 2011, Ying</td>
<td>Prospective and retrospective cohorts</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>2310</td>
<td>RR 0.16 (0.12, 0.22)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (Fang 2013, Vogel 2016)</td>
<td>Prospective cohorts</td>
<td>Very serious(^2)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^5)</td>
<td>239</td>
<td>RR 1.44 (1.02, 2.01)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Percentage of people who gained 15 letters or more at 6 to 12 months (visual acuity <20 letters (6/120) vs VA≥6/120 (20 letters))**

1. Downgraded one level for non-randomised study design but large sample size included in the analysis.
2. Downgraded two levels for non-randomised study design.
3. Downgraded one level for inconsistency (\(i^2>50\%\))
4. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
5. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference

Note: visual acuity 6/12 equivalents to 70 ETDRS letters, and 6/96 equivalents to 25 ETDRS letters.
## Mean visual acuity at 1 year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VA better than 6/12</th>
<th>VA ≥6/9 to &lt;6/12</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Writing committee for the UK AMD EMR user group 2014</td>
<td>17.3</td>
<td>5.42</td>
<td>2322</td>
<td>53.52</td>
</tr>
<tr>
<td>Yang 2013</td>
<td>77.7</td>
<td>13.9</td>
<td>387</td>
<td>12.6</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2276</td>
<td>9165</td>
<td>16.52 [13.41, 19.64]</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Tau² = 3.17, df = 1, P = 0.05, I² = 74%

Test for overall effect: Z = 10.39 (P < 0.00001)

### Change in visual acuity

#### Change in visual acuity (letters) at 1 year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VA worse than 6/6</th>
<th>VA &gt;6/9 to &lt;6/12</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Williams 2011</td>
<td>-0.5</td>
<td>1.6</td>
<td>88</td>
<td>6.43</td>
</tr>
<tr>
<td>Writing committee for the UK AMD EMR user group 2014</td>
<td>-3.39</td>
<td>3.11</td>
<td>2322</td>
<td>33.33</td>
</tr>
<tr>
<td>Yang 2013</td>
<td>5.7</td>
<td>3.2</td>
<td>307</td>
<td>2.3</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2047</td>
<td>9172</td>
<td>106.0% [93.39, 118.64]</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 1.17, df = 2, P = 0.56, I² = 0%

Test for overall effect: Z = 12.66 (P < 0.00001)

### Change in visual acuity at 6 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VA worse than 6/6</th>
<th>VA &gt;6/9 to &lt;6/12</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Fang 2013</td>
<td>13.2</td>
<td>3.7</td>
<td>112</td>
<td>9.9</td>
</tr>
<tr>
<td>Writing committee for the UK AMD EMR user group 2014</td>
<td>11.4</td>
<td>3.1</td>
<td>411</td>
<td>35.6</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>434</td>
<td>8598</td>
<td>100.0% [78.44, 121.12]</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 0.13, df = 1, P = 0.72, I² = 0%

Test for overall effect: Z = 6.52 (P < 0.00001)

### Change in visual acuity at 6 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VA worse than 6/6</th>
<th>VA &gt;6/9 to &lt;6/12</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Fang 2013</td>
<td>13.2</td>
<td>3.7</td>
<td>112</td>
<td>9.9</td>
</tr>
<tr>
<td>Writing committee for the UK AMD EMR user group 2014</td>
<td>11.4</td>
<td>3.1</td>
<td>411</td>
<td>35.6</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>434</td>
<td>8598</td>
<td>100.0% [78.44, 121.12]</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 0.13, df = 1, P = 0.72, I² = 0%

Test for overall effect: Z = 6.52 (P < 0.00001)

### Percentage of people who gained ≥15 letter at 1 year

#### People with good baseline vision vs people with VA between 6/12 and 6/69

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VA better than 6/12</th>
<th>VA ≥6/9 to &lt;6/12</th>
<th>Risk Ratio</th>
<th>M-H, Found, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>El-Mohajaneen 2013</td>
<td>0</td>
<td>30</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>Riquillo 2015</td>
<td>7</td>
<td>122</td>
<td>162</td>
<td>43.8</td>
</tr>
<tr>
<td>Williams 2011</td>
<td>1</td>
<td>80</td>
<td>153</td>
<td>52.7</td>
</tr>
<tr>
<td>Yang 2013</td>
<td>28</td>
<td>597</td>
<td>269</td>
<td>708</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>577</td>
<td>1733</td>
<td>100.0% [90.12, 120.22]</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 6.68, df = 2, P = 0.13, I² = 47%

Test for overall effect: Z = 11.03 (P < 0.00001)
People with poor baseline vision vs people with baseline vision ≥6/120 (20 letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VA &lt;6/120</th>
<th>VA 6/120 or better</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Fang 2013</td>
<td>10</td>
<td>28</td>
<td>121</td>
<td>41.2%</td>
</tr>
<tr>
<td>Vogel 2018</td>
<td>17</td>
<td>30</td>
<td>85</td>
<td>59.8%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>53</strong></td>
<td><strong>126</strong></td>
<td><strong>186</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 27

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%
Test for overall effect: Z = 2.13 (P = 0.04)
### Adjunctive therapies

RQ13: What is the effectiveness of adjunctive therapies for the treatment of late AMD (wet active)?

#### H.6.3.1 Anti-VEGF + PDT vs anti-VEGF

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-VEGF + PDR vs anti-VEGF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA (ETDRS letters ≤3 months) - positive values favour combination</td>
<td>1 (Lazic)*</td>
<td>RCT</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>106</td>
<td>MD -7.25 (-19.82, 5.31)</td>
</tr>
<tr>
<td>BCVA (ETDRS letters &gt;3 months) - positive values favour combination</td>
<td>11 (Datseris; Bashshur; Hatz; Kaiser; Krebs; Larsen; Semeraro*; Weingessel; Williams; Gomi; Koh)</td>
<td>RCT</td>
<td>Not serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1025</td>
<td>MD -0.54 (-1.29, 0.21)</td>
</tr>
<tr>
<td>BCVA (proportion gain ≥15 letters, &gt;3 months) - values greater than 1 favour combination</td>
<td>9 (Datseris; Bashshur; Hatz; Kaiser; Larsen; Vallance; Williams; Gomi; Koh)</td>
<td>RCT</td>
<td>Not serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>923</td>
<td>RR 0.76 (0.63, 0.92)</td>
</tr>
<tr>
<td>Reinjections (&gt;3 months) - positive values favour monotherapy</td>
<td>5 (Datseris; Bashshur; Larsen; Gomi; Koh)</td>
<td>RCT</td>
<td>Serious⁴</td>
<td>Serious⁵</td>
<td>Not serious</td>
<td>Not serious</td>
<td>488</td>
<td>MD -1.43 (-2.42, -0.45)</td>
</tr>
<tr>
<td>Total number of injections (&gt;3 months) - positive values favour monotherapy</td>
<td>6 (Lim; Krebs;</td>
<td>RCT</td>
<td>Serious⁴</td>
<td>Serious⁵</td>
<td>Not serious</td>
<td>Not serious</td>
<td>474</td>
<td>MD -0.94</td>
</tr>
</tbody>
</table>
### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larsen; Semeraro; Weignessel, Williams</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Hatz)</td>
<td>RCT</td>
<td>Serious(^6)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>40</td>
<td>RR 0.69 (0.42, 1.13)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Proportion needing retreatment (&gt;3 months) - values greater than 1 favour combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (Lazic; Bashshur; Hatz; Kaiser; Larsen)</td>
<td>RCT</td>
<td>Not serious(^3)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>762</td>
<td>RR 1.03 (0.88, 1.21)</td>
<td>HIGH</td>
</tr>
<tr>
<td><strong>Proportion having ocular adverse events - values greater than 1 favour combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Larsen)</td>
<td>RCT</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>255</td>
<td>RR 1.03 (0.82, 1.29)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Proportion having non-ocular adverse events - values greater than 1 favour combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Downgraded one level for study design (open label, single blinded)
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.
3. Some individual studies at high-risk of bias, but overall risk of bias rated low due to consistency of effect size estimates between high and low quality studies.
4. Downgraded one level for includes open label studies; lack of appropriate assessor masking.
5. Downgraded one level for heterogeneity (i\(^2\)>50%).
6. Downgraded one level for selection bias (differences in baseline characteristics between treatment groups)

*visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters × -0.02).
Meta-analysis: Anti-VEGF + PDT vs anti-VEGF

Visual acuity

Letters (>3 month follow-up)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>anti-VEGF + PDT</th>
<th>anti-VEGF</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total Mean</td>
<td>Total Weight</td>
</tr>
<tr>
<td>Danis et al 2015</td>
<td>5.37</td>
<td>3.83</td>
<td>39.84 ± 17.12</td>
<td>0.19%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0.19</td>
<td>0.27</td>
<td>-0.27 [5.67, 6.14]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect Z = 0.10 (P = 0.62)

1.3.2 Ranibizumab

Sriwijaya 2015
56.6 ± 14.76 20 65.8 ± 13.8 21 0.09% 0.20 [1.47, 31.19]
Max 2015
53.5 ± 23.8 12 75.8 ± 13.9 18 0.48% 0.02 [0.01, 0.04]
Keshp 2013
46.56 ± 28.8 17 57.9 ± 24.9 25 0.4% 0.1 [0.01, 0.03]
Lazarus 2012
25.4 ± 18.8 13 42.1 ± 14.9 21 0.33% 0.15 [0.01, 0.03]
Sermore 2015
25.4 ± 7.2 24 25 ± 17.6 16 0.02% -1.59 [-16.5, 12.5]
Veitkiss 2015
26.4 ± 10.9 29 79.9 ± 23.9 21 0.04% -1.7 [18.55, 3.95]

Subtotal (95% CI) 456
84% 94% -0.29 [-1.85, 1.06]

Heterogeneity: Chi² = 15.60, df = 7 (P = 0.04), I² = 36%

Test for overall effect Z = 1.44 (P = 0.15)

1.3.3 Ranibizumab PCV

Gori 2015
5.1 ± 1.8 30 6.1 ± 1.8 29 0.07% -0.7 [1.81, 2.1]
Koh 2012
15.8 ± 10.9 10 9.2 ± 12.4 9 0.1% 1.7 [0.51, 0.01]
Subtotal (95% CI) 49
50 68.6% -0.66 [-1.9, 0.24]

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52), I² = 6%

Test for overall effect Z = 1.44 (P = 0.15)

Total (95% CI) 541
81 100.0% -0.64 [-1.2, 0.21]

