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

Agreement outcomes: Interobserver agreement

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
AREDS 17 (2006) Case-control study	AREDS 9-step severity scale	Serious[1]	Not applicable (N/A)	Not serious	Not serious	1225 eyes from the Age Related Eye Disease Study (AREDS)	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).	MODERATE
Danis et al (2013) Retrospective cohort	AREDS 9-step severity scale	Serious[1]	N/A	Not serious	Not serious	1335 eyes from the AREDS2 study	Contemporaneous regrades, (interobserver agreement) (n=1335) Agreement: 96% Weighted Kappa (SE): 0.76 (0.01)	MODERATE

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
							Historical AREDS Temporal Drift (AREDS Report 6 and 17), (n=119) Agreement: 94% Weighted Kappa (SE): 0.73 (0.01)	
AREDS 6, (2001) Retrospective cohort	AREDS 4-step severity scale	Serious[1]	N/A	Not serious	Not serious	1230 eyes from the AREDS study	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)	MODERATE
Seddon 2006 Retrospective cohort	CARMS	Serious[1]	N/A	Not serious	Not serious	492 eyes recruited for the Progression of Age-Related Macular Degeneration Study	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) Agreement between 2 observers assessments of Age-Related Maculopathy.	MODERATE

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
							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)	
Hamada (2006) Retrospective cohort	The Modified International Classification of ARM	Serious[1]	N/A	Not serious	Not serious	164 images of 106 patients taken from consecutive patients referred to the Retinal Research Unit at King's College Hospital.	Interobserver consistency between the two graders: Kappa value of 0.82 (SE 0.34).	MODERATE
Leeuwen (2003) Retrospective cohort	The Modified International Classification of ARM	Serious[1]	N/A	Not serious	Not serious	91 subjects in the EUREYE study. 131 images of eyes taken to represent the full range of AMD.	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 On the 5 main stages: 35-mm film Agreement: 72.3% Weighted kappa: 0.79	MODERATE

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Klein (2014) Retrospective cohort	Harmonized Three Continent AMD Consortium Severity Scale	Serious[1]	N/A	Not serious	Not serious	60 images from participants of the Beaver Dam Eye Study	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	MODERATE
1. Downgraded one level for risk of bias due to lack of clarity regarding baseline characteristics of included participants								

Agreement outcomes: Intraobserver Agreement

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Danis et al (2013) Retrospective cohort	AREDS 9-step severity scale	Serious[1]	N/A	Not serious	Not serious	1335 eyes from the AREDS2 study	AREDS2 Temporal Drift Regrade Year 4 Compared to BL, (intraobserver agreement) (n=88) Agreement: 92% Weighted Kappa (SE): 0.73 (0.02)	MODERATE
AREDS 6, (2001) Retrospective cohort	AREDS 4-step severity scale	Serious[1]	N/A	Not serious	Not serious	1230 eyes from the AREDS study	Intraobserver temporal reproducability AMD severity level Agreement- 88.2% Agreement within 1 step: 98.3% Kappa, unweighted (SE)- 0.83 (0.04) Kappa, weighted (SE)- 0.88 (0.04)	MODERATE

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Seddon 2006 Retrospective cohort	Clinical Age-Related Maculopathy Staging (CARMS) system	Serious[1]	N/A	Not serious	Not serious	492 eyes recruited for the Progression of Age-Related Macular Degeneration Study	Intraobserver agreement Agreement: 94% Agreement within 1 step: 100% Kappa, unweighted (95% CI): 0.92 (0.58-1.3) Kappa, weighted (95% CI): 0.97 (0.49-1.4)	MODERATE

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

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

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Interobserver agreement								
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).								
Cohen (2007) Prospective cohort	CAMRS	Very serious[1, 3, 4]	N/A	Not serious	Serious[2]	207 patients with newly diagnosed exudative AMD	Lesion classification: Kappa: 0.59 Location of lesion: Kappa: 0.52	VERY LOW
(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, ICG and OCT)								
Coscas (2014) Prospective cohort	CAMRS	Very Serious[1, 3,]	N/A	Not serious	Serious[7]	99 consecutive Japanese eyes and 94 consecutive French eyes with exudative AMD	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%	VERY LOW

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
							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% Range, French patients (n= 94) AMD with type 1 CNV: 95.8 - 97.9% AMD with type 1+2 CNV: 68.4 - 89.5% AMD with type 2 CNV: 60.0 - 100% Chorioretinal anastomosis: 80.0- 100% PCV without type 1 or 2 CNV: 66.6-87.5% Other: 75-100%	
(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)								
Coscas (2014) Prospective cohort	CAMRS	Very Serious[1, 3,]	N/A	Not serious	Serious[7]	99 consecutive Japanese eyes and 94 consecutive French eyes with exudative AMD	Crude agreement with final diagnosis: Range, Kyoto patients (n= 99) AMD with type 1 CNV: 79.4 – 82.3%	VERY LOW

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
							AMD with type 1+2 CNV: 16.6- 66.6% AMD with type 2 CNV: 40-80% Chorioretinal anastomosis: 66.6- 83.3% PCV with type 1 or 2 CNV: 33.3% PCV without type 1 or 2 CNV: 56.5-91.3% Other: 66.6-88.8% Range, French patients (n= 94) AMD with type 1 CNV: 89.5% AMD with type 1+2 CNV: 36.8- 78.9% AMD with type 2 CNV: 60.0- 100% Chorioretinal anastomosis (RAP): 60-80% PCV without type 1 or 2 CNV: 33.3-75% Other: 50-100%	
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								
Jung (2014)	CARMS	Serious[1, 6]	N/A	Serious[5]	Not serious	374 treatment naïve patients with neovascular AMD in at least 1 eye	Agreement between FA and anatomic classification: Kappa 0.65	LOW

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Prospective cohort								
1) Classic only, 2) occult only, 3) mixed, or 4) unable to determine								
Friedman (2000) Retrospective cohort	CARMS	Very serious[1, 3, 4, 6]	N/A	Serious[2]	Not serious	6 fluorescein angiograms read by 21 ophthalmologists	Membrane type Mean agreement, % (SD): 72.5 (23.0) Mean kappa (SD): 0.64 (0.30)	VERY LOW
1) classic, 2) occult, or 3) mixed with classic component less or equal/greater than 50%								
Holz (2003) Prospective cohort	CARMS	Very serious[1, 3, 4]	N/A	Serious[2]	Not serious	40 patients with neovascular ARMD, graded by 16 retinal specialists.	Mean kappa agreement (SD): Randomised series A: 0.40 (0.05) Randomised series B: 0.37 (0.05)	VERY LOW
Predominantly classic, minimally classic, or occult								
Olsen (2004) Retrospective cohort	CAMRS	Very serious[1, 4, 6]	N/A	Serious[2]	Not serious	200 cases of nAMD from 2 centres	kappa agreement: 0.63	VERY LOW
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	Serious[1]	N/A	Serious[2]	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%								
Holz (2003)	CAMRS	Very serious[1, 3, 4]	N/A	Serious[2]	Not serious	40 patients with neovascular ARMD,	Mean kappa agreement (SD): 0.64 (SD 0.11)	VERY LOW

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Prospectiv e cohort						graded by 16 retinal specialists.		

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

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
CAPT classification of late dry AMD								
Brader (2011) Retrospec tive cohort	CAMRS	Serious[1]	N/A	Serious[2]	Not serious	Sample of 15 photographic sets, some of which included lesions that met the new criteria but not the previously used criteria. Regraded 6m.	Interobserver variability kappa: 0.536	LOW
Intraobserver agreement								
classic, occult, or mixed with classic component less or equal/greater than 50%								
Brader (2011) Retrospec tive cohort	CAMRS	Serious[1]	N/A	Serious[2]	Not serious	Sample of 15 photographic sets, some of which included lesions that met the new criteria but not the previously used criteria. Regraded 6m.	Intraobserver agreement kappa: 0.845	LOW

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
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

Studies	Classification system	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Units	Effect	Quality
Risk of developing neovascular AMD									
Simple Severity Score									
Perlee et al (2013) Prospective cohort study	Simple severity score	Very serious [1, 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) 2) 12.66 (6.87-23.36) 3) 26.56 (14.53-48.58) 4) 35.89 (19.75-65.21)	LOW
Sandberg 4-point scale									
Sandberg (1998) Prospective cohort study	Sandberg 4-point scale	Very Serious [1, 2, 3]	N/A	Not serious	Very serious7	patients with unilateral neovascular AMD (127)	HR (95% CI)	Hazards ratio for development of choroidal neovascular membrane (95% confidence intervals) 1.76 (1.18-2.73)	VERY LOW

Studies	Classification system	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Units	Effect	Quality
Risk of developing geographic atrophy									
Simple Severity Score									
Perlee et al (2013) Prospective cohort study	Simple severity score	Very serious [1, 2, 5]	N/A	Not serious	Nots serious	Participants in the Age-Related Eye Disease Study (n=2415)	HR (95% CI)	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) 4) 34.81 (16.02-75.65)	LOW
Risk of developing advanced AMD									
Simple Severity Score									
Klein et al (2011) Prospective cohort study	Simple severity score	Very serious [1, 2, 3]	N/A	Not serious	Not serious	Participants in the Age-Related Eye Disease Study (n=2846)	HR (95% CI)	Hazard Ratios for Progression to Advanced Age-Related Macular Degeneration at 2, 5, and 10 Years (95% Confidence Interval) Simple scale score 0- referent	LOW

Studies	Classification system	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Units	Effect	Quality
								1- 6.38 (3.48-11.69) 2- 14.12 (8.06-24.75) 3- 34.53 (19.79-60.26) 4- 50.65 (28.86-88.89)	

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, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Low dose aspirin								
Christen (2001) Prospective cohort	22,071	Very serious[1,2,3]	N/A	Not serious	Serious[5]	HR (95% CI)	0.77 (0.54, 1.11)	VERY LOW
Low dose aspirin								
Christen (2009) Prospective cohort	39,876	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	1.03 (0.88, 1.21)	LOW
Ethnicity (risk of non-exudative AMD) – white as reference category								
van der Beek (2011) Prospective cohort	1,772,962	Very serious[1,2,3,4]	N/A	Not serious	Not serious	HR (95% CI)	Black - age 60: 0.75 (0.71, 0.79) Black - age 80: 0.56 (0.52, 0.60) Latino - age 60: 0.99 (0.94, 1.04) Latino - age 80: 0.82 (0.76, 0.88)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							Asian American - age 60: 1.28 (1.20, 1.36) Asian American - age 80 0.92 (0.83, 1.02)	
Stein (2011) Prospective cohort	44,103	Very serious[1,2,3,4]	N/A	Not serious	Not serious	HR (95% CI)	Vietnamese: 1.15 (0.96, 1.38) Japanese: 0.71 (0.59, 0.85) Chinese: 1.63 (1.50, 1.77) Filipino: 0.96 (0.76, 1.22) Korean: 1.11 (0.92, 1.34) Indian: 0.99 (0.85, 1.16) Pakistani: 1.97 (1.40, 2.77)	LOW
Exercise (km/day)								
Williams 2009 Prospective cohort	41,708	Very serious[1,2,3,4]	N/A	Not serious	Not serious	HR (95% CI)	0.90 (0.83, 0.97)	LOW
Cardiorespiratory fitness (10-k performance times) (m/s)								
Williams 2009 Prospective cohort	41,708	Very serious[1,2,3,4]	N/A	Not serious	Serious[5]	HR (95% CI)	0.92 (0.60, 1.39)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Alcohol (<1drink/week as reference category)								
Ajani (1999) Prospective cohort	21,041	Very serious[1,2]	N/A	Not serious	Serious[3]	HR (95% CI)	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)	VERY LOW
Alpha carotene, per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	0.99 (0.94, 1.06)	LOW
Beta carotene, per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	1.00 (0.94, 1.06)	LOW
Beta cryptoxanthin, per standard deviation increase								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Leeuwen (2005) Prospective cohort	Participants of the Rotterdam study (2005)	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	1.01 (0.92, 1.10)	LOW
Lutein/zeaxanthin, per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	1.01 (0.93, 1.09)	LOW
Lycopene, per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	1.01 (0.97, 1.04)	LOW
Vitamin A (retinol equivalents), per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	0.95 (0.86, 1.05)	LOW
Vitamin C, per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	1.02 (0.94, 1.10)	LOW
Vitamin E, per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	0.92 (0.84, 1.00)	MODERATE
Trace elements Iron, per standard deviation increase								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	0.95 (0.86, 1.04)	LOW
Zinc, per standard deviation increase								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	0.91 (0.83, 0.98)	MODERATE
Combined intake of 4 predefined antioxidant nutrients (vitamins C and E, beta carotene, and zinc) – medium intake as reference category								
Leeuwen (2005) Prospective cohort	4,170	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	Low: 1.20 (0.92, 1.56) High: 0.65 (0.46, 0.92)	MODERATE

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
3. Downgraded one level for non-significant effect

H.2.1.1 Development of early AMD in people at risk: risk outcomes for developing early AMD

Ocular risk factors

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Large drusen								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen > 125µm vs <63µm in diameter: 5.5 (3.5, 8.7)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Soft distinct drusen vs hard distinct drusen								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Soft distinct drusen vs hard distinct drusen: 3.0 (2.2, 4.1)	MODERATE
Drusen area								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen area >16877 μm² vs ≤2596 μm²: 5.2 (3.7, 7.5)	MODERATE

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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Gender								
Klein (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Female: 2.8 (1.6, 4.9)	MODERATE
Increasing education								
Klein (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Serious[5]	Time-adjusted odds ratios (95% CI)	Increasing education 0.6 (0.4, 0.8)	LOW
Obesity (BMI)								
Howard (2014)	2,641	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Female, non-smoker: BMI (per 2.5 kg/m²): 1.10 (1.02, 1.19)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							Male, non-smoker: BMI (per 2.5 kg/m²): 0.90 (0.75, 1.07) Female smoker BMI (per 2.5 kg/m²): 1.07 (0.98, 1.17) Male smoker BMI (per 2.5 kg/m²): 1.00 (0.90, 1.10)	
Long term use of aspirin								
Klein (2012) Prospecti ve cohort	4,926	Not serious	N/A	Not serious	Serious[6]	HR (95% CI)	Regular aspirin use: 0.86 (0.71, 1.05)	MODERATE
Age								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 2.3 (2.1, 2.6)	MODERATE
Age								
Klein (2008) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	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)	MODERATE
Smoking								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Klein (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Serious[5]	Time-adjusted odds ratios (95% CI)	Past vs never smokers: 1.16 (0.91, 1.48) Current vs never smokers: 1.47 (1.08, 1.99)	LOW
Smoking								
Seddon (2015)* Prospective cohort	2,951	Very Serious[1,2,3,4]	N/A	Not serious	Not serious	HR (95% CI)	Past: 1.1 (1.0, 1.3) Current: 1.8 (1.4, 2.3)	LOW
Smoking								
Klein (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Serious[5]	Time-adjusted odds ratios (95% CI)	Current vs never smoker 1.9 (1.03, 3.6) Past vs never smoker 1.4 (0.9, 2.3)	LOW
Smoking								
Seddon (2013)* Prospective cohort	2,914	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Past: 1.2 (1.1, 1.4) Current: 1.6 (1.3, 2.1)	MODERATE
Smoking								
Seddon (2013)* Prospective cohort	980	Serious[1,2]	N/A	Not serious	Serious[6]	HR (95% CI)	Past: 1.0 (0.8, 1.4) Current: 2.2 (1.4, 3.3)	LOW
Diabetes history								
Klein (2008)	3,917	Serious[1,2]	N/A	Not serious	Serious[5]	Time-adjusted odds ratios (95% CI)	0.1 (0.02, 0.8)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
History of MI								
Klein (2013) Prospecti ve cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.13 (0.60, 2.14)	VERY LOW
History of stroke								
Klein (2013) Prospecti ve cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.25 (0.46, 3.38)	VERY LOW
History of CVD								
Klein (2013) Prospecti ve cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	0.79 (0.46, 1.37)	VERY LOW
History of angina								
Klein (2013) Prospecti ve cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	0.90 (0.48, 1.71)	VERY LOW
Exercise								
Knudtson et al (2006) Prospecti ve cohort	3,684	Very Serious[1,2,3]	N/A	Not serious	Serious[5]	Time-adjusted odds ratios (95% CI)	Sedentary: reference Active: 0.9 (0.7, 1.1)	VERY LOW

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)

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality

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 fros the ARED2 study

Diet and nutrition

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Increased wine drinking								
Klein (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Serious[3]	Time-adjusted odds ratios (95% CI)	Increased wine drinking 0.6 (0.3, 1.1)	LOW
Daily Alcohol consumption, g (none as reference category)								
Boekhoorn (2008) Prospective cohort	4,229	Serious[1,2]	N/A	Not serious	Serious[4]	HR (95% CI)	≤10: 1.00 (0.76, 1.30) >10 to ≤20: 0.98 (0.70, 1.36) >20: 1.10 (0.80, 1.51)	LOW
Beta-carotene (quartile 1 as reference category)								
Chiu (2009) Prospective cohort	2,924	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	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)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							Q4 (>3.2 mg/day): 0.97 (0.77, 1.21)	
Docosahexaenoic acid (quartile 1 as reference category)								
Chiu (2009) Prospective cohort	2,924	Serious[1]	N/A	Not serious	Serious[4]	HR (95% CI)	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 (>64.0 mg/day): 1.09 (0.88, 1.35)	LOW
Eicosapentaenoic acid (quartile 1 as reference category)								
Chiu (2009) Prospective cohort	2,924	Serious[1]	N/A	Not serious	Serious[4]	HR (95% CI)	Q2 (12.7–24.6 mg/day): 1.07 (0.90, 1.28) Q3 (24.6–42.3 mg/day): 1.01 (0.84, 1.21) Q4 (>42.3 mg/day): 1.01 (0.83, 1.23)	LOW
Low Glycaemic Index (>81.5 as reference category)								
Chiu (2009)	2,924	Serious[1]	N/A	Not serious	Serious[4]	HR (95% CI)	78.6–81.5: 1.15 (0.96, 1.38) 75.2–78.6: 1.05 (0.87, 1.28) 75.2: 1.03 (0.83, 1.29)	LOW

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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Cataract surgery								
Chew (2009) Prospective cohort	5,841	Very serious[1,2]	N/A	Not serious	Serious[5]	HR (95% CI)	Right eye: 0.80 (0.61, 1.06) Left eye: 0.95 (0.71, 1.26)	VERY LOW
Hyperpigmentation (none as reference category)								
CAPT (2008) Prospective cohort	1,052	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	<250 um: 2.82 (1.30, 6.12) >=250 um: 10.4 (4.51, 24.0)	MODERATE
Hyperpigmentation								
Klein (2007)	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Increased pigment present vs absent: 15.8 (7.6, 32.8)	MODERATE
Retinal pigment epithelium depigmentation								
Klein (2007) Prospective cohort	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	RPE depigmentation present vs absent: 11.1 (5.0, 24.4)	MODERATE
Retinal pigment epithelium depigmentation								
CAPT (2008) Prospective cohort	1,052	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	2.64 (1.26, 5.53)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Pigmentary changes								
Finger (2014) Retrospective cohort	200	Very serious[1,3,4]	N/A	Not serious	Not serious	HR (95% CI)	Pigmentary Changes: 5.75 (2.09, 15.84)	LOW
Pigmentary abnormalities								
Klein (2007) Prospective cohort	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Pigmentary abnormalities present vs absent: 15.2 (7.3, 31.6)	MODERATE
% of area covered by drusen (<10 as reference category)								
CAPT (2008) Prospective cohort	1,052	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	10-24%: 2.39 (1.44, 3.97) >=25%: 5.10 (2.57, 10.1)	MODERATE
Drusen area								
Klein (2007) Prospective cohort	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen area >16877 µm² vs ≤2596 µm²: 24.0 (3.2, 179)	MODERATE
Large drusen								
Finger (2014) Retrospective cohort	200	Very serious[1,3,4]	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥125µm: 11.73 (1.47, 93.81)	LOW
Large drusen								
Klein (2007)	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen > 125µm vs <63µm in diameter: 14.5 (5.9, 35.7)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
Soft distinct drusen vs hard distinct drusen								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,3]	N/A	Not serious	Very serious[6]	Time-adjusted odds ratios (95% CI)	1.2 (0.3, 5.7)	VERY LOW
Soft indistinct vs soft distinct drusen or hard distinct drusen								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	14.6 (6.8, 31.1)	MODERATE
Reticular drusen vs Soft distinct drusen								
Klein (2008) Prospecti ve cohort	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	41.78 (9.43, 185.14)	MODERATE
Reticular drusen vs Soft indistinct drusen								
Klein (2008) Prospecti ve cohort	3,917	Serious[1,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	6.23 (1.70, 22.73)	MODERATE
Reticular pseudodrusen								
Finger (2014) Retrospec tive cohort	200	Very serious[1,3,4]	N/A	Not serious	Not serious	HR (95% CI)	Reticular pseudodrusen: 4.93 (1.06, 22.93)	LOW
Baseline visual acuity (20/25-20/40 as reference category)								
Grunwald (2014)	1,024	Serious[3]	N/A	Not serious	Not serious	HR (95% CI)	20/50–20/80: 1.66 (1.14, 2.44)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospective cohort							20/100–20/160: 1.70 (1.10, 2.62) 20/200–20/320: 2.65 (1.43, 4.93)	
Retinal angiomatous proliferation lesion								
Grunwald (2014) Prospective cohort	1,024	Serious[3]	N/A	Not serious	Not serious	HR (95% CI)	1.69 (1.16, 2.47)	MODERATE
Geographic atrophy in fellow eye								
Grunwald (2014) Prospective cohort	1,024	Serious[3]	N/A	Not serious	Not serious	HR (95% CI)	2.07 (1.40, 3.08)	MODERATE

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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Hypertension								
CAPT (2008)	1,052	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	Suspected: 1.01 (0.76, 1.35)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							Definite: 1.98 (1.16, 3.39)	
Age (50-59 years as reference category)								
CAPT (2008) Prospecti ve cohort	1,052	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	60-69 years: 6.09 (1.72, 21.5) 70-79 years: 4.12 (1.18, 14.4) >79: 6.39 (1.64, 24.9)	MODERATE
Age								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 4.2 (2.9, 6.1)	MODERATE
Diabetes mellitus								
Hahn (2013) Retrospec tive cohort	6,621	Very Serious[1,3,4,5]	N/A	Not serious	Serious[6]	HR (95% CI)	1.03 (0.97 1.09)	VERY LOW
Long term use of aspirin								
Klein (2012) Prospecti ve cohort	4,926	Not serious	N/A	Not serious	Serious[6]	HR (95% CI)	Regular aspirin use: 1.65 (0.91, 2.99)	MODERATE
Smoking								
Klein (2008) Prospecti ve cohort	2,119	Serious[1,2]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	Past vs never smokers: 0.88 (0.41, 1.88)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							Current vs never smokers: 0.18 (0.02, 1.40)	
History of MI								
Klein (2013) Prospecti ve cohort	1,700	Serious[2]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	0.61 (0.07, 5.34)	VERY LOW
History of CVD								
Klein (2013) Prospecti ve cohort	1,700	Serious[2]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.31 (0.32, 5.27)	VERY LOW
History of angina								
Klein (2013) Prospecti ve cohort	1,700	Serious[2]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.53 (0.30, 7.85)	VERY LOW
Exercise (sedentary as reference group)								
Knudtson (2006) Prospecti ve cohort	3,684	Very Serious[1,2,3]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	Active: 1.1 (0.5, 2.3)	VERY LOW

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)

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
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 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								

Diet and nutrition

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Daily Alcohol consumption, g (0 as reference category)								
Boekhoorn (2008) Prospective cohort	4,229	Serious[1,2]	N/A	Not serious	Serious[4]	HR (95% CI)	≤10: 1.10 (0.32, 3.80) >10 to ≤20 1.38 (0.31, 6.16) >20: 3.27 (0.88, 12.19)	LOW
Total Fat, g (quintile 1 as reference category)								
Reynolds (2013) Prospective cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	Quintile 2: 1.14 (0.82, 1.59) Quintile 3: 0.99 (0.70, 1.39) Quintile 4: 1.54 (1.13, 2.11) Quintile 5: 1.18 (0.85, 1.64)	VERY LOW
Saturated Fat, g (quintile 1 as reference category)								
Reynolds (2013)	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	Quintile 2: 1.09 (0.78, 1.51) Quintile 3:	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							1.42 (1.03, 1.95) Quintile 4: 1.18 (0.85, 1.64) Quintile 5: 1.19 (0.87, 1.64)	
Monounsaturated Fat g (quintile 1 as reference category)								
Reynolds (2013) Prospecti ve cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	Quintile 2: 1.37 (0.98, 1.91) Quintile 3: 1.22 (0.86 , 1.71) Quintile 4: 1.38 (0.99, 1.94) Quintile 5: 1.47 (1.05 , 2.05)	LOW
Total Polyunsaturated Fatty Acids g (quintile 1 as reference category)								
Reynolds (2013) Prospecti ve cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	Quintile 2: 0.95 (0.68, 1.33) Quintile 3: 1.10 (0.80, 1.52) Quintile 4: 1.34 (0.97,1.85) Quintile 5: 1.13 (0.82, 1.55)	VERY LOW
Omega-3 fatty acids, Eicosapentaenoic Acid (EPA) - quintile 1 as reference category								
Reynolds (2013) Prospecti ve cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	Quintile 2: 0.92 (0.65, 1.30) Quintile 3: 1.16 (0.86, 1.58) Quintile 4: 1.00 (0.71, 1.39)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							Quintile 5: 0.84 (0.59, 1.18)	
Omega-3 fatty acids, Docosahexaenoic Acid (DHA) (g) - quintile 1 as reference category								
Reynolds (2013) Prospecti ve cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	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)	VERY LOW
Omega-3 fatty acids, DHA + EPA (g) - quintile 1 as reference category								
Reynolds (2013) Prospecti ve cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	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)	VERY LOW
Omega-3 fatty acids, Linolenic Acid (g) - quintile 1 as reference category								
Reynolds (2013)	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	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: 1.08(0.80, 1.46)	VERY LOW
Omega-6 Fatty Acids, linoleic acid (g) - quintile 1 as reference category								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Reynolds (2013) Prospective cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	Quintile 2: 0.98 (0.70, 1.37) Quintile 3: 1.04 (0.75, 1.44) Quintile 4: 1.36 (0.99, 1.87) Quintile 5: 1.11 (0.81, 1.53)	VERY LOW
Omega-6 Fatty Acids, Arachidonic Acid (g) - quintile 1 as reference category								
Reynolds (2013) Prospective cohort	4,165	Very serious[1,2,3]	N/A	Not serious	Serious[4]	HR (95% CI)	Quintile 2: 0.92 (0.67, 1.26) Quintile 3: 0.85 (0.62, 1.17) Quintile 4: 0.91 (0.66, 1.25) Quintile 5: 0.84 (0.62, 1.14)	VERY LOW

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

H.2.1.3 Development of choroidal neovascularisation (CNV) due to AMD: risk outcomes for developing CNV

Ocular risk factors

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
5 or more drusen								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Macular photocoagulation study group (1997) Prospective cohort	670	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	2.1 (1.3, 3.5)	LOW
1 or more large drusen								
Macular photocoagulation study group (1997) Prospective cohort	670	Very serious[1,2,3]	N/A	Not serious	Serious[6]	HR (95% CI)	1.5 (1.0, 2.2)	VERY LOW
Large drusen								
Bressler 1990 Prospective cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Large drusen (≥50µm): 2.4 (1.1, 5.1)	LOW
Large Drusen								
Finger (2014) Retrospective cohort	200	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥125µm: 1.96 (1.14, 3.36)	LOW
Large drusen								
Klein (2007)	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen > 125µm vs <63µm in diameter: 60.4 (17.7, 206)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
No. of large drusen (quartile 1 as reference category)								
Sandberg (1998) Prospecti ve cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Quartile 2: 2.09 (0.66, 7.84) Quartile 3: 0.83 (0.20, 3.52) Quartile 4: 3.25 (1.11, 11.75)	LOW
Drusen area								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen area >16877 μm² vs ≤2596 μm²: 40.4 (5.5, 297)	MODERATE
Soft distinct drusen vs hard distinct drusen								
Klein et al (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Soft distinct drusen vs hard distinct drusen: 7.4 (2.4, 22.6)	MODERATE
Soft indistinct vs soft distinct drusen or hard distinct drusen								
Klein et al (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Soft indistinct vs soft distinct drusen or hard distinct drusen: 18.3 (8.9, 37.4)	MODERATE
Reticular drusen vs Soft distinct drusen								
Klein et al (2008) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	9.89 (2.16, 45.23)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Reticular drusen vs Soft indistinct drusen								
Klein et al (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Very serious[7]	Time-adjusted odds ratios (95% CI)	2.82 (0.66, 12.01)	VERY LOW
Reticular pseudodrusen								
Finger (2014) Retrospective cohort	200	Very serious[1,2,4]	N/A	Not serious	Serious[6]	HR (95% CI)	Reticular pseudodrusen: 1.19 (0.72, 1.94)	VERY LOW
Confluent drusen								
Bressler 1990 Prospective cohort	127	Very serious[1,2,4]	N/A	Not serious	Serious[6]	HR (95% CI)	1.8 (0.8, 3.9)	VERY LOW
Hyperpigmentation								
Macular photocoagulation study group (1997) Prospective cohort	670	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	2.0 (1.4, 2.9)	LOW
Hyperpigmentation								
Bressler 1990 Prospective cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	2.5 (1.3, 4.9)	LOW
Hyperpigmentation (none/questionable as reference category)								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
CAPT (2008) Prospective cohort	1,052	Serious[2]	N/A	Not serious	Not serious	HR (95% CI)	<250 um: 1.28 (0.94, 1.75) >=250 um: 1.84 (1.22, 2.76)	MODERATE
Hyperpigmentation								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Increased pigment present vs absent: 5.8 (2.9, 11.7)	MODERATE
Retinal pigment epithelium depigmentation								
Klein et al (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	RPE depigmentation present vs absent: 7.8 (3.6, 16.6)	MODERATE
Pigmentary changes								
Finger (2014) Retrospective cohort	200	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Pigmentary Changes: 2.49 (1.51, 4.10)	LOW
Pigmentary abnormalities								
Klein et al (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Pigmentary abnormalities present vs absent: 15.2 (7.3, 31.6)	MODERATE
Cataract surgery								
Chew (2009) Prospective cohort	5,841	Very serious[2,5]	N/A	Not serious	Serious[6]	HR (95% CI)	Right eye 1.20 (0.82, 1.75) Left eye 1.07 (0.72, 1.58)	VERY LOW

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 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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Definite systemic hypertension								
Macular photocoagulation study group (1997) Prospective cohort	670	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	1.7 (1.2, 2.4)	LOW
Hypertension (normal as reference category)								
CAPT (2008) Prospective cohort	1,052	Serious[2]	N/A	Not serious	Serious[6]	HR (95% CI)	Suspect: 0.69 (0.45, 1.07) Definite: 1.23 (0.90, 1.68)	LOW
Age (50-59 years as reference category)								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
CAPT (2008) Prospective cohort	1,052	Serious[2]	N/A	Not serious	Not serious	HR (95% CI)	60-69 years: 2.06 (1.06, 3.97) 70-79 years: 2.61 (1.39, 4.92) >79 years: 2.81 (1.33, 5.94)	MODERATE
Age								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 2.9 (2.2, 3.8)	MODERATE
Age								
Sandberg (1998) Prospective cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Age, y, continuous: 1.08 (1.02, 1.14)	LOW
Smoking (never as reference category)								
CAPT (2008) Prospective cohort	1,052	Serious[2]	N/A	Not serious	Not serious	HR (95% CI)	Former: 1.01 (0.76, 1.35) Current: 1.98 (1.16, 3.39)	MODERATE
Smoking								
Wilson (2004) Retrospective cohort	326	Serious[5]	N/A	Not serious	Not serious	HR (95% CI)	Current smoker: 1.77 (1.06, 2.97)	MODERATE
Smoking								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Klein (2008) Prospective cohort	2,119	Serious[1,2]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	Past vs never smokers: 1.12 (0.62, 2.01) Current vs never smokers: 0.69 (0.27, 1.76)	VERY LOW
Diabetes								
Hahn (2013) Prospective cohort	6,621	Very serious[2,3,4,5]	N/A	Not serious	Serious[6]	HR (95% CI)	1.11 (0.97, 1.27)	VERY LOW
Long term use of aspirin (no regular use as reference category)								
Klein (2012) Prospective cohort	4,926	Not serious	N/A	Not serious	Serious[6]	HR (95% CI)	Regular aspirin use: 1.07 (0.68, 1.67)	MODERATE
Aspirin user								
Wilson (2004) Retrospective cohort	326	Serious[5]	N/A	Not serious	Not serious	HR (95% CI)	0.63 (0.40, 0.98)	MODERATE
History of MI								
Klein (2013) Prospective cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.56 (0.48, 5.08)	VERY LOW
History of CVD								
Klein (2013)	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.66 (0.65, 4.26)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
History of angina								
Klein (2013) Prospecti ve cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	0.92 (0.27, 3.13)	VERY LOW
Exercise								
Knudtson (2006) Prospecti ve cohort	3,684	Very Serious[1,2,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Sedentary: reference Active: 0.3 (0.1, 0.7)	LOW
Ethnicity (white as reference category)								
van der Beek (2011) Prospecti ve cohort	1,772,962	Very Serious[1,2,3,5]	N/A	Not serious	Not serious	HR (95% CI)	Black at age 60: Exudative AMD: 0.70 (0.59, 0.83) Blacks at age 80: Exudative AMD: 0.45 (0.37, 0.54) Latinos at age 60: Exudative AMD: 1.28 (1.13, 1.45) Latinos at age 80: Exudative AMD: 0.89 (0.76, 1.05) Asian Americans at age 60:	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							Exudative AMD: 1.08 (0.89, 1.31) Asian Americans at age 80: Exudative AMD: 0.54 (0.40, 0.73)	
Stein (2011) Prospecti ve cohort	44,103	Very Serious[1,2,3,5]	N/A	Not serious	Very Serious[7]	HR (95% CI)	Vietnamese: 0.70 (0.37, 1.35) Japanese: 0.64 (0.40, 1.04) Chinese: 0.95 (0.71, 1.27) Filipino: 1.18 (0.67, 2.09) Korean: 0.97 (0.56, 1.66) Indian: 1.08 (0.71, 1.62) Pakistani: 0.45 (0.06, 3.21)	VERY LOW

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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference								

Diet and nutrition

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Alcohol use (<1 drink/week as reference category)								
Ajani (1999) Prospective cohort	21,041	Very serious[1,2]	N/A	Not serious	Serious[4]	HR (95% CI)	1 drink/week: 1.12 (0.47, 2.68) 2-4 drinks/week: 0.88 (0.39, 1.96) 5-6 drinks/week: 1.20 (0.52, 2.78) ≥1 drink/day: 1.33 (0.70, 2.50)	VERY LOW
Daily Alcohol consumption, g (0 as reference category)								
Boekhoorn (2008) Prospective cohort	4,229	Serious[1,3]	N/A	Not serious	Serious[4]	HR (95% CI)	≤10: 0.96 (0.45, 2.03) >10 to ≤20: 0.60 (0.21, 1.72) >20: 0.40 (0.13, 1.25)	LOW

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. Downgraded one level for non-significant effect

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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Large drusen								
Finger (2014) Retrospective cohort	200	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥125µm: 2.08 (1.25, 3.49)	LOW
Large drusen in the fellow eye (<250 µm in diameter in the fellow eye as the reference category)								
SST (2009) Prospective cohort	370	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥250 µm in diameter in the fellow eye: 2.32 (1.49, 3.61)	MODERATE
Large drusen								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen > 125µm vs <63µm in diameter: 29.6 (14.4, 60.7)	MODERATE
Large drusen								
Klein (2011) Prospective cohort	2,846	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	1.79 (1.50, 2.14)	LOW
Largest drusen size in non-advanced eye (<63 µm as reference category)								
Seddon (2011)* Prospective cohort	2,937	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	63-124: 4.1 (1.9, 9.2) 125-249: 7.3 (3.4,15.8) ≥250: 11.7 (5.4, 25.3)	MODERATE
Large drusen in the fellow eye with CNV (<250 µm as reference category)								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
SST (2009) Prospective cohort	370	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥250 µm in diameter: 1.73 (1.12, 2.66)	MODERATE
Size of drusen for those with no advanced AMD in either eye (<63 µm in both eyes as reference category)								
Seddon (2011)* Prospective cohort	2,937	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	L eye, R eye 63–124, <63: 3.5 (1.9, 6.3) 63–124, 63–124: 7.6 (4.2, 13.5) 125–249,<63: 7.8 (4.1, 14.7) 125–249, 63–124: 15.1 (8.8, 25.7) 125–249, 125–249: 26.0 (15.4, 43.7) ≥ 250, <124: 28.0 (15.2, 51.6) ≥ 250, 125–249: 43.9 (26.1, 73.9) ≥ 250, ≥250: 53.7 (32.2, 89.4)	MODERATE
Drusen area								
Klein (2011)	2,846	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	Drusen area >16877 µm² vs ≤2596 µm²:	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							32.3 (7.8, 133)	
Advanced AMD in one eye: largest drusen size in non-advanced eye, µm (<63 as reference category)								
Seddon (2015)* Prospecti ve cohort	2,951	Very Serious[1,2,4,5]	N/A	Not serious	Not serious	HR (95% CI)	63–124: 3.9 (1.7, 8.6) 125–249: 8.4 (3.9, 18.3) ≥250: 13.8 (6.4, 29.5)	LOW
No advanced AMD: largest drusen size in each eye, µm (<63 µm in both eyes as reference category)								
Seddon (2015)* Prospecti ve cohort	2,951	Very Serious[1,2,4,5]	N/A	Not serious	Not serious	HR (95% CI)	L eye, R eye 63–124, none to <63: 3.0 (1.7, 5.3) 63–124, 63–124: 7.9 (4.5, 13.8) 125–249, none to <63: 7.2 (3.9, 13.3) 125–249, 63–124: 15.2 (9.1, 25.2) 125–249, 125–249: 29.0 (17.7, 47.5) 250, ≤124: 31.0 (17.2, 55.9) 250, 125–249: 50.3 (30.8, 82.2)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							250, ≥250: 72.0 (44.7, 116.2)	
Soft distinct drusen vs hard distinct drusen								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Soft distinct drusen vs hard distinct drusen: 3.6 (1.5, 8.6)	MODERATE
Soft indistinct vs soft distinct drusen or hard distinct drusen								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	17.5 (10.3, 29.8)	MODERATE
Reticular drusen vs Soft distinct drusen								
Klein (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	28.29 (9.48, 84.44)	MODERATE
Reticular drusen vs Soft indistinct drusen								
Klein (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	6.34 (2.28, 17.63)	MODERATE
Reticular pseudodrusen								
Finger (2014) Retrospective cohort	200	Very serious[1,2,3]	N/A	Not serious	Serious[6]	HR (95% CI)	1.20 (0.76, 1.89)	VERY LOW
Pigmentary changes								
Finger (2014)	200	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	2.55 (1.64, 3.96)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Retrospective cohort								
Pigmentary abnormalities								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Pigmentary abnormalities present vs absent: 10.8 (6.5, 18.0)	MODERATE
Hyperpigmentation								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Increased pigment present vs absent: 9.8 (5.9, 16.3)	MODERATE
Hyperpigmentation in a fellow eye with CNV (no focal hyperpigmentation as reference category)								
SST (2009) Prospective cohort	370	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Mild/moderate focal hyperpigmentation: 1.43 (0.86, 2.40) Severe focal hyperpigmentation: 2.26 (1.30, 3.94)	MODERATE
Retinal pigment epithelium depigmentation								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	RPE depigmentation present vs absent: 10.5 (5.9, 18.5)	MODERATE
Retinal pigment epithelium depigmentation								
SST (2009) Prospective cohort	370	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	1.79 (1.14, 2.82)	MODERATE
Advanced age related macular degeneration in 1 eye								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Klein (2011) Prospective cohort	2,846	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	1.21 (1.02, 1.45)	MODERATE
Advanced AMD in 1 eye								
Seddon (2011)* Prospective cohort	2,937	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	1 eye with geographic atrophy: 7.3 (2.9, 18.4) 1 eye with neovascular disease: 5.1 (2.1, 12.2)	MODERATE
Advanced AMD in one eye								
Seddon (2015)* Prospective cohort	2,951	Very Serious[1,2,4,5]	N/A	Not serious	Not serious	HR (95% CI)	Grade 4: 8.3 (3.2, 19.9) Grade 5: 5.8 (2.3, 13.2)	LOW
Geographic atrophy in the fellow eye with CNV								
SST (2009) Prospective cohort	370	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	1.82 (1.08, 3.08)	MODERATE

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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
*Seddon (2011), Seddon (2013) and Seddon (2015) all report the same participants fros the ARED2 study								

Demographic and medical risk factors

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Low dose aspirin								
Christen (2009) Prospective cohort	39,876	Very serious[1,2,3]	N/A	Not serious	Serious[6]	HR (95% CI)	0.90 (0.53, 1.52)	VERY LOW
Long term use of aspirin								
Klein (2012) Prospective cohort	4,926	Not serious	N/A	Not serious	Serious[6]	HR (95% CI)	Regular aspirin use: 1.21 (0.84, 1.74)	MODERATE
Obesity (BMI)								
Howard (2014) Prospective cohort	2,641	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Female, non-smoker BMI (per 2.5 kg/m²): 1.31 (1.15, 1.50) Male, non-smoker BMI (per 2.5 kg/m²): 0.86 (0.61, 1.20) Female smoker BMI (per 2.5 kg/m²): 0.99 (0.81, 1.21)	MODERATE
Obesity (BMI)								
Lechanteur (2012)	108	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Overweight (25–30): 1.3 (0.8, 2.1) Obese (≥30):	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							2.2 (1.1, 4.1)	
Obesity (BMI) - <25 as reference category								
Seddon (2003) Prospecti ve cohort	261	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	25-29: 2.32 (1.32, 4.07) ≥30: 2.35 (1.27, 4.34)	MODERATE
Obesity (BMI) - <25 as reference category								
Seddon (2011)* Prospecti ve cohort	2,937	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	25–29: 1.1 (0.9, 1.3) ≥30: 1.3 (1.1, 1.6)	MODERATE
Obesity (BMI) - <25 as reference category								
Seddon (2013)* Prospecti ve cohort	2,914	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	25–29: 1.1 (0.9, 1.3) ≥30: 1.3 (1.1, 1.6)	MODERATE
Obesity (BMI) - <25 as reference category								
Seddon (2015)* Prospecti ve cohort	2,951	Very serious[1,2,3,4]	N/A	Not serious	Not serious	HR (95% CI)	25–29: 1.1 (0.9, 1.3) ≥30: 1.2 (1.0, 1.5)	LOW
Current smoker								
Klein (2011) Prospecti ve cohort	2,846	Very serious[1,2,5]	N/A	Not serious	Not serious	HR (95% CI)	1.78 (1.37, 2.31)	LOW
Smoking								
Seddon (2003)	261	Serious[1]	N/A	Not serious	Serious[6]	HR (95% CI)	Past: 1.32 (0.82, 2.12) Current: 1.99 (0.90, 4.43)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
Smoking (pack years) – 0 to 1 as reference category								
Lechante ur (2012) Prospecti ve cohort	108	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	1 to 40: 2.4 (1.3, 4.5) ≥40: 4.4 (1.4, 14.3)	MODERATE
Smoking								
Seddon (2011)* Prospecti ve cohort	2,937	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	Past: 1.1 (1.0, 1.3) Current: 1.8 (1.4, 2.3)	MODERATE
Family History of AMD								
Klein (2011) Prospecti ve cohort	2,846	Very serious[1,2,5]	N/A	Not serious	Not serious	HR (95% CI)	1.40 (1.16, 1.70)	LOW
Age								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 3.5 (2.8, 4.4)	MODERATE
Age (<65 as reference category)								
Lechante ur (2012) Prospecti ve cohort	108	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	65 to 70: 1.2 (0.5, 2.7) 70 to 75: 1.5 (0.7, 3.1) 75 to 80: 2.6 (1.3, 5.3) ≥80: 5.0 (2.0, 12.5)	MODERATE
Age (<65 as reference category)								
Seddon (2011)*	2,937	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	65–74: 1.4 (1.1, 1.7) ≥75: 1.8 (1.5, 2.3)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
Age (<65 as reference category)								
Seddon (2013)* Prospecti ve cohort	2,914	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	65-74: 1.4 (1.1, 1.7) ≥75: 2.0 (1.6, 2.5)	MODERATE
Age (<65 as reference category)								
Seddon (2013)* Prospecti ve cohort	980	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	65-74: 1.5 (1.0, 2.3) ≥75: 2.6 (1.7, 4.1)	MODERATE
Age (≥75 as reference category)								
Seddon (2015)* Prospecti ve cohort	2,951	Very serious[1,2,3,4]	N/A	Not serious	Not serious	HR (95% CI)	65–74: 0.8 (0.6, 0.9) 55–64: 0.6 (0.5, 0.7)	LOW
History of MI								
Klein (2013) Prospecti ve cohort	1,700	Serious[1]	N/A	Not serious	Very serious[7]	Time-adjusted odds ratios (95% CI)	1.04 (0.36, 3.02)	VERY LOW
History of CVD								
Klein (2013) Prospecti ve cohort	1,700	Serious[1]	N/A	Not serious	Very serious[7]	Time-adjusted odds ratios (95% CI)	1.33 (0.59, 3.01)	VERY LOW
History of angina								
Klein (2013)	1,700	Serious[1]	N/A	Not serious	Very serious[7]	Time-adjusted odds ratios (95% CI)	0.89 (0.32, 2.50)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
Cardiovascular disease								
Seddon (2003) Prospecti ve cohort	261	Serious[1]	N/A	Not serious	Serious[6]	HR (95% CI)	1.21 (0.73, 2.02)	LOW
Gender (male as reference category)								
Lechante ur (2012) Prospecti ve cohort	108	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Female: 2.6 (1.4, 5.0)	MODERATE
Gender (female as reference category)								
Seddon (2011)* Prospecti ve cohort	2,937	Serious[1]	N/A	Not serious	Serious[6]	HR (95% CI)	Male: 1.0 (0.9, 1.2)	LOW
Gender (female as reference category)								
Seddon (2013)* Prospecti ve cohort	2,914	Serious[1,2]	N/A	Not serious	Serious[6]	HR (95% CI)	Male: 1.0 (0.8, 1.1)	LOW
Gender (female as reference category)								
Seddon (2013)* Prospecti ve cohort	980	Serious[1,2]	N/A	Not serious	Serious[6]	HR (95% CI)	Male: 1.0 (0.8, 1.2)	LOW
Gender (female as reference category)								
Seddon (2015)*	2,951	Very serious[1,2,3,4]	N/A	Not serious	Serious[6]	HR (95% CI)	Male: 1.1 (0.9, 1.2)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospective cohort								
Education (≤ high school as reference category)								
Lechantenur (2012) Prospective cohort	108	Serious[1,2]	N/A	Not serious	Serious[6]	HR (95% CI)	> high school: 0.6 (0.4, 1.1)	LOW
Education (≤ high school as reference category)								
Seddon (2011)* Prospective cohort	2,937	Serious[1]	N/A	Not serious	Serious[6]	HR (95% CI)	> high school: 0.9 (0.8, 1.0)	LOW
Education (≤ high school as reference category)								
Seddon (2013)* Prospective cohort	2,914	Serious[1,2]	N/A	Not serious	Serious[6]	HR (95% CI)	> high school: 0.9 (0.8, 1.0)	LOW
Education (≤ high school as reference category)								
Seddon (2013)* Prospective cohort	980	Serious[1,2]	N/A	Not serious	Serious[6]	HR (95% CI)	> high school: 0.8 (0.6, 1.0)	LOW
Education (high school as reference category)								
Seddon (2015)* Prospective cohort	2,951	Very serious[1,2,3,4]	N/A	Not serious	Serious[6]	HR (95% CI)	> high school: 0.9 (0.8, 1.0)	VERY LOW

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)

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
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 fros the ARED2 study								

Diet and nutrition

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Daily Alcohol consumption, g (0 as reference category)								
Boekhoorn (2008) Prospective cohort	4,229	Serious[1,2]	N/A	Not serious	Serious[3]	HR (95% CI)	≤10: 1.00 (0.53, 1.89) >10 to ≤20: 0.77 (0.33, 1.80) >20: 1.01 (0.46, 2.21)	LOW
Dietary glycaemic index (quintile 1 as reference category)								
Chiu (2007) Prospective cohort	3,977	Serious[1,2]	N/A	Not serious	Not serious	HR (95% CI)	Quintile 2: 1.12 (0.90, 1.40) Quintile 3: 1.14 (0.90, 1.44) Quintile 4: 1.20 (0.94, 1.52) Quintile 5: 1.39 (1.08, 1.79)	MODERATE
Low dietary glycaemic index (>81.5 as reference category)								
Chiu (2009)	2,924	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	78.6–81.5: 0.80 (0.67, 0.97)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospective cohort							75.2–78.6: 0.77 (0.63, 0.94) 75.2: 0.76 (0.60, 0.96)	
Beta-carotene (quartile 1 as reference category)								
Chiu (2009) Prospective cohort	2,924	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	Q2 (1.5–2.2 mg/day): 0.97 (0.80, 1.19) Q3 (2.2–3.2 mg/day): 1.11 (0.90, 1.37) Q4 (>3.2 mg/day): 1.24 (0.96, 1.59)	LOW
Docosahexaenoic acid (quartile 1 as reference category)								
Chiu (2009) Prospective cohort	2,924	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	Q2 (26.0–41.9 mg/day): 0.97 (0.80, 1.18) Q3 (41.9–64.0 mg/day): 1.04 (0.85, 1.28) Q4 (>64.0 mg/day): 0.73 (0.57, 0.94)	MODERATE
Eicosapentaenoic acid (quartile 1 as reference category)								
Chiu (2009) Prospective cohort	2,924	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	Q2 (12.7–24.6 mg/day): 0.91 (0.75, 1.11) Q3 (24.6–42.3 mg/day): 1.03 (0.85, 1.24) Q4 (>42.3 mg/day): 0.74 (0.59, 0.94)	MODERATE
Total fat (quartile 1 as reference category)								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	2nd quartile: 1.27 (0.63, 2.53) 3rd quartile: 2.29 (1.08, 4.88) 4th quartile: 2.90 (1.15, 7.32)	MODERATE
Animal fat (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	2nd quartile: 0.81 (0.41, 1.57) 3rd quartile: 1.14 (0.55, 2.37) 4th quartile: 2.29 (0.91, 5.72)	LOW
Vegetable fat (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	2nd quartile: 1.64 (0.86, 3.13) 3rd quartile: 2.27 (1.12, 4.59) 4th quartile: 3.82 (1.58, 9.28)	MODERATE
Saturated fat (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	2nd quartile: 0.97 (0.49, 1.93) 3rd quartile: 1.46 (0.66, 3.20) 4th quartile: 2.09 (0.83, 5.28)	LOW
Monounsaturated fat (quartile 1 as reference category)								
Seddon (2003)	261	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	2nd quartile:	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospective cohort							1.27 (0.65, 2.45) 3rd quartile: 2.13 (1.03, 4.43) 4th quartile: 2.21 (0.90, 5.47)	
Polyunsaturated fat (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	2nd quartile: 1.57 (0.82, 3.02) 3rd quartile: 1.90 (0.94, 3.84) 4th quartile: 2.28 (1.04, 4.99)	MODERATE
Transunsaturated fat (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	2nd quartile: 1.67 (0.83, 3.36) 2nd quartile: 3.22 (1.63, 6.36) 3rd quartile: 2.39 (1.10, 5.17)	LOW
No. of servings of fish a week (<1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	1: 1.30 (0.78, 2.16) ≥2: 0.88 (0.49, 1.60)	LOW
High-fat dairy (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	2nd quartile: 2.08 (1.09, 3.97) 3rd quartile: 1.80 (0.96, 3.38) 4th quartile:	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							1.91 (0.98, 3.73)	
Meat (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	2nd quartile: 1.75 (0.91, 3.34) 3rd quartile: 1.62 (0.81, 3.24) 4th quartile: 2.09 (0.98, 4.47)	LOW
Processed baked goods (quartile 1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Not serious	HR (95% CI)	2nd quartile: 1.21 (0.69, 2.26) 3rd quartile: 2.02 (1.06, 3.85) 4th quartile: 2.42 (1.21, 4.84)	MODERATE
Number of servings of nuts per week (<1 as reference category)								
Seddon (2003) Prospective cohort	261	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	1: 0.69 (0.40, 1.17) ≥2: 0.60 (0.32, 1.02)	LOW
Taking antioxidants (clinical trial)								
Seddon (2011)* Prospective cohort	2,937	Serious[1]	N/A	Not serious	Serious[3]	HR (95% CI)	0.9 (0.8, 1.0)	LOW

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 non-significant effect

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
*Seddon (2011), Seddon (2013) and Seddon (2015) all report the same participants fros 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 by the Cochrane Eyes and Vision group and the NICE Internal Clinical Guidelines Team.

Statin for age-related macular degeneration

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
AMD progression								
1 (Guymer 2013)	RCT	Serious[1]	N/A	Not serious	Serious[2]	114	RR 0.78 (0.50, 1.02)	LOW
Adverse outcomes								
1 (Guymer 2013)	RCT	Serious[1]	N/A	Not serious	Serious[2]	114	RR 0.64 (0.39, 0.92)	LOW

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

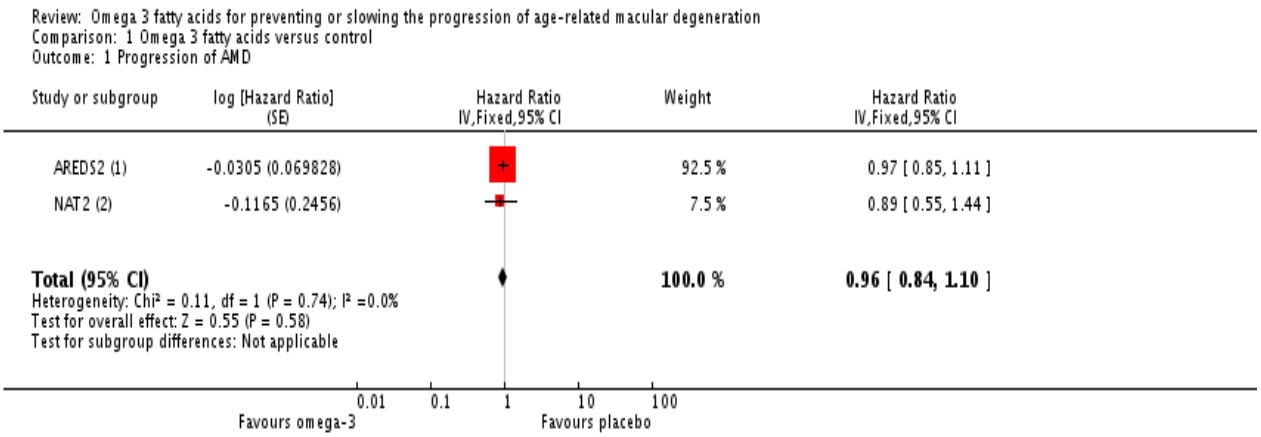
Omega 3 fatty acids compared to placebo for slowing the progression of age-related macular degeneration

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Loss of 3 or more lines of visual acuity at 24 months								
1 (ARES2)	RCT	Not serious	N/A	Not serious	Very serious[1]	236	RR 1.14, (0.53, 2.45)	LOW
Loss of 3 or more lines of visual acuity at 36 months								
1 (ARES2)	RCT	Not serious	N/A	Not serious	Very serious[1]	230	RR 1.25, (0.69, 2.26)	LOW
Incidence of CNV at 24 months								
1 (NAT 2013)	RCT	Not serious	N/A	Not serious	Very serious[1]	224	RR 1.06, (0.47,2.40)	LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Incidence of CNV at 36 months								
1 (NAT 2013)	RCT	Not serious	N/A	Not serious	Very serious[1]	195	RR 1.12, (0.53 , 2.38)	LOW
Progression of AMD over 5 years								
2 (ARES and NAT)	RCT	Not serious	Not serious	Not serious	Not serious	2343	HR 0.96 (0.84, 1.1)	HIGH
Adverse effects								
2 (ARES and NAT)	RCT	Not serious	Not serious	Not serious	Not serious	2343	RR 1.01, (0.94 ,1.09)	HIGH
Visual acuity (ETDRS letters; higher is better)								
1 (Ute E K 2015)	RCT	Serious[3]	N/A	Not serious	Not serious	79	MD 1.00 (-2.50 ,4.50)	MODERATE

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)

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



(1) Progression over 5 years; unit of analysis eye, adjusted for within person correlation.

(2) Incidence of CNV 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

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Development of CNV								
11 (CAPT, DLS, Figueroa 1994, Little 1995, Olk 1999, PTAMD bilateral 2009, CNVPT, Fremensson 1995, Fremesson 2009, Laser to Drusen study 1995, PTAMD unilateral 2002)	RCT	Not serious	Not serious	Not serious	Serious[1]	2159 (3580 eyes)	RR* 1.03, (0.83, 1.27)	MODERATE
Development of geographic atrophy								
2 (CNVPT, laser to Drusen study 1995)	RCT	Not serious	Not serious	Not serious	Very serious[2]	148 (148 eyes)	RR* 1.27 (0.41, 3.94)	LOW
Visual loss of 2-3+ lines of visual acuity at 3-year follow-up								
9 (CAPT, DLS, Figueroa 1994, PTAMD bilateral 2009, CNVPT, Laser to Drusen Study 1995, Olk 1999, PTAMD unilateral 2002)	RCT	Serious[3]	Not serious	Not serious	Not serious	2002 (3486 eyes)	RR* 0.99 (0.83, 1.18)	MODERATE
Drusen reduction								
3 (CNVPT, PTAMD bilateral	RCT	Not serious	Serious[4]	Not serious	Not Serious	570 (944 eyes)	RR* 4.47 (1.64, 12.19)	MODERATE

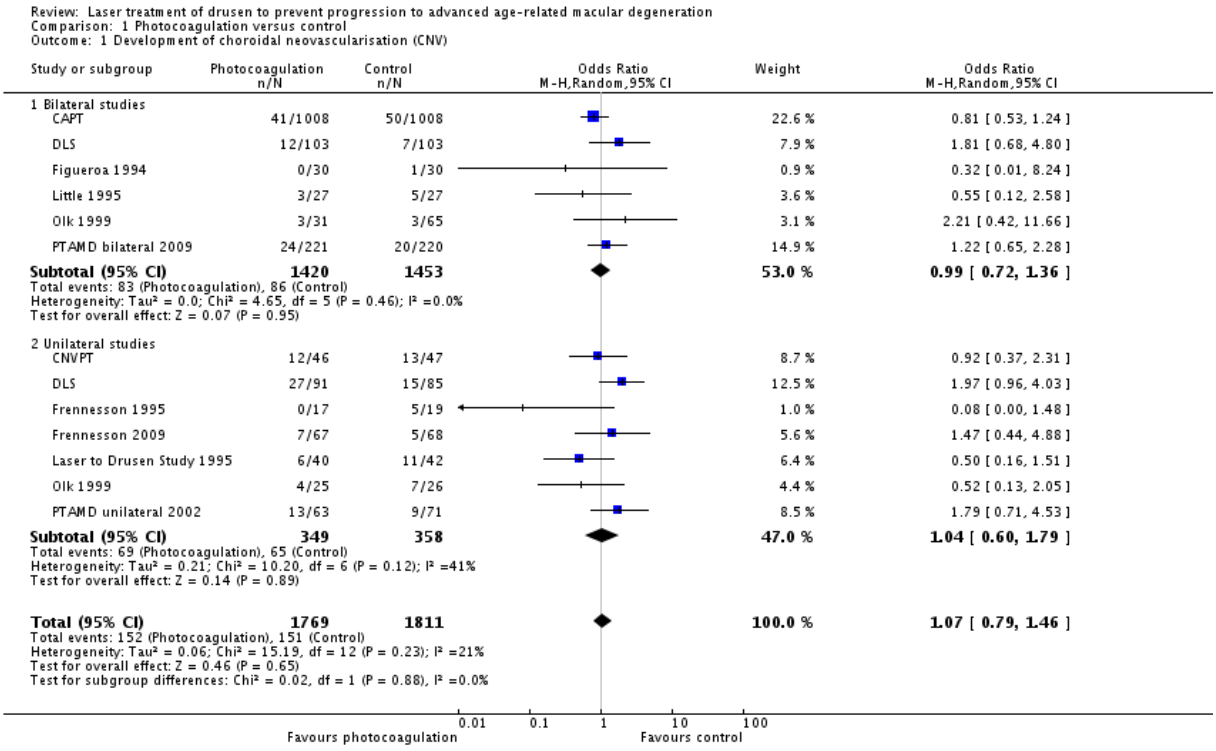
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
2009, PTAMD unilateral 2002)								

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 (i^2=89%)

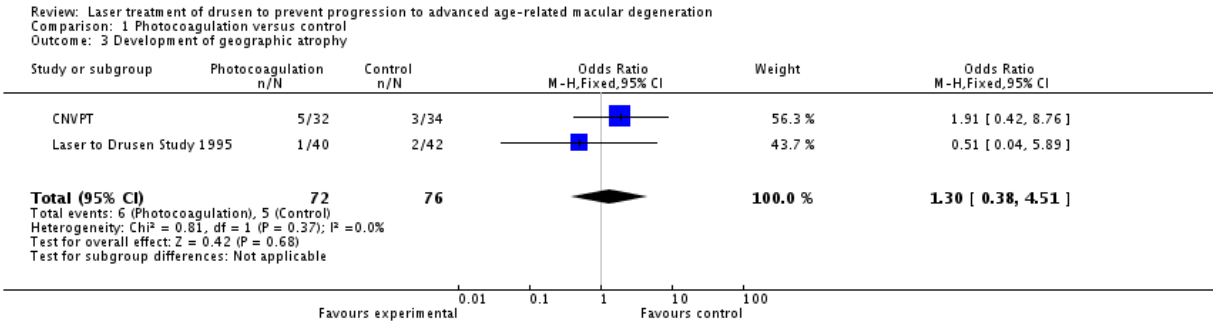
*Converted from odds ratios reported in included Cochrane review

Meta-analysis: Laser treatment of drusen to prevent progression to advanced AMD

Development of CNV[1]

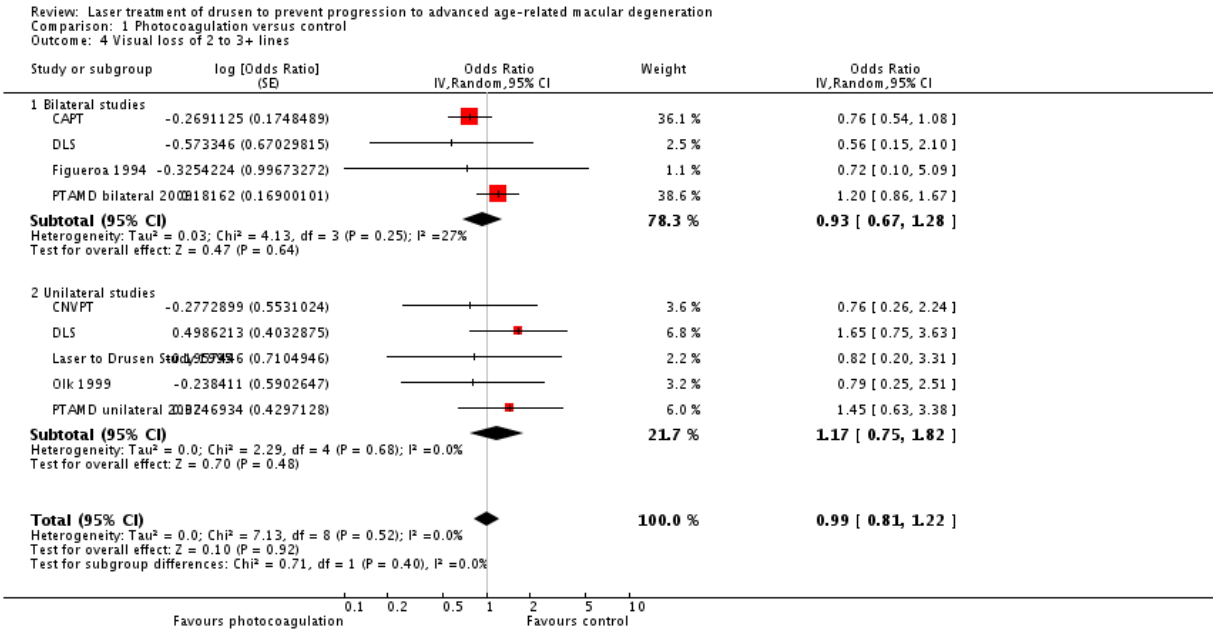


Development of geographic atrophy

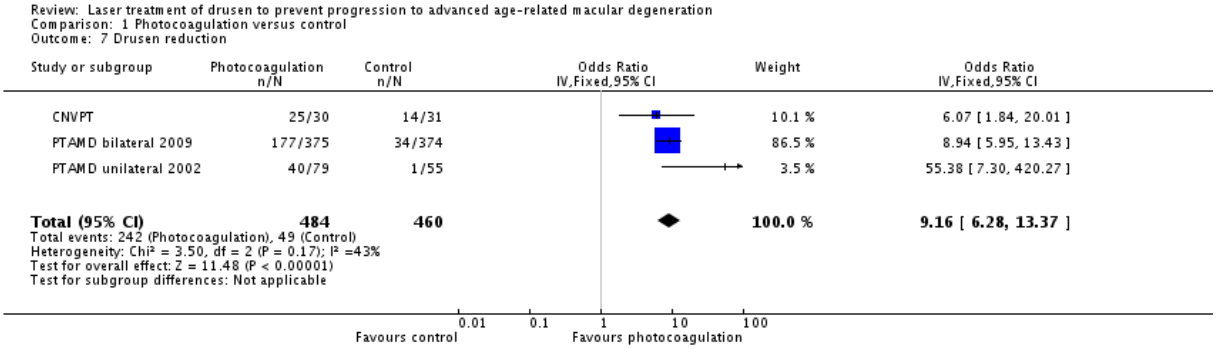


[1] Meta-analysis were extracted form the Cochrane review, and odds ratios were reported in Cochrane review.