Heterogeneity: Chi² = 15.63, df = 10 (P = 0.01), I² = 36%

Test for overall effect Z = 1.44 (P = 0.15)

Test for subgroup differences: Chi² = 0.22, df = 2 (P = 0.99), I² = 0%

Letters gained (proportion 15 or more letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>anti-VEGF + PDT</th>
<th>anti-VEGF</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M, H, Fixed, 95% CI</td>
<td>M, H, Fixed, 95% CI</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Weight</td>
<td>Mean</td>
</tr>
<tr>
<td>Danis et al 2015</td>
<td>21</td>
<td>49</td>
<td>49</td>
<td>13.11% 0.99 [0.62, 1.56]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>21</td>
<td>49</td>
<td>13.11% 0.99 [0.62, 1.56]</td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect Z = 0.06 (P = 0.95)

1.4.2 Ranibizumab

Beckers 2011
2 20 5 20 3.2% 0.49 [0.03, 1.63]
Max 2015
5 19 8 21 4.9% 0.33 [0.05, 1.95]
Kahun 2012
58 200 46 112 23.8% 0.98 [0.49, 1.92]
Lasking 2012
22 121 34 112 20.7% 0.71 [0.44, 1.14]
Valsec et al 2010
1 9 1 9 8.9% 1.89 [0.07, 13.64]
Williams 2012
3 29 9 27 5.9% 0.93 [0.04, 1.98]
Subtotal (95% CI) 407
321 73.4% 0.74 [0.56, 0.99]

Total events 98 103

Heterogeneity: Chi² = 3.33, df = 5 (P = 0.63), I² = 0%

Test for overall effect Z = 1.39 (P = 0.09)

1.4.3 Ranibizumab PCV

Gori 2015
13 29 13 31 9.2% 0.93 [0.54, 1.60]
Koh 2012
4 19 7 21 4.2% 0.53 [0.02, 1.32]
Subtotal (95% CI) 48
62 13.0% 0.83 [0.51, 1.36]

Total events 17 22

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%

Test for overall effect Z = 0.73 (P = 0.47)

Total (95% CI) 504
419 100.0% 0.76 [0.63, 0.92]

Total events 135 145

Heterogeneity: Chi² = 3.53, df = 8 (P = 0.90), I² = 0%

Test for overall effect Z = 2.06 (P = 0.04)

Test for subgroup differences: Chi² = 1.73, df = 2 (P = 0.42), I² = 0%

Macular Degeneration

Appendix H: Grade tables and meta-analysis results

166
### Number of injections: reinjections

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>anti-VEGF + PDT</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Ranibizumab</td>
<td>Dauthors 2015</td>
<td>4.4</td>
<td>1.03</td>
<td>46</td>
<td>0.96</td>
<td>1.87</td>
<td>46</td>
<td>21.5%</td>
<td>-2.51 [-3.15, -1.87]</td>
<td>-2.51 [-3.15, -1.87]</td>
<td>-2.51 [-3.15, -1.87]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>40</td>
<td>24</td>
<td>184</td>
<td>36</td>
<td>1.60</td>
<td>184</td>
<td>75.0%</td>
<td>0.96 [-1.03, 2.07]</td>
<td>0.96 [-1.03, 2.07]</td>
<td>0.96 [-1.03, 2.07]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td>Test for overall effect:</td>
<td>Z = 7.08 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1.2 Ranibizumab</td>
<td>Baschsher 2011</td>
<td>2.08</td>
<td>2.04</td>
<td>26</td>
<td>2.09</td>
<td>2.09</td>
<td>26</td>
<td>16.8%</td>
<td>-1.10 [-2.30, 0.10]</td>
<td>-1.10 [-2.30, 0.10]</td>
<td>-1.10 [-2.30, 0.10]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Larsen 2012</td>
<td>1.0</td>
<td>1.2</td>
<td>121</td>
<td>2.2</td>
<td>132</td>
<td>22.3%</td>
<td>-0.39 [-0.79, 0.01]</td>
<td>-0.39 [-0.79, 0.01]</td>
<td>-0.39 [-0.79, 0.01]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>152</td>
<td>152</td>
<td>304</td>
<td>152</td>
<td>152</td>
<td>304</td>
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<td>-0.09 [0.05, 0.19]</td>
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<td>256</td>
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### Number of injections: total number of injections

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<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<td>168</td>
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<td>Larsen 2012</td>
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<td>121</td>
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<td>2.1</td>
<td>132</td>
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<td>-0.26 [4.76, 0.19]</td>
<td>-0.26 [4.76, 0.19]</td>
<td>-0.26 [4.76, 0.19]</td>
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<td>1.0</td>
<td>14</td>
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<td>1.4</td>
<td>16</td>
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<td>-0.50 [4.10, 0.04]</td>
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<td>Williams 2012</td>
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<td>184</td>
<td>304</td>
<td>224</td>
<td>177</td>
<td>304</td>
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<td>Z = 2.91 (P = 0.001)</td>
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<td>252</td>
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<td>232</td>
<td>252</td>
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<td>93.0%</td>
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<td>Test for sub-bars differences:</td>
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<td>Test for sub-bars differences:</td>
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### Ocular adverse events

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<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Weight</th>
<th>Risk Ratio H, 95% CI</th>
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<tr>
<td>Latark 2007</td>
<td>7</td>
<td>52</td>
<td>54</td>
<td>9.4%</td>
<td>0.48</td>
<td>[0.22, 1.06]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>54</td>
<td>9.4%</td>
<td>0.48</td>
<td>[0.22, 1.06]</td>
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#### 5.1.2 Ranibizumab

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<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Weight</th>
<th>Risk Ratio H, 95% CI</th>
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<td>Estefan 2011</td>
<td>0</td>
<td>20</td>
<td>20</td>
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<td>4.90</td>
<td>[0.07, 16.56]</td>
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<tr>
<td>Hafez 2015</td>
<td>18</td>
<td>15</td>
<td>11</td>
<td>8.7%</td>
<td>1.00</td>
<td>[0.59, 1.91]</td>
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<td>Kusser 2012</td>
<td>11</td>
<td>209</td>
<td>60</td>
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<td>[0.85, 3.21]</td>
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<td>Larsen 2012</td>
<td>51</td>
<td>122</td>
<td>74</td>
<td>33.2%</td>
<td>1.03</td>
<td>[0.77, 1.36]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>280</td>
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<td>1.09</td>
<td>[0.89, 1.32]</td>
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<td>Total events</td>
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#### Meta-analysis (excluded study population with previous treatment history)

### Visual acuity

#### Letters (>3 month follow-up)

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<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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<td>Danesh 2015</td>
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<td>49</td>
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<td>40</td>
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<td>-0.27</td>
<td>[5.67, 5.13]</td>
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<td>[5.67, 5.13]</td>
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#### 5.3.2 Ranibizumab

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<th>SD</th>
<th>Total</th>
<th>Weight</th>
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<td>100</td>
<td>0.1</td>
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<td>-2.05</td>
<td>[0.76, 0.28]</td>
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<td>67.09</td>
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</table>

#### 5.3.3 Ranibizumab PCV

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>anti-VEGF</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oomi 2015</td>
<td>8.1</td>
<td>1.2</td>
<td>31</td>
<td>8.8</td>
<td>1.1</td>
<td>29</td>
<td>0.3%</td>
<td>-0.20</td>
<td>[1.81, 0.21]</td>
<td></td>
</tr>
<tr>
<td>Kusser 2012</td>
<td>10.3</td>
<td>18.3</td>
<td>19</td>
<td>9.2</td>
<td>13.4</td>
<td>21</td>
<td>1.3%</td>
<td>1.70</td>
<td>[5.81, 0.01]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>49</td>
<td></td>
<td></td>
<td>81.3%</td>
<td>-0.66</td>
<td>[1.57, 0.24]</td>
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</tr>
<tr>
<td>Heterogeneity</td>
<td>Chi² = 0.01, df = 1 (P = 0.52); P = 0%</td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 1.44 (P = 0.15)</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>515</td>
<td>430</td>
<td>100.0%</td>
<td>-0.90</td>
<td>[1.73, 0.07]</td>
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</tr>
<tr>
<td>Heterogeneity</td>
<td>Chi² = 5.41, df = 9 (P = 0.71); P = 0%</td>
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<tr>
<td>Test for overall effect: Z = 2.12 (P = 0.03)</td>
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<td></td>
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</tr>
<tr>
<td>Test for subgroup differences: Chi² = 2.94, df = 2 (P = 0.33); P = 10.9%</td>
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</tbody>
</table>
### Letters gained (proportion 15 or more letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>anti-VEGF + PDT Events</th>
<th>Total</th>
<th>anti-VEGF Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.1 Bevacizumab</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Darnars 2015</td>
<td>21</td>
<td>49</td>
<td>20</td>
<td>48</td>
<td>14.3%</td>
<td>0.94 [0.82, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>49</td>
<td>46</td>
<td>11.3%</td>
<td>0.99 [0.62, 1.65]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total events</td>
<td>21</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 0.08 (P = 0.93)</td>
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<tr>
<td>1.4.2 Ranibizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baethier 2011</td>
<td>2</td>
<td>20</td>
<td>5</td>
<td>19</td>
<td>0.3%</td>
<td>0.49 [0.09, 0.83]</td>
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</tr>
<tr>
<td>Holt 2016</td>
<td>6</td>
<td>18</td>
<td>8</td>
<td>21</td>
<td>0.8%</td>
<td>0.83 [0.35, 1.68]</td>
<td></td>
</tr>
<tr>
<td>Kalina 2012</td>
<td>20</td>
<td>20</td>
<td>12</td>
<td>32</td>
<td>41.1%</td>
<td>0.99 [0.46, 1.64]</td>
<td></td>
</tr>
<tr>
<td>Larsen 2012</td>
<td>22</td>
<td>121</td>
<td>34</td>
<td>132</td>
<td>22.5%</td>
<td>0.71 [0.44, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Vailance 2010</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.7%</td>
<td>1.00 [0.30, 3.34]</td>
<td></td>
</tr>
<tr>
<td>Williams 2012</td>
<td>20</td>
<td>29</td>
<td>9</td>
<td>27</td>
<td>8.4%</td>
<td>0.94 [0.44, 1.99]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>360</td>
<td>360</td>
<td>71.1%</td>
<td>0.71 [0.39, 1.31]</td>
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<tr>
<td>Total events</td>
<td>90</td>
<td>90</td>
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<tr>
<td>Heterogeneity: Chi² = 0.86, df = 3 (P = 0.88), P = 6%</td>
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<tr>
<td>Test for overall effect: Z = 2.70 (P = 0.007)</td>
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</tr>
<tr>
<td>1.4.3 Ranibizumab PCV</td>
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<tr>
<td>Borni 2015</td>
<td>13</td>
<td>28</td>
<td>15</td>
<td>31</td>
<td>10.9%</td>
<td>0.93 [0.54, 1.60]</td>
<td></td>
</tr>
<tr>
<td>Koch 2012</td>
<td>4</td>
<td>18</td>
<td>7</td>
<td>21</td>
<td>4.8%</td>
<td>0.93 [0.22, 3.92]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>48</td>
<td>52</td>
<td>11.6%</td>
<td>0.83 [0.51, 1.36]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total events</td>
<td>128</td>
<td>132</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52), P = 6%</td>
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<tr>
<td>Test for overall effect: Z = 0.73 (P = 0.47)</td>
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<tr>
<td>Test for subgroups differences: Chi² = 1.56, df = 2 (P = 0.46), P = 6%</td>
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### Total number of injections