Visual acuity (loss of at least 2 lines)



Drusen reduction



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

Multivitamin supplement

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Progression to Late AMD (wet active or geographic atrophy)								
3 (AREDS 2001, CARMA 2013, CARMIS 2011)	RCT	Not serious	Not serious	Not serious	Serious[1]	2140	RR* 0.77 (0.67 ,0.89)	MODERATE
Progression to Late AMD (wet active)								
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious[1]	1206	RR* 0.67 (0.53, 0.85)	MODERATE
Progression to Late AMD (geographic atrophy)								
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious[1]	1206	RR* 0.76 (0.53 ,1.10)	MODERATE
Progression to visual loss (loss of 3 or more lines on logMAR chart)								
1 (ARED 2001)	RCT	Not serious	N/A	Not serious	Serious[1]	1807	RR* 0.83 (0.70,0.97)	MODERATE
Quality of lifeassessed with change in NEI-VFQ score (higher scores indicate better QoL)								
1 (CARMIS 2011)	RCT	Serious[2]	N/A	Not serious	Serious[1]	110	MD=12.30 (4.24, 20.36)	LOW
Visual acuity (logMAR score) (lower values indicate better vision)								
4 (AMDSG 1996, CARMA 2013, Bartlett 2007, Veterans LAST study 2004)	RCT	Serious[2]	Not serious	Not serious	Serious[1]	979	SMD=0.01[2] (-0.12,0.13)	LOW

[2] 0.01 logMAR= - 0.5 letters, 95%CI -6.5 to 6 letters

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

1. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
2. Downgraded for risk of bias (randomisation and allocation; blinding; incomplete outcome)

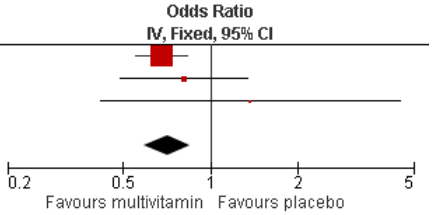
*Converted from odds ratios reported in included Cochrane review

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	Multivitamin Total	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
AREDS 2001 (1)	-0.3857	0.1041	904	903	83.7%	0.68 [0.55, 0.83]
CARMA 2013 (2)	-0.2107	0.2564	230	228	13.8%	0.81 [0.49, 1.34]
CARMIS 2011 (3)	0.3164	0.6036	103	42	2.5%	1.37 [0.42, 4.48]
Total (95% CI)			**1237**	**1173**	**100.0%**	**0.71 [0.59, 0.85]**

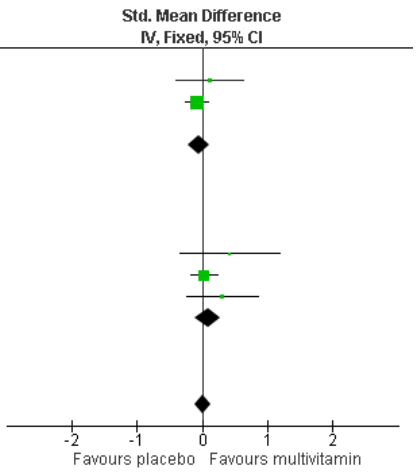
Heterogeneity: Chi² = 1.63, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 3.61 (P = 0.0003)



Footnotes
(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up
(2) Follow-up: 12 months
(3) Follow-up: 24 months

Mean visual acuity

Study or Subgroup	Multivitamin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.5.1 Mean visual acuity at end of study								
AMDSG 1996 (1)	0.33	0.41	35	0.29	0.24	24	5.9%	0.11 [-0.41, 0.63]
CARMA 2013 (2)	79.7	8.9	243	80.4	9.8	250	50.7%	-0.07 [-0.25, 0.10]
Kaiser 1995 (3)	-0.67	0.2	9	-0.6	0.22	11	0.0%	-0.32 [-1.20, 0.57]
Subtotal (95% CI)			**278**			**274**	**56.5%**	**-0.06 [-0.22, 0.11]**
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%								
Test for overall effect: Z = 0.65 (P = 0.52)								
1.5.2 Change in visual acuity								
Bartlett 2007 (4)	0.01	0.07	20	-0.02	0.07	10	2.7%	0.42 [-0.35, 1.18]
CARMA 2013	-0.1	7	172	-0.3	7.7	173	35.5%	0.03 [-0.18, 0.24]
Veterans LAST study 2004 (5)	-0.03	0.24	25	-0.14	0.44	27	5.3%	0.30 [-0.24, 0.85]
Subtotal (95% CI)			**217**			**210**	**43.5%**	**0.08 [-0.11, 0.28]**
Heterogeneity: Chi² = 1.61, df = 2 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.87 (P = 0.38)								
Total (95% CI)			**495**			**484**	**100.0%**	**0.01 [-0.12, 0.13]**
Heterogeneity: Chi² = 3.23, df = 4 (P = 0.52); I² = 0%								
Test for overall effect: Z = 0.09 (P = 0.93)								
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 18 months
(2) Number of letters read at 4m at 12 months
(3) Study eye: Snellen acuity (expressed as decimal) at six months,
(4) Study eye: Change in logMAR score (EDTRS chart) over 9 months
(5) Right eye: Change in logMAR score (converted from Snellen decimal acuity) over 12 months

Lutein/zeaxanthin

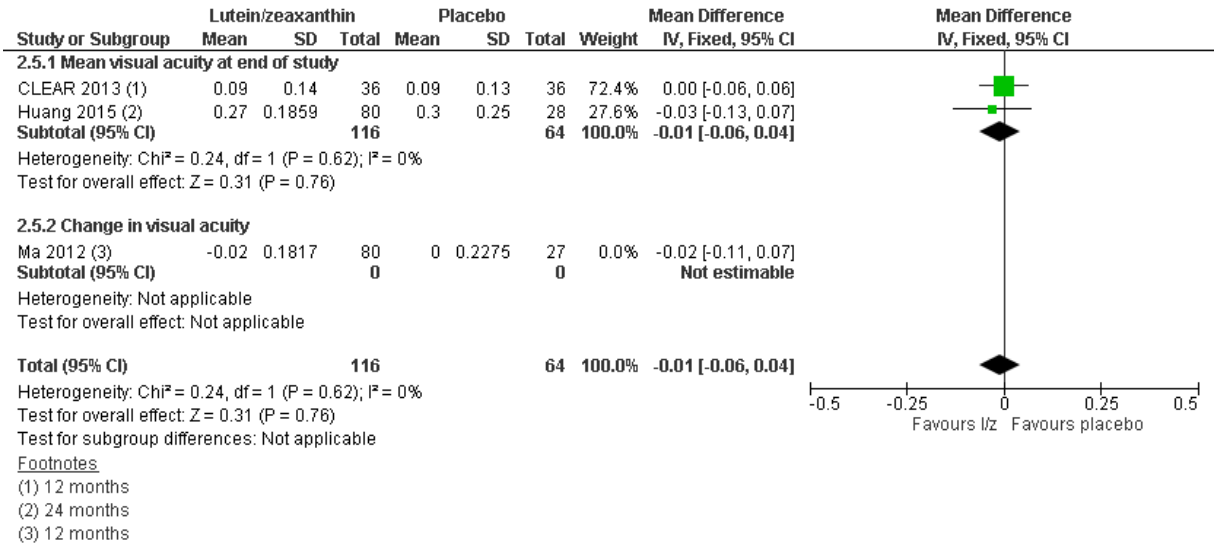
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Progression to Late AMD (wet active or geographic atrophy)								
1 (AREDS2 2013)	RCT	Not serious	N/A	Serious[1]	Serious[2]	6891	RR 0.94 (0.87, 1.01)	LOW
Progression to Late AMD (wet active)								
1 (AREDS2 2013)	RCT	Not serious	N/A	Serious[1]	Serious[2]	6891	RR 0.92 (0.84,1.02)	LOW
Progression to Late AMD (geographic atrophy)								
1 (AREDS2 2013)	RCT	Not serious	N/A	Serious[1]	Serious[2]	6891	RR 0.92 (0.80 ,1.05)	LOW
Quality of lifeassessed with change in NEI-VFQ score (higher scores better)								
1 (Huang 2015)	RCT	Not serious	N/A	Not serious	Serious[2]	108	MD 1.48 (-5.53 , 8.49)	MODERATE
Visual acuity (logMAR score) (lower values better)								
2 (CLEAR 2013, Huang 2015)	RCT	Not serious	Not serious	Not serious	Not Serious	180	MD -0.01[3] (-0.06, 0.04)	HIGH

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

Meta-analysis: Lutein and zeaxanthin

Distance visual acuity mean (logMAR)



Study or Subgroup	Lutein/zeaxanthin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.5.1 Mean visual acuity at end of study								
CLEAR 2013 (1)	0.09	0.14	36	0.09	0.13	36	72.4%	0.00 [-0.06, 0.06]
Huang 2015 (2)	0.27	0.1859	80	0.3	0.25	28	27.6%	-0.03 [-0.13, 0.07]
Subtotal (95% CI)			**116**			**64**	**100.0%**	**-0.01 [-0.06, 0.04]**
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 0.31 (P = 0.76)								
2.5.2 Change in visual acuity								
Ma 2012 (3)	-0.02	0.1817	80	0	0.2275	27	0.0%	-0.02 [-0.11, 0.07]
Subtotal (95% CI)			**0**			**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: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 0.31 (P = 0.76)								
Test for subgroup differences: Not applicable								

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

Zinc supplement

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

1. Although there were risk of bias due to incomplete outcome date 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%)

*Converted from odds ratios reported in included Cochrane review

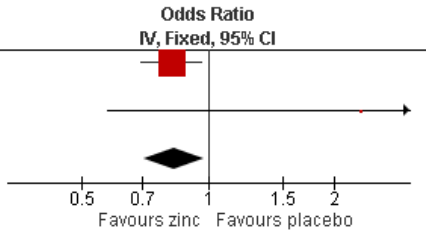
[4] -0.09logMAR=+4.5 letters, 95%CI: -11.5 to 20.5

Meta-analysis: Zinc supplements

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

Study or Subgroup	log[Odds Ratio]	SE	Zinc Total	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
AREDS 2001 (1)	-0.1985	0.0843	1792	1848	98.6%	0.82 [0.70, 0.97]
Holz 1993 (2)	-0.6931	1.1533	28	30	0.0%	0.50 [0.05, 4.79]
Stur 1996 (3)	0.8391	0.7073	37	41	1.4%	2.31 [0.58, 9.26]
Total (95% CI)			**1829**	**1889**	**100.0%**	**0.83 [0.71, 0.98]**

Heterogeneity: Chi² = 2.12, df = 1 (P = 0.15); I² = 53%
Test for overall effect: Z = 2.20 (P = 0.03)

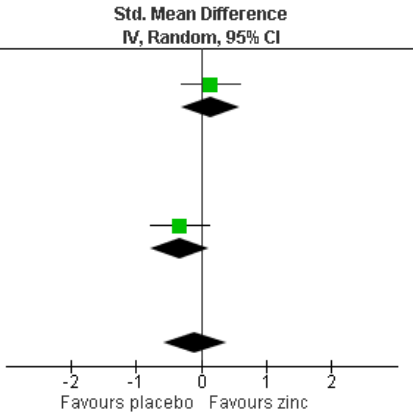


Footnotes
(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up
(2) By person: "new exudative or dry macular lesions" over 12 to 24 months
(3) Study eye: incidence of exudative AMD over 24 months

Visual acuity

Study or Subgroup	Zinc Mean	Zinc SD	Zinc Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.5.1 Mean visual acuity at end of study								
Stur 1996 (1)	0.05	0.12	37	0.03	0.14	41	50.3%	0.15 [-0.29, 0.60]
Subtotal (95% CI)			**37**			**41**	**50.3%**	**0.15 [-0.29, 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.51)								
3.5.2 Change in visual acuity								
Newsome 1988 (2)	4.1	6.2	40	7.1	10.95	37	49.7%	-0.34 [-0.79, 0.11]
Subtotal (95% CI)			**40**			**37**	**49.7%**	**-0.34 [-0.79, 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.47 (P = 0.14)								
Total (95% CI)			**77**			**78**	**100.0%**	**-0.09 [-0.57, 0.39]**

Heterogeneity: Tau² = 0.07; Chi² = 2.29, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Chi² = 2.29, df = 1 (P = 0.13), I² = 56.3%



Footnotes
(1) Study eye: LogMAR score (Bailey-Lovie chart) at 24 months
(2) Study eye: Change in number of correct letters (EDTRS chart) 19 to 24 months

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?

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Blurred vision											
1 (Hesselund)	Prospective cohort	1,683	83% (80, 86%)	26% (24, 29%)	**LR+**	1.12 (1.07, 1.18)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
					LR-	0.65 (0.53, 0.80)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
Central dark spot											
1 (Hesselund)	Prospective cohort	1,683	46% (42, 50%)	68% (65, 71%)	**LR+**	1.45 (1.28, 1.64)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
					LR-	0.79 (0.72, 0.86)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
Metamorphosia											
1 (Hesselund)	Prospective cohort	1,683	51% (47, 55%)	60% (57, 63%)	**LR+**	1.27 (1.13, 1.41)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
					LR-	0.80 (0.75, 0.91)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
Micropsia											
1 (Hesselund)	Prospective cohort	1,683	10% (8, 113%)	89% (87, 91%)	**LR+**	0.88 (0.65, 1.20)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
					LR-	1.01 (0.98, 1.05)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
Dyschromatopsia											

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Hesselund)	Prospective cohort	1,683	18% (15, 22%)	89% (87, 90%)	**LR+**	1.62 (1.27, 2.05)	Very serious[1]	N/A	Serious[2]	Serious[3]	VERY LOW
					LR-	0.92 (0.88, 0.96)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
Sudden onset											
1 (Hesselund)	Prospective cohort	1,683	36% (32, 40%)	73% (70, 75%)	**LR+**	1.31 (1.13, 1.51)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
					LR-	0.88 (0.82, 0.95)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
Worsening of symptoms											
1 (Hesselund)	Prospective cohort	1,683	62% (58, 66%)	46% (43, 49%)	**LR+**	1.15 (1.05, 1.25)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW
					LR-	0.83 (0.73, 0.94)	Very serious[1]	N/A	Serious[2]	Not serious	VERY LOW

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

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?

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Diagnostic tools for use in detecting drusen											
Fundus photograph (grading criteria) to detect drusen											
1 (Lim 2002)	Prospective case series	33 eyes (17 people)	50.0% (9.4, 90.6)	98.4% (79.4, 99.9)	LR+	32.00 (1.64, 626.10)	Very serious[1,2]	N/A	Not serious	Serious[3]	VERY LOW
					LR-	0.51 (0.16, 1.58)	Very serious[1,2]	N/A	Not serious	Serious[3]	VERY LOW
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 (Mokwa 2013)	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 serious[4]	N/A	Not serious	Not serious	LOW
					LR-	0.14 (0.07, 0.28)	Very serious[4]	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 (Mokwa 2013)	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 serious[4]	N/A	Serious[5]	Not serious	VERY LOW
					LR-	0.10 (0.04, 0.21)	Very serious[4]	N/A	Serious[5]	Not serious	VERY LOW

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Diagnostic tools for use in detecting dry age-related macular degeneration											
Fundus photography vs clinical assessment to detect geographic atrophy											
1 (Pirbhai 2004)	Prospective case series	223 eyes (118 people)	66.0% (51.5, 78.0)	86.9% (81.1, 91.2)	LR+	5.05 (3.27, 7.78)	Serious[4]	N/A	Serious[5]	Not serious	LOW
					LR-	0.39 (0.26, 0.59)	Serious[4]	N/A	Serious[5]	Serious[3]	VERY LOW
Diagnostic tools for use in detecting pigment epithelial detachment(PED)											
Fundus photography vs clinical assessment to detect pigment epithelial detachment(PED)											
1 (Pirbhai 2004)	Prospective case series	223 eyes (118 people)	40.0% (21.44, 61.6)	94.1% (90.5, 96.9)	LR+	6.77 (3.14, 14.58)	Serious[4]	N/A	Serious[5]	Not serious	LOW
					LR-	0.64 (0.45, 0.91)	Serious[4]	N/A	Serious[5]	Serious[3]	VERY LOW
Fundus photograph (grading criteria) to detect pigment epithelial detachment (PED)											
1 (Lim 2002)	Prospective cross sectional	33 eyes(17 people)	50.0% (18.5, 81.5)	98.2% (77.0, 99.9)	LR+	28.00 (1.63, 481. 68)	Very serious[1,2]	N/A	Not serious	Serious[3]	VERY LOW
					LR-	0.51 (0.24, 1.07)	Very serious[1,2]	N/A	Not serious	Serious[3]	VERY LOW
Diagnostic tools for use in detecting neovascular age-related macular degeneration/choroidal neovascularation											
Optical coherence tomography vs fluorescein angiography to detect choroidal neovascularisation (see figure 1, meta analysis)											
4 (Talks 2007; Wilde 2015; Mathew 2014; Mokwa 2013)	Retrospective	30/128/ 476/130 /120 eyes (759 people)	93.5% (72.2, 98.8)	89.2% (74.8, 95.8)	LR+	6.72 (3.19, 14.14)	Serious[4]	Serious[6]	Not serious	Not serious	LOW
					LR-	0.08 (0.02, 0.30)	Serious[4]	Serious[6]	Not serious	Not serious	LOW

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
3 (Do 2012; Padnick 2012; Sandhu 2005)	Prospective cohort	295 eyes: 87/77/131 eyes (282 people)	84.4% (49.0, 96.8)	75.0% (48.6, 90.5)	LR+	3.27 (1.27, 8.43)	Serious[7]	Serious[6]	Not serious	Serious[3]	VERY LOW
					LR-	0.21 (0.05, 0.96)	Serious[7]	Serious[6]	Not serious	Serious[3]	VERY LOW
Optical coherence tomography angiography vs fluorescein angiography to detect choroidal neovascularisation											
1 (De Carlo 2015)	Retrospective	30 eyes (24 people)	50.0% (20, 80%)	90.9% (70, 97.9%)	LR+	5.50 (1.24, 24.5)	Serious[4]	N/A	Not serious	Serious[3]	LOW
					LR-	0.55 (0.27, 1.11)	Serious[4]	N/A	Not serious	Serious[3]	LOW
Optical coherence tomography angiography vs fluorescein angiography to detect neovascular AMD											
1 (Gong 2016)	Retrospective	86 eyes (53 people)	86.5% (76.1-94.3%)	79.4% (64.5-91.0%)	**LR+**	4.20 (2.15,8.20)	Serious[8]	N/A	Not serious	Not serious	MODERATE
					LR-	0.17 (0.08, 0.35)	Serious[8]	N/A	Not serious	Not serious	MODERATE
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)											
1 (Talks 2007)	Retrospective audit	111 people	93.5% (87.9, 97.4)	96.2% (81.5,100.0)	LR+	24.31 (1.60, 368.47)	Very serious[4,8]	N/A	Not serious	Serious[3]	VERY LOW
					LR-	0.07 (0.03, 0.14)	Very serious[4,8]	N/A	Not serious	Not serious	LOW
Fundus photography vs Fluorescein angiography to detect neovascular age-related macular degeneration – cohort study											
1 (Maberley 2005)	Prospective cross sectional	74 eyes (40 people)	97.0% (89.1, 99.9)	86.6% (74.8, 95.1)	LR+	7.23 (3.31, 15.77)	Serious[9]	N/A	Not serious	Not serious	MODERATE
					LR-	0.03 (0.01, 0.24)	Serious[9]	N/A	Not serious	Not serious	MODERATE

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Fundus photography vs Fluorescein angiography to detect neovascular age-related macular degeneration – case-control study											
1 (Mokwa 2013)	Retrospective case control	120 eyes (66 people)	77.9% (67.4, 86.9)	98.1% (93.0, 100)	LR+	40.53 (5.79, 283,49)	Very serious[4]	N/A	Not serious	Not serious	LOW
					LR-	0.22 (0.14, 0.35)	Very serious[4]	N/A	Not serious	Not serious	LOW
Fundus photography + clinical information vs Fluorescein angiography to detect neovascular age-related macular degeneration											
1 (Maberley 2005)	Prospective cross sectional	74 eyes (40 people)	98.5% (92.7, 100)	76.2% (62.4, 87.6)	LR+	4.14 (2.41, 7.12)	Serious[9]	N/A	Not serious	Not serious	MODERATE
					LR-	0.02 (0.00, 0.30)	Serious[9]	N/A	Not serious	Not serious	MODERATE
Fundus photography vs clinical assessment to detect neovascular age-related macular degeneration											
1 (Pirbhai 2004)	Prospective case series	223 eyes (118 people)	82.1% (43.3, 89.5)	79.1% (72.0, 85.5)	LR+	3.94 (2.81, 5.53)	Serious[4]	N/A	Not serious	Not serious	MODERATE
					LR-	0.23 (0.14, 0.36)	Serious[4]	N/A	Not serious	Not serious	MODERATE
Fundus photograph (grading criteria) to detect CNV											
1 (Lim 2002)	Prospective cross sectional	33 eyes (17 people)	64.0% (44.7, 81.2)	87.5% (59.0, 99.6)	LR+	5.12 (0.80, 32.78)	Very serious[1,2]	N/A	Not serious	Serious[3]	VERY LOW
					LR-	0.41 (0.23, 0.74)	Very serious[1,2]	N/A	Not serious	Serious[3]	VERY LOW
Fundus autofluoresence vs fluorescein angiography to detect CNV											
1 (Cachulo 2011)	Prospective cohort	58 eyes (52 people)	88.2% (63.2, 97.0)	94.3% (79.8, 98.6)	LR+	15.44 (3.98, 59,97)	Very serious[1,8]	N/A	Not serious	Not serious	LOW
					LR-	0.12 (0.03, 0.46)	Very serious[1,8]	N/A	Not serious	Not serious	LOW

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
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 serious[4,8]	Not serious	Not serious	Serious[3]	VERY LOW
					LR-	0.49 (0.36, 0.66)	Very serious[4,8]	Not serious	Not serious	Serious[3]	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 serious[4]	N/A	Not serious	Not serious	LOW
					LR-	0.06 (0.02, 0.23)	Very serious[4]	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)	Serious[1]	N/A	Not serious	Serious	LOW
					LR-	0.73 (0.55, 0.98)	Serious[1]	N/A	Not serious	Not serious	MODERATE
Flash fundus camera-based indocyanine green angiography vs confocal scanning laser ophthalmoscope-based iIndocyanine green angiography (grading criteria) to detect polypoidal choroidal vasculopathy (PCV)											
1 (Cheung et al. 2015)	Retrospective comparative	241 eyes (230 people)	78.6% (71.2, 85.2)	87.3% (80.5, 92.8)	LR+	6.18 (3.76. 10.16)	Very serious[4,2]	N/A	Not serious	Not serious	LOW
					LR-	0.24 (0.18, 0.34)	Very serious[4,2]	N/A	Not serious	Not serious	LOW
Fundus photography vs clinical assessment to detect choroidal neovascular membrane											
1 (Pirbhai 2004)	Prospective case series	223 eyes	89.2% (81.9, 93.8)	85.7% (77.9, 91.1)	LR+	6.24 (3.95, 9.87)	Serious[4]	N/A	Not serious	Not serious	MODERATE

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
		(118 people)			LR-	0.13 (0.07, 0.22)	Serious[4]	N/A	Not serious	Not serious	MODERATE

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

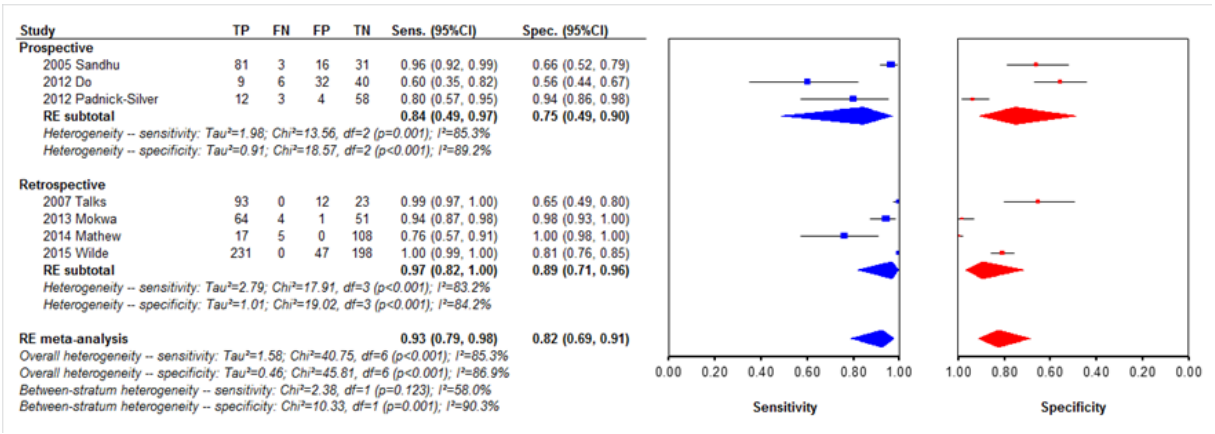
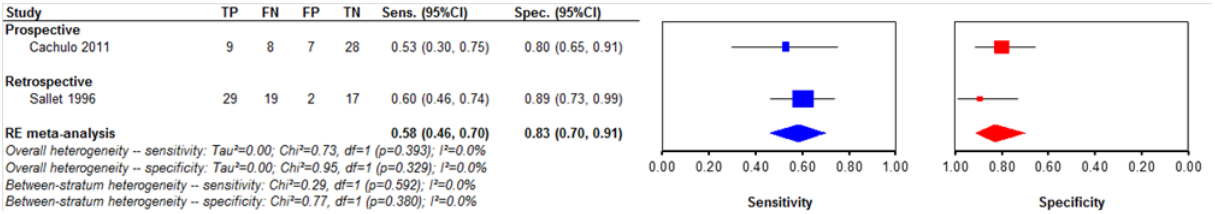


Figure 2: Indocyanine green angiography vs fluorescein angiography to detect CNV



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?

Models of care

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Diagnosis agreement between optometrist and ophthalmologist								
Rapid access referral form (history finding (reduction in vision, distortion, central scotoma)								
1 (Muen 2011)	Prospective cohort	Serious[1]	N/A	Not serious	Serious[2]	54 (referrals)	57.4% (n=31) (44.2 to 70.6%)	VERY LOW
Rapid access referral form (accuracy in detecting Exudative AMD)								
1 (Muen 2011)	Prospective cohort	Serious[1]	N/A	Not serious	Serious[2]	54 (referrals)	37.0% (n=20) (24.1 to 50.0%)	VERY LOW
Vignette (no. of correctly classified nAMD)								
1 (Reeves 2016)	RCT	Serious[3]	N/A	Not serious	Not serious	2016 images	RR 1.01 (0.99 to 1.04)	MODERATE
Vignette (no. of correctly classified as reactivated)								
1 (Reeves 2016)	RCT	Serious[3]	N/A	Not serious	Not serious	994 images	RR 0.93 (0.88 to 0.97)	MODERATE
Vignette (no. of error occurred that classified as reactivated)								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
1 (Reeves 2016)	RCT	Serious[3]	N/A	Not serious	Very serious[4]	994 images	RR 1.09 (0.77 to 1.54)	VERY LOW
Vignette (no. of correctly classified as quiescent/suspicious)								
1(Reeves 2016)	RCT	Serious[3]	N/A	Not serious	Not serious	1022 images	RR 1.09 (1.06 to 1.11)	MODERATE
Number of patients referred								
Routine eye examination (patients with no symptoms being referred for AMD)								
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	1084	2.7% (n=30) (1.7 to 3.7%)	VERY LOW
Routine eye examination (patients with symptoms being referred for AMD)								
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	2992	5.1% (n=153) (4.3 to 6.0%)	VERY LOW
Routine eye examination (number of patients without symptoms vs no. of patients with symptoms being referred for AMD)								
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	4,076	RR 0.54 (0.37 to 0.80)	VERY LOW
Teleretinal screening								
1 (Chasan 2014)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	1935	24.0% (n=465) (22.1 to 25.9%)	VERY LOW
Electronically referrals resulting in a hospital appointment (with vs without attached images)								
1 (Goudie 2014)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	1152 (referrals)	RR 0.73 (0.73 to 0.79)	VERY LOW
Anti-VEGF injection administration								
% of injection cycles were uninterrupted injection (by retinal specialist)								
1 (Engman 2011)	Chart review	Serious[7]	N/A	Not serious	Not serious	175 injection cycles	76.5% (70.2 to 82.8%)	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Visual acuity								
Community vs hospital follow-up								
% of people had a gain of 15 ETDRS letters								
1 (Tschuor 2013)	Prospective cohort	Serious[8]	N/A	Not serious	Serious[5]	62 people (72 eyes)	RR 9.00 (1.17 to 68.92)	VERY LOW
% of eyes had a loss of 15 letters								
1 (Tschuor 2013)	Prospective cohort	Serious[8]	N/A	Not serious	Very serious[4]	62 people (72 eyes)	RR 0.43 (0.12 to 1.59)	VERY LOW
Visual change over 6 visits, ETDRS letters (higher values better)								
1 (Tschuor 2013)	Prospective cohort	Serious[8]	N/A	Not serious	Serious[5]	62 people (72 eyes)	MD 1.20 (-4.00 to 6.40)	VERY LOW
Improvement in service provision (after vs before)								
% of patients had a gain of 15 letter or more								
1 (Ghazala 2013)	Audit study	Serious[7,8]	N/A	Not serious	Serious[5]	113	RR 3.53 (1.05 to 11.85)	VERY LOW
% patients maintained vision								
1 (Ghazala 2013)	Audit study	Serious[7,8]	N/A	Not serious	Serious[5]	113	RR 1.11 (0.94 to 1.45)	VERY LOW
Chronic model of care vs usual care								
VA at the end of follow-up (12 months) (ETDRS letters; higher scores indicate better vision)								
1 (Markun 2015)	RCT	Serious[10]	N/A	Not serious	Serious[5]	169	MD -4.80 letters (-11.31 to 1.71)	LOW
Teleconsultation network vs usual care								
VA after treatment (logMAR; lower scores indicate better vision)								
Azzolini 2013	Prospective cohort	Serious[8]	n/a	Not serious	Very serious[11]	360	MD -0.05	VERY LOW
Time interval (diagnosis interval, treatment interval)								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Improvement in service provision (after vs before)								
% of patients being referred to 1st assessment within 1 week								
1 (Ghazala 2013)	Audit study	Serious[7]	n/a	Not serious	Not serious	120	RR 2.14 (1.33 to 3.45)	VERY LOW
Teleophthalmology vs routine								
Time from referral to diagnosis (diagnostic image), days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Serious[13]	106	MD 4.5 (-2.80 to 11.80)	LOW
Time from referral to treatment, days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Serious[13]	106	MD 8.7 (-5.29 to 22.69)	LOW
Time to recurrence, days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Serious[13]	63	MD -4.2 (-47.77 to 39.15)	LOW
Recurrence to treatment, days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Not serious	63	MD 13.5 (9.0 to 18.2)	MODERATE
Teleconsultation network vs usual care (time from first visit to treatment), days								
1 (Azzolini 2013)	Prospective cohort	Serious[8]	N/A	Not serious	Not serious	360	MD=-23.20 (-23.66 to -22.74)	VERY LOW

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

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

Evidence on association between diagnosis/treatment time and visual acuity

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Time interval and visual acuity								
Visual acuity score change (longest vs shortest time to treatment)								
1 (Arias 2009)	Retrospective cohort	Serious[1]	N/A	Serious[2]	Not serious	100	Correlation r 0.3534 (p=0.0004)	VERY LOW
Visual acuity change treatment and baseline, BCVA decimal (higher values better)								
1 (Rauch 2012) (symptoms duration <1m)	Case series	Serious[1]	N/A	Serious[2]	Not serious	22	MD 0.09 (-0.03 to 0.21)	VERY LOW
1 (Rauch 2012) (symptoms duration 1-6m)	Case series	Serious[1]	N/A	Serious[2]	Not serious	17	MD 0.07 (-0.04 to 0.18)	VERY LOW
1 (Rauch 2012) (symptoms duration >6m)	Case series	Serious[1]	N/A	Serious[2]	Not serious	6	MD 0.06 (-0.05 to 0.19)	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
VA change between diagnosis and treatment (longer vs shorter treatment waiting time) (ETDRS letters; higher scores indicate better vision)								
1 (Real 2013)	Case series	Serious[1]	N/A	Serious[2]	Serious[3]	78	MD -7.55[5] (-12.94 to -2.16)	VERY LOW
1 (Rasmussen 2015)	Case series	Serious[1]	N/A	Serious[2]	Serious[3]	1185	MD -4.24[6] (-5.93 to -2.55)	VERY LOW
% of people had a gain of more than 2 lines (10 letters)								
Longer (>21 w) vs shorter (<7 w) delay from symptom to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[3]	109	RR 0.53 (0.29 to 1.00)	VERY LOW
Longer (>3w) vs shorter (<1w) delay from diagnosis to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[5]	134	RR 0.77 (0.41 to 1.43)	VERY LOW
% of people had a loss of more than 2 lines (10 letters)								
Longer (>21w) vs shorter (7w) delay from symptom to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[5]	109	RR 1.19 (0.43 to 3.31)	VERY LOW
Longer (>3w) vs shorter (<1w) delay from diagnosis to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[5]	134	RR 0.84 (0.34 to 2.10)	VERY LOW
Vison loss during latency (ETDRS letters; higher scores indicate better vision)								
1 (Muether 2013)	Non-randomised trial	Serious[6]	N/A	Serious[2]	Not serious	83	MD -1.79 (-3.71 to 0.13)	VERY LOW
Vision loss with time delay (between initial referral and assessment and treatment								

[5] Time difference=long waiting time (averge 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.