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>anti-VEGF + PDT Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Weight</th>
<th>Mean Difference M-H, Random, 95% CI</th>
<th>Mean Difference M-H, Random, 95% CI</th>
</tr>
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<tbody>
<tr>
<td>3.2.1 Bevacizumab</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lee 2012</td>
<td>3.25</td>
<td>0.58</td>
<td>23</td>
<td>3.2</td>
<td>0.42</td>
<td>18</td>
<td>0.0%</td>
<td>-0.06 [-0.26, 0.16]</td>
<td>-0.06 [-0.26, 0.16]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Not applicable</td>
<td></td>
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<tr>
<td>3.2.2 Ranibizumab</td>
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</tr>
<tr>
<td>Krebs 2013</td>
<td>4.7</td>
<td>1.0</td>
<td>20</td>
<td>6.6</td>
<td>2.4</td>
<td>24</td>
<td>18.7%</td>
<td>-1.69 [-2.14, -1.26]</td>
<td>-1.69 [-2.14, -1.26]</td>
</tr>
<tr>
<td>Larsen 2012</td>
<td>4.0</td>
<td>2.2</td>
<td>20</td>
<td>5.1</td>
<td>2.7</td>
<td>12</td>
<td>27.2%</td>
<td>-0.30 [-0.67, 0.07]</td>
<td>-0.30 [-0.67, 0.07]</td>
</tr>
<tr>
<td>Semeraro 2015</td>
<td>5.8</td>
<td>1.3</td>
<td>25</td>
<td>7.8</td>
<td>1.4</td>
<td>16</td>
<td>24.0%</td>
<td>-2.68 [-3.18, -2.18]</td>
<td>-2.68 [-3.18, -2.18]</td>
</tr>
<tr>
<td>Williams 2015</td>
<td>6.9</td>
<td>1.1</td>
<td>14</td>
<td>7.4</td>
<td>1.4</td>
<td>16</td>
<td>29.4%</td>
<td>-1.50 [-1.89, -1.10]</td>
<td>-1.50 [-1.89, -1.10]</td>
</tr>
<tr>
<td>Williams 2012</td>
<td>3.3</td>
<td>0.9</td>
<td>20</td>
<td>6.0</td>
<td>0.9</td>
<td>27</td>
<td>31.1%</td>
<td>-2.30 [-4.60, 0.00]</td>
<td>-2.30 [-4.60, 0.00]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>209</td>
<td>221</td>
<td>100.0%</td>
<td>1.23</td>
<td>2.20, 0.27</td>
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<tr>
<td>Heterogeneity: Tau² = 0.92, Chi² = 21.56, df = 4 (P = 0.0003), P = 81%</td>
<td></td>
<td>221</td>
<td>100.0%</td>
<td>1.23</td>
<td>2.20, 0.27</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.91 (P = 0.00)</td>
<td></td>
<td>221</td>
<td>100.0%</td>
<td>1.23</td>
<td>2.20, 0.27</td>
<td></td>
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</tr>
<tr>
<td>Test for subgroups differences: Not applicable</td>
<td></td>
<td>221</td>
<td>100.0%</td>
<td>1.23</td>
<td>2.20, 0.27</td>
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</table>
## Proportion of people had ocular adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Anti-VEGF + PDT</th>
<th>Anti-VEGF</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>5.1.1 Bosozizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lazic 2007</td>
<td>7</td>
<td>52</td>
<td>16.2%</td>
<td>0.48 [0.22, 1.09]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>52</td>
<td>94</td>
<td>15.2%</td>
<td>0.48 [0.22, 1.09]</td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.75 (P = 0.08)</td>
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</table>

5.1.2 Ranibizumab

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Anti-VEGF + PDT</th>
<th>Anti-VEGF</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
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<tr>
<td>Bahnhofer 2011</td>
<td>8</td>
<td>20</td>
<td>6.9%</td>
<td>4.09 [0.97, 16.66]</td>
</tr>
<tr>
<td>Halz 2015</td>
<td>10</td>
<td>19</td>
<td>6.9%</td>
<td>1.50 [0.56, 4.16]</td>
</tr>
<tr>
<td>Kaiser 2014</td>
<td>119</td>
<td>209</td>
<td>54.1%</td>
<td>1.06 [0.86, 1.31]</td>
</tr>
<tr>
<td>Lantins 2012</td>
<td>51</td>
<td>122</td>
<td>33.9%</td>
<td>1.53 [0.77, 1.38]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>301</td>
<td>245</td>
<td>89.9%</td>
<td>1.05 [0.88, 1.29]</td>
</tr>
<tr>
<td>Total events</td>
<td>170</td>
<td>114</td>
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<tr>
<td>Heterogeneity: Ch² = 0.03, df = 1 (P = 0.85), I² = 0%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.50 (P = 0.60)</td>
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</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Anti-VEGF + PDT</th>
<th>Anti-VEGF</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>383</td>
<td>299</td>
<td>100.0%</td>
<td>0.99 [0.84, 1.17]</td>
</tr>
<tr>
<td>Total events</td>
<td>177</td>
<td>126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 3.47, df = 2 (P = 0.18), I² = 42%</td>
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<tr>
<td>Test for overall effect: Z = 0.96 (P = 0.33)</td>
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<tr>
<td>Test for subgroups: Ch² = 3.33, df = 1 (P = 0.07), I² = 70.0%</td>
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Favours monotherapy

Favours combination
### H.6.3.2 Anti-VEGF + steroids vs anti-VEGF

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF vs anti-VEGF steroids</td>
<td></td>
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<tr>
<td><strong>BCVA (ETDRS letters &gt;3 months) - positive values favour combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (Ahmadieh; Kuppermann; Ranchod)</td>
<td>RCT</td>
<td>Not serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not serious</td>
<td>267</td>
<td>MD 0.82 (-1.91, 3.55)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>BCVA (proportion gain ≥15 letter, &gt;3 months) - values greater than 1 favour combination</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2 (Kuppermann; Ranchod)</td>
<td>RCT</td>
<td>Serious&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Very serious&lt;sup&gt;4&lt;/sup&gt;</td>
<td>152</td>
<td>RR 1.20 (0.53, 2.70)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Total number of injections (&gt;3 months) - positive values favour combination</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Ranchod)</td>
<td>RCT</td>
<td>Serious&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;5&lt;/sup&gt;</td>
<td>37</td>
<td>MD -0.50 (-1.30, 0.30)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Proportion needing retreatment (&gt;3 months) - values greater than 1 favour combination</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 (Ahmadieh)</td>
<td>RCT</td>
<td>Serious&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>115</td>
<td>RR 0.65 (0.42, 1.00)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Proportion having ocular adverse events - values greater than 1 favour combination</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Kuppermann)</td>
<td>RCT</td>
<td>Serious&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N/A</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;6&lt;/sup&gt;</td>
<td>333</td>
<td>RR 1.20 (0.91, 1.59)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Some individual studies at high-risk of bias, but overall risk of bias rated low due to consistency of effect size estimates between high and low quality studies.
2. Downgraded one level for unclear about cataract status of study population.
3. Downgraded one level for study design (open label, single blinded)
4. Downgraded one level for confidence interval crossing 2 lines of a defined minimal important difference.
5. Downgraded one level for non-significant effect.
6. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.

*visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters × -0.02).
Meta-analysis: anti-VEGF + steroids vs anti-VEGF

Visual acuity

Letters (>3 month follow-up)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Study or Subgroup</th>
<th>anti-VEGF + steroids</th>
<th>anti-VEGF</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>2.1 Ranibizumab + triamcinolone</td>
<td>Ahn et al. 2014</td>
<td>11.3</td>
<td>17.2</td>
<td>65</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>65</td>
<td>59</td>
<td>26.6%</td>
<td>2.60 (3.42, 8.62)</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.89 (P = 0.37)</td>
<td></td>
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</tr>
<tr>
<td>2.1.2 Ranibizumab + dexamethasone implant</td>
<td>Kuppermann 2015</td>
<td>1.5</td>
<td>10.8</td>
<td>68</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>58</td>
<td>57</td>
<td>81.1%</td>
<td>-1.10 (-4.69, 2.39)</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.82 (P = 0.41)</td>
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</tr>
<tr>
<td>2.1.3 Ranibizumab + dexamethasone injection</td>
<td>Randolf 2013</td>
<td>11.1</td>
<td>9.08</td>
<td>17</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>17</td>
<td>20</td>
<td>10.3%</td>
<td>5.20 (1.16, 11.56)</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.80 (P = 0.11)</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>138</td>
<td>137</td>
<td>100.0%</td>
<td>0.82 (1.41, 3.55)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Test for subgroup differences: $\chi^2 = 3.31$, df = 2 (P = 0.19), $\phi^2 = 0.59$, $P = 0.19$</td>
<td></td>
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</tr>
</tbody>
</table>

Test for overall effect: $Z = 0.62$ (P = 0.26)

Letters gained (proportion 15 or more letters)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Study or Subgroup</th>
<th>anti-VEGF + steroids</th>
<th>anti-VEGF</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2.1 Ranibizumab + dexamethasone implant</td>
<td>Kuppermann 2015</td>
<td>58</td>
<td>5</td>
<td>57</td>
<td>57.8%</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>58</td>
<td>57</td>
<td>57.8%</td>
<td>0.79 (0.22, 2.70)</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.57 (P = 0.57)</td>
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</tr>
<tr>
<td>2.2.2 Ranibizumab + dexamethasone injection</td>
<td>Randolf 2013</td>
<td>17</td>
<td>4</td>
<td>20</td>
<td>42.2%</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>17</td>
<td>20</td>
<td>42.2%</td>
<td>1.76 (0.59, 5.24)</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.02 (P = 0.31)</td>
<td></td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>75</td>
<td>77</td>
<td>100.0%</td>
<td>1.20 (0.53, 2.70)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Test for subgroup differences: $\chi^2 = 0.31$, df = 1 (P = 0.57)</td>
<td></td>
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</tr>
</tbody>
</table>

Test for overall effect: $Z = 0.44$ (P = 0.66)

Test for subgroup differences: $\chi^2 = 0.31$, df = 1 (P = 0.57), $P = 0.60$
### Anti-VEGF +PDT vs anti-VEGF steroid + PDT

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF + PDT vs anti-VEGF steroids + PDT</td>
<td></td>
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</tr>
<tr>
<td><strong>BCVA (ETDRS letters &gt;3 months) – positive values favour triple therapy</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Piri)*</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>84</td>
<td>MD 0.50 (-6.04, 7.04)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Reinjections (&gt;3 months) – positive values favour triple therapy</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (Piri)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>84</td>
<td>MD -0.40 (-0.83, 0.03)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Proportion needing retreatment (&gt;3 months) – values greater than 1 favour triple therapy</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Piri)</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>84</td>
<td>RR 0.84 (0.71, 0.98)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for unclear about cataract status of study population
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.

*visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters × -0.02).
### H.6.4 Switching and stopping antiangiogenic treatment for late AMD (wet)

RQ11: What are the indicators for treatment failing and switching?

RQ14: What factors indicate that treatment for neovascular AMD should be stopped?

RQ15: What is the effectiveness of switching therapies for neovascular AMD if the first-line therapy is contraindicated or has failed?

This review was undertaken by the National Clinical Guideline team.

#### H.6.4.1 The effectiveness of switching therapies

**Anti-VEGF switching**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ranibizumab to aflibercept vs continuing on ranibizumab</strong></td>
<td></td>
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</tr>
<tr>
<td>Visual acuity (ETDRS letters [change score] (Better indicated by higher values)</td>
<td>1 (Mantel 2016)</td>
<td>RCT</td>
<td>Very serious(^1)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>21</td>
<td>MD -2.5 (-4.87 to -0.13)</td>
</tr>
<tr>
<td><strong>Ranibizumab to bevacizumab vs bevacizumab to ranibizumab</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Best corrected visual acuity (logMAR) - 12 months (Better indicated by lower values)</td>
<td>1 (Kucukerdon mez 2015)</td>
<td>Cohort study</td>
<td>Very serious(^1)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>87</td>
<td>MD 0.05 (-2.84 to 2.94)</td>
</tr>
<tr>
<td>Best corrected visual acuity (logMAR) - ≥ 12 months (Better indicated by lower values)</td>
<td>1 (Kucukerdon mez 2015)</td>
<td>Cohort study</td>
<td>Very serious(^1)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^2)</td>
<td>87</td>
<td>MD 0.16 (-0.88 to 1.20)</td>
</tr>
<tr>
<td><strong>Bevacizumab to ranibizumab</strong></td>
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<tr>
<td>Visual acuity (logMAR) - ≤ 3 months (Better indicated by lower values)</td>
<td>1 (Moisseiev Before–after)</td>
<td>Very serious(^1)</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious(^3)</td>
<td>110</td>
<td>MD- 0.02</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>
# Appendix H: Grade tables and meta-analysis results

## Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Sample size | Effect (95% CI) | Quality |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>2015) study</td>
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<tr>
<td>Visual acuity (logMAR) – at least 4 months (Better indicated by lower values)</td>
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</tr>
<tr>
<td>1 (Moisseiev 2015) Before–after study Very serious¹ N/A Not serious Serious³ 110 MD -0.04 (-0.06 to 0.14) VERY LOW</td>
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<tr>
<td>Bevacizumab to aflibercept</td>
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<tr>
<td>Best corrected visual acuity (ETDRS) - &gt; 3 months and &lt;12 months (Better indicated by higher values)</td>
<td></td>
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</tr>
<tr>
<td>1 (Tiosano 2017) Before–after study Very serious¹ N/A Not serious Serious³ 47 MD 2.8 (-2.35, 7.95) VERY LOW</td>
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<tr>
<td>Best corrected visual acuity (ETDRS) - ≥ 12 months (Better indicated by higher values)</td>
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</tr>
<tr>
<td>1 (Pinheiro-Costa 2015) Observational study Very serious¹ N/A Not serious Serious³ 39 MD -2.4 (-10.15 to 5.35) VERY LOW</td>
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<td></td>
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<tr>
<td>Bevacizumab and/or ranibizumab to aflibercept</td>
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<tr>
<td>Best corrected visual acuity (logMAR) - After 1 injection (Better indicated by lower values)</td>
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</tr>
<tr>
<td>2 (Maksys 2017, Yonekawa 2013) Observational study Very serious¹ Not serious Not serious Serious³ 134 MD 0.02 (-0.06 to 0.09) VERY LOW</td>
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<tr>
<td>Best corrected visual acuity (logMAR) - After 2 injections (Better indicated by lower values)</td>
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<td></td>
</tr>
<tr>
<td>1 (Maksys 2017) Observational study Very serious¹ N/A Not serious Serious³ 32 MD 0.00 (-0.16 to 0.16) VERY LOW</td>
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<tr>
<td>Best corrected visual acuity (logMAR) - After 3 injections (Better indicated by lower values)</td>
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<td></td>
</tr>
<tr>
<td>1 (Maksys 2017) Observational study Very serious¹ N/A Not serious Serious³ 32 MD -0.10 (-0.27 to 0.07) VERY LOW</td>
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</tr>
<tr>
<td>Best corrected visual acuity (logMAR) - &gt; 3 months and &lt;12 months (Better indicated by lower values)</td>
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<td></td>
</tr>
<tr>
<td>6 (Bakall 2013, Chan 2014, Grewal 2014, Hall 2014, Major Observational study Very serious¹ N/A Not serious Serious³ 413 MD -0.07 (-0.10 to -0.04) VERY LOW</td>
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</tbody>
</table>
### Macular Degeneration

### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015, Yonekawa 2013)</td>
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<tr>
<td><strong>Best corrected visual acuity (logMAR) - ≥ 12 months (Better indicated by lower values)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5 (Grewal 2014, Hall 2014, Homer 2015, Jorstad 2017, Major 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>159</td>
<td>MD 0.00 (-0.01 to 0.02)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Best corrected visual acuity (ETDRS) - After 1 injections (Better indicated by higher values)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Hariri 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>31</td>
<td>MD 3.1 (-4.06 to 10.26)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Best corrected visual acuity (ETDRS) - After 3 injections (Better indicated by higher values)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (Gharbiya 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>31</td>
<td>MD -0.2 (-5.95 to 5.55)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Best corrected visual acuity (ETDRS) - &gt; 3 months and &lt;12 months (Better indicated by higher values)</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>2 (Gharbiya 2014, Thorell 2014)</td>
<td>Observational studies</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>104</td>
<td>MD 0.44 (-2.59 to 3.48)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2. Downgraded one level for non-significant effect.
3. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
### Meta-analysis (forest plots) for bevacizumab and/or ranibizumab to aflibercept

#### Best corrected visual acuity (logMAR)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>aflibercept</th>
<th>bevacizumab</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD Total</td>
<td>Mean</td>
<td>SD Total</td>
</tr>
<tr>
<td>2.1.1 After 1 injection</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mavridis 2017</td>
<td>0.4</td>
<td>0.3</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Yokoyama 2013</td>
<td>0.44</td>
<td>0.38</td>
<td>0.46</td>
<td>0.3</td>
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<tr>
<td>Overall</td>
<td>1.24</td>
<td></td>
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<tr>
<td></td>
<td>Heterogeneity: Ch² = 0.04, df = 1, P = 0.83, 95% CI 0.0%</td>
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<tr>
<td></td>
<td>Test for overall Z: 0.19 (P = 0.9)</td>
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<tr>
<td>2.1.2 After 2 injections</td>
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<tr>
<td>Makris 2017</td>
<td>0.4</td>
<td>0.3</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Overall</td>
<td>0.32</td>
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<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
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<td></td>
<td>Test for overall Z: 0.38 (P = 1.0)</td>
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<tr>
<td>2.1.3 After 3 injections</td>
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<tr>
<td>Makris 2017</td>
<td>0.3</td>
<td>0.3</td>
<td>1.3</td>
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<tr>
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<td>0.32</td>
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<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
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<td>Test for overall Z: 0.38 (P = 1.0)</td>
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<tr>
<td>2.1.4 3 months and &lt;12 months</td>
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<td>Bakal 2013</td>
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<td>Chiang 2014</td>
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<td>0.1</td>
<td>0.6</td>
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<td>Overall</td>
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<td>Test for overall Z: 1.15 (P = 0.26)</td>
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<tr>
<td>2.1.5 12 months</td>
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<td>0.8</td>
<td>0.1</td>
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<td>Heterogeneity: Not applicable</td>
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<td></td>
<td>Test for overall Z: 0.12 (P = 0.97)</td>
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</table>

#### Best corrected visual acuity (ETDRS)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>aflibercept</th>
<th>bevacizumab</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD Total</td>
<td>Mean</td>
<td>SD Total</td>
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<tr>
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<tr>
<td>Hracek 2014</td>
<td>0.5</td>
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<td>1.5</td>
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<tr>
<td>Overall</td>
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<td></td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
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<td>Test for overall Z: 0.36 (P = 0.49)</td>
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<tr>
<td>2.2.2 After 3 injections</td>
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<tr>
<td>Gribby 2014</td>
<td>0.4</td>
<td>0.3</td>
<td>1.2</td>
<td>0.3</td>
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<tr>
<td>Overall</td>
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<td>1.2</td>
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<td>Heterogeneity: Not applicable</td>
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<tr>
<td></td>
<td>Test for overall Z: 0.36 (P = 0.49)</td>
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<tr>
<td>2.2.3 3 months and &lt;12 months</td>
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<tr>
<td>Gribby 2014</td>
<td>0.4</td>
<td>0.3</td>
<td>1.2</td>
<td>0.3</td>
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<tr>
<td>Overall</td>
<td>0.4</td>
<td></td>
<td>1.2</td>
<td></td>
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<tr>
<td></td>
<td>Heterogeneity: Ch² = 0.10, df = 1, P = 0.95, 95% CI 0.0%</td>
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<tr>
<td></td>
<td>Test for overall Z: 0.36 (P = 0.78)</td>
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</tbody>
</table>
### Number of studies

#### Design

### Risk of bias

### Inconsistency

### Indirectness

### Imprecision

### Sample size

### Effect size (95% CI)

### Quality

### Ranibizumab to aflibercept

#### Best corrected visual acuity (logMAR) - After 1 injection (Better indicated by lower values)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Heussen 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>71</td>
<td>MD -0.02 (-0.17 to 0.13)</td>
<td>VERY LOW</td>
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</tbody>
</table>

#### Best corrected visual acuity (logMAR) - After 2 injections (Better indicated by lower values)

<table>
<thead>
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<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Heussen 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>66</td>
<td>MD 0.01 (-0.14 to 0.16)</td>
<td>VERY LOW</td>
</tr>
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</table>

#### Best corrected visual acuity (logMAR) - After 3 injections (Better indicated by lower values)

<table>
<thead>
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<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (Gokce 2016, Kumar 2013, Heussen 2014)</td>
<td>Observational studies</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>123</td>
<td>MD -0.07 (-0.11 to -0.02)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

#### Best corrected visual acuity (logMAR) - After 4 injections (Better indicated by lower values)

<table>
<thead>
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<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Heussen 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>12</td>
<td>MD -0.22 (-0.58 to 0.14)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

#### Best corrected visual acuity (logMAR) - > 3 months and <12 months (Better indicated by lower values)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (Gerding 2015, Kawshima 2015, Kumar 2013)</td>
<td>Observational studies</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>115</td>
<td>MD -0.07 (-0.19 to 0.04)</td>
<td>VERY LOW</td>
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</tbody>
</table>

#### Best corrected visual acuity (logMAR) - ≥ 12 months (Better indicated by lower values)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Narayan 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>80</td>
<td>MD -0.03 (-0.12 to 0.07)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

#### Best corrected visual acuity (ETDRS) - > 3 months and <12 months (Better indicated by higher values)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (Chang 2015, Hatz)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>216</td>
<td>MD 0.57 (-0.43 to 1.56)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>
### Macular Degeneration

**Appendix H: Grade tables and meta-analysis results**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect size (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016, Sarao 2016, Wykoff 2014</td>
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<tr>
<td><strong>Best corrected visual acuity (ETDRS) - ≥ 12 months (Better indicated by lower values)</strong></td>
<td></td>
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</tr>
<tr>
<td>2 (Chang 2015, Sarao 2016)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>141</td>
<td>MD 3.06 (-0.86 to 6.92)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Ranibizumab to pegaptanib</strong></td>
<td></td>
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<tr>
<td><strong>Best corrected visual acuity (logMAR) - ≥ 12 months (Better indicated by lower values)</strong></td>
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</tr>
<tr>
<td>1 (Shiragami 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>50</td>
<td>MD -0.07 (-0.23 to 0.09)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2. Downgraded by 1 increment if the confidence interval crossing 1 MID or by 2 increments if the confidence interval crossing both MIDs.
### Meta-analysis (forest plots) for ranibizumab to aflibercept

#### Best corrected visual acuity (logMAR)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
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<td><strong>Best corrected visual acuity (logMAR)</strong></td>
<td></td>
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<tr>
<td><strong>3.1.1 After 1 injection</strong></td>
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<tr>
<td>Heeren2014</td>
<td>0.65</td>
<td>0.48</td>
<td>71</td>
<td>0.67</td>
<td>0.48</td>
<td>71</td>
<td>100.9%</td>
<td>-0.63 [0.017, 0.13]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td><strong>Heterogeneity: Not applicable</strong></td>
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<tr>
<td>Test for overall effect Z = 0.15 (P = 0.86)</td>
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<tr>
<td><strong>3.1.2 After 2 injections</strong></td>
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<td>Heeren2014</td>
<td>0.6</td>
<td>0.43</td>
<td>66</td>
<td>0.59</td>
<td>0.42</td>
<td>66</td>
<td>100.9%</td>
<td>-0.61 [0.014, 0.16]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td><strong>Heterogeneity: Not applicable</strong></td>
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<tr>
<td><strong>3.1.3 After 3 injections</strong></td>
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</tr>
<tr>
<td>Odkere2016 (1)</td>
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<td>0.46</td>
<td>23</td>
<td>0.74</td>
<td>0.46</td>
<td>23</td>
<td>37.2%</td>
<td>-3.97 [0.14, 0.01]</td>
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<tr>
<td>Odkere2016 (2)</td>
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<td>21</td>
<td>0</td>
<td>0.24</td>
<td>21</td>
<td>21.1%</td>
<td>-6.01 [0.05, 0.06]</td>
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<tr>
<td>Heeren2014</td>
<td>0.63</td>
<td>0.45</td>
<td>45</td>
<td>0.58</td>
<td>0.21</td>
<td>45</td>
<td>24.4%</td>
<td>-0.13 [0.21, 0.05]</td>
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<tr>
<td>Kumar2013</td>
<td>0.62</td>
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<td>34</td>
<td>0.57</td>
<td>0.38</td>
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<td>9.3%</td>
<td>-0.63 [0.22, 0.13]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td><strong>Heterogeneity: Chisquare = 4.26, df = 3 (P = 0.30), I^2 = 30%</strong></td>
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<tr>
<td>Test for overall effect Z = 2.10 (P = 0.042)</td>
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<tr>
<td><strong>3.1.4 After 4 injections</strong></td>
<td></td>
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<tr>
<td>Heeren2014</td>
<td>0.25</td>
<td>0.47</td>
<td>12</td>
<td>0.67</td>
<td>0.43</td>
<td>12</td>
<td>100.9%</td>
<td>-0.22 [0.05, 0.14]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td><strong>Heterogeneity: Not applicable</strong></td>
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<tr>
<td>Test for overall effect Z = 1.22 (P = 0.22)</td>
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<tr>
<td><strong>3.1.5 &gt;3 months and &lt;12 months</strong></td>
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<tr>
<td>Gerding2015</td>
<td>0.64</td>
<td>1.77</td>
<td>40</td>
<td>0.65</td>
<td>2.09</td>
<td>40</td>
<td>1.9%</td>
<td>0.62 [0.77, 0.93]</td>
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<tr>
<td>Kharbatia2015</td>
<td>0.26</td>
<td>0.41</td>
<td>41</td>
<td>0.4</td>
<td>0.37</td>
<td>41</td>
<td>47.8%</td>
<td>-6.01 [0.022, 0.12]</td>
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</tr>
<tr>
<td>Kumar2013</td>
<td>0.67</td>
<td>0.22</td>
<td>24</td>
<td>0.57</td>
<td>0.26</td>
<td>24</td>
<td>59.5%</td>
<td>-0.61 [0.26, 0.04]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td><strong>Heterogeneity: Chisquare = 0.20, df = 2 (P = 0.88), I^2 = 0%</strong></td>
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<tr>
<td>Test for overall effect Z = 1.24 (P = 0.21)</td>
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<td><strong>3.1.6 &gt;12 months</strong></td>
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<tr>
<td>Narayen2015</td>
<td>0.65</td>
<td>0.36</td>
<td>90</td>
<td>0.64</td>
<td>0.31</td>
<td>90</td>
<td>100.9%</td>
<td>-0.03 [0.12, 0.07]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td><strong>Heterogeneity: Not applicable</strong></td>
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<tr>
<td>Test for overall effect Z = 0.55 (P = 0.58)</td>
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</table>

**Forest plots:**
- **(1)** Complete ranibizumab resistance
- **(2)** Treatment failure

#### Best corrected visual acuity (letter)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ranibizumab</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best corrected visual acuity (letter)</strong></td>
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<tr>
<td><strong>3.2.1 &gt; 3 months and &lt;12 months</strong></td>
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<tr>
<td>Chang2016</td>
<td>67.4</td>
<td>13.37</td>
<td>49</td>
<td>69.5</td>
<td>16.2</td>
<td>49</td>
<td>2.9%</td>
<td>6.93 [1.04, 12.76]</td>
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<tr>
<td>Heo2016</td>
<td>0.9</td>
<td>12.3</td>
<td>20</td>
<td>58.8</td>
<td>13.3</td>
<td>20</td>
<td>2.2%</td>
<td>1.10 [0.65, 1.75]</td>
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<tr>
<td>Sanaa2016</td>
<td>55.9</td>
<td>13.64</td>
<td>92</td>
<td>52.9</td>
<td>17.8</td>
<td>92</td>
<td>5.2%</td>
<td>3.10 [1.25, 7.45]</td>
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<tr>
<td>Widfurth2014</td>
<td>0.2</td>
<td>2.67</td>
<td>2545</td>
<td>0</td>
<td>2.67</td>
<td>2545</td>
<td>0</td>
<td>0.20 [0.06, 1.26]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td><strong>Heterogeneity: Chisquare = 0.23, df = 3 (P = 0.90), I^2 = 52%</strong></td>
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<tr>
<td>Test for overall effect Z = 1.11 (P = 0.27)</td>
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<tr>
<td><strong>3.2.2 &gt;12 months</strong></td>
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<tr>
<td>Chang2015</td>
<td>69.2</td>
<td>13.35</td>
<td>49</td>
<td>69.5</td>
<td>16.2</td>
<td>49</td>
<td>4.3%</td>
<td>4.70 [1.19, 10.58]</td>
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<tr>
<td>Sanaa2016</td>
<td>54.8</td>
<td>17.74</td>
<td>92</td>
<td>52.9</td>
<td>17.8</td>
<td>92</td>
<td>6.7%</td>
<td>1.80 [1.03, 3.43]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td><strong>Heterogeneity: Chisquare = 0.63, df = 1 (P = 0.47), I^2 = 0%</strong></td>
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<tr>
<td>Test for overall effect Z = 1.95 (P = 0.12)</td>
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</tbody>
</table>

**Forest plots:**
- **(1)** Complete ranibizumab resistance
- **(2)** Treatment failure
### Bevacizumab to bevacizumab + triamcinolone acetonide

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best corrected visual acuity (logMAR) - ≤ 3 months (Better indicated by lower values)</strong></td>
<td>1 (Tao 2010)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>31</td>
<td>MD -0.11 (-0.3 to 0.08)</td>
</tr>
<tr>
<td><strong>Best corrected visual acuity (logMAR) - &gt; 3 months and &lt;12 months (Better indicated by lower values)</strong></td>
<td>1 (Tao 2010)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>31</td>
<td>MD -0.07 (-0.26 to 0.12)</td>
</tr>
<tr>
<td></td>
<td>1 (Tao 2010)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>31</td>
<td>MD -0.02 (-0.21 to 0.17)</td>
</tr>
</tbody>
</table>

1. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2. Downgraded by 1 increment if the confidence interval crossing 1 MID or by 2 increments if the confidence interval crossing both MIDs
H.7 Monitoring

H.7.1 Frequency of monitoring

RQ19: How often should people with early age-related macular degeneration (AMD), indeterminate AMD, or advanced geographic atrophy be reviewed?