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
1 (Oliver-Fermandez 2005)	Case series	Serious[8]	N/A	Serious[2]	Not serious	38	Coefficient -0.00674 (a decrease of 0.00674 logMAR with every one day delay) (-0.010 to -0.003)	VERY LOW
Time delay in first treatment, days								
People with visual loss vs no visual loss								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Not serious	69	MD 7.6 (1.07 to 14.13)	VERY LOW
People had a loss of more than 1 line vs no visual loss more than 1 line								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Serious[7]	69	MD 11.0 (-0.27 to 22.27)	VERY LOW
Time days in recurrent treatment, days								
People with visual loss vs no visual loss								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Serious[7]	21	MD 5.4 (-3.54 to 14.34)	VERY LOW
People had a loss of more than 1 line vs no visual loss more than 1 line								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Not serious	21	MD 32.0 (10.05 to 53.93)	VERY LOW

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

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Vision-related quality of life (NEI-VFQ-25) (higher values better)								
Chronic model of care vs usual care								
Markun 2015	RCT	Serious[1]	N/A	Not serious	Serious[2]	169	MD 2.10 (-0.96 to 5.16)	LOW
1.Downgraded one level for open label study 2. Downgraded oned level for confidence interal 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)

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Depression at 6 months (better indicated by lower values)								
1 (Rovner 2007)	RCT	Serious[1]	N/A	Not serious	Serious[2]	206	RR 0.74 (0.44, 1.24)	LOW
Mean difference in Hamilton Depression Rating Score (6 months) (better indicated by lower values)								
1 (Rovner 2007)	RCT	Serious[1]	N/A	Not serious	Serious[3]	206	MD 0.01 (-1.14, 1.16)	LOW
No. of lost activities at 6 months (better indicated by lower values)								
1 (Rovner 2007)	RCT	Serious[1]	N/A	Not serious	Serious[2]	206	RR 0.66 (0.45, 0.98)	LOW
Mean difference in NEI VFQ-17 score at 6 months (better indicated by higher values)								
1 (Rovner 2007)	RCT	Serious[1]	N/A	Not serious	Serious[2]	206	MD 1.48 (-1.05, 4.01)	LOW

1. Downgraded one level for single-masked design
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
3. Downgraded one level for non-significant result

Problem solving treatment vs supportive therapy

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Targeted Vision Function at 6 months (better indicated by lower values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 0.03	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
							(-0.21, 0.27)	
Activities Inventory at 6 months (better indicated by lower values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 0.01 (-0.29, 0.31)	VERY LOW
NEI-VFQ total score at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Very serious[3]	141	MD 1.60 (-2.71, 5.91)	VERY LOW
NEI-VFQ QoL Social Functioning at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 2.53 (-4.19, 9.25)	VERY LOW
NEI-VFQ QoL Mental Health (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 5.50 (-1.14, 12.14)	VERY LOW
NEI-VFQ QoL Role Functioning at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD -0.70 (-6.17, 4.77)	VERY LOW
NEI-VFQ QoL Dependency at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 6.10 (-1.55, 13.75)	VERY LOW
Control strategies: selective primary control at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Not serious	141	MD -1.00 (-1.79, -0.21)	LOW
Control strategies: compensatory primary control at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 0.20 (-1.40, 1.80)	VERY LOW
Control strategies: selective secondary control at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 0.10	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
							(-1.30, 1.50)	
Control strategies: compensatory secondary control at 6 months (better indicated by higher values)								
1 (Rovner 2013)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 1.20 (-0.02, 2.42)	VERY LOW

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

Psychosocial intervention programme vs usual care

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Mean difference Positive affect (PANAS) score at 7-9 weeks follow up (better indicated by lower values)								
1 (Birk 2004)	Non-randomised trial	Very serious[1]	N/A	Not serious	Serious[2]	22	MD -0.12 (-0.58, 0.34)	VERY LOW
Mean difference negative affect (PANAS) score at 7-9 weeks (better indicated by higher values)								
1 (Birk 2004)	Non-randomised trial	Very serious[1]	N/A	Not serious	Not serious	22	MD 0.53 (0.13, 0.93)	LOW
Mean difference geriatric depression scale (GDS) score at 7-9 weeks (better indicated by higher values)								
1 (Birk 2004)	Non-randomised trial	Very serious[1]	N/A	Not serious	Not serious	22	MD 1.45 (0.31, 2.59)	LOW
Mean difference activities of daily living score at 7-9 weeks (better indicated by higher values)								
1 (Birk 2004)	Non-randomised trial	Very serious[1]	N/A	Not serious	Not serious	22	MD 6.10 (1.18, 11.02)	LOW
Mean difference perceived autonomy at 7-9 weeks (better indicated by lower values)								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
1 (Birk 2004)	Non-randomised trial	Very serious[1]	N/A	Not serious	Serious[2]	20	MD -1.80 (-3.62, 0.02)	VERY LOW
Mean difference active problem orientation score at 7-9 weeks (better indicated by lower values)								
1 (Birk 2004)	Non-randomised trial	Very serious[1]	N/A	Not serious	Serious[2]	20	MD -3.50 (-7.22, 0.22)	VERY LOW

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

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Mean difference total profile of mood states (POMS) score at 6 months (better indicated by lower values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[2]	214	MD -11.78 (-18.43, -5.13)	LOW
Mean difference NEI-VFQ-25 total score at 6 months (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[2]	213	MD 2.63 (0.23, 5.03)	LOW
Mean difference AMD self-efficacy scale total score at 6 months (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Not serious	213	MD 5.64 (2.11, 9.17)	MODERATE
Mean difference in POMS total score at 6 months among those with depression at baseline (better indicated by lower values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Not serious	51	MD -26.24 (-42.40, -10.08)	MODERATE
Mean difference in total NEI-VFQ-25 at 6 months among those with depression at baseline (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[2]	50	MD 6.12 (0.12, 12.12)	LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Mean difference in POMS total score at 6 months among those without depression at baseline (better indicated by lower values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[2]	162	MD 2.67 (-3.76, 9.10)	LOW
Mean difference in total NEI-VFQ-25 at 6 months among those without depression at baseline (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[2]	161	MD -0.83 (-3.29, 1.63)	LOW
Mean difference in AMD self-efficacy score at 6 months amongst those with depression at baseline (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Not serious	66	MD 9.87 (2.31, 17.43)	MODERATE
Mean difference in AMD self-efficacy score at 6 months amongst those without depression at baseline (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[3]	161	MD 1.42 (-2.22, 5.06)	LOW
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)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[3]	32	MD -1.82 (-4.40, 0.56)	LOW
Mean difference Duke Social Support Index-11 score at 6 months among those with depression at baseline (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[3]	32	MD 5.72 (-3.37, 14.81)	LOW
Mean difference life orientation test at 6-months amongst those with depression at baseline (better indicated by higher values)								
1 (Brody 2002)	RCT	Serious[1]	N/A	Not serious	Serious[3]	32	MD -0.87 (-3.72, 1.98)	LOW

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

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

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Mean difference total profile of mood states (POMS) score at 6 months (better indicated by lower values)								
1 (Rovner 2014)	RCT	Very serious[1]	N/A	Not serious	Serious[2]	188	RR 0.59 (0.29, 1.17)	VERY LOW

1. Downgraded two levels for single masked; differences in baseline characteristics between those who did and did not complete follow-up
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference

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

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
ADL step scale 0-9, rate "0" as least dependence , 28 months follow-up (health education programme vs individual programme)								
1 (Eklund 2008)	RCT	Very serious[1,6]	N/A	Not serious	Serious[2]	131	RR 1.78 (1.03, 3.08)	VERY LOW
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)								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Not serious[4]	124	MD 0.04 (-0.02, 0.11)	HIGH
Self rated restriction score, enhanced low vision rehabilitation by community care worker vs conventional low vision rehabilitation								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious[3]	130	MD -0.00 (-0.06, 0.06)	MODERATE
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)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious[3]	150	MD -0.72 (-2.30, 0.87)	MODERATE
Melbourne low vision activities of daily living, part 1 (performance of ADL dependent on vision), standard prisms vs placebo (higher values better)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious[3]	155	MD 0.45 (-1.11, 2.01)	MODERATE
Melbourne low vision activities of daily living, part 2 (self assessment of ADL performance), custom prisms vs placebo (higher values better)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious[3]	150	MD -0.14 (-0.67, 0.39)	MODERATE

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
Melbourne low vision activities of daily living, part 2 (self assessment of ADL performance), standard prisms vs placebo (higher values better)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious[3]	155	MD -0.07 (-0.59, 0.45)	MODERATE
Melbourne low vision activities of daily living index (part 2), 8 weeks (eccentric viewing vs control) (higher values better)								
1 (Vukicevic 2009)	RCT	Serious[5]	N/A	Not serious	Not serious	48	MD 6.25 (3.72, 8.78)	MODERATE

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 baise 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

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
Perceived security in the performance of daily activities, 28 months follow-up (health education programme vs individual programme)								
1 (Eklund 2004)	RCTs	Very serious[1,3]	N/A	Not serious	Not serious	131	MD[2] 0.42 (0.19, 0.65)	LOW

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

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
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)								
1 (Eklund 2008)	RCT	Very serious[1,3]	N/A	Not serious	Very serious[2]	131	RR 0.97 (0.52, 1.83)	VERY LOW
Visual acuity logMAR at 1 year (prisms correction vs control) (lower values indicate better vision)								
1 (Parodi 2004)	RCT	Serious[1]	N/A	Not serious	Not serious	28	MD -0.40 (-0.52, -0.28)	MODERATE
Visual acuity at 3 month (prism spectacle vs placebo)								
Visual acuity logMAR at 3 month (custom prism spectacle vs placebo) (lower values indicate better vision)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Not serious	150	MD -0.02 (-0.07, 0.02)	HIGH
Visual acuity logMAR at 3 month (standard prism spectacle vs placebo) (lower values indicate better vision)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Not serious	155	MD -0.02 (-0.06, 0.03)	HIGH
Visual acuity logMAR at 8-week follow up (eccentric viewing vs control) (lower values indicate better vision)								
1 (Vukicevic 2009)	RCT	Serious[4]	N/A	Not serious	Not serious	48	MD -0.38 (-0.47, -0.29)	MODERATE

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

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
Vision-specific QoL, 12 months follow-up (enhanced low vision rehabilitation by rehabilitation officer or community worker vs conventional low vision rehabilitation)								
Vision specific quality of life score (enhanced low vision rehabilitation vs conventional low vision rehabilitation) (higher scores indicate poorer QoL)								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious[1]	124	MD 0.06 (-0.17, 0.30)	MODERATE
Vision specific quality of life score, enhanced low vision rehabilitation by community worker vs conventional low vision rehabilitation (higher scores indicate poorer QoL)								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious[1]	130	MD -0.05 (-0.29, 0.18)	MODERATE
NEI-VFQ-25 at 3 months								
NEI-VFQ-25, custom prisms vs placebo (higher scores indicate better QoL)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious[2]	150	MD 1.25 (-1.98, 4.47)	MODERATE
NEI-VFQ-25, standard prisms vs placebo (higher scores indicate better QoL)								
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious[2]	155	MD 0.29 (-2.90, 3.49)	MODERATE

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

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
SF-36, percentage of people reporting "excellent" health 28 month follow-up (health promotion programme vs individual programme)								

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
1 (Eklund 2008)	RCT	Serious[1]	N/A	Not serious	Serious[2]	131	RR 6.68 (0.83, 53.93)	LOW
SF-36, percentage of people reporting "bad" health 28 month follow-up (health education programme vs individual programme)								
1 (Eklund 2008)	RCT	Vert serious[1,4]	N/A	Not serious	Serious[2]	131	RR 0.56 (0.31, 0.98)	VERY LOW
SF-36 (enhanced low vision rehabilitation by rehabilitation officer or community worker vs conventional low vision rehabilitation), 12 months follow-up								
SF-36, physical health (enhanced low vision rehabilitation by rehabilitation officer vs conventional low vision rehabilitation) (higher values indicate better HRQoL)								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious[2]	124	MD -6.05 (-10.2, -1.91)	MODERATE
SF-36, physical (enhanced low vision rehabilitation by community worker vs conventional low vision rehabilitation) (higher values indicate better HRQoL)								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious[3]	130	MD -2.27 (-6.29, 1.76)	MODERATE
SF-36, mental health (enhanced low vision rehabilitation by rehabilitation officer vs conventional low vision rehabilitation) (higher values indicate better HRQoL)								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious[2]	124	MD -4.04 (-7.44, -0.65)	MODERATE
SF-36, physical (enhanced low vision rehabilitation by community worker vs conventional low vision rehabilitation) (higher values indicate better HRQoL)								
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious[3]	130	MD -1.48 (-4.69, 1.73)	MODERATE

1. Downgraded one level for masking of study populations not reported in the study
2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
3. Downgraded one level for non-significant effect
4. Downgraded one level for high dropout rate (75%)

Reading performance

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
Reading rate, at 3-months (prism spectacle vs control) (higher scores indicate better reading)								
1 (Smith 2005)	RCTs	Not serious	N/A	Not serious	Serious[1]	250	MD 6.50 (-7.84, 20.84)	MODERATE

1. Downgraded one level for non-significant effect

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

Outcomes	**Illustrative comparative risks*** **(95% CI)**		**Relative effect**	**No of Participants**	**Quality of the evidence**
	Corresponding risk	**Assumed risk**	**(95% CI)**	**(studies)**	**(GRADE)**
	Intervention (photodynamic therapy with verteporfin)	Control (photodynamic therapy with 5% dextrose in water)			
Loss of 3 or more lines (15 or more letter) visual acuity ETDRS at 24 months	487 per 1000 (445 to 536)	609 per 1000	RR 0.8, 0.73 to 0.89	1381 (4 studies)	⊕⊕⊕⊖ Moderate[1]
Loss of 6 or more lines (30 or more letter) visual acuity ETDRS at 24 months	220 per 1000 (176 to 276)	333 per 1000	RR 0.66, 0.55 to 0.78	1381 (4 studies)	⊕⊕⊕⊕ High
Gain of 3 or more lines (15 or more	80 per 1000	36 per 1000	RR 2.59,	941	⊕⊕⊕⊕

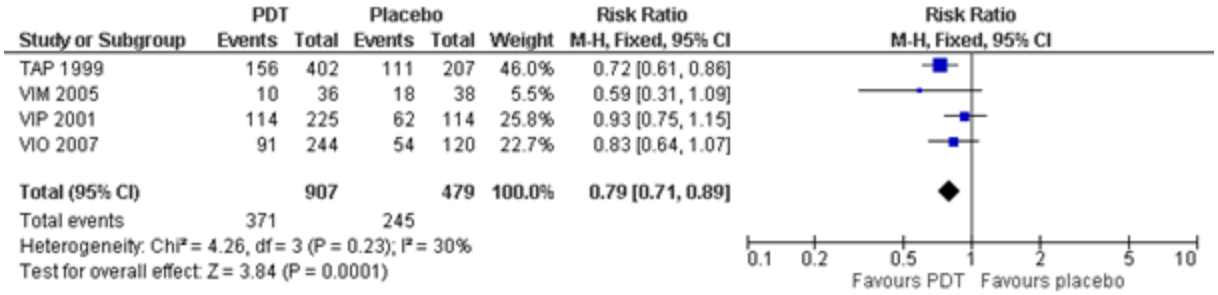
letter) visual acuity ETDRS at 24 months	(43 to 151)		1.33 to 5.06	(3 studies)	High
Adverse effects: acute severe visual acuity decrease (follow-up: 7 days)	11 per 1000 (3 to 48)	3 per 1000	RR 3.75 0.87 to 16.12	1075 (3 studies)	⊕⊕⊕⊖ Moderate[1]
Adverse effects: visual disturbance	270 per 1000	170 per 1000	RR 1.56 1.21 to 2.01	1075 (3 studies)	⊕⊕⊕⊖ Moderate[1]
Adverse effects: injection site	120 per 1000	60 per 1000	RR 1.36 0.50 to 3.71	1075 (3 studies)	⊕⊖⊖⊖ Very low[2]
Adverse effects: infusion-related back pain	20 per 1000 (6 to 70)	2 per 1000	RR 9.93 (2.82 to 35.02)	1439 (4 studies)	⊕⊕⊕⊕ High[3]
Adverse effects: allergic reactions	17 per 1000	19 per 1000	RR 0.94 (0.35 to 2.51)	948 (2 studies)	⊕⊕⊖⊖ Low[4]
Adverse effects: photosensitivity reactions	24 per 1000	3 per 1000	RR 2.73 (0.08 to 97.96)	948 (2 studies)	⊕⊖⊖⊖ Very low[2]

*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.

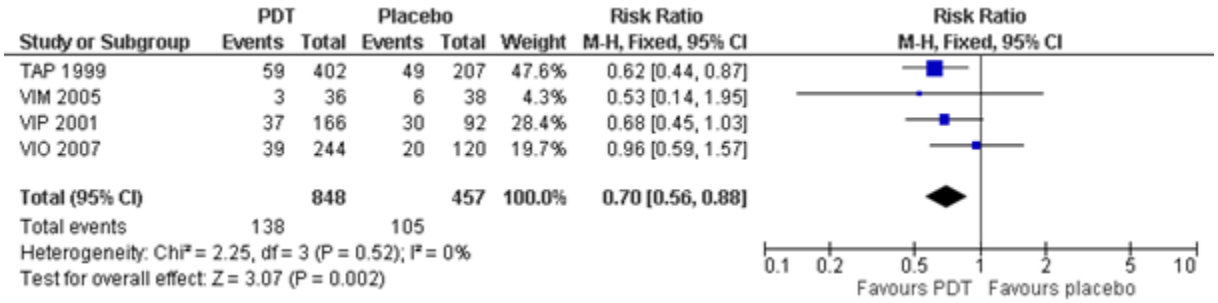
Visual acuity

One year

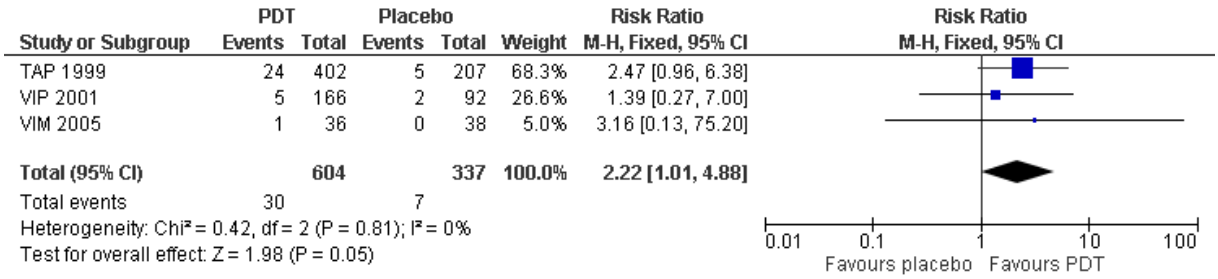
Visual acuity (loss of 3 or more lines ETDRS)



Visual acuity (loss of 6 or more lines ETDRS)



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

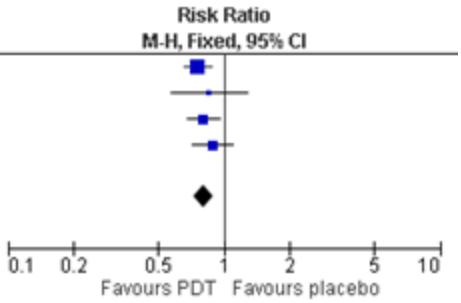


Two years

Visual acuity (loss of 3 or more line ETDRS)

Study or Subgroup	PDT Events	PDT Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
TAP 1999	189	402	129	207	45.2%	0.75 [0.65, 0.88]
VIM 2005	17	32	23	37	5.7%	0.85 [0.57, 1.29]
VIP 2001	121	225	76	114	26.8%	0.81 [0.68, 0.96]
VIO 2007	114	244	63	120	22.4%	0.89 [0.72, 1.11]
Total (95% CI)		**903**		**478**	**100.0%**	**0.80 [0.73, 0.89]**
Total events	441		291			

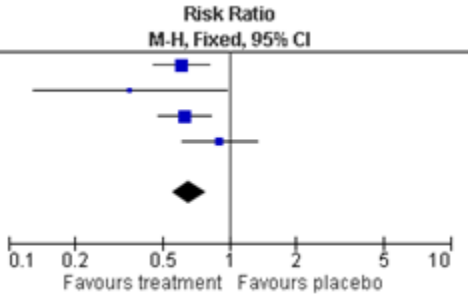
Heterogeneity: Chi² = 1.64, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 4.34 (P < 0.0001)



Visual acuity (loss of 6 or more lines ETDRS)

Study or Subgroup	Treatment Events	Treatment Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
TAP 1999	73	402	62	207	39.8%	0.61 [0.45, 0.81]
VIM 2005	4	32	13	37	5.9%	0.36 [0.13, 0.98]
VIP 2001	67	225	54	114	34.8%	0.63 [0.48, 0.83]
VIO 2007	55	244	30	120	19.5%	0.90 [0.61, 1.33]
Total (95% CI)		**903**		**478**	**100.0%**	**0.66 [0.55, 0.78]**
Total events	199		159			

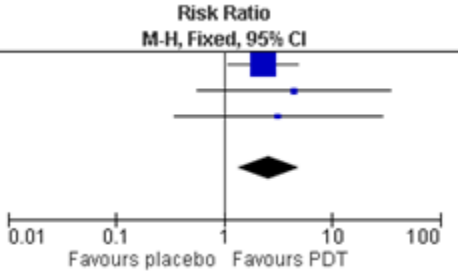
Heterogeneity: Chi² = 4.35, df = 3 (P = 0.23); I² = 31%
Test for overall effect: Z = 4.64 (P < 0.00001)



Visual acuity (gain of 3 or more lines ETDRS)

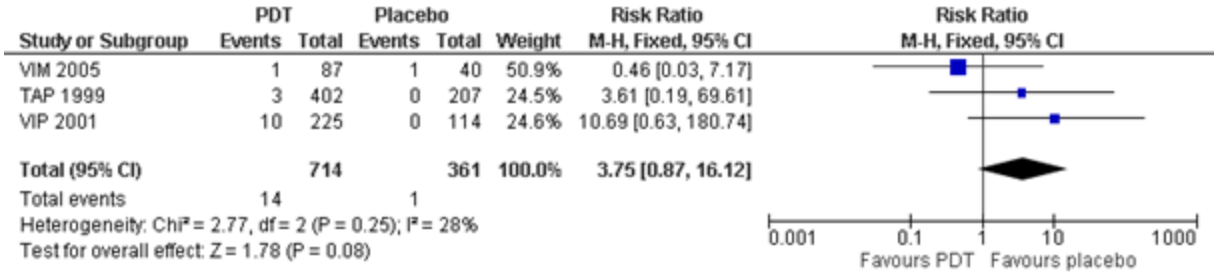
Study or Subgroup	PDT Events	PDT Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
TAP 1999	36	402	8	207	82.4%	2.32 [1.10, 4.89]
VIP 2001	8	166	1	92	10.0%	4.43 [0.56, 34.90]
VIM 2005	3	36	1	38	7.6%	3.17 [0.35, 29.06]
Total (95% CI)		**604**		**337**	**100.0%**	**2.59 [1.33, 5.06]**
Total events	47		10			

Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005)

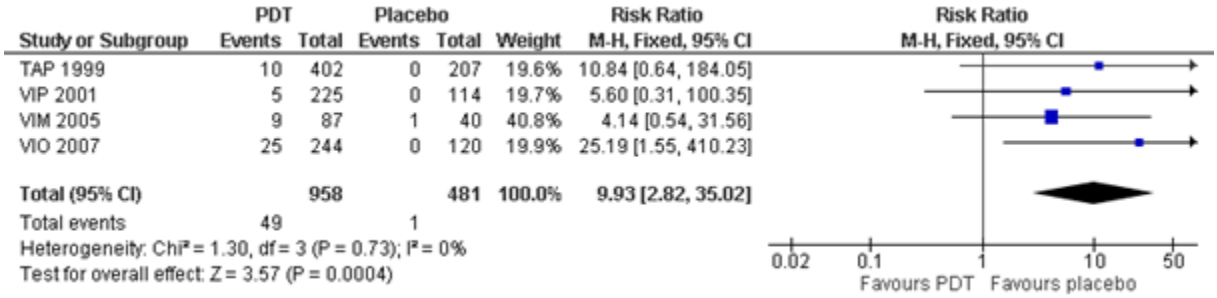


Adverse effects

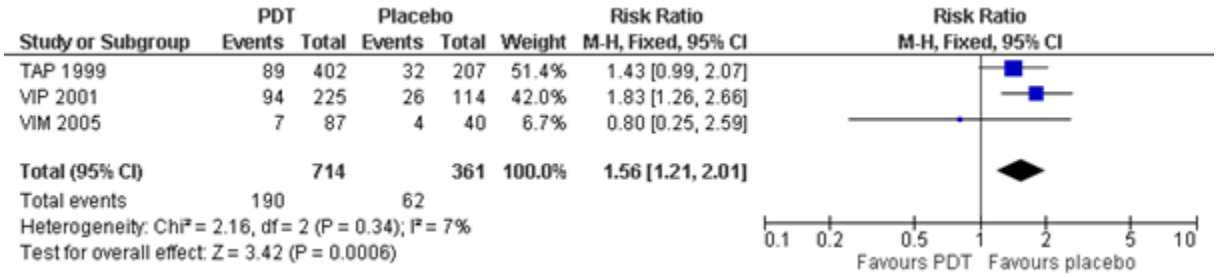
Acute severe visual acuity decrease



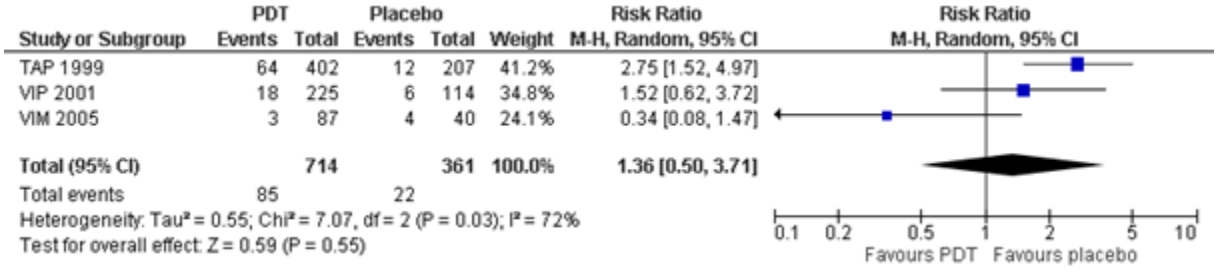
Infusion-related back pain



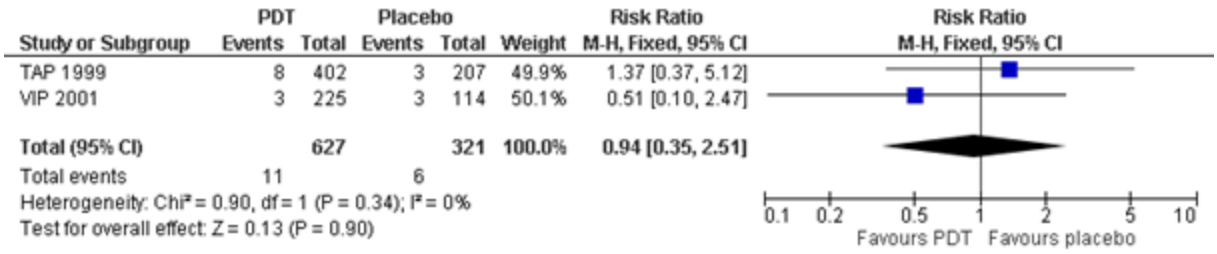
Visual disturbance



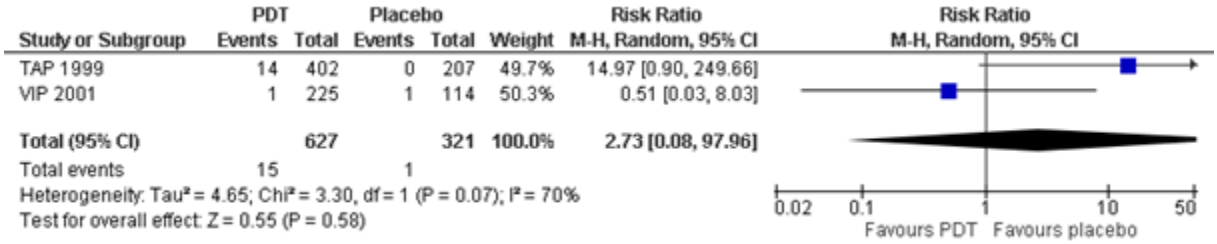
Injection site



Allergic reactions



Photosensitivity reactions



H.6.1.2 Bevacizumab vs control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants	Quality of the evidence	Comments
	Corresponding risk	**Assumed risk**	**(95% CI)**	**(studies)**	**(GRADE)**	
	Bevacizumab	Control				
Gain of 15 letters or more visual acuity at one year	293 per 1000 (92 to 937)	38 per 1000	RR 8.43 (2.65 to 26.80)	159 (2 studies)	⊕⊕⊕⊖ Moderate[1]	
Loss of fewer than 15 letters visual acuity at one year	896 per 1000 (763 to 1000)	700 per 1000	RR 1.32 (1.13 to 1.54)	159 (2 studies)	⊕⊕⊖⊖ Low[2]	
Mean change in visual acuity at one year (number of letters)	-	-	-	-	.	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

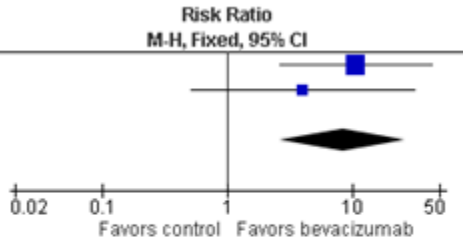
						letters on average
Serious systemic adverse events at one year	31 per 1000	15 per 1000	RR 2.03 (0.19 to 21.85)	131 (1 study)	⊕⊕⊖⊖ Low[3]	
Serious ocular adverse events at one year	169 per 1000	91 per 1000	RR 1.86 (0.73 to 4.74)	131 (1 study)	⊕⊕⊖⊖ Low[3]	

*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)

Study or Subgroup	Bevacizumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ABC 2010 (1)	21	65	2	66	66.5%	10.66 [2.60, 43.64]
Sacu 2009 (2)	4	14	1	14	33.5%	4.00 [0.51, 31.46]
Total (95% CI)		**79**		**80**	**100.0%**	**8.43 [2.65, 26.80]**
Total events	25		3			

Heterogeneity: Chi² = 0.61, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 3.61 (P = 0.0003)

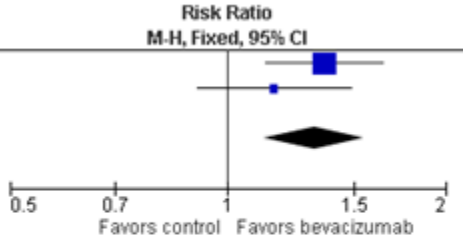


Footnotes
(1) Control group in the ABC study received standard therapy including pegaptanib injections, verteporfin PDT, or sham injection
(2) Control group in the Sacu 2009 study received verteporfin photodynamic therapy plus same day 4 mg intravitreal triamcinolone...

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

Study or Subgroup	Bevacizumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ABC 2010 (1)	59	65	44	66	77.7%	1.36 [1.13, 1.64]
Sacu 2009 (2)	14	14	12	14	22.3%	1.16 [0.91, 1.48]
Total (95% CI)		**79**		**80**	**100.0%**	**1.32 [1.13, 1.54]**
Total events	73		56			

Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 3.44 (P = 0.0006)



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)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants	Quality of the evidence	Comments
	Corresponding risk	**Assumed risk**	**(95% CI)**	**(studies)**	**(GRADE)**	
	Ranibizumab	Control				
Gain of 15 letters or more visual acuity at one year	230 per 1000 (93 to 566)	59 per 1000	RR 3.25 (1.44 to 7.33)	1415 (4 studies)	⊕⊕⊕⊖ Moderate[1]	
Loss of fewer than 15 letters visual acuity at one year	934 per 1000 (861 to 1000)	610 per 1000	RR 1.51 (1.41 to 1.63)	1415 (4 studies)	⊕⊕⊕⊕ High	
Mean change in visual acuity at one year (number of letters)	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)	The mean change across control groups ranged from a loss 10 to 16 letter	MD 17.81 (15.94 to 19.67)	1322 (3 studies)	⊕⊕⊕⊕ High	
Mean change in vision-related quality of life	The mean change in vision related quality of life in the ranibizumab groups ranged from 5 to 7 points	The mean change across control groups in vision-related quality of life scores ranged from -3 to 2 points	MD 6.69 (3.38 to 9.99)	1134 (2 studies)	⊕⊕⊕⊕ High	Using the NEI-VFQ questionnaire with a 10-point difference considered as being clinically meaningful.
Serious systemic adverse events at one year	Range of 0 to 55 per 1000	Range of 5 to 83 per 1000 for various systematic adverse events	Range of RR 0.17 (0.01 to 4.24) to 2.08 (0.23 to 18.45)	603 (2 studies)		
Myocardial infarction	10 per 1000	< 10 per 1000	RR 2.08 (0.23, 18.45)	603 (2 studies)	⊕⊕⊖⊖ Low[2]	

Stroke or cerebral infarction	< 10 per 1000	< 10 per 1000	RR 1.04 (0.09, 11.38)	603 (2 studies)	⊕⊕⊖⊖ Low[2]	
Treatment-emergent hypertension	60 per 1000	80 per 1000	RR 0.67 (0.36, 1.24)	603 (2 studies)	⊕⊕⊕⊖ Moderate[3]	
Non-ocular hemorrhage	60 per 1000	30 per 1000	RR 1.90 (0.78, 4.62)	603 (2 studies)	⊕⊕⊖⊖ Low[2]	
Serious ocular adverse events at one year	Range of 3 to 118 per 1000	Range of 0 to 68 per 1000 for various systematic adverse events	Range of RR 0.52 (0.03 to 8.25) to 2.71 (1.36 to 5.42)	603 (2 studies)		
Ocular inflammation	120 per 1000	40 per 1000	RR 2.71 (1.36 to 5.42)	603 (2 studies)	⊕⊕⊕⊕ High	
Elevated intraocular pressure (30 mmHg or more increase)	80 per 1000	30 per 1000	RR 2.22 (0.99, 4.98)	603 (2 studies)	⊕⊕⊕⊖ Moderate[3]	
Cataract	100 per 1000	70 per 1000	RR 1.48 (0.83, 2.66)		⊕⊕⊕⊖ Moderate[3]	

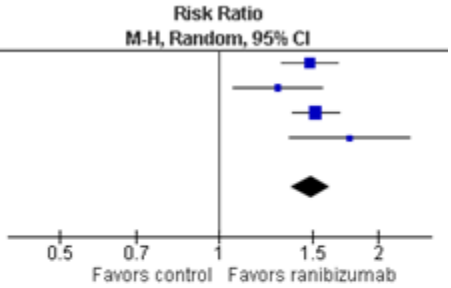
*The basis for the assumed risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
1. Downgrade one level for inconsistency due to heterogeneity (i2>=50%).
2. Downgrade two levels for serious imprecision.
3. Downgrade one level for imprecision.

One year

Visual acuity (loss of fewer than 15 letters)

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ANCHOR 2006 (1)	266	279	92	143	32.0%	1.48 [1.31, 1.68]
LAPTOP 2013	43	46	34	47	16.7%	1.29 [1.07, 1.57]
MARINA 2006 (2)	452	478	148	238	41.3%	1.52 [1.37, 1.68]
PIER 2008 (3)	105	121	31	63	9.9%	1.76 [1.36, 2.29]
Total (95% CI)		**924**		**491**	**100.0%**	**1.49 [1.37, 1.62]**
Total events	866		305			

Heterogeneity: Tau² = 0.00; Chi² = 4.04, df = 3 (P = 0.26); I² = 26%
Test for overall effect: Z = 9.00 (P < 0.00001)

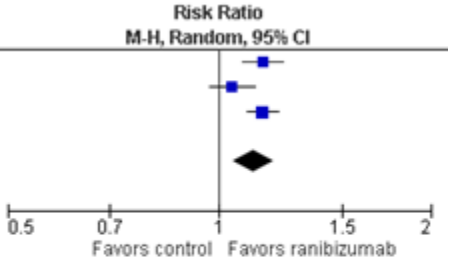


Footnotes
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
(3) Control group in the PIER study received sham injections

Visual acuity (loss of fewer than 30 letters)

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ANCHOR 2006 (1)	279	279	124	143	32.8%	1.15 [1.08, 1.23]
LAPTOP 2013	46	46	45	47	30.3%	1.04 [0.97, 1.12]
MARINA 2006 (2)	473	478	204	238	36.9%	1.15 [1.10, 1.22]
Total (95% CI)		**803**		**428**	**100.0%**	**1.12 [1.05, 1.19]**
Total events	798		373			

Heterogeneity: Tau² = 0.00; Chi² = 6.33, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 3.43 (P = 0.0006)

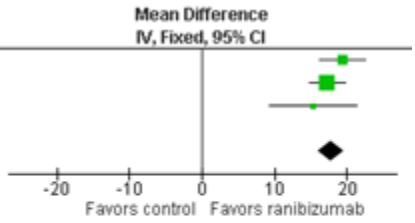


Footnotes
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections

Mean change in visual acuity (number of letters)

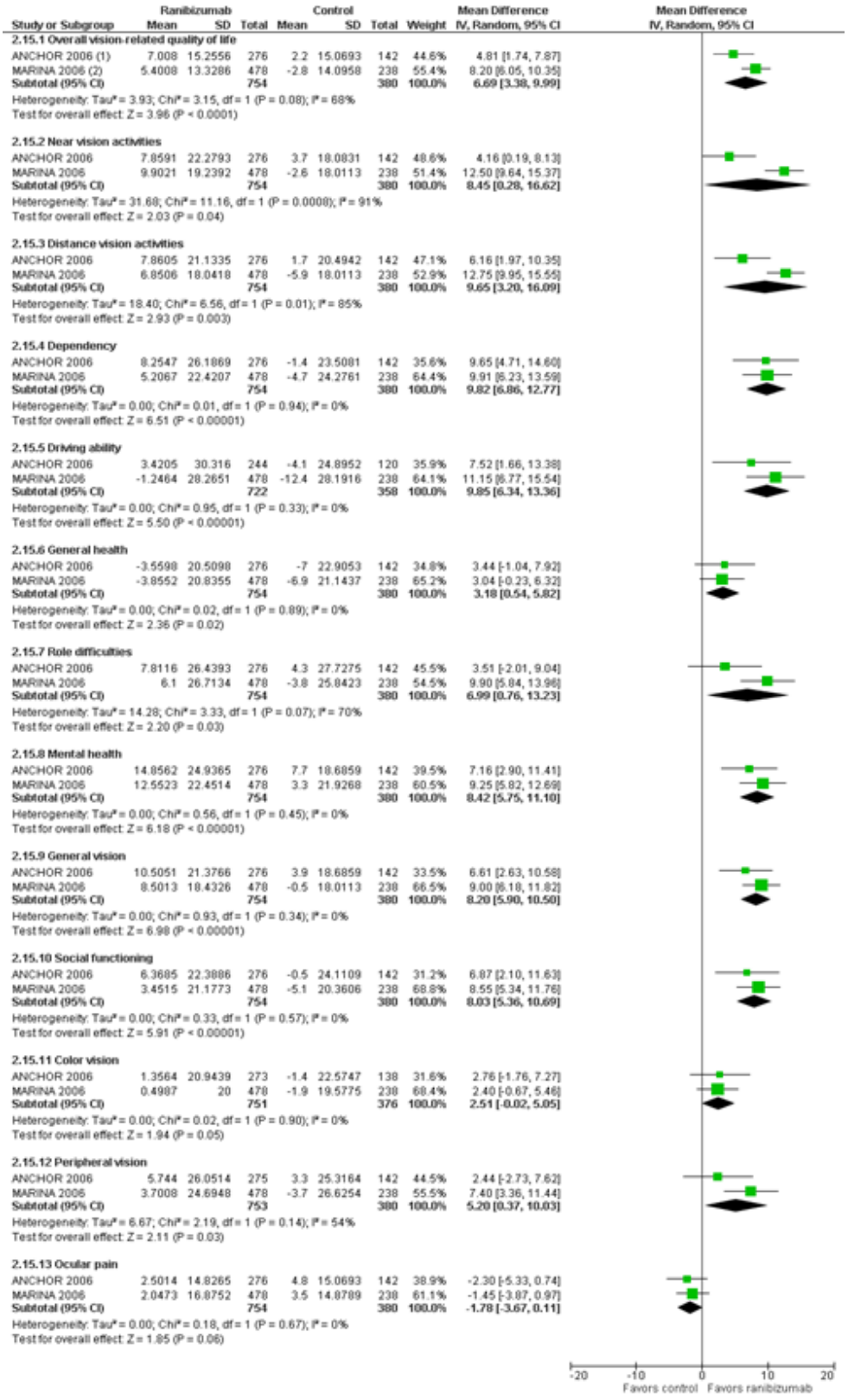
Study or Subgroup	Ranibizumab Mean	Ranibizumab SD	Ranibizumab Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
ANCHOR 2006 (1)	9.895	14.641	279	-9.5	16.4	143	34.1%	19.39 [16.20, 22.59]
MARINA 2006 (2)	6.8515	13.5705	478	-10.4	17	238	56.4%	17.25 [14.77, 19.73]
PIER 2008 (3)	-0.8942	14.0856	121	-16.3	22.3	63	9.5%	15.41 [9.35, 21.46]
Total (95% CI)			**878**			**444**	**100.0%**	**17.81 [15.94, 19.67]**

Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 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

Quality of life score



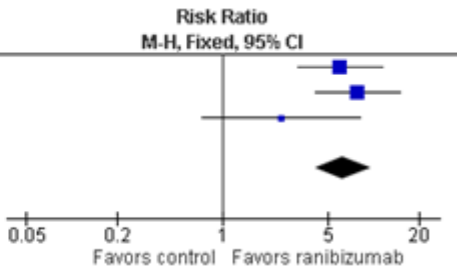
Footnotes
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections

Two years

Visual acuity (gain of 15 letters or more ETDRS)

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ANCHOR 2006 (1)	105	279	9	143	42.7%	5.98 [3.12, 11.46]
MARINA 2006 (2)	142	478	9	238	43.1%	7.86 [4.08, 15.13]
PIER 2008 (3)	14	121	3	63	14.2%	2.43 [0.73, 8.14]
Total (95% CI)		**878**		**444**	**100.0%**	**6.29 [4.09, 9.66]**
Total events	261		21			

Heterogeneity: Chi² = 2.84, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 8.39 (P < 0.00001)

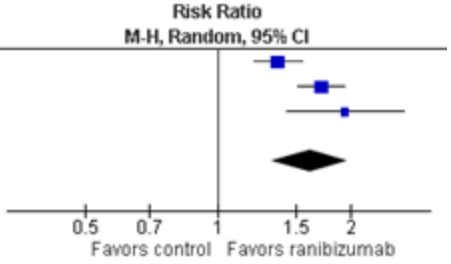


Footnotes
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
(3) Control group in the PIER study received sham injections

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

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ANCHOR 2006 (1)	251	279	94	143	38.9%	1.37 [1.21, 1.55]
MARINA 2006 (2)	435	478	126	238	39.0%	1.72 [1.52, 1.94]
PIER 2008 (3)	97	121	26	63	22.1%	1.94 [1.43, 2.64]
Total (95% CI)		**878**		**444**	**100.0%**	**1.62 [1.32, 1.98]**
Total events	783		246			

Heterogeneity: Tau² = 0.02; Chi² = 9.02, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 4.69 (P < 0.00001)

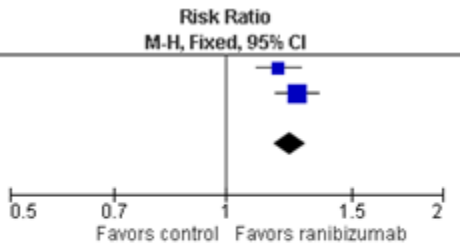


Footnotes
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections
(3) Control group in the PIER study received sham injections

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

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ANCHOR 2006 (1)	277	279	120	143	39.2%	1.18 [1.10, 1.27]
MARINA 2006 (2)	464	478	184	238	60.8%	1.26 [1.17, 1.35]
Total (95% CI)		**757**		**381**	**100.0%**	**1.23 [1.17, 1.29]**
Total events	741		304			

Heterogeneity: Chi² = 1.38, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 7.78 (P < 0.00001)

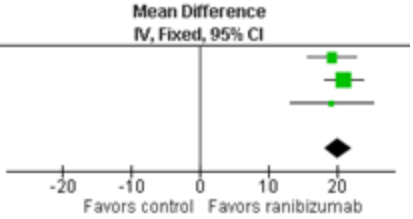


Footnotes
(1) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
(2) Control group in the MARINA study received sham injections

Mean change in visual acuity (number of letters)

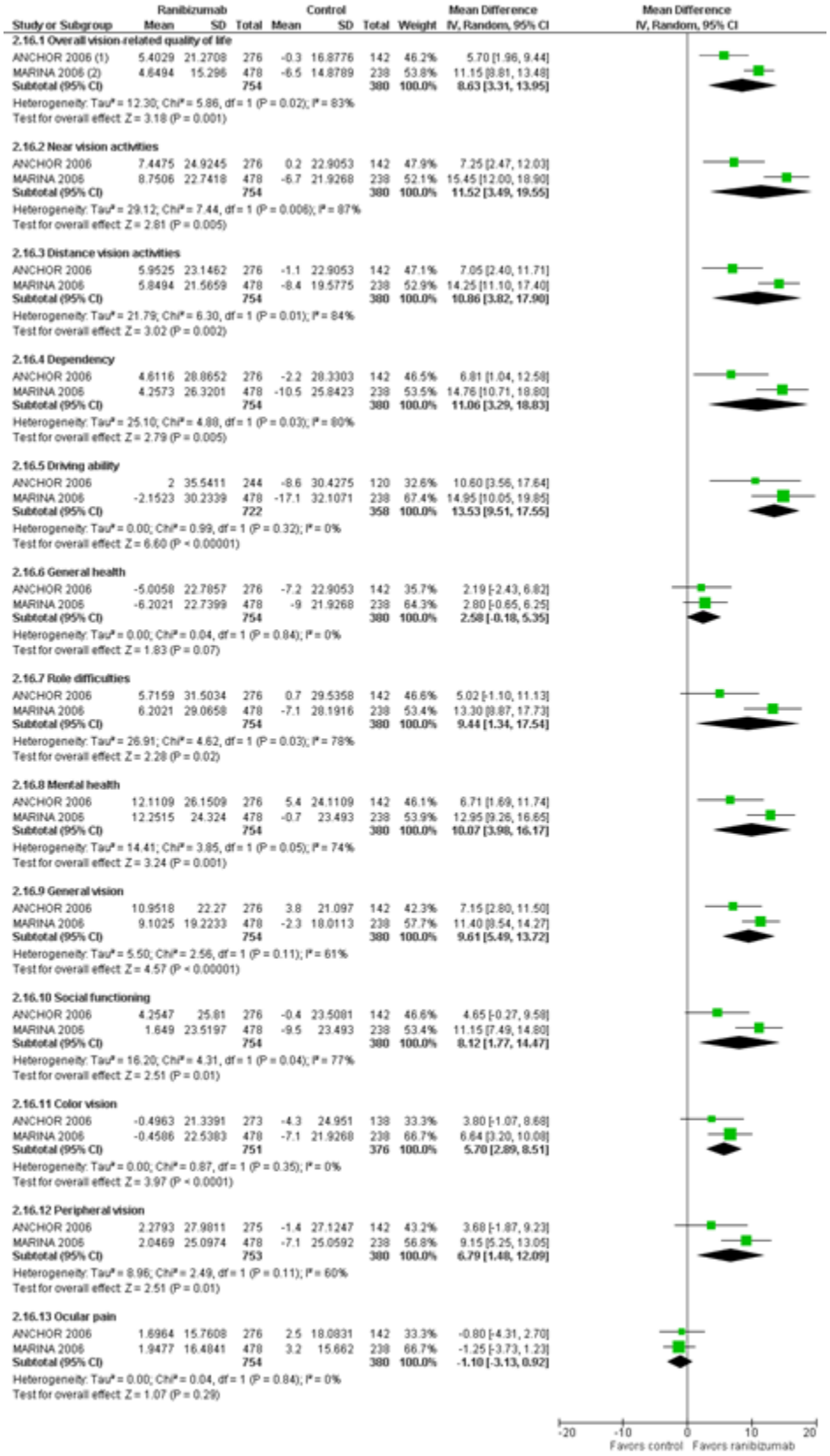
Study or Subgroup	Ranibizumab Mean	Ranibizumab SD	Ranibizumab Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
ANCHOR 2006 (1)	9.3953	16.3726	279	-9.8	17.6	143	34.5%	19.20 [15.73, 22.66]
MARINA 2006 (2)	6.0025	15.8608	478	-14.9	18.7	238	54.0%	20.90 [18.13, 23.67]
PIER 2008 (3)	-2.2504	14.9444	121	-21.4	21.8	63	11.5%	19.15 [13.14, 25.16]
Total (95% CI)			**878**			**444**	**100.0%**	**20.11 [18.08, 22.15]**

Heterogeneity: Chi² = 0.68, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 19.37 (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



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

H.6.1.4 Bevacizumab vs ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants	Quality of the evidence	Comments
	Corresponding risk	**Assumed risk**	**(95% CI)**	**(studies)**	**(GRADE)**	
	Ranibizumab	Bevacizumab				
Gain of 15 letters or more visual acuity at one year	238 per 1000 (202 to 279)	258 per 1000	RR 0.96 (0.85 to 1.08)	3101 (8 studies)	⊕⊕⊕⊕ High	
Loss of fewer than 15 letters visual acuity at one year	942 per 1000 (923 to 960)	942 per 1000	RR 1.00 (0.98 to 1.02)	2817 (7 studies)	⊕⊕⊕⊕ High	
Mean change in visual acuity at one year (number of letters)	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)	The mean change across ranibizumab groups ranged from gains of 3 to 8 letters	MD -0.48 (-1.47 to 0.51)	3101 (8 studies)	⊕⊕⊕⊕ High	
Serious systemic adverse events at one year	148 per 1000 (150 to 206)	175 per 1000 with at least one serious systemic adverse event	RR 1.18 (1.01 to 1.39)	3038 (5 studies)	⊕⊕⊕⊖ Moderate[1]	
Gastrointestinal disorders	10 per 1000	20 per 1000	RR 1.85 (1.01, 3.40)	3038 (5 studies)	⊕⊕⊕⊖ Moderate[1]	
Myocardial infarction	<10 per 1000	<10 per 1000	RR 0.51 (0.22 to 1.19)	3038 (5 studies)	⊕⊕⊖⊖ Low[2]	
Stroke or cerebral infarction	<10 per 1000	<10 per 1000	RR 0.65 (0.25 to 1.67)	3038 (5 studies)	⊕⊕⊖⊖ Low[2]	
Venous thrombotic event	<10 per 10000	<10 per 1000	RR 2.04 (0.61 to 6.75)	2721 (4 studies)	⊕⊕⊖⊖ Low[2]	

Serious ocular adverse events at one year	< 5 per 1000	<5 per 1000	Range of RRs 0.51 (0.05 to 5.62) to 7.05 (0.36 to 136.28)	Range 1670 to 2280 (2 to 3 studies)		Studies reported different ocular adverse events
Retinal detachment	0	<10 per 1000	RR 7.05 (0.36 to 136.28)	1670 (2 studies)	⊕⊕⊖⊖ Low[2]	
Severe uveitis	< 10 per 1000	<10 per 1000	RR 4.14 (0.46 to 36.97)	1795 (2 studies)	⊕⊕⊖⊖ Low[2]	
Endophthalmitis	<10 per 1000	<10 per 1000	RR 1.68 (0.40 to 7.00)	2111 (3 studies)	⊕⊕⊖⊖ Low[2]	
Retinal pigment epithelial tear	<10 per 1000	<10 per 1000	RR 1.37 (0.31 to 6.12)	2236 (3 studies)	⊕⊕⊖⊖ Low[2]	
cataract	<10 per 1000	<10 per 1000	RR 0.51 (0.05 to 5.62	2280 (3 studies)	⊕⊕⊖⊖ Low[2]	

*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 vent 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 studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Bevacizumab vs ranibizumab							
Number of injections							
5 studies (CATT 2011, Biswas 2011, GEFAL 2013, LUCAS 2015, MANTA 2013)	Serious[1]	Not serious	Not serious	Not serious	1660	MD=0.60 (0.33, 0.87)	Moderate

1. Downgrade for masking of participants and incomplete outcome data.

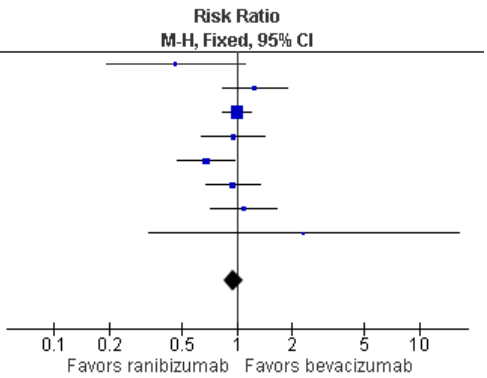
Bevacizumab vs ranibizumab

One year

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

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	Ranibizumab Events	Ranibizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Biswas 2011 (1)	6	50	14	54	3.4%	0.46 [0.19, 1.11]
BRAMD study 2016	39	161	32	166	8.0%	1.26 [0.83, 1.90]
CATT 2011	159	536	168	569	41.4%	1.00 [0.84, 1.21]
GEFAL 2013	39	191	39	183	10.1%	0.96 [0.65, 1.42]
IVAN 2013	40	251	64	273	15.6%	0.68 [0.48, 0.97]
LUCAS 2015	47	184	50	187	12.6%	0.96 [0.68, 1.35]
MANTA 2013	36	154	35	163	8.6%	1.09 [0.72, 1.64]
Subramanian 2010	5	15	1	7	0.3%	2.33 [0.33, 16.41]
Total (95% CI)		**1542**		**1602**	**100.0%**	**0.96 [0.85, 1.08]**
Total events	371		403			

Heterogeneity: Chi² = 9.31, df = 7 (P = 0.23); I² = 25%
Test for overall effect: Z = 0.71 (P = 0.48)

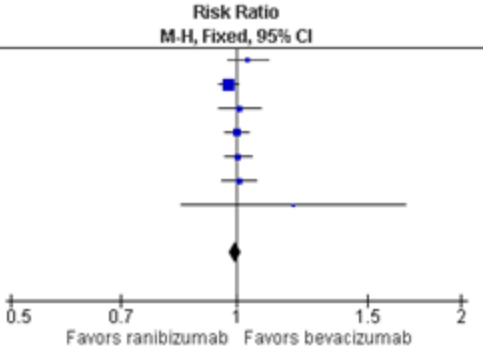


Footnotes
(1) follow-up was 18 months

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

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	Ranibizumab Events	Ranibizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Biswas 2011 (1)	50	50	52	54	3.8%	1.04 [0.97, 1.11]
CATT 2011	497	536	540	569	39.5%	0.98 [0.95, 1.01]
GEFAL 2013	174	191	165	183	12.7%	1.01 [0.95, 1.08]
IVAN 2013	240	251	260	273	18.8%	1.00 [0.97, 1.04]
LUCAS 2015	177	184	179	187	13.4%	1.00 [0.96, 1.05]
MANTA 2013	146	154	153	163	11.2%	1.01 [0.96, 1.07]
Subramanian 2010	15	15	6	7	0.7%	1.19 [0.84, 1.68]
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); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

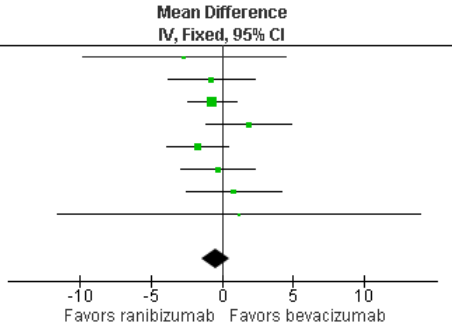


Footnotes
(1) follow-up was 18 months

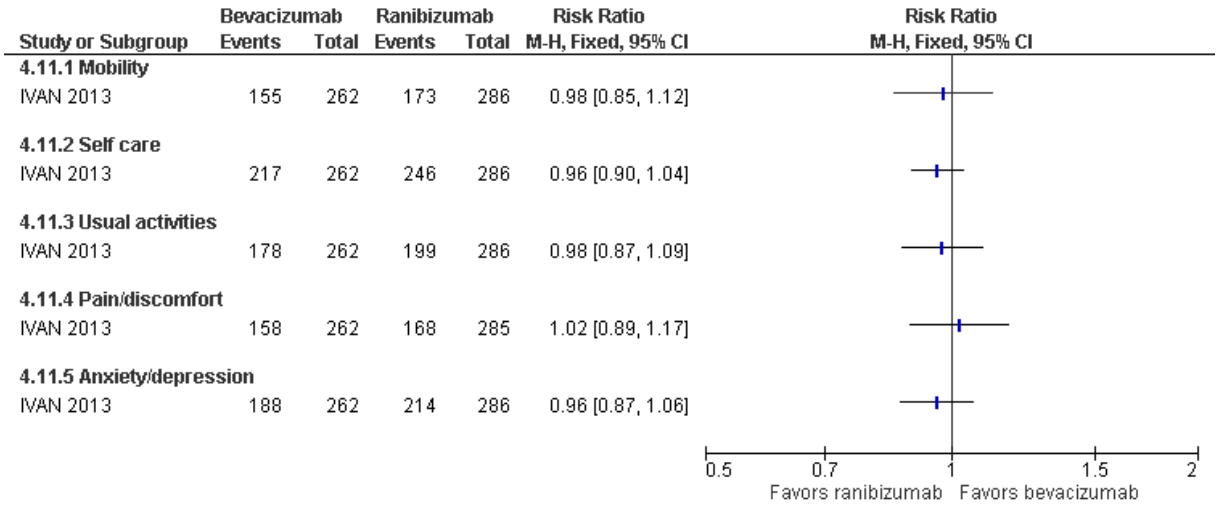
Visual acuity (mean change in number of letters)

Study or Subgroup	Bevacizumab Mean	Bevacizumab SD	Bevacizumab Total	Ranibizumab Mean	Ranibizumab SD	Ranibizumab Total	Weight	Mean Difference IV, Fixed, 95% CI
Biswas 2011	0.52	18.67	50	3.22	18.67	54	1.9%	-2.70 [-9.88, 4.48]
BRAMD study 2016	6.06	13.67	142	6.82	12.63	142	10.5%	-0.76 [-3.82, 2.30]
CATT 2011	6.9382	15.7698	536	7.6485	13.6229	569	32.4%	-0.71 [-2.45, 1.03]
GEFAL 2013	4.82	14.85	191	2.93	15.09	183	10.7%	1.89 [-1.15, 4.93]
IVAN 2013	4.7	12.5	251	6.4	12.8	273	21.0%	-1.70 [-3.87, 0.47]
LUCAS 2015	7.9	13.4	184	8.2	12.5	187	14.2%	-0.30 [-2.94, 2.34]
MANTA 2013	4.9	15.27	154	4.1	15.23	163	8.7%	0.80 [-2.56, 4.16]
Subramanian 2010	7.5	15.4	15	6.3	13.7	7	0.6%	1.20 [-11.60, 14.00]
Total (95% CI)			**1523**			**1578**	**100.0%**	**-0.48 [-1.47, 0.51]**

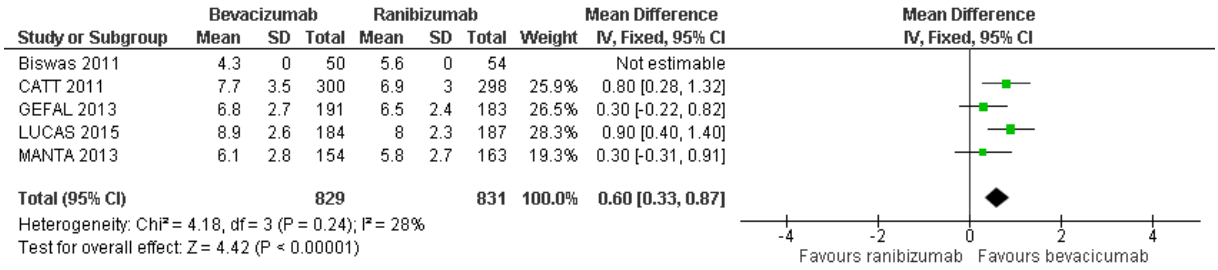
Heterogeneity: Chi² = 4.67, df = 7 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)



Quality of life (no problem in quality of life)