RQ20: How often should people with early AMD, indeterminate AMD, or advanced geographic atrophy have their non-affected eye reviewed?

RQ21: In people with neovascular AMD who are not being actively treated, how often should they be reviewed?

RQ22: How often should people with neovascular AMD have their non-affected eye reviewed?

No evidence was found for these review questions.
### H.7.2 Self monitoring

RQ23a: What strategies and tools are useful for self-monitoring for people with AMD?

<table>
<thead>
<tr>
<th>Number of RCTs</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>Effect (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual acuity (ETDRS letter)</strong> change from baseline to CNV event (higher values indicate better vision)**</td>
<td></td>
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<tr>
<td>1 (Chew E Y 2014)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>81</td>
<td>MD=5.20 (-1.48, 11.88)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Visual acuity (ETDRS letter)</strong> at CNV event (higher values indicate better vision)**</td>
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<tr>
<td>1 (Chew E Y 2014)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>81</td>
<td>MD=4.2 (-2.69, 11.09)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Percentage of participants maintaining 20/40 or better visual acuity</strong></td>
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<tr>
<td>1 (Chew E Y 2014)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>81</td>
<td>RR=1.31 (0.94, 1.81)</td>
<td>LOW</td>
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<tr>
<td><strong>CNV detection rate</strong></td>
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<tr>
<td>1 (Chew E Y 2014)</td>
<td>RCT</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>1520</td>
<td>RR=1.63 (1.06, 2.52)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Frequency of self-monitoring (VMS journal vs usual care control group)</strong></td>
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<tr>
<td>1 (Bittner A K 2014)</td>
<td>RCT</td>
<td>Very serious³,⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>198</td>
<td>RR=1.61 (1.25, 1.82)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>No confidence in self-monitoring (VMS journal vs usual care control group)</strong></td>
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<tr>
<td>1 (Bittner A K 2014)</td>
<td>RCT</td>
<td>Very serious³,⁴</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>198</td>
<td>RR=0.31 (0.12, 0.69)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Downgraded one level for risk of bias due to early stoppage;
2. Downgraded one level for 95% confidence interval of estimated effect crossing 1 line of a defined minimal important difference
3. Downgraded one level for masking of participants and personnel not reported.
4. Downgraded one level for selection bias (baseline participants’ characteristics not reported)
5. Note: Frequency of self-monitoring and no confidence in self-monitoring were reported as odd ratio (OR), which was converted to relative risk (RR). RR=OR/(1-probability +probability *OR)
### Monitoring strategies and tools for people with late age-related macular degeneration (wet active)

RQ23b: What strategies and tools are useful for monitoring for people with late AMD (wet active)?

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LR+</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascularisation (fluid)</td>
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<tr>
<td>SD - Optical coherence tomography vs FA</td>
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<tr>
<td>2 studies (Giani, Khurana,)</td>
<td>Retrospective</td>
<td>152 eyes (149 people)</td>
<td>92.3% (83.9, 96.5%)</td>
<td>35.8% (25.3, 47.8%)</td>
<td>LR+</td>
<td></td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>LR-</td>
<td>0.22 (0.10, 0.50)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<td>TD - Optical coherence tomography vs FA</td>
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<tr>
<td>3 studies (Eter, Khurana, van velthoven)</td>
<td>Retrospective</td>
<td>149 eyes (146 people)</td>
<td>69.6% (59.7, 78.0%)</td>
<td>63.1% (48.2, 75.9%)</td>
<td>LR+</td>
<td>1.58 (1.04, 2.39)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<tr>
<td></td>
<td>Prospective</td>
<td>1 x Prospective (van velthoven)</td>
<td>237 sets of OCT and FA (66 people), up to 12 months follow-up</td>
<td>95.9% (91.1, 98.1%)</td>
<td>51.8% (41.4, 62.1%)</td>
<td>LR+</td>
<td>1.85 (1.51, 2.28)</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
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<td></td>
<td>LR-</td>
<td>0.08 (0.03, 0.17)</td>
<td>Serious³</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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<tr>
<td>OCT-A vs multimodal imaging (FA, ICG, OCT)</td>
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<tr>
<td>1 (Coscas)</td>
<td>Retrospective</td>
<td>80 eyes (73 people)</td>
<td>96.6% (90.6, 99.6%)</td>
<td>86.4% (69.6, 97.0%)</td>
<td>LR+</td>
<td>7.08 (2.47, 20.29)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Sample size</td>
<td>Sensitivity (95%CI)</td>
<td>Specificity (95%CI)</td>
<td>LRs</td>
<td>Effect size (95%CI)</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Quality</td>
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<tr>
<td>Neovascular AMD activities (PED)</td>
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<tr>
<td>SD-Optical coherence tomography vs FA</td>
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<tr>
<td>1 (Giani)</td>
<td>Retrospective</td>
<td>93 eyes (93 people)</td>
<td>38.5% (25.8, 51.9%)</td>
<td>68.3% (53.5, 81.4%)</td>
<td>LR+</td>
<td>1.21 (0.69, 2.14)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>MODERATE</td>
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<tr>
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<td></td>
<td></td>
<td>LR-</td>
<td>0.90 (0.67, 1.22)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>LOW</td>
</tr>
<tr>
<td>TD-Optical coherence tomography vs FA</td>
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<tr>
<td>1 (Van de Moere)</td>
<td>Retrospective</td>
<td>121 eyes (121 people)</td>
<td>6.3% (2.0, 13.0%)</td>
<td>99.0% (95.2, 100.0%)</td>
<td>LR+</td>
<td>6.59 (0.36, 119.77)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious⁴</td>
<td>VERY LOW</td>
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<td></td>
<td>LR-</td>
<td>0.95 (0.89, 1.01)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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<tr>
<td>Neovascular AMD activities (intraretinal fluid)</td>
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<td>SD-Optical coherence tomography vs FA</td>
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</tr>
<tr>
<td>1 (Khurana)</td>
<td>Retrospective</td>
<td>59 eyes (56 people)</td>
<td>65.5% (47.6, 81.4%)</td>
<td>63.3% (45.7, 79.3%)</td>
<td>LR+</td>
<td>1.79 (1.04, 3.06)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>LR-</td>
<td>0.54 (0.31, 0.96)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
</tr>
<tr>
<td>TD-Optical coherence tomography vs FA</td>
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<tr>
<td>2 (Khurana, van de moere)</td>
<td>Retrospective</td>
<td>180 eyes (177 people)</td>
<td>67.6% (56.3, 77.1%)</td>
<td>59.9% (48.6, 70.2%)</td>
<td>LR+</td>
<td>1.71 (1.28, 2.27)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<tr>
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<td></td>
<td>LR-</td>
<td>0.65 (0.48, 0.88)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
</tr>
<tr>
<td>TD-Optical coherence tomography vs FA (analysis unit: sets of OCT and FA)</td>
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</table>
### Neovascular AMD activities (subretinal fluid)

#### SD-Optical coherence tomography vs FA

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LR+</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Khurana)</td>
<td>Retrospective</td>
<td>59 eyes (56 people)</td>
<td>69.0% (51.3, 84.1%)</td>
<td>76.7% (60.3, 89.7%)</td>
<td>LR+</td>
<td>2.96 (1.48, 5.91)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>LR-</td>
<td>0.41 (0.23, 0.72)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### TD-Optical coherence tomography vs FA

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LR+</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (Khurana, van de moere)</td>
<td>Retrospective</td>
<td>180 eyes (117 people)</td>
<td>47.5% (37.9, 57.3%)</td>
<td>83.9% (74.3, 90.4%)</td>
<td>LR+</td>
<td>2.96 (1.73, 5.09)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>LR-</td>
<td>0.63 (0.51, 0.77)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

### Neovascular AMD activities (retinal cystoid abnormalities)
## Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Khurana)</td>
<td>Retrospective</td>
<td>59 eyes (56 people)</td>
<td>58.6% (40.6, 75.5%)</td>
<td>56.7% (38.9, 73.6%)</td>
<td><strong>LR+</strong> 1.35 (0.81, 2.26)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<td></td>
<td><strong>LR-</strong> 0.73 (0.43, 1.25)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
<td></td>
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</tbody>
</table>

**TD-Optical coherence tomography vs FA**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Khurana)</td>
<td>Retrospective</td>
<td>59 eyes (56 people)</td>
<td>73.3% (56.5, 87.3%)</td>
<td>55.6% (32.9, 77.0%)</td>
<td><strong>LR+</strong> 1.29 (0.60, 2.81)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<td></td>
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<td></td>
<td><strong>LR-</strong> 0.89 (0.64, 1.26)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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</table>

**Neovascular AMD activities (cystoid macular oedema)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (van de moere)</td>
<td>Retrospective</td>
<td>121 eyes (121 people)</td>
<td>22.9% (13.9, 33.3%)</td>
<td>98.0% (92.9, 99.9%)</td>
<td><strong>LR+</strong> 11.66 (1.60, 85.1)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td><strong>LR-</strong> 0.79 (0.69, 0.90)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
<td></td>
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</tbody>
</table>

**Neovascular AMD activities (cystoid spaces)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Eter)</td>
<td>Retrospective</td>
<td>60 eyes (60 people)</td>
<td>80% (66.7, 88.9%)</td>
<td>80% (45.9, 95.0%)</td>
<td><strong>LR+</strong> 4.00 (1.15 to 13.92)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>LOW</td>
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<td></td>
<td><strong>LR-</strong> 0.25 (0.13 to 0.47)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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</table>

**SD-Optical coherence tomography vs FA**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Giani)</td>
<td>Retrospective</td>
<td>93 eyes (93 people)</td>
<td>51.9% (38.5, 65.0%)</td>
<td>43.9% (29.7, 59.2%)</td>
<td><strong>LR+</strong> 0.93 (0.64 to 1.35)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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<tr>
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<td></td>
<td></td>
<td><strong>LR-</strong> 1.09</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
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</table>
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>LRs</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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<tbody>
<tr>
<td>(0.70 to 1.71)</td>
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</table>

1. Downgraded for study design (retrospective study)
2. Downgraded for imprecision because 95%CI of the positive likelihood ratio crossing 1 line of defined minimal importance difference
3. Downgraded for overall results of diagnostic accuracy based on sets of OCT and FA with no individual time point result
4. Downgraded for imprecision because 95%CI of the positive likelihood ratio crossing 2 lines of defined minimal importance difference
### H.8 Information

#### H.8.1 Barriers and facilitators to appointment attendance and update of treatment for people with age-related macular degeneration

RQ17: What are the barriers and facilitators to appointment attendance and uptake of treatment for people with AMD?