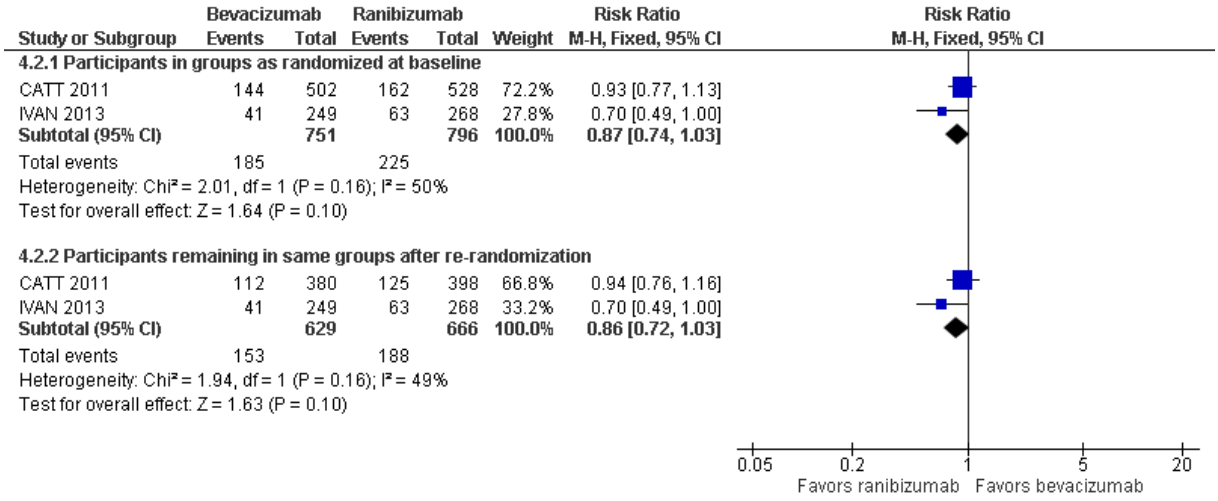


Number of injections

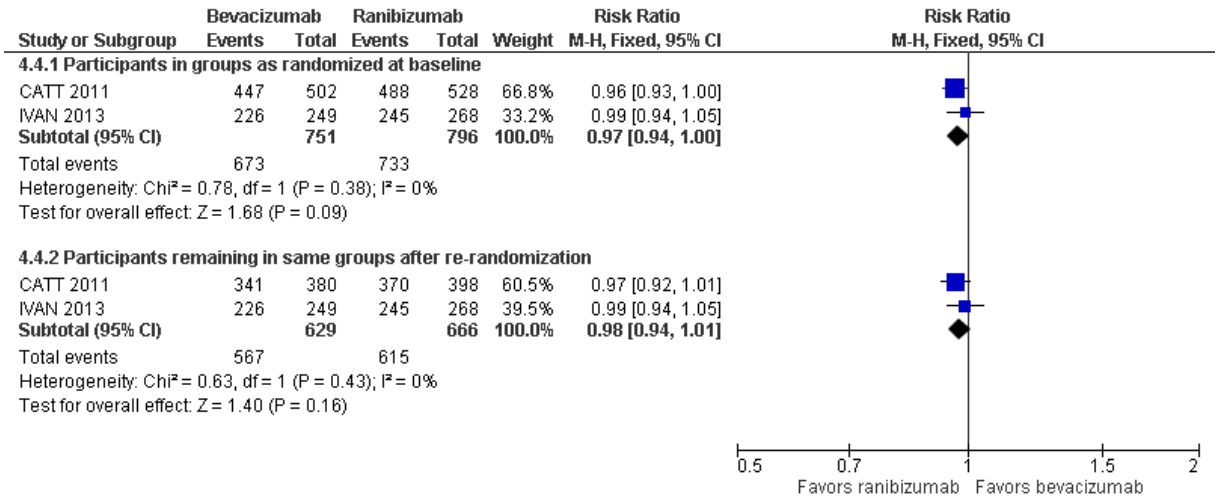


Two years

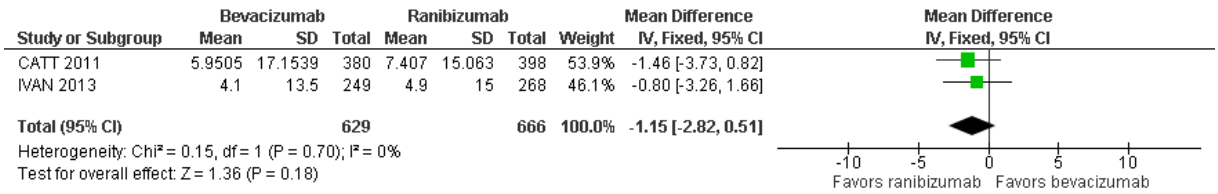
Visual acuity (gain of 15 letters or more)



Visual acuity (loss of fewer than 15 letters)

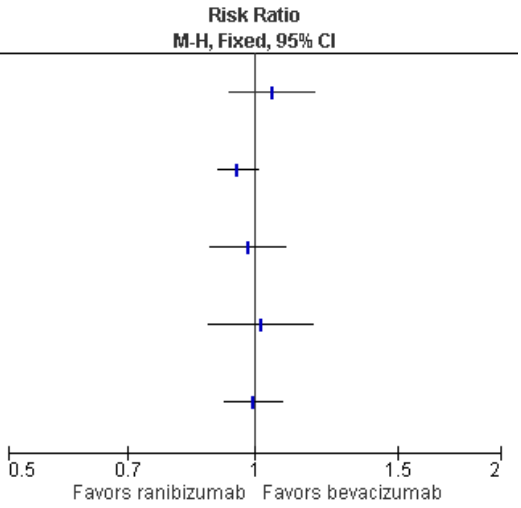


Visual acuity (mean change in number of letters)



Quality of life (no problem in quality of life)

Study or Subgroup	Bevacizumab Events	Total	Ranibizumab Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.12.1 Mobility					
IVAN 2013	171	247	176	267	1.05 [0.93, 1.18]
4.12.2 Self care					
IVAN 2013	218	247	247	267	0.95 [0.90, 1.01]
4.12.3 Usual activities					
IVAN 2013	179	247	197	267	0.98 [0.88, 1.09]
4.12.4 Pain/discomfort					
IVAN 2013	145	247	154	267	1.02 [0.88, 1.18]
4.12.5 Anxiety/depression					
IVAN 2013	203	247	220	267	1.00 [0.92, 1.08]



H.6.1.5 Aflibercept vs ranibizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants	Quality of the evidence	Comments
	Corresponding risk	**Assumed risk**	**(95% CI)**	**(studies)**	**(GRADE)**	
	Alfibercept	Ranibizumab				
Mean change in BCVA in ETDRS letters at 1 year	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)	Mean change in visual acuity across ranibizumab groups ranged from gains of 8.57 letters to 8.71 letters	MD -0.15 (-1.47 to 1.17)	2412 (2 studies)	⊕⊕⊕⊕ High	
Gain of 15 of BCVA at one year	314 per 1000 (275 to 360)	324 per 1000	RR 0.97 (0.85 to 1.11)	2412 (2 studies)	⊕⊕⊕⊕ High	
Quality of life measures at 1 year (national eye institute-visual function questionnaire)	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)	Mean improvement in composite NEI-VQF score ranged across control groups from 4.9 to 6.3 points	MD -0.39 (-1.71 to 0.93)	2412 (2 studies)	⊕⊕⊕⊕High	
Adverse events (serious systemic events at 1 year)	138 per 1000 (110 to 174)	139 per 1000	RR 0.99 (0.79 to 1.25)	2419 (2 studies)	⊕⊕⊕⊖ Moderate[1]	
Adverse events (serious ocular events at 1 year)	20 per 1000 (12 to 34)	32 per 1000	RR 0.62 (0.36 to 1.07)	2419 (2 studies)	⊕⊕⊕⊖ Moderate[1]	

*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 vent 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

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
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							
2 (VIEW 1, VIEW2)	Not serious	Serious[1]	Not serious	Not serious	1193	RR 0.97 (0.86, 1.10)	MODERATE
NEI-VFQ-25 subscale score changes from baseline to week 52 (higher scores indicate better QoL)							
General vision	Not serious	Not serious	Not serious	Not serious	1193	MD 0.06 (-2.00, 2.13)	HIGH
Near activities	Not serious	Not serious	Not serious	Not serious	1193	MD -0.62 (-3.09, 1.86)	HIGH
Distance activities	Not serious	Not serious	Not serious	Serious[2]	1193	MD 0.08 (-2.43, 2.58)	MODERATE
Mental health	Not serious	Not serious	Not serious	Serious[2]	1193	MD 0.14 (-2.41, 2.70)	MODERATE
Role difficulities	Not serious	Not serious	Not serious	Serious[2]	1193	MD 1.09 (-2.04, 4.23)	MODERATE
Dependency	Not serious	Not serious	Not serious	Serious[2]	1193	MD -1.29 (-4.00, 1.43)	MODERATE
Social funictioning	Not serious	Not serious	Not serious	Serious[2]	1193	MD 0.18 (-2.35, 2.70)	MODERATE
Driving	Not serious	Not serious	Not serious	Serious[2]	1193	MD 1.51 (-1.15, 4.17)	MODERATE
Colour vision	Not serious	Not serious	Not serious	Not serious	1193	MD -2.04 (-4.33, 0.26)	HIGH

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Ocular pain	Not serious	Not serious	Not serious	Not serious	1193	MD -0.94 (-3.21, 1.32)	HIGH
Peripheral vision	Not serious	Not serious	Not serious	Not serious	1193	MD 0.86 (-3.73, 2.00)	HIGH
General health	Not serious	Not serious	Not serious	Not serious	1193	MD -0.23 (-2.56, 2.10)	HIGH

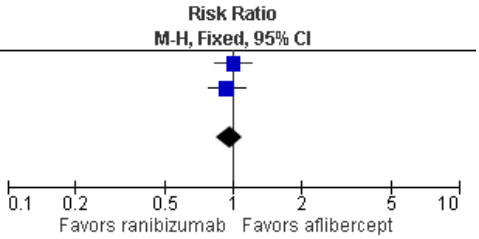
1. Downgraded one level for inconsistency due to heterogenioty (i2>50%)
2. Downgraded one level for imprecision due to 95%CI of estimated effect crossing 1 line of a defined minimal important difference (2.3 point)

Aflibercept vs ranibizumab (one year)

Gain of ≥ 15 letters of BCVA

Study or Subgroup	Aflibercept Events	Total	Ranibizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VIEW 1	281	906	94	304	48.4%	1.00 [0.83, 1.22]
VIEW 2	290	911	99	291	51.6%	0.94 [0.78, 1.13]
Total (95% CI)		**1817**		**595**	**100.0%**	**0.97 [0.85, 1.11]**
Total events	571		193			

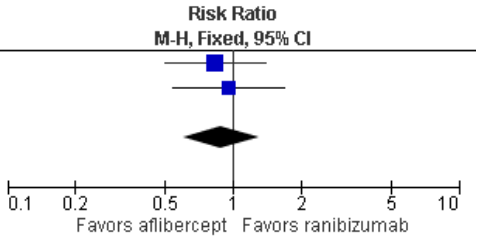
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)



Loss of ≥15 letters of BCVA

Study or Subgroup	Aflibercept Events	Total	Ranibizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VIEW 1	47	906	19	304	55.6%	0.83 [0.50, 1.39]
VIEW 2	45	911	15	291	44.4%	0.96 [0.54, 1.69]
Total (95% CI)		**1817**		**595**	**100.0%**	**0.89 [0.61, 1.30]**
Total events	92		34			

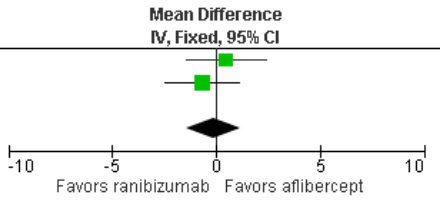
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)



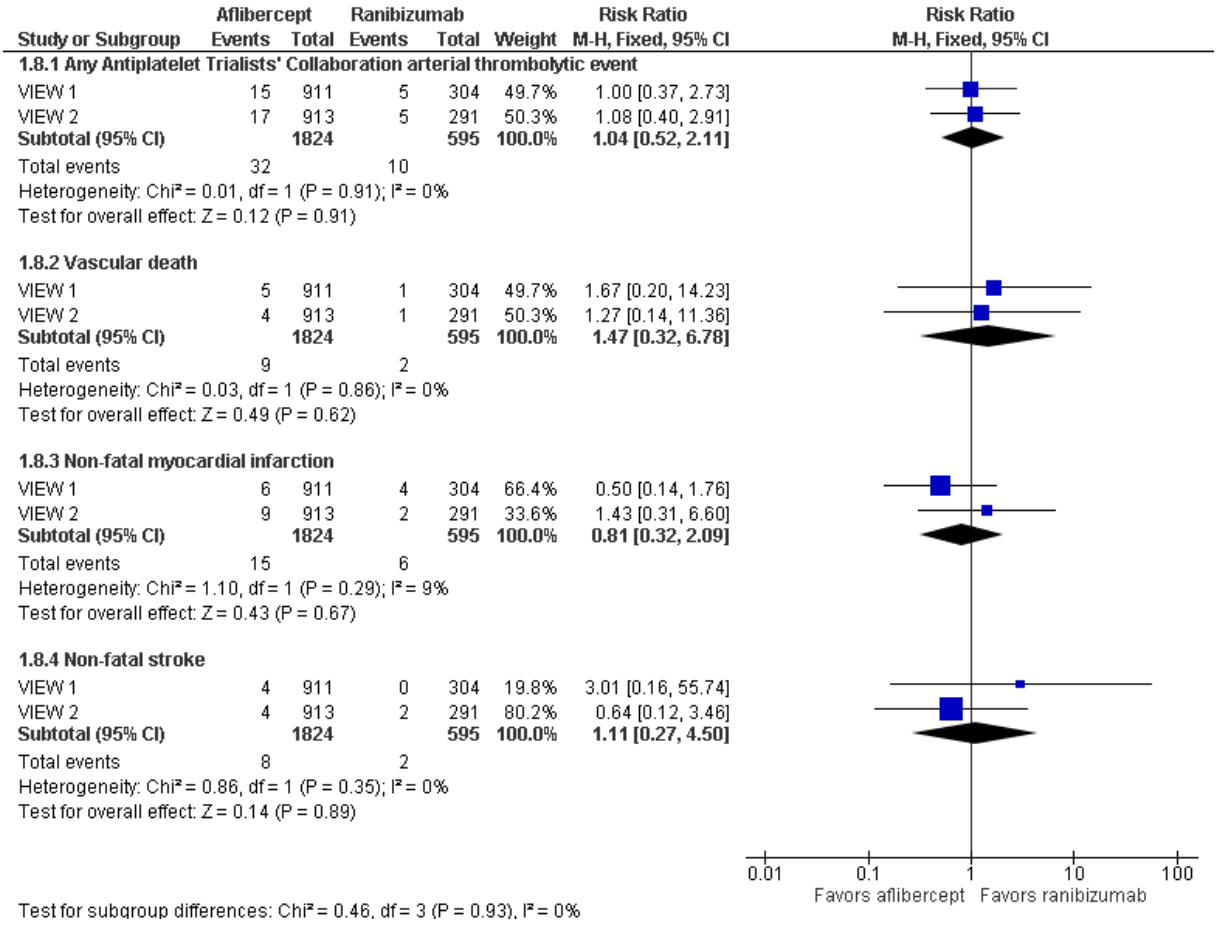
Mean change in BCVA in ETDRS letters

Study or Subgroup	Aflibercept Mean	SD	Total	Ranibizumab Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
VIEW 1	8.5744	14.1693	906	8.1	15.3	304	45.7%	0.47 [-1.48, 2.43]
VIEW 2	8.719	13.7271	911	9.4	13.5	291	54.3%	-0.68 [-2.47, 1.11]
Total (95% CI)			**1817**			**595**	**100.0%**	**-0.15 [-1.47, 1.17]**

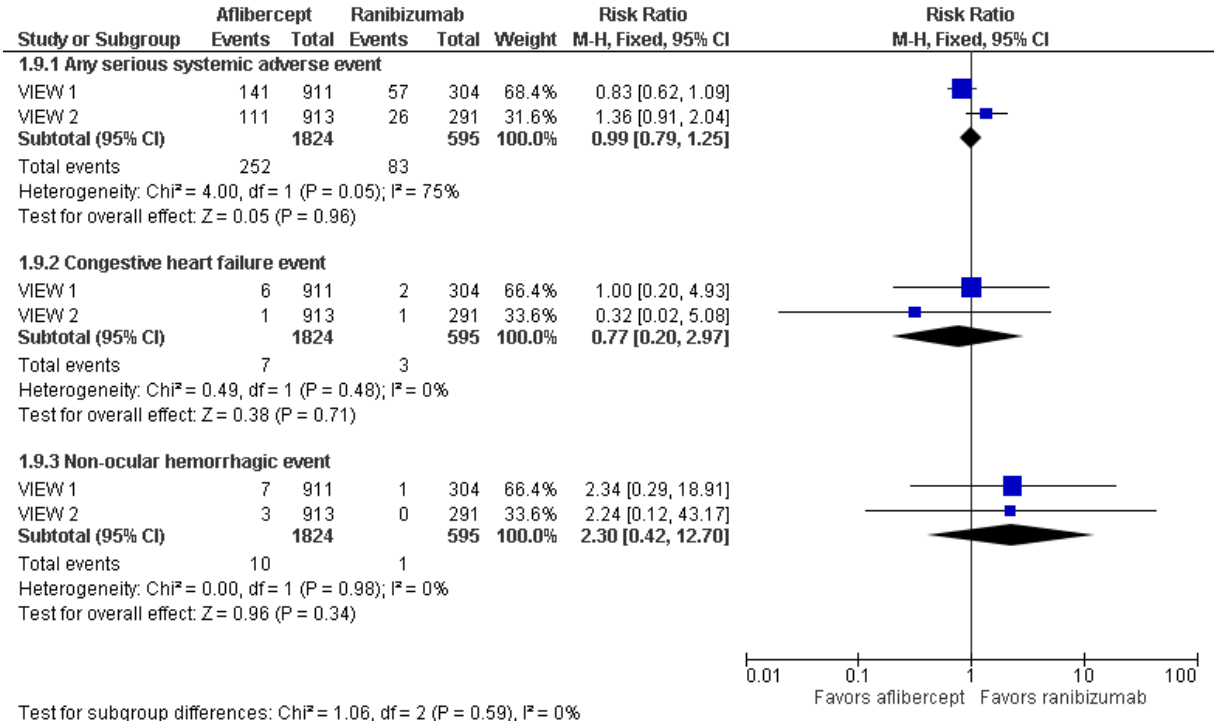
Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



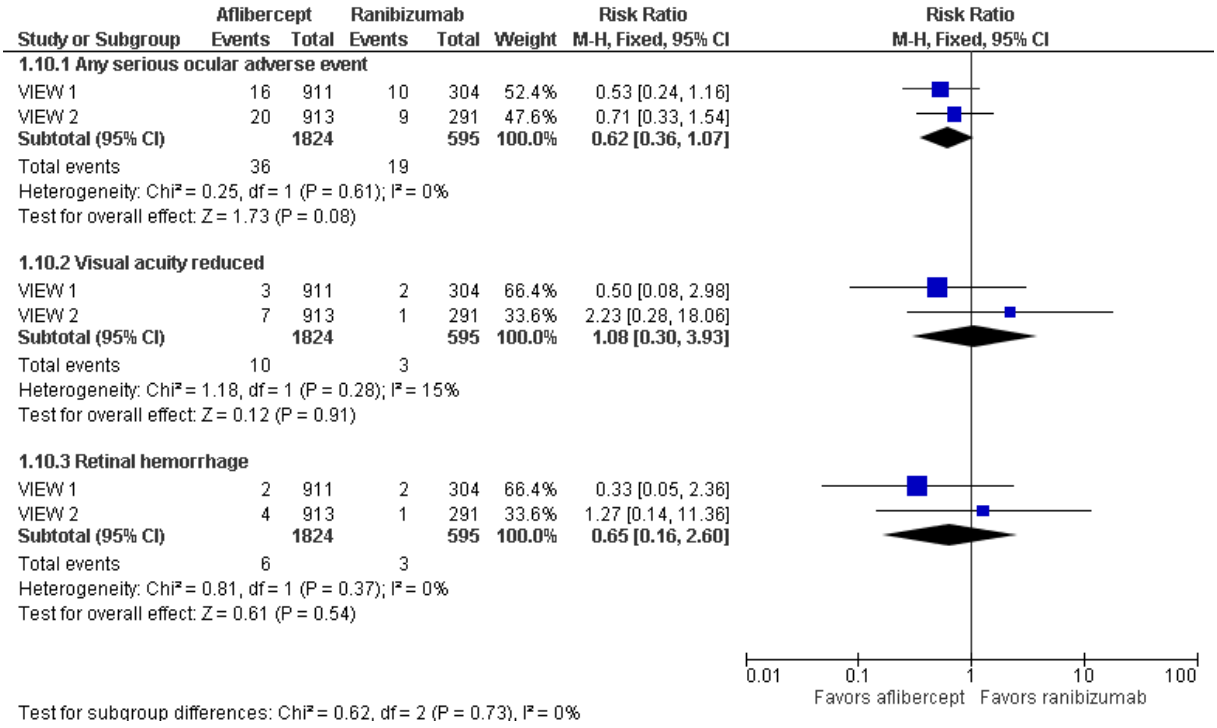
Arterial thrombotic events



Serious systemic events



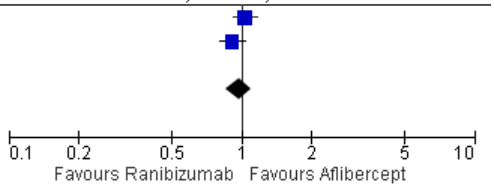
Serious ocular events



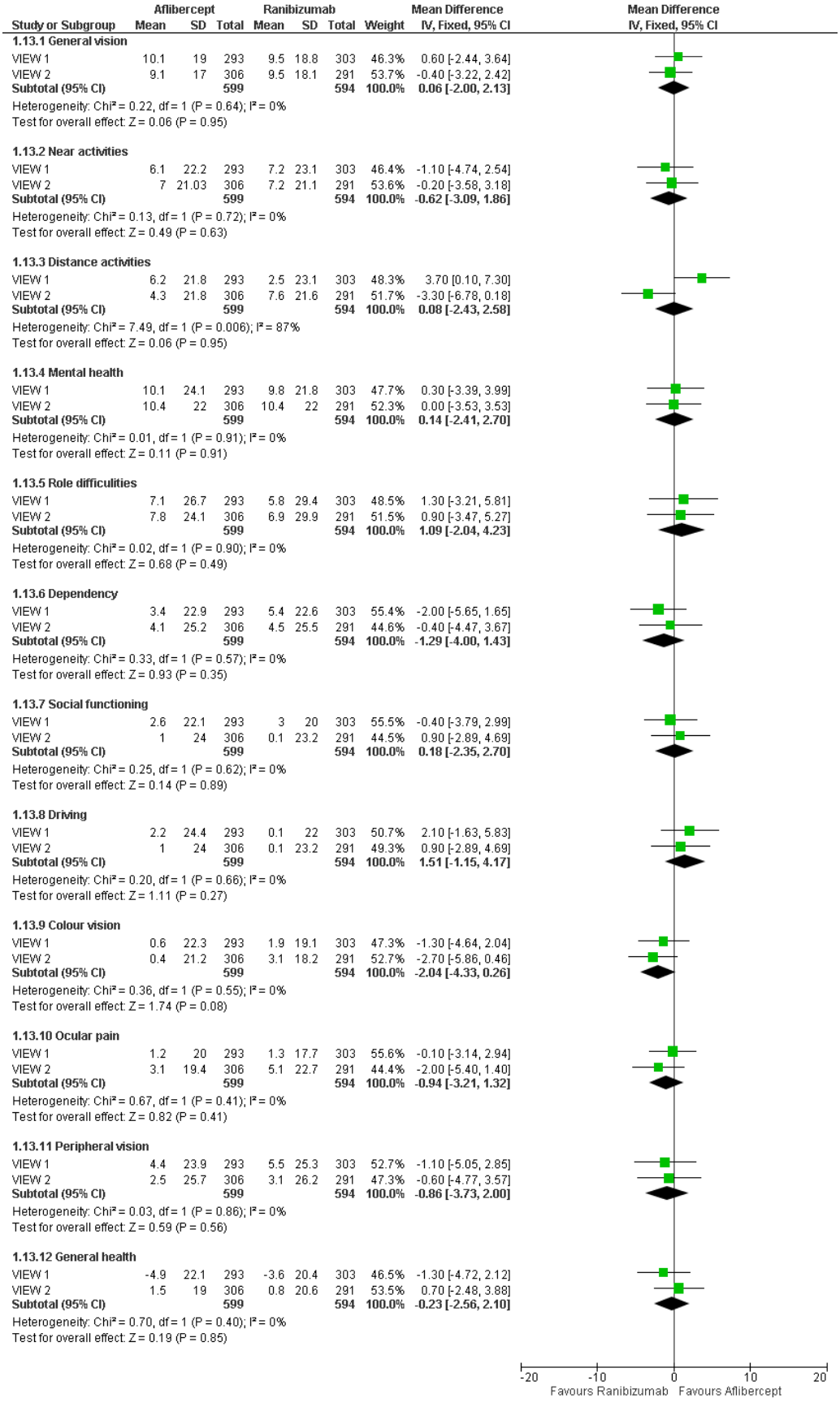
Proportion of people had gain more than 5 ETDRS letters and had clinical improvement in NEI-VFQ compsite score (more than 6-point)

Study or Subgroup	Aflibercept Events	Total	Ranibizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
VIEW 1	192	293	192	303	51.1%	1.03 [0.92, 1.17]
VIEW 2	182	306	190	291	48.9%	0.91 [0.80, 1.03]
Total (95% CI)		**599**		**594**	**100.0%**	**0.97 [0.86, 1.10]**
Total events	374		382			

Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.45 (P = 0.65)



Mean change in NEI-VFQ subscale score


Aflibercept
Ranibizumab
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
1.13.1 General vision
VIEW 1 10.1 19 293 9.5 18.8 303 46.3% 0.60 [-2.44, 3.64]
VIEW 2 9.1 17 306 9.5 18.1 291 53.7% -0.40 [-3.22, 2.42]
Subtotal (95% CI) 599 594 100.0% 0.06 [-2.00, 2.13]
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
1.13.2 Near activities
VIEW 1 6.1 22.2 293 7.2 23.1 303 46.4% -1.10 [-4.74, 2.54]
VIEW 2 7 21.03 306 7.2 21.1 291 53.6% -0.20 [-3.58, 3.18]
Subtotal (95% CI) 599 594 100.0% -0.62 [-3.09, 1.86]
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)
1.13.3 Distance activities
VIEW 1 6.2 21.8 293 2.5 23.1 303 48.3% 3.70 [0.10, 7.30]
VIEW 2 4.3 21.8 306 7.6 21.6 291 51.7% -3.30 [-6.78, 0.18]
Subtotal (95% CI) 599 594 100.0% 0.08 [-2.43, 2.58]
Heterogeneity: Chi² = 7.49, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 0.06 (P = 0.95)
1.13.4 Mental health
VIEW 1 10.1 24.1 293 9.8 21.8 303 47.7% 0.30 [-3.39, 3.99]
VIEW 2 10.4 22 306 10.4 22 291 52.3% 0.00 [-3.53, 3.53]
Subtotal (95% CI) 599 594 100.0% 0.14 [-2.41, 2.70]
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
1.13.5 Role difficulities
VIEW 1 7.1 26.7 293 5.8 29.4 303 48.5% 1.30 [-3.21, 5.81]
VIEW 2 7.8 24.1 306 6.9 29.9 291 51.5% 0.90 [-3.47, 5.27]
Subtotal (95% CI) 599 594 100.0% 1.09 [-2.04, 4.23]
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.49)
1.13.6 Dependency
VIEW 1 3.4 22.9 293 5.4 22.6 303 55.4% -2.00 [-5.65, 1.65]
VIEW 2 4.1 25.2 306 4.5 25.5 291 44.6% -0.40 [-4.47, 3.67]
Subtotal (95% CI) 599 594 100.0% -1.29 [-4.00, 1.43]
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
1.13.7 Social functioning
VIEW 1 2.6 22.1 293 3 20 303 55.5% -0.40 [-3.79, 2.99]
VIEW 2 1 24 306 0.1 23.2 291 44.5% 0.90 [-2.89, 4.69]
Subtotal (95% CI) 599 594 100.0% 0.18 [-2.35, 2.70]
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
1.13.8 Driving
VIEW 1 2.2 24.4 293 0.1 22 303 50.7% 2.10 [-1.63, 5.83]
VIEW 2 1 24 306 0.1 23.2 291 49.3% 0.90 [-2.89, 4.69]
Subtotal (95% CI) 599 594 100.0% 1.51 [-1.15, 4.17]
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
1.13.9 Colour vision
VIEW 1 0.6 22.3 293 1.9 19.1 303 47.3% -1.30 [-4.64, 2.04]
VIEW 2 0.4 21.2 306 3.1 18.2 291 52.7% -2.70 [-5.86, 0.46]
Subtotal (95% CI) 599 594 100.0% -2.04 [-4.33, 0.26]
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)
1.13.10 Ocular pain
VIEW 1 1.2 20 293 1.3 17.7 303 55.6% -0.10 [-3.14, 2.94]
VIEW 2 3.1 19.4 306 5.1 22.7 291 44.4% -2.00 [-5.40, 1.40]
Subtotal (95% CI) 599 594 100.0% -0.94 [-3.21, 1.32]
Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
1.13.11 Peripheral vision
VIEW 1 4.4 23.9 293 5.5 25.3 303 52.7% -1.10 [-5.05, 2.85]
VIEW 2 2.5 25.7 306 3.1 26.2 291 47.3% -0.60 [-4.77, 3.57]
Subtotal (95% CI) 599 594 100.0% -0.86 [-3.73, 2.00]
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)
1.13.12 General health
VIEW 1 -4.9 22.1 293 -3.6 20.4 303 46.5% -1.30 [-4.72, 2.12]
VIEW 2 1.5 19 306 0.8 20.6 291 53.5% 0.70 [-2.48, 3.88]
Subtotal (95% CI) 599 594 100.0% -0.23 [-2.56, 2.10]
Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
-20
-10
0
10
20
Favours Ranibizumab
Favours Aflibercept

H.6.1.6 Treatment frequency: PRN vs routine injection

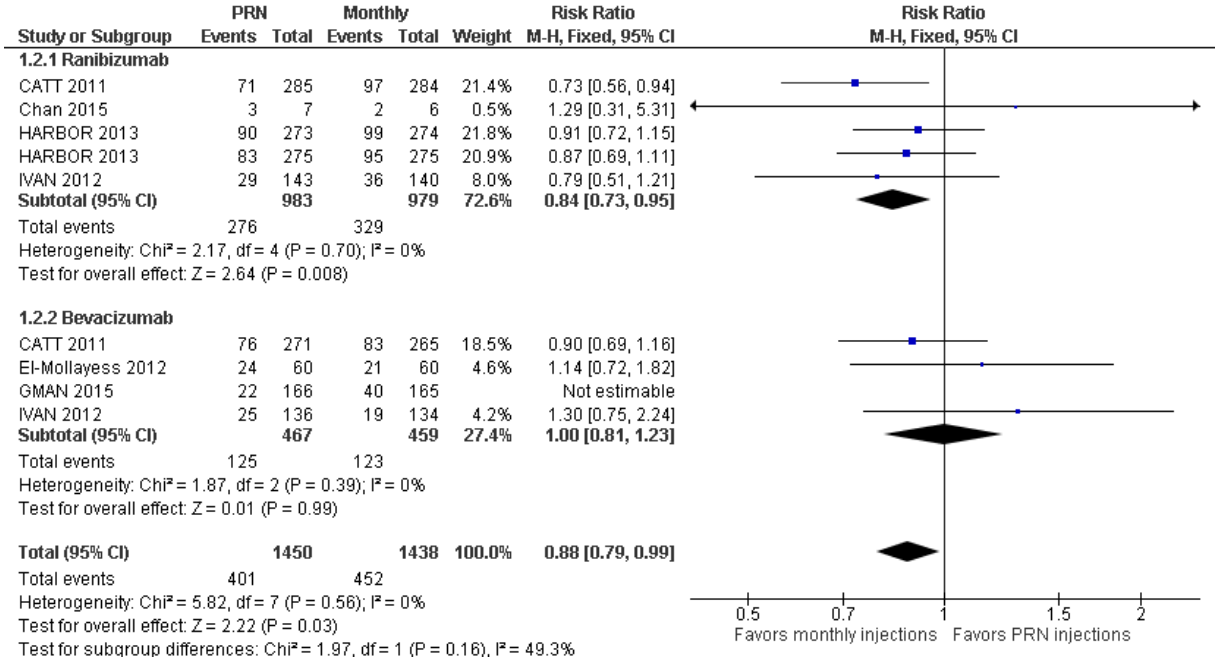
Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
PRN vs routine injections							
Gain of ≥15 letters at one year							
5 studies (CATT 2011, HARBOUR 2013, El-Mollayess 2012, IVAN 2012, Chan 2015)	Serious[1]	Not serious	Not serious	serious[3]	2888	RR 0.88 (0.79, 0.99)	LOW
Loss of <15 letters at one year							
3 studies (CATT 2011, IVAN 2012, HARBOUR 2013)	Serious[1,2]	Not serious	Not serious	Not serious	2755	RR 0.99 (0.97, 1.01)	MODERATE
Mean change in BCVA in ETDRS letters at one year (higher values indicate better vision)							
4 studies (CATT 2011, HARBOUR 2013, , El-Mollayess 2012, IVAN 2012)	Serious[1]	Not serious	Not serious	Not serious	2874	MD -1.45 (-2.45, -0.45)	MODERATE
Mean number of injections at one year							
2 studies (CATT 2011, , HARBOUR 2013)	Serious[1]	Serious[4]	Not serious	Not serious	2202	MD -4.22 (-4.72, -3.73)	LOW
Adverse events (serious systemic events at one year)							
2 studies (CATT 2011, HARBOUR 2013,)	Serious[1]	Serious[4]	Not serious	Serious[5]	2280	RR 1.07 (0.70, 1.63)	VERY LOW
Adverse events (serious ocular events at one year)							
2 studies (CATT 2011, HARBOUR 2013,)	Serious[1]	Serious[4]	Not serious	not serious	2280	RR 0.31 (0.13, 0.78)	LOW

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 crossing1 line of a defined minimal important difference
4. Downgraded for inconsistency due to heterogeneity (i2>50%)

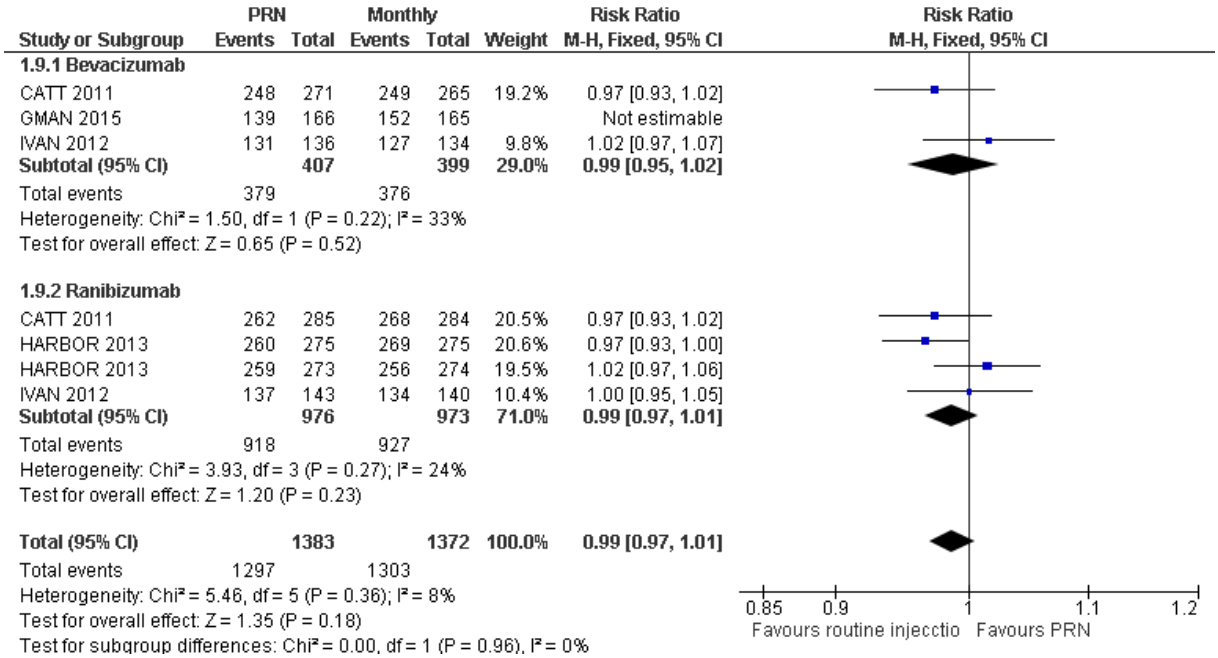
Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
5. Downgrade one level for imprecision due to 95%CI of the effect cannot be estimated							

PRN vs routine injections

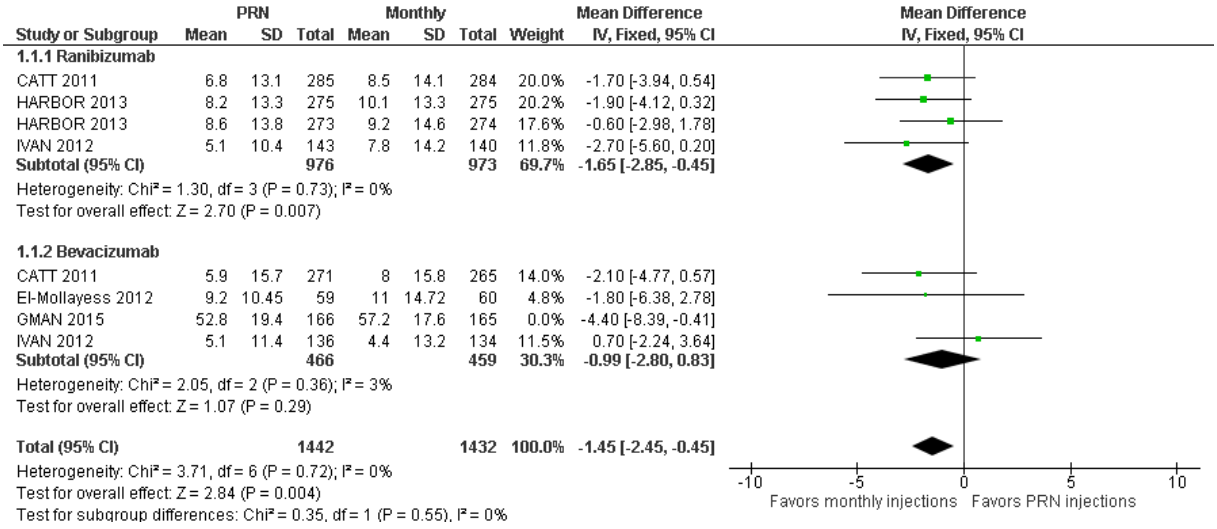
Gain of 15 or more letters ETDRS



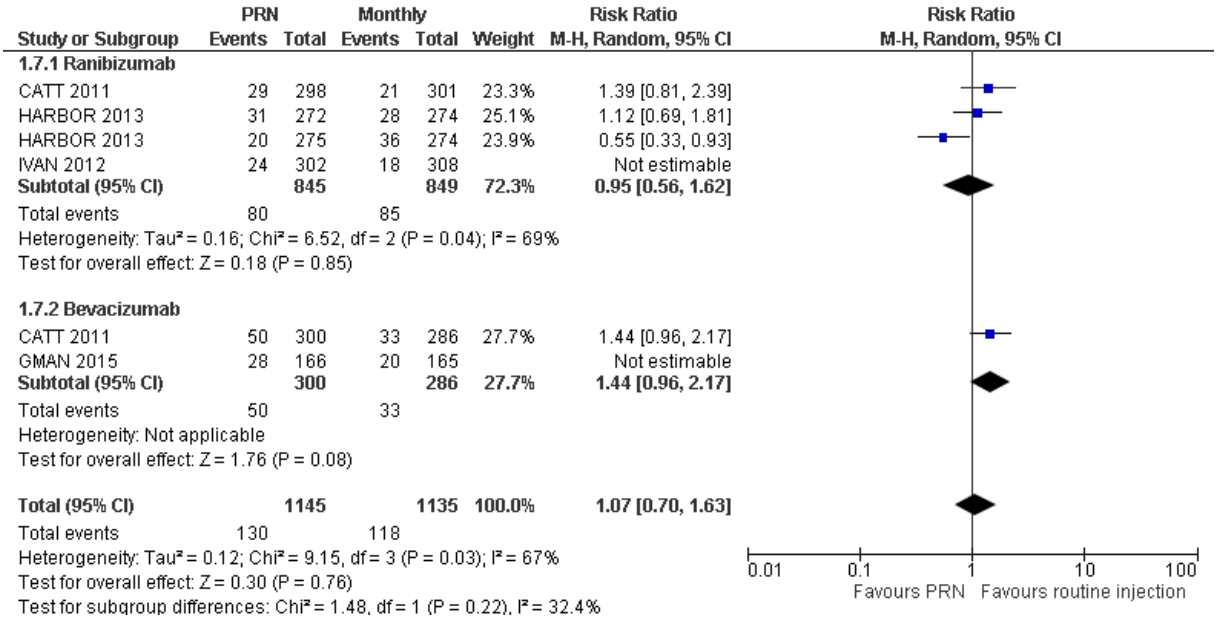
Loss of fewer than15 letters ETDRS



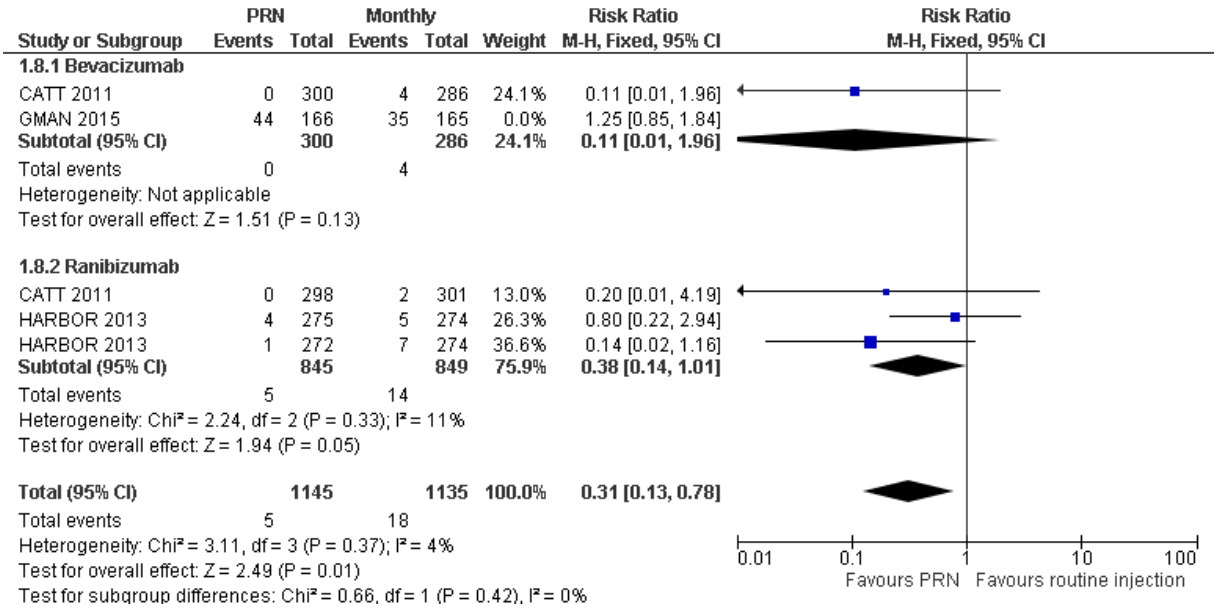
Mean change in BCVA of EDTRS letters



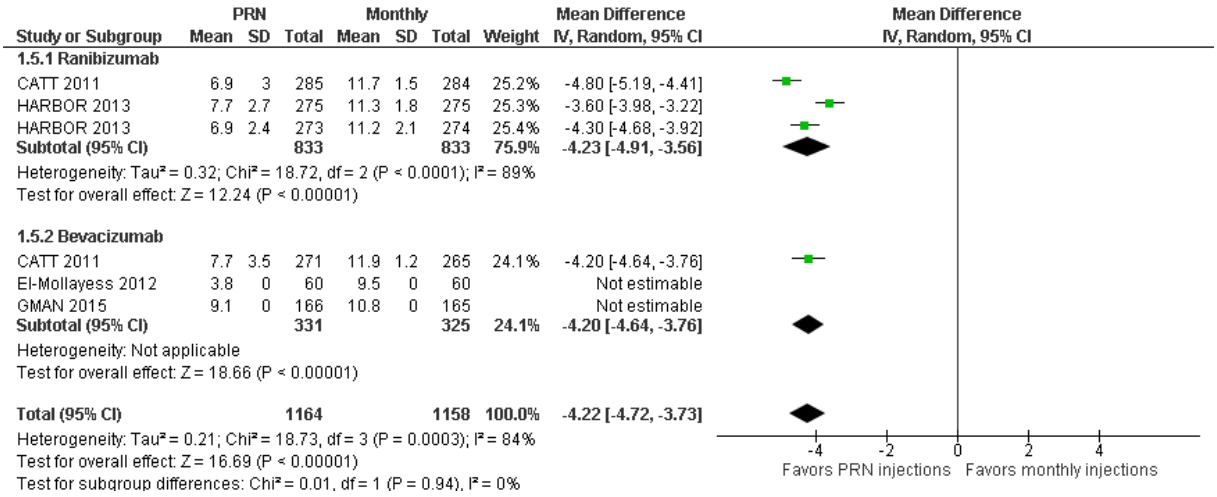
Serious systemic events



Serious ocular events



Number of injections



H.6.1.7 Treatment frequency: ≤6 weeks vs >6 weeks treatment intervals

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
PRN vs (6 and/or 12 weeks) interval injections							
Gain of ≥15 letters at one year							
1 study (GMAN 2015)	Serious[1]	N/A	Not serious	Serious[2]	231	RR 0.55 (0.34 to 0.88)	LOW
Loss of <15 letters at one year							
1 study (GMAN 2015)	Serious[1]	N/A	Not serious	Not serious	231	RR 0.91 (0.84 to 0.99)	MODERATE
Mean change in BCVA in ETDRS letters at one year(higher values indicate better vision)							
1 study (GMAN 2015)	Serious[1]	N/A	Not serious	Serious[2]	231	MD -4.40 (-8.39 to -0.41)	LOW
Adverse events (serious systemic events at one year)							
1 study (GMAN 2015)	Serious[1]	N/A	Not serious	Serious[2]	231	RR 1.39 (0.82 to 2.37)	LOW
Adverse events (serious ocular events at one year)							
1 study (GMAN 2015)	Serious[1]	N/A	Not serious	Serious[2]	231	RR 1.25 (0.85 to 1.84)	LOW
Routine injections (interval 6 weeks or less vs more than 6 weeks)							
Gain of ≥15 letters at one year							
4 studies (Lushchyk 2013, NATTB 2012, VIEW 2012, EXCITE)	Serious[3]	Not serious	Not serious	Serious[2]	1276	RR 1.28 (1.08, 1.52)	LOW
Loss of <15 letters at one year							
3 studies (Lushchyk 2013, NATTB 2012, EXCITE)	Serious[3]	Serious[4]	Not serious	not serious	671	RR 0.99 (0.92, 1.06)	LOW
Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)							

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
4 studies (Lushchyk 2013, NATTB 2012, VIEW 2012, EXCITE 2010)	Serious[3]	Serious[4]	Not serious	Not serious	1276	MD 1.87 (0.36, 3.39)	LOW
Adverse events (serious systemic events at one year)							
2 studies (Lushchyk 2013, VIEW 2012)	Serious[5]	Not serious	Not serious	Serious[2]	798	RR 0.77 (0.53, 1.11)	LOW
Adverse events (serious ocular events at one year)							
3 studies (Lushchyk 2013, NATTB 2012, VIEW 2012)	Serious[3]	Not serious	Not serious	Serious[2]	983	RR 1.52 (0.86, 2.69)	LOW

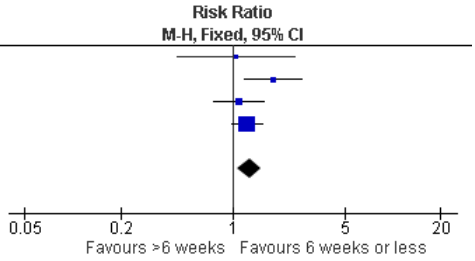
1. Downgraded one level for risk of bias due to masking of participants (patients, treating clinicians, and other staff involved in the study were not masked)
2. Downgraded one level for imprecision due to 95%CI of estimated effect crossing of 1 line of defined minimal important difference
3. Downgrade 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)

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

Gain of 15 or more letters of visual acuity

Study or Subgroup	6 weeks or less Events	Total	more than 6 weeks Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lushchyk 2013	14	103	7	54	5.8%	1.05 [0.45, 2.44]
EXCITE 2010	33	115	38	238	15.6%	1.80 [1.19, 2.71]
NATTB 2012	35	79	33	82	20.4%	1.10 [0.77, 1.58]
VIEW 2012	114	304	92	301	58.2%	1.23 [0.98, 1.53]
Total (95% CI)		**601**		**675**	**100.0%**	**1.28 [1.08, 1.52]**
Total events	196		170			

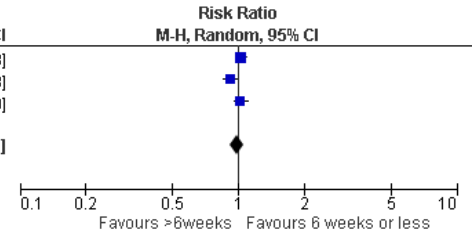
Heterogeneity: Chi² = 3.65, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 2.86 (P = 0.004)



Loss of fewer than 15 letters of visual acuity

Study or Subgroup	6 weeks or less Events	Total	more than 6 weeks Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
EXCITE 2010	109	115	220	238	35.5%	1.03 [0.97, 1.08]
Lushchyk 2013	94	103	54	54	32.9%	0.92 [0.86, 0.98]
NATTB 2012	76	79	77	82	31.7%	1.02 [0.95, 1.10]
Total (95% CI)		**297**		**374**	**100.0%**	**0.99 [0.92, 1.06]**
Total events	279		351			

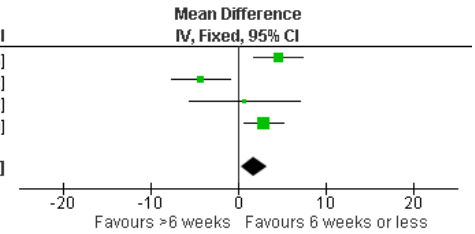
Heterogeneity: Tau² = 0.00; Chi² = 7.77, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 0.32 (P = 0.75)



Mean visual change in BCVA (EDTRS letters)

Study or Subgroup	6 weeks or less Mean	SD	Total	more than 6 weeks Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
EXCITE 2010	8	11.27	115	3.4	14.33	238	30.4%	4.60 [1.85, 7.35]
Lushchyk 2013	1.73	12.25	103	6	8.9	54	20.4%	-4.27 [-7.62, -0.92]
NATTB 2012	49.4	21.6	79	48.6	19.2	82	5.7%	0.80 [-5.52, 7.12]
VIEW 2012	10.9	13.8	304	7.9	15	301	43.5%	3.00 [0.70, 5.30]
Total (95% CI)			**601**			**675**	**100.0%**	**1.87 [0.36, 3.39]**

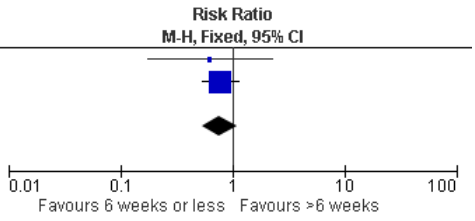
Heterogeneity: Chi² = 17.72, df = 3 (P = 0.0005); I² = 83%
Test for overall effect: Z = 2.43 (P = 0.02)



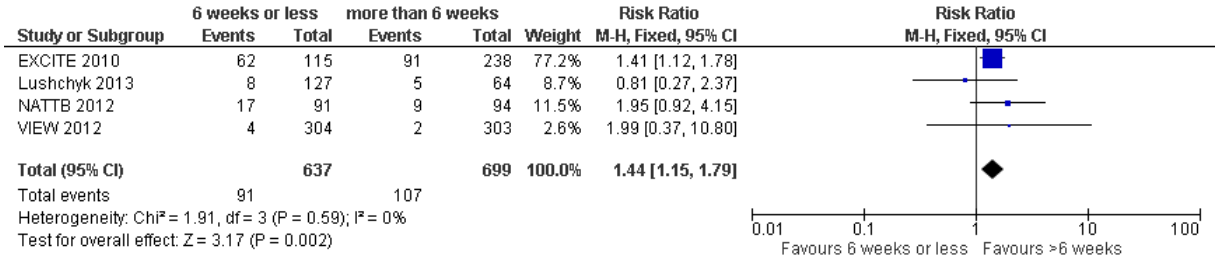
Serious systemic events

Study or Subgroup	6 weeks or less Events	Total	more than 6 weeks Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lushchyk 2013	5	127	4	64	9.4%	0.63 [0.18, 2.27]
VIEW 2012	40	304	51	303	90.6%	0.78 [0.53, 1.15]
Total (95% CI)		**431**		**367**	**100.0%**	**0.77 [0.53, 1.11]**
Total events	45		55			

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)



Serious ocular events



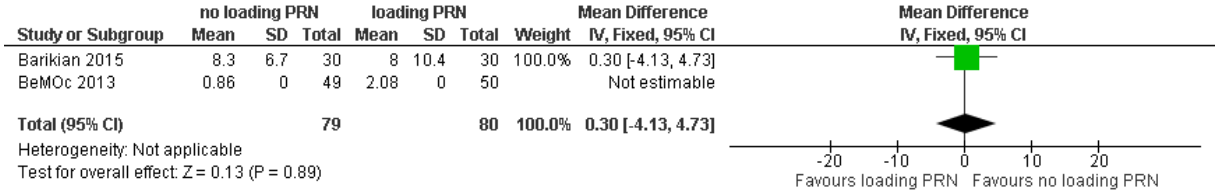
H.6.1.8 Treatment frequency: PRN loading

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
PRN (no loading vs loading)							
Gain of ≥15 letters at one year							
1 study (Barikian 2015)	Serious[1]	N/A	Not serious	Very serious[2]	60	RR 0.83 (0.43, 1.63)	VERY LOW
Gain of ≥10 letters at one year							
1 study (BeMoc 2013)	Serious[1]	N/A	Not serious	Very serious[2]	99	RR 0.93 (0.38, 2.25)	VERY LOW
Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)							
2 studies (Barikian 2015, BeMoc 2013)	Serious[1]	Not serious	Not serious	Serious[3]	189	MD 1.20 (-2.51, 4.91)	LOW
Mean number of injections at one year							
2 studies (Barikian 2015, BeMoc 2013)	Serious[1]	Not serious	Not serious	Serious[3]	189	MD -0.30 (-1.92, 1.32)	LOW
Quality of life measures at one year (VFQ-25) (higher values indicate better QoL)							
1 studiy (BeMoc 2013)	Serious[1]	N/A	Not serious	Serious[4]	99	MD -0.06	LOW
PRN with 4 week vs 12 weeks loading phase							
Gain of ≥15 letters at one year							
1 study (CLEART-IT 2011)	Serious[1]	N/A	Not serious	Very serious[2]	126	RR 0.94 (0.51, 1.72)	VERY LOW
Loss of <15 letter at one year							
1 study (CLEART-IT 2011)	Serious[1]	N/A	Not serious	Not serious	126	RR 1.05 (0.94, 1.18)	MODERATE

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Mean change in BCVA (ETDRS letters)							
1 study (CLEART-IT 2011)	Serious[1]	N/A	Not serious	Serious[5]	126	MD 3.41 (-0.16, 6.98)	LOW

1. Downgraded for risk of bias due to randomisation, allocation concealment, masking of participants, and selective report were unclear
2. Downgrade two levesl 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)



H.6.1.9 Treatment frequency: treat-and-extend vs routine month injection

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Gain of ≥15 letters at one year							
1 study (TREX-AMD 2015)	Serious[1]	N/A	Not serious	Very serious[2]	60	RR 1.67 (0.52, 5.39)	VERY LOW
Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)							
1 study (TREX-AMD 2015)	Serious[1]	N/A	Not serious	Serious[3]	60	MD 2.70 (-4.38, 9.78)	LOW
Mean number of injections at one year							
1 study (TREX-AMD 2015)	Serious[1]	N/A	Not serious	Serious[4]	60	MD -2.90	LOW
Adverse events (serious systemic events at one year)							
1 study (TREX-AMD 2015)	Serious[1]	N/A	Not serious	Very serious[2]	60	RR 5.63 (0.33, 97.10)	VERY LOW
Adverse events (serious ocular events at one year)							
1 study (TREX-AMD 2015)	Serious[1]	N/A	Not serious	Very serious[2]	60	RR 2.50 (0.60, 10.34)	VERY LOW

1. Downgraded one level for risk of bias due to masking of participants (method of random sequence generation was not reported).
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 a defined minimal important difference
4. Downgrade one level for imprecision due to 95%CI of the effect cannot be estimated

H.6.1.10 Treatment frequency: PRN-and-extend vs PRN

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Gain of ≥15 letters at one year							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Very serious[2]	67	RR 1.48 (0.72, 3.05)	VERY LOW
Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)							
1 study (Elden 2015)	Serious[1]	N/A	Not serious	Serious[3]	67	MD 4.50 (-3.78, 12.78)	LOW
Mean number of injections at one year							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Serious[4]	67	MD 1.1	LOW
Adverse events (serious systemic events at one year)							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Very serious[2]	67	RR 1.71 (0.44, 6.66)	VERY LOW
Adverse events (ocular events at one year)							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Very serious[2]	67	RR 0.99 (0.70, 1.38)	VERY LOW

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 estmate confidence interval of the effect

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

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean change in BCVA at 12 months								
25	RCT	10,054	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with anti-VEGF	Not serious	Not serious	Not serious	Not serious	HIGH
			Anti-VEGF frequency – PRN compared with routine injection	Serious[2]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious[3]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – different frequencies of routine treatment	Serious[4]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – treat-and-extend compared with routine or PRN	Serious[2]	Not serious	Not serious	Serious[1]	LOW
			Anti-VEGF frequency – PRN-and-extend compared with routine or PRN	Serious[3]	Not serious	Not serious	Serious[1]	LOW
Mean change in BCVA at 24 months								
10	RCT	7,041	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Not serious	HIGH
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with anti-VEGF	Not serious	Not serious	Not serious	Not serious	HIGH
			Anti-VEGF frequency – PRN compared with monthly	Not serious	Serious[6]	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious[3]	Not serious	Not serious	Not serious	MODERATE
Categorical change in BCVA[7] (change in ETDRS letters) at 12months								
24	RCT	9,950	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with anti-VEGF	Not serious	Not serious	Not serious	Not serious	HIGH
			Anti-VEGF frequency – PRN compared with routine treatment	Serious[3]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious[3]	Not serious	Not serious	Not serious	MODERATE

[7] The estimated effects=z score * 13.7 (standard deviation) at 12 months; and z score *15.1(standard deviation) at 24 months

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			Anti-VEGF frequency – different frequencies of routine treatment	Serious[4]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – treat-and-extend compared with routine or PRN	Serious[2]	Not serious	Not serious	Serious[1]	LOW
			Anti-VEGF frequency – PRN-and-extend compared with routine or PRN	Serious[3]	Not serious	Not serious	Serious[1]	LOW
Categorical change in BCVA (change in ETDRS letters) at 24 months								
10	RCT	7,041	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Not serious	HIGH
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with anti-VEGF	Not serious	Not serious	Not serious	Not serious	HIGH
			Anti-VEGF frequency – PRN compared with monthly	Not serious	Serious[6]	Not serious	Not serious	MODEATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious[3]	Not serious	Not serious	Not serious	MODERATE

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).

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
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?

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
Visual acuity at 1 year (visual acuity ≥ 6/12 vs VA<6/12 to VA>6/96) (ETDRS letters; higher scores indicate better vision)								
2 (Writing committee for the UK AMD EMR user group 2014, Ying 2013)	Cohort study	Serious[1]	Serious[3]	Not serious	Not serious	11,914	MD 16.52 (13.41, 19.64)	LOW
Visual acuity at 1 year (visual acuity ≤6/96 vs VA<6/12 to VA>6/96) (ETDRS letters; higher scores indicate better vision)								
1 (Writing committee for the UK AMD EMR user group 2014)	Cohort study	Serious[1]	N/A	Not serious	Not serious	8,888	MD -17.23 (-22.36, -12.10)	MODERATE
Change in visual acuity at 1 year (visual acuity ≥ 6/12 vs VA<6/12 to VA>6/96) (ETDRS letters; higher scores indicate better vision)								
3 (Writing committee for the UK AMD EMR user group 2014, William 2011, Ying 2013)	Cohort study	Serious[1]	Not serious	Not serious	Not serious	12,529	MD -6.34 (-7.33, -5.36)	MODERATE
Change in visual acuity at 1 year (visual acuity <6/96 vs VA<6/12 letters to VA≥6/96) (ETDRS letters; higher scores indicate better vision)								

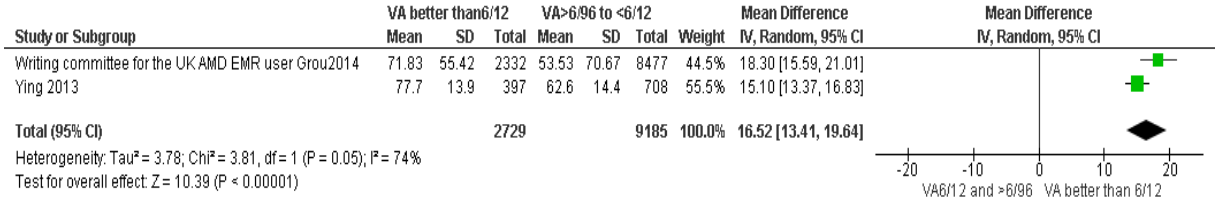
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
1 (Writing committee for the UK AMD EMR user group 2014)	Cohort study	Serious[1]	N/A	Not serious	Not serious	8888	MD 13.99 (10.39, 17.59)	MODERATE
Change in visual acuity at 6 months (visual acuity <6/96 vs VA≥6/96) (Fang 2013, vision threshold up to≥60 letters) (ETDRS letters; higher scores indicate better vision)								
2 (Fang 2013, Writing committee for the UK AMD EMR user group 2014)	Cohort study	Serious[1]	Not serious	Not serious	Not serious	9032	MD 7.77 (5.44, 10.10)	MODERATE
Change in visual acuity at 5 years (visual acuity ≥ 6/12 vs VA <6/12 to VA≥6/60) (ETDRS letters; higher scores indicate better vision)								
1 (Zhu 2015)	Case series	Very serious[2]	N/A	Not serious	Not serious	186	MD -11.75 (-18.98, -4.52)	LOW
Percentage of people who lost 15 letters or more at 1 year (visual acuity ≥6/12 vs VA <6/12to VA >6/100 (23 letter)								
2 (Buckle 2014, El-Mollagyess 2013)	Prospective cohorts	Serious[1]	Serious[3]	Not serious	Very serious[4]	1389	RR 0.41 (0.04, 3.94)	VERY LOW
Percentage of people who lost less than 15 letters at 1 year (visual acuity ≥6/12 vs VA <6/12to VA ≥6/196)								
1 (William 2011)	Prospective cohort	Very serious[2]	N/A	Not serious	Not serious	615	RR 10.01 (0.95, 1.08)	LOW
Percentage of people who gained 15 letters or more at 1 year (visual acuity≥6/12 vs VA<6/12)								
4 (El-Mollagyess	Prospective and	Serious[1]	Not serious	Not serious	Not serious	2310	RR 0.16 (0.12, 0.22)	MODERATE

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect	Quality
2013, Regillo 2015, William 2011, Ying 2013)	retrospective cohorts							
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)								
2 (Fang 2013, Vogel 2016)	Prospective cohorts	Very serious[2]	Not serious	Not serious	Serious[5]	239	RR 1.44 (1.02, 2.01)	VERY LOW

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

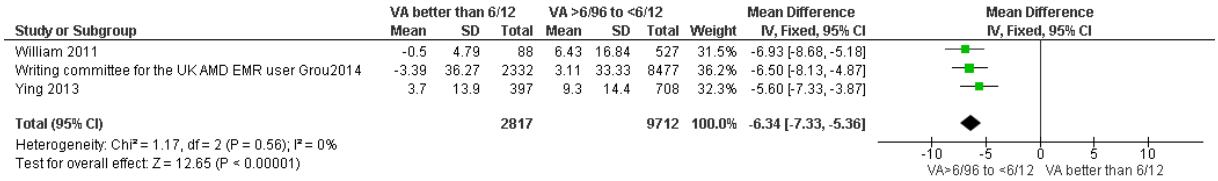
Note: visual acuity 6/12 equivalents to 70 ETDRS letters, and 6/96 equivalents to 25 ETDRS letters.