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burden of periodic follow-up visits (3 studies)</strong></td>
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<tr>
<td>1 (Boulanger-Scemama 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>20 lost to follow-up and no longer receiving care</td>
<td>15% (n=3) (5%, 36%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Varano Monic 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>910 treated for wet AMD</td>
<td>8.6% (n=78) (7%, 10.7%)</td>
<td>LOW</td>
</tr>
<tr>
<td>1 (Vaze 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious³</td>
<td>Not serious</td>
<td>248 began anti-VEGF treatment</td>
<td>0.8% (n=2) (0.2%, 2.9%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Travel problem (4 studies)</strong></td>
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</tr>
<tr>
<td>1 (Boulanger-Scemama 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>58 lost to follow-up</td>
<td>51.7% (n=30) (39.2%, 64.1%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Droege 2013)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious³</td>
<td>Serious²</td>
<td>19 stopped visits and interviewed</td>
<td>26.3% (n=5) (11.8%, 48.8%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Nunes 2010)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>19 answered phone questionnaire</td>
<td>5.3% (n=1) (0.9%, 24.6%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Vaze 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious³</td>
<td>Not serious</td>
<td>248 began anti-VEGF treatment</td>
<td>10.9%(n=27) (7.6%, 15.2%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Comorbidities (5 studies)</strong></td>
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<td></td>
</tr>
<tr>
<td>1 (Boulanger-Scemama 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>58 lost to follow-up</td>
<td>1.7% (n=1)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>
# Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scemama 2015)</td>
<td>study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>up</td>
<td>(0.3%, 9.1%)</td>
<td></td>
</tr>
<tr>
<td>1 (Droege 2013)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>19 stopped visits and interviewed</td>
<td>15.8% (n=3) (5.5%, 37.6%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Nunes 2010)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>19 answered phone questionnaire</td>
<td>15.8% (n=3) (5.5%, 37.6%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date</td>
<td>23.5% (n=24) (16.3%, 32.6%)</td>
<td>LOW</td>
</tr>
<tr>
<td>1 (Vaze A 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Not serious</td>
<td>248 began anti-VEGF</td>
<td>4.4% (n=11) (2.5%, 7.8%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Treatment related emotion (pain/discomfort/fear/dissatisfaction with treatment benefit) (4 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Boulanger-Scemama 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>20 lost to follow-up and no longer receiving care</td>
<td>50% (n=10) (29.9%, 70.1%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Droege 2013)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>19 stopped visits and interviewed</td>
<td>36.8% (n=7) (19.1%, 59.0%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Varano 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>910 treated for wet AMD</td>
<td>3.0% (n=27) (2.0%, 4.3%)</td>
<td>LOW</td>
</tr>
<tr>
<td>1 (Vaze A 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Not serious</td>
<td>248 began anti-VEGF</td>
<td>1.2% (n=3) (0.4%, 3.5%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Lack of information (2 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Mitchell 2002)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Serious⁵</td>
<td>Not serious</td>
<td>604 completed and answered</td>
<td>43.4% (n=262) (39.5%, 47.4%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>
## Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Nunes 2010)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>Not Serious</td>
<td>Not serious</td>
<td>Serious²</td>
<td>19 answered phone questionnaire</td>
<td>26.3% (n=5) (11.8%, 48.8%)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

### Specialist’s attitudes (dismissive, patronising, brusque, unfeeling, uninterested in patients, using jargon) (1 study)

| 1 (Mitchell 2002) | Observational study | Serious¹ | N/A | Serious⁵ | Not serious | 604 completed and answered the question | 43.5%(n=263) (39.6%, 47.5%) | LOW |

### Poor visual results (2 studies)

| 1 (Nunes 2010)    | Observational study | Very serious¹ | N/A | Not serious | Serious² | 19 answered phone questionnaire | 42.1%(n=8) (23.1%, 63.7%) | VERY LOW |
| 1 (Vaze 2014)     | Observational study | Very serious¹ | N/A | Serious⁴ | Not serious | 248 began anti-VEGF | 2.4% (n=6) (1.1%, 5.2%) | VERY LOW |

### Difficulty in re-scheduling (2 studies)

| 1 (Nunes 2010)    | Observational study | Very serious¹ | N/A | Not serious | Serious² | 19 answered phone questionnaire | 10.5% (n=2) (2.9%, 31.3%) | VERY LOW |
| 1 (Thompson 2015) | Observational study | Serious¹ | N/A | Serious⁴ | Not serious | 102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date | 37.3% (n=38) (28.5%, 46.9%) | LOW |

### Carer cannot take the patient to the appointment (2 studies)

| 1 (Varano 2015)   | Observational study | Very serious¹ | N/A | Not serious | Not serious | 910 treated for wet AMD | 23.5% (n=214) (20.9%, 26.4%) | LOW |
### Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date</td>
<td>21.6% (n=22) (14.7%, 30.5%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

**Financial burden (4 studies)**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Boulanger-Scemama 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>58 lost to follow-up</td>
<td>8.6% (n=5) (3.7%, 18.6%)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date</td>
<td>25.5% (n=26) (18.0%, 34.7%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Varano 2015)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>910 treated for wet AMD</td>
<td>5.0% (n=45) (3.7%, 6.5%)</td>
<td>LOW</td>
</tr>
<tr>
<td>1 (Vaze 2014)</td>
<td>Observational study</td>
<td>Very serious¹</td>
<td>N/A</td>
<td>Serious³</td>
<td>Not serious</td>
<td>248 began anti-VEGF</td>
<td>0.8% (n=2) (0.2%, 2.9%)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Long wait time (1 study)**

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date</td>
<td>52.0% (n=53) (42.3%, 61.4%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>
### Facilitators to appointment attendance and uptake of treatment (1 study)

#### Pre-appointment reminder (by phone, text, email)

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>240 participants answered the question</td>
<td>81.7% (n=153) (70.6%, 93.9%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Parking vouchers

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>240 participants answered the question</td>
<td>47.9% (n=115) (41.7%, 54.2%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Transportation service to and from the clinic

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>240 participants answered the question</td>
<td>44.6% (n=107) (38.4%, 50.9%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Mobile eye care van

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>240 participants answered the question</td>
<td>32.1% (n=77) (26.5%, 38.2%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Networking with other patients with the same eye diseases

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>240 participants answered the question</td>
<td>41.3% (n=99) (35.2%, 47.5%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### More education on eye disease/the importance of follow-up

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Thompson 2015)</td>
<td>Observational study</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>240 participants answered the question</td>
<td>70.8% (n=170) (64.8, 76.2%)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

---

1. Downgraded one level for study design; downgraded two levels for retrospective design;
2. Downgraded one level for wide 95%CI;
3. Downgraded one level for patients were from a single institute (i.e. practice, clinic);
Macular Degeneration
Appendix H: Grade tables and meta-analysis results

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Sample size</th>
<th>% (n) reported (95%CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Downgraded one level for 86 of a total of 240 participants had AMD;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>5. Downgraded one level for participants were member of macular society and not all had AMD</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### CERQual tables

<table>
<thead>
<tr>
<th>Review finding</th>
<th>Contributing studies</th>
<th>Confidence in the evidence</th>
<th>Explanation of confidence in the evidence assessment</th>
</tr>
</thead>
</table>
McCloud C, et al. 2014                                                          | Moderate confidence            | This review finding is rated as moderate, because there are two studies with minor to moderate methodological limitations (one only had 7 participants who were volunteers; one recruited participants through a nonprobability, convenience sampling). Minor concern about coherence. Fairly adequate and relevant data from one UK and Australian study. |
McCloud C, et al. 2014                                                          | Moderate confidence            | This review finding is rated as moderate, because there are two studies with minor to moderate methodological limitations (one only had 7 participants who were volunteers; one recruited participants through a nonprobability, convenience sampling). Minor concern about coherence. Fairly adequate and relevant data from one UK and Australian study. |
Burton A E, Shaw R L, and Gibson J M. 2013. BMJ Open                            | Moderate confidence            | This review finding is rated as moderate, because there are two studies with minor to moderate methodological limitations (one only had 7 participants who were volunteers; one recruited participants through a nonprobability, convenience sampling). Minor concern about coherence. Fairly adequate and relevant data from one UK and Australian study. |
| **The nature of treatment/treatment regimen**                                  | McCloud C, et al. 2014                                                              | Low confidence               | This review finding is rated as low, because there is one study with minor to moderate methodological limitations (participants were recruited through a nonprobability, |
### Facilitators to appointment attendance and uptake of treatment

#### Knowledge and treatment experience

Patients felt treatments were not as distressing as originally feared at their later appointments. They shared their treatment experiences with others, helping to ease concerns and reduce unnecessary distress.

- **Confidence in the evidence**: Moderate confidence
- **Explanation of confidence in the evidence assessment**: This review finding is rated as moderate, because there is a study with moderate methodological limitations (only had 7 participants who were volunteers). Coherence could not be assessed as only 1 study. High relevance with fairly adequate data from the study in the UK.

#### Regular monitoring

Patients expressed a desire for regular monitoring by healthcare professionals. It seemed that traditional view of healthcare professionals prevailed and therefore knowing that they were under the care of the hospital gave a sense of security.

- **Burton A E, Shaw R L, and Gibson J M. 2013. BMJ Open**
- **Confidence in the evidence**: Moderate confidence
- **Explanation of confidence in the evidence assessment**: This review finding is rated as moderate, because there is one study with minor methodological limitations (13 participants). Coherence could not be assessed as only 1 study. High relevance with fairly adequate data from the study in the UK.

Patients highlighted the need to self-advocate; they were expected to identify advancing vision loss and seek appropriate support as and when it was necessary.

#### Relationship with healthcare providers

Some patients described building relationship with healthcare professionals (i.e. nurses) as a way to manage the distress treatment caused. Patients preferred appointments that exemplified balanced relationships, mutual respect, and professional friendship and that left them feeling empowered about decisions they could make regarding treatment and management of their condition.

- **Confidence in the evidence**: Moderate confidence
- **Explanation of confidence in the evidence assessment**: This review finding is rated as moderate, because there is a study with moderate methodological limitations (only had 7 participants who were volunteers). Coherence could not be assessed as only 1 study. High relevance with fairly adequate data from the study in the UK.
### Review finding

<table>
<thead>
<tr>
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<th>Explanation of confidence in the evidence assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment outcome (vision acuity)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients expressed a clear willingness to endure their treatments if they continued to gain or maintain their vision.</td>
<td>McCloud C, et al. 2014</td>
<td>Low confidence</td>
<td>This review finding is rated as low, because there is one study with minor to moderate methodological limitations (participants were recruited through a nonprobability, convenience sampling). Coherence could not be assessed as only 1 study. Adequate data with minor concern about relevance.</td>
</tr>
</tbody>
</table>
### Informational needs of people with suspected or confirmed AMD and their family members/carers

**RQ3a:** What information do people with suspected AMD and their family members or carers find useful, and in what format and when?

**RQ3b:** What information do people with confirmed AMD and their family members or carers find useful, and in what format and when?

<table>
<thead>
<tr>
<th>Review finding</th>
<th>Contributing studies</th>
<th>Confidence in the evidence</th>
<th>Explanation of confidence in the evidence assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Theme 1: Information required and when</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Timing: Before diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information about types of AMD and risk factors/causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients and carers want increased public awareness of the causes and symptoms of AMD (Burton, Vukicevic).</td>
<td>Burton (2013) Vukicevic (2016)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because there were two studies with minor methodological limitations. The studies were internally and externally coherent. There were no serious problems with relevance and fairly adequate data from UK and Australia.</td>
</tr>
<tr>
<td>• This could provide a context for diagnosis, could help people seek advice earlier (Burton).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• This could help improve public interaction with people with AMD (more understanding of the challenges facing the visually impaired) (Vukicevic).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At the opticians - detection of possible AMD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients reported very different experiences at the opticians when they were told that they may have a severe eye condition. The way a person was told and what they were told appeared to have a big effect on the anxiety and fear they feel prior to formal diagnosis.</td>
<td>Burton (2013)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because was one study with minor methodological limitations. The study was internally coherent. There were no serious problems with relevance and fairly adequate data from UK.</td>
</tr>
<tr>
<td><strong>Timing: At or following diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• The information at diagnosis needs to be matched to the person’s disease stage: early AMD patients needed information about monitoring their condition and spotting changes; wet AMD patients needed to know about available treatments and outcomes; patients with advanced disease needed to hear about support services and equipment</td>
<td>Burton (2013)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because was one study with minor methodological limitations. The study was internally coherent. There were no serious problems with relevance and fairly adequate data from UK.</td>
</tr>
</tbody>
</table>

**Information about types of AMD and frequency of diagnosis**
<table>
<thead>
<tr>
<th>Review finding</th>
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<th>Confidence in the evidence</th>
<th>Explanation of confidence in the evidence assessment</th>
</tr>
</thead>
</table>
| • Patients were confused about the different names and types of AMD (Dahlin Ivanoff)  
• Patients were unaware that AMD was so common (Burton, Dahlin Ivanoff).   | Burton (2013) Dahlin Ivanoff (1996)       | High confidence            | This review finding is rated as high because there were two studies with minor methodological limitations. The studies were internally and externally coherent. There were no serious problems with relevance and adequate data from UK and Sweden. |
| **Information about potential causes and risk factors**                       |                                           |                            |                                                                                                                     |
| • Patients often lacked a clear understanding of the potential causes and risk factors associated with AMD (Burton, Crossland, Dahlin Ivanoff).  
• Most patients were not aware of the potential effects of smoking on disease development and progression, while those patients that mentioned smoking as a cause did not necessarily believe it (Crossland).  
• Patients often linked AMD to wear and tear and ageing (Crossland, McCloud).  
• The role of genetic susceptibility in developing AMD was not widely understood (Crossland). | Burton (2013) Crossland (2007) Dahlin Ivanoff (1996) McCloud (2015) | High confidence            | This review finding is rated as high, because there were 4 studies with minor methodological limitations. The studies were internally and externally coherent. There were no serious problems with relevance and adequate data from UK, Sweden and Australia. |
| **Information about disease progression**                                     |                                           |                            |                                                                                                                     |
| • Patients were suffering unnecessarily due to inaccurate/insufficient information about disease progression, leaving them to worry about going completely blind (Burton, McCloud, Dahlin Ivanoff).  
• Patients discussed a need for accurate information to help them plan for the future and avoid unrealistic expectations (Burton, Dahlin Ivanoff,  
• Patients reported giving up favourite pastimes to help preserve their vision (Burton). | Burton (2013) Dahlin Ivanoff (1996) McCloud (2015) | High confidence            | This review finding is rated as high, because there were 3 studies with minor methodological limitations. The studies were internally and externally coherent. There were no serious problems with relevance and adequate data from UK, Sweden and Australia. |
<p>| <strong>Information about treatment regimens</strong>                                      |                                           |                            |                                                                                                                     |
| • Patients often had unrealistic expectations of treatment outcomes and this was not helped by inaccurate information | Burton (2013) | Moderate confidence | This review finding is rated as moderate because there were three studies with minor methodological limitations. |</p>
<table>
<thead>
<tr>
<th>Review finding</th>
<th>Contributing studies</th>
<th>Confidence in the evidence assessment</th>
<th>Explanation of confidence in the evidence assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>from neighbours/family members (Burton).</td>
<td>Dahlin Ivanoff (1996) McCloud (2015)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because there was one study with minor methodological limitations. The studies were internally coherent, but with limited overlap. There were no serious problems with relevance and adequate data from UK, Sweden and Australia.</td>
</tr>
<tr>
<td>Patients did not necessarily understand the importance of the use of vitamins and food to promote eye health and when they could be useful during disease progression (Burton, Dahlin Ivanoff).</td>
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<td>Patients did not understand why glasses were not able to correct their vision problems (Dahlin Ivanoff).</td>
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<td>Patients were often unaware of the purpose of hospital visits and medical procedures (Burton).</td>
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<td>An understanding of the processes involved in treatment and the short-term side effects allowed patients to plan their post-treatment activities to cope with these problems (McCloud).</td>
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<tr>
<td>Information about abnormal outcomes and when to seek help would also be useful (McCloud).</td>
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<tr>
<td>Good communication regarding changes in treatment regimens was linked to better patient experience (McCloud).</td>
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<tr>
<td>Other non-NHS support services/ financial help</td>
<td>Burton (2013)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because there was one study with minor methodological limitations. The study was internally coherent. There were no serious problems with relevance and fairly adequate data from UK.</td>
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<tr>
<td>Patients were unaware of support groups or unlikely to attend them for fear of associating with depressed people.</td>
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<tr>
<td>Patients were not necessarily aware of sources of financial help (e.g. attendance allowance) or the advantages associated with being registered as partially sighted.</td>
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<tr>
<td>Monitoring of symptoms- when to seek help?</td>
<td>Burton (2013)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because there was one study with minor methodological limitations. The study was internally coherent. There were no serious problems with relevance and fairly adequate data from UK.</td>
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<tr>
<td>Patients who were not being regularly monitored were expected to identify advancing vision loss and seek appropriate support as and when it was necessary. However, they did not understand what constituted a serious change and were worried about wasting doctor’s valuable time and NHS resources. They were also relatively unlikely to attend accident and emergency if their vision changed as they did not associate A and E with this type of care.</td>
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<tr>
<td>Review finding</td>
<td>Contributing studies</td>
<td>Confidence in the evidence</td>
<td>Explanation of confidence in the evidence assessment</td>
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<tr>
<td><strong>Theme 2: Format of information</strong></td>
<td>Burton (2013)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because there was one study with minor methodological limitations. The study was internally coherent. There were no serious problems with relevance and fairly adequate data from UK.</td>
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<tr>
<td>• Verbal communication of information was problematic for many patients as they struggled to understand and retain the information given to them in hospital consultations. They also reported problems with hearing and understanding the doctors’ accents.</td>
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<td>• The use of written sources of information was potentially problematic as patients could be confused by the volume of information and find it hard to read the documents.</td>
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<td>• Patients reported finding the language use by medical staff to be confusing and inaccessible.</td>
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<td><strong>Theme 3: Additional sources of information</strong></td>
<td>Burton (2013)</td>
<td>Moderate confidence</td>
<td>This review finding is rated as moderate, because there was one study with minor methodological limitations. The study was internally coherent. There were no serious problems with relevance and fairly adequate data from UK.</td>
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<tr>
<td>• These were varied and not always accurate. In particular, information from neighbours and friends could be very misleading and discourage people from seeking help in a timely manner or lead them to have unrealistic expectations from treatment.</td>
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<td>• Support groups could be useful sources of information, but patients were not necessarily aware of them.</td>
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<td>• Public presentations were raised as a useful source of information, but required pro-active patients.</td>
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<td><strong>Theme 4: Caregiver perspectives and needs</strong></td>
<td>Vukicevic (2016)</td>
<td>High confidence</td>
<td>This review finding is rated as high, because there was one study with minor methodological limitations. The study was internally coherent. High relevance with adequate sample size from an Australian study.</td>
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<td>• Carers need sufficient information to allow them to understand the condition and the physical/emotional effects on the person’s wellbeing.</td>
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<td>• Caregivers raised the point that since AMD has a genetic component it is important that all family members of AMD sufferers are aware of their increased risk and have regular eye tests.</td>
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<td>• They lack information about support services and respite care</td>
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<td>Review finding</td>
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<td>options.</td>
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</tbody>
</table>

**Additional points**

- Patients were unaware that medical research was being carried out (Dahlin Ivanoff).
- Patient experiences were more positive if they received reassurance, support and caring communication from medical staff (McCloud).

<table>
<thead>
<tr>
<th>Dahlin Ivanoff (1996)</th>
<th>Moderate confidence</th>
<th>This review finding is rated as moderate because there were two studies with minor methodological limitations. The studies were internally coherent, but with limited overlap. There were no serious problems with relevance and fairly adequate data from UK and Australia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCloud (2015)</td>
<td></td>
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</tbody>
</table>
GRADE tables and meta-analysis results