Mean visual acuity at 1 year

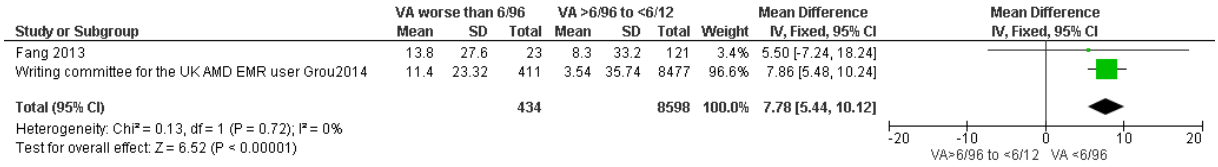


Change in visual acuity

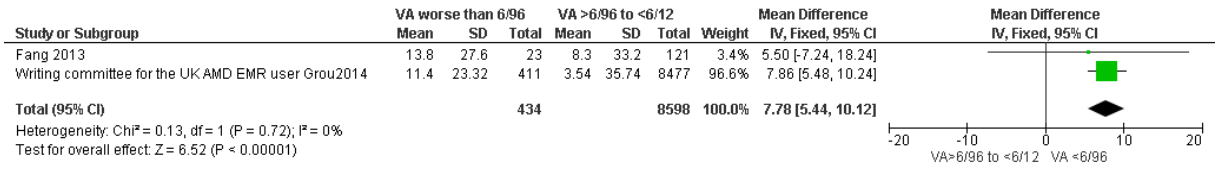
Change in visual acuity (letters) at 1 year



Change in visual acuity at 6 months

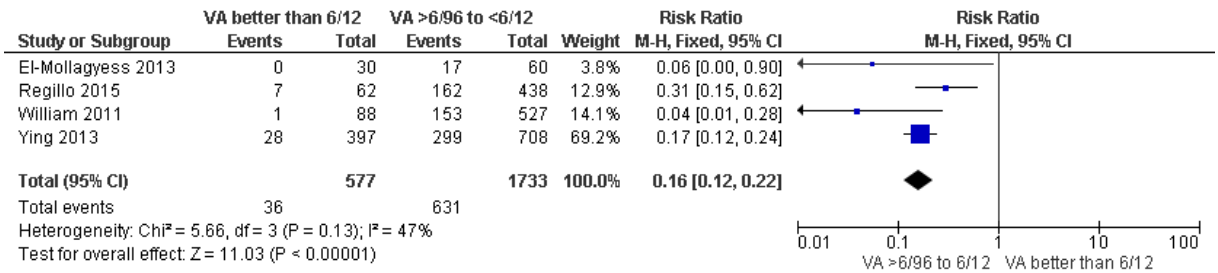


Change in visual acuity at 6 months

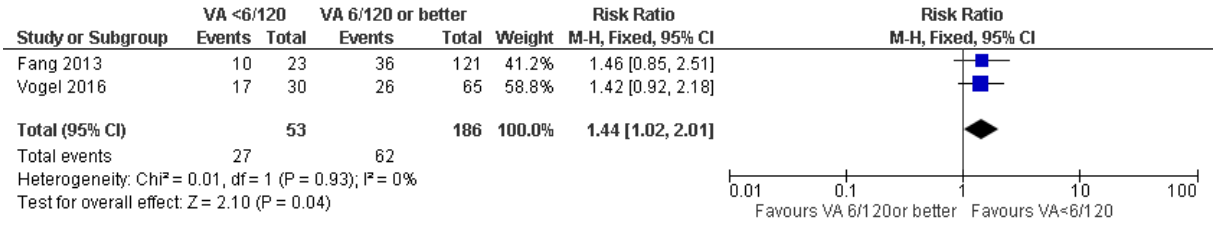


Percentage of people who gained ≥15 letter at 1 year

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



People with poor baseline vision vs people with baseline vision≥6/120 (20 letters)



H.6.3 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

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Anti-VEGF + PDR vs anti-VEGF								
BCVA (ETDRS letters ≤3 months) - positive values favour combination								
1 (Lazic)*	RCT	Serious[1]	Not serious	Not serious	Serious[2]	106	MD -7.25 (-19.82, 5.31)	LOW
BCVA (ETDRS letters >3 months) - positive values favour combination								
11 (Datseris; Bashshur; Hatz; Kaiser; Krebs; Larsen; Semeraro*; Weingessel; Williams: Gomi; Koh)	RCT	Not serious[3]	Not serious	Not serious	Not serious	1025	MD -0.54 (-1.29, 0.21)	HIGH
BCVA (proportion gain ≥15 letters, >3 months) - values greater than 1 favour combination								
9 (Datseris; Bashshur; Hatz; Kaiser; Larsen; Vallance; Williams: Gomi; Koh)	RCT	Not serious[3]	Not serious	Not serious	Serious[2]	923	RR 0.76 (0.63, 0.92)	MODERATE
Reinjections (>3 months) - positive values favour monotherapy								
5 (Datseris; Bashshur; Larsen; Gomi; Koh)	RCT	Serious[4]	Serious[5]	Not serious	Not serious	488	MD -1.43 (-2.42, -0.45)	LOW
Total number of injections (>3 months) - positive values favour monotherapy								

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
6 (Lim; Krebs; Larsen; Semeraro; Weignessel, Williams)	RCT	Serious[4]	Serious[5]	Not serious	Not serious	474	MD -0.94 (-1.76, -0.12)	LOW
Proportion needing retreatment (>3 months) - values greater than 1 favour combination								
1 (Hatz)	RCT	Serious[6]	N/A	Not serious	Serious[2]	40	RR 0.69 (0.42, 1.13)	LOW
Proportion having ocular adverse events - values greater than 1 favour combination								
5 (Lazic; Bashshur; Hatz; Kaiser; Larsen)	RCT	Not serious[3]	Not serious	Not serious	Not serious	762	RR 1.03 (0.88, 1.21)	HIGH
Proportion having non-ocular adverse events - values greater than 1 favour combination								
1 (Larsen)	RCT	Not serious	N/A	Not serious	Serious[2]	255	RR 1.03 (0.82, 1.29)	MODERATE

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)

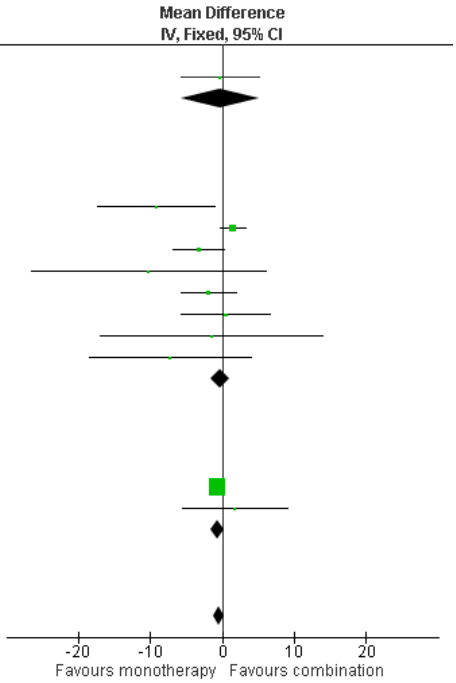
*visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters × -0.02).

Meta-analysis: Anti-VEGF + PDT vs anti-VEGF

Visual acuity

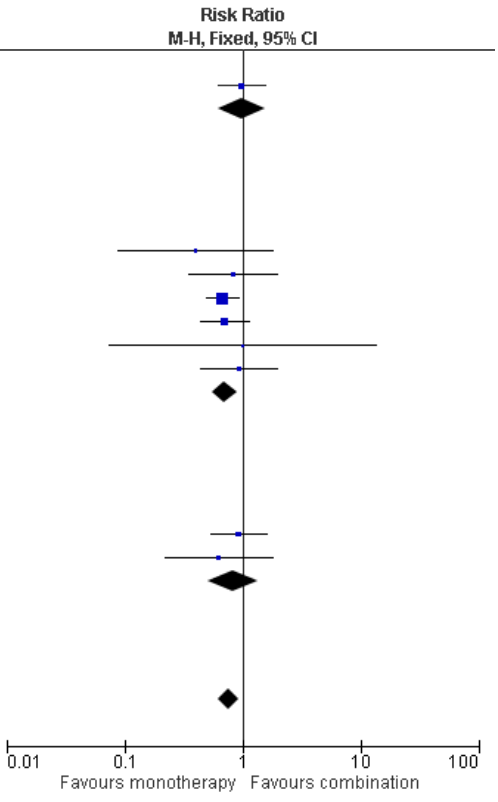
Letters (>3 month follow-up)

Study or Subgroup	anti-VEGF + PDT Mean	SD	Total	anti-VEGF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Bevacizumab								
Datseris 2015	8.37	12.39	49	8.64	14.32	46	1.9%	-0.27 [-5.67, 5.13]
Subtotal (95% CI)			**49**			**46**	**1.9%**	**-0.27 [-5.67, 5.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.3.2 Ranibizumab								
Bashshur 2011	56.6	14.76	20	65.8	11.18	20	0.9%	-9.20 [-17.31, -1.09]
Hatz 2015	9	2.8	19	7.5	2.9	21	17.9%	1.50 [-0.27, 3.27]
Kaiser 2012	4.8478	15.5995	209	8.1	15.1	112	4.6%	-3.25 [-6.76, 0.25]
Krebs 2013	46.89	28.3	19	57.09	24.61	22	0.2%	-10.20 [-26.56, 6.16]
Larsen 2012	2.5	14.8	121	4.4	15.9	132	3.9%	-1.90 [-5.68, 1.88]
Semeraro 2015	24.5	7	25	24	14	25	1.5%	0.50 [-5.64, 6.64]
Weingessel 2016	57.2	24.4	14	58.7	17.6	16	0.2%	-1.50 [-16.92, 13.92]
Williams 2012	2.6	18.53	29	9.9	23.88	27	0.4%	-7.30 [-18.55, 3.95]
Subtotal (95% CI)			**456**			**375**	**29.6%**	**-0.28 [-1.65, 1.10]**
Heterogeneity: Chi² = 15.00, df = 7 (P = 0.04); I² = 53%								
Test for overall effect: Z = 0.39 (P = 0.69)								
1.3.3 Ranibizumab PCV								
Gomi 2015	8.1	1.8	31	8.8	1.8	29	67.4%	-0.70 [-1.61, 0.21]
Koh 2012	10.9	10.9	18	9.2	12.4	21	1.0%	1.70 [-5.61, 9.01]
Subtotal (95% CI)			**49**			**50**	**68.5%**	**-0.66 [-1.57, 0.24]**
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 1.44 (P = 0.15)								
Total (95% CI)			**554**			**471**	**100.0%**	**-0.54 [-1.29, 0.21]**
Heterogeneity: Chi² = 15.63, df = 10 (P = 0.11); I² = 36%								
Test for overall effect: Z = 1.42 (P = 0.16)								
Test for subgroup differences: Chi² = 0.22, df = 2 (P = 0.89), I² = 0%								

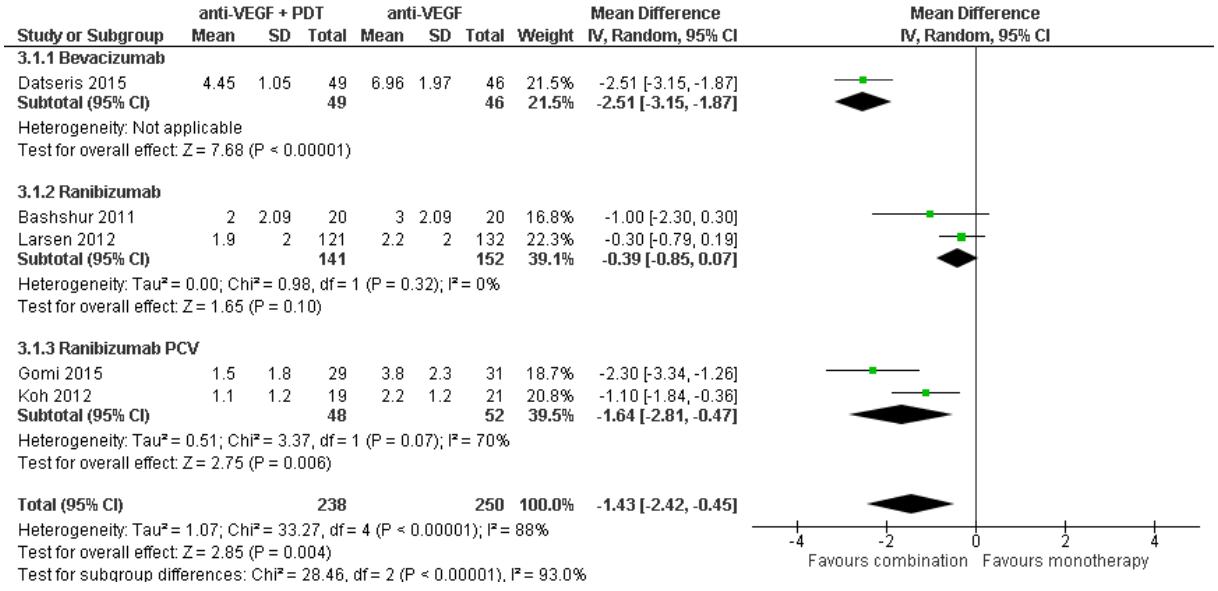


Letters gained (proportion 15 or more letters)

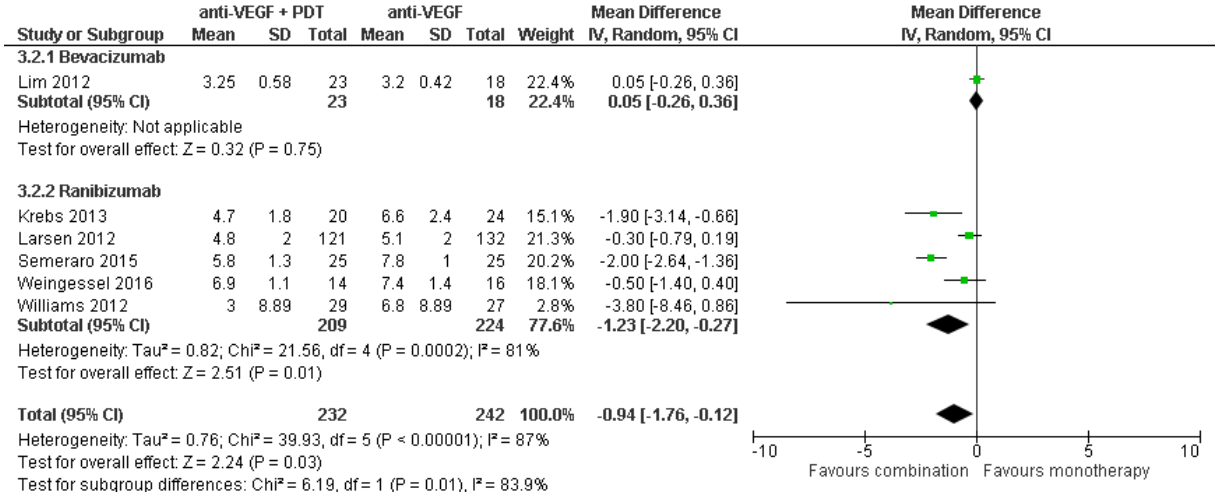
Study or Subgroup	anti-VEGF + PDT Events	Total	anti-VEGF Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Bevacizumab						
Datseris 2015	21	49	20	46	13.1%	0.99 [0.62, 1.56]
Subtotal (95% CI)		**49**		**46**	**13.1%**	**0.99 [0.62, 1.56]**
Total events	21		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.4.2 Ranibizumab						
Bashshur 2011	2	20	5	20	3.2%	0.40 [0.09, 1.83]
Hatz 2015	6	19	8	21	4.8%	0.83 [0.35, 1.95]
Kaiser 2012	58	209	46	112	38.1%	0.68 [0.49, 0.92]
Larsen 2012	22	121	34	132	20.7%	0.71 [0.44, 1.14]
Vallance 2010	1	9	1	9	0.6%	1.00 [0.07, 13.64]
Williams 2012	9	29	9	27	5.9%	0.93 [0.44, 1.99]
Subtotal (95% CI)		**407**		**321**	**73.4%**	**0.71 [0.56, 0.89]**
Total events	98		103			
Heterogeneity: Chi² = 1.33, df = 5 (P = 0.93); I² = 0%						
Test for overall effect: Z = 2.91 (P = 0.004)						
1.4.3 Ranibizumab PCV						
Gomi 2015	13	29	15	31	9.2%	0.93 [0.54, 1.60]
Koh 2012	4	19	7	21	4.2%	0.63 [0.22, 1.82]
Subtotal (95% CI)		**48**		**52**	**13.5%**	**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	136		145			
Heterogeneity: Chi² = 3.53, df = 8 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.80 (P = 0.005)						
Test for subgroup differences: Chi² = 1.73, df = 2 (P = 0.42), I² = 0%						



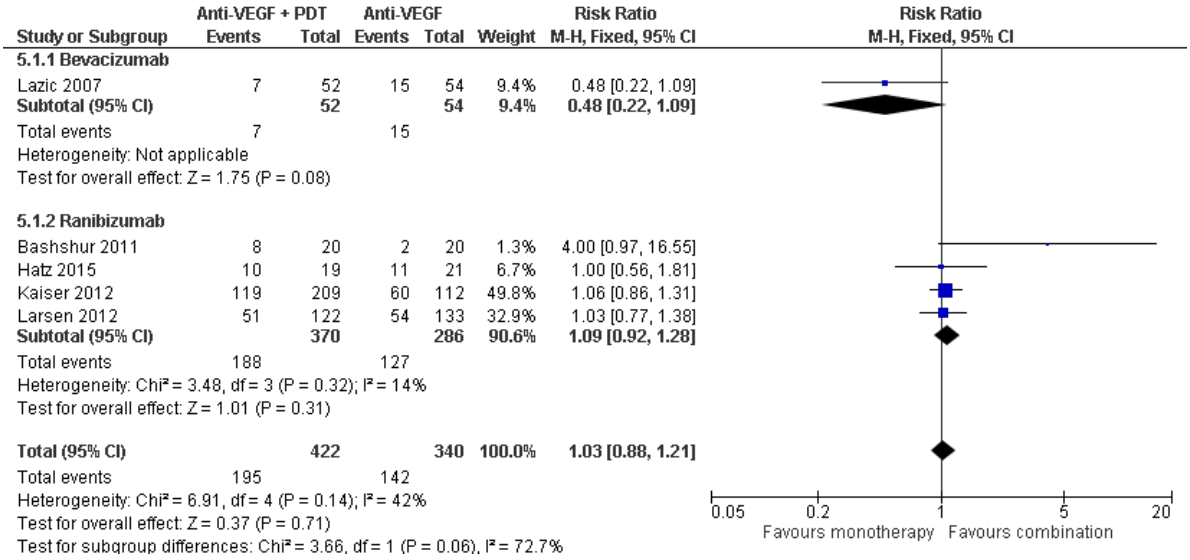
Number of injections: reinjections



Number of injections: total number of injections



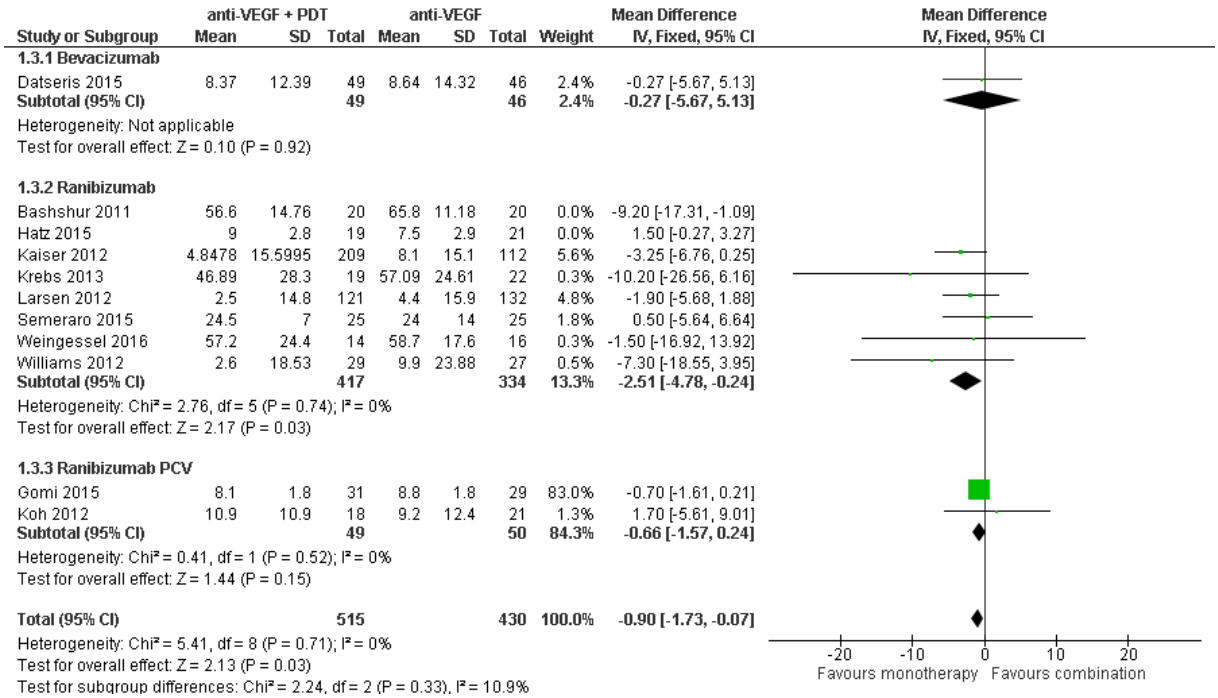
Ocular adverse events



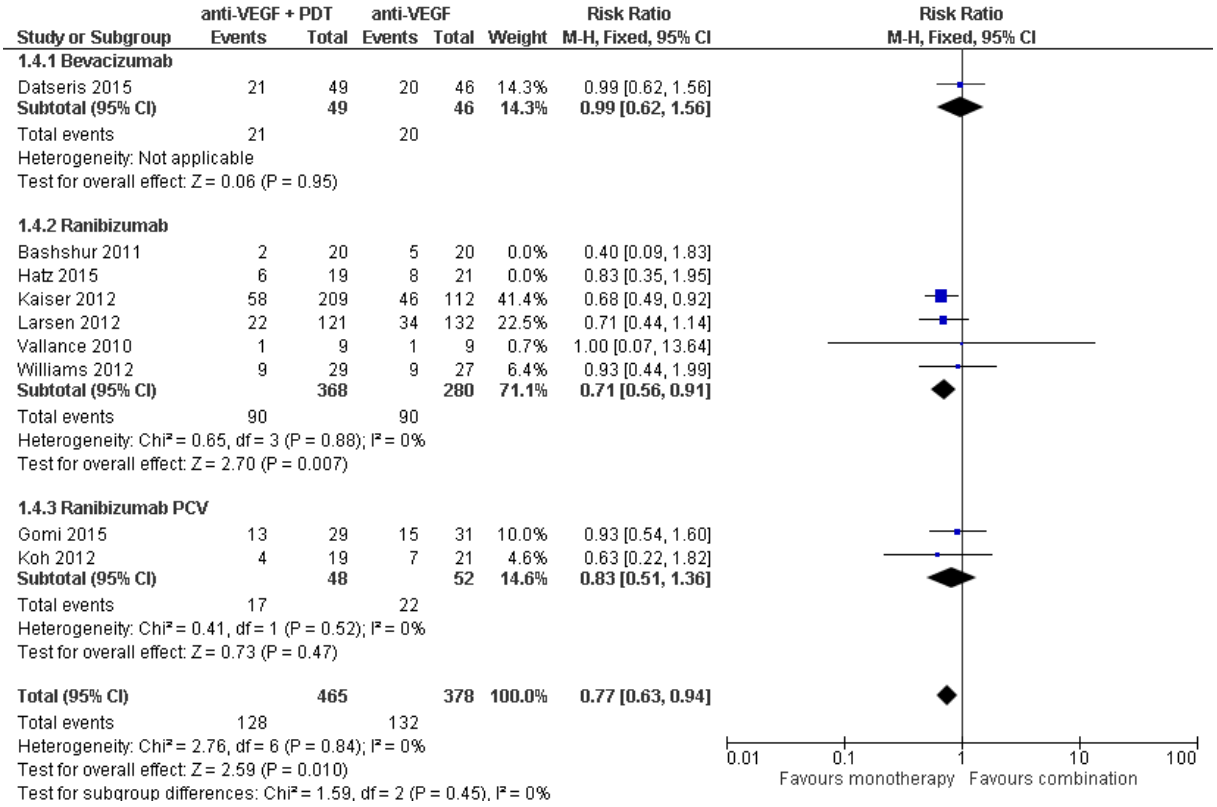
Meta-analysis (excluded study population with previous treatment history)

Visual acuity

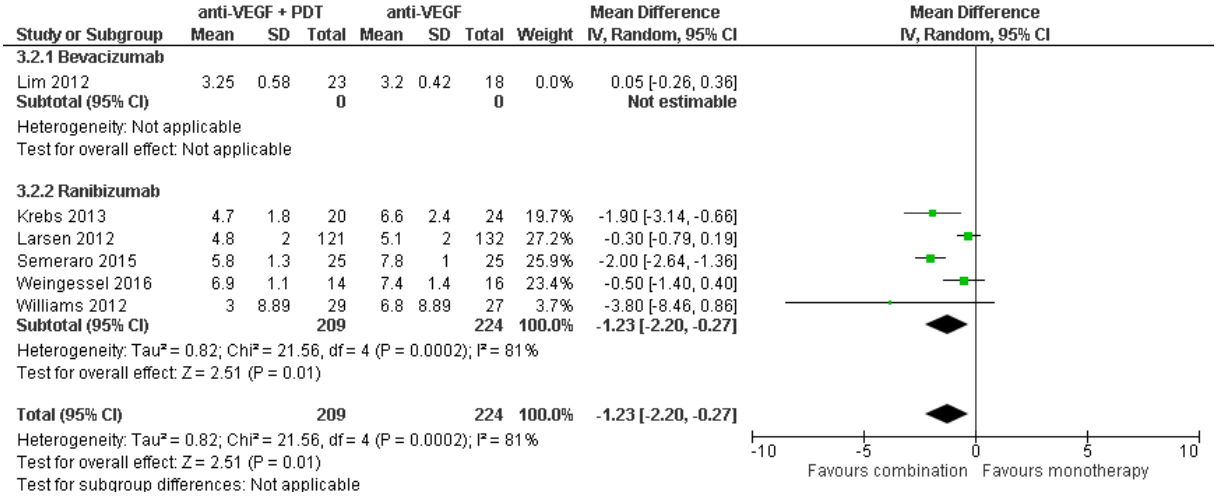
Letters (>3 month follow-up)



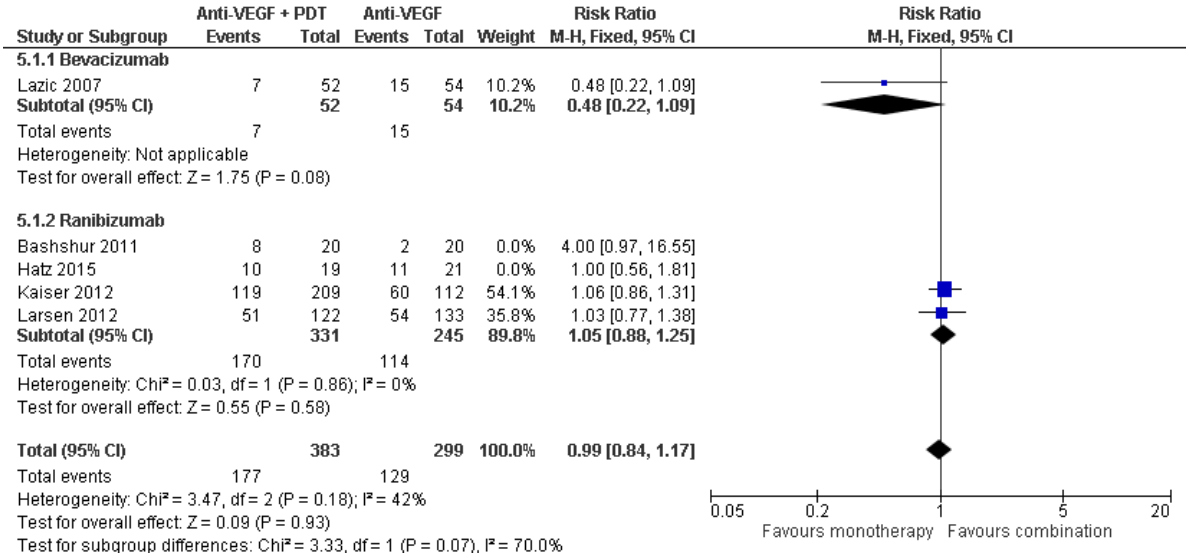
Letters gained (proportion 15 or more letters)



Total number of injections



Proportion of people had ocular adverse events



H.6.3.2 Anti-VEGF + steroids vs anti-VEGF

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

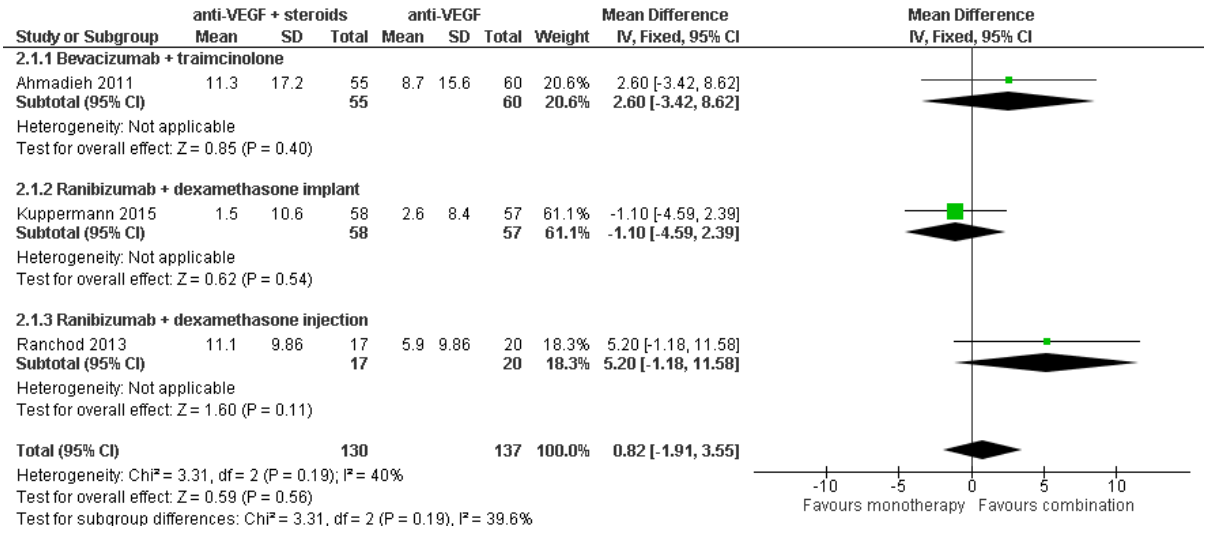
1. Some individual studies at high-risk of bias, but overall risk of bias rated low due to consistency of effect size estimates between high and low quality studies.
2. Downgraded one level for unclear about cataract status of study population.
3. Downgraded one level for study design (open label, single 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).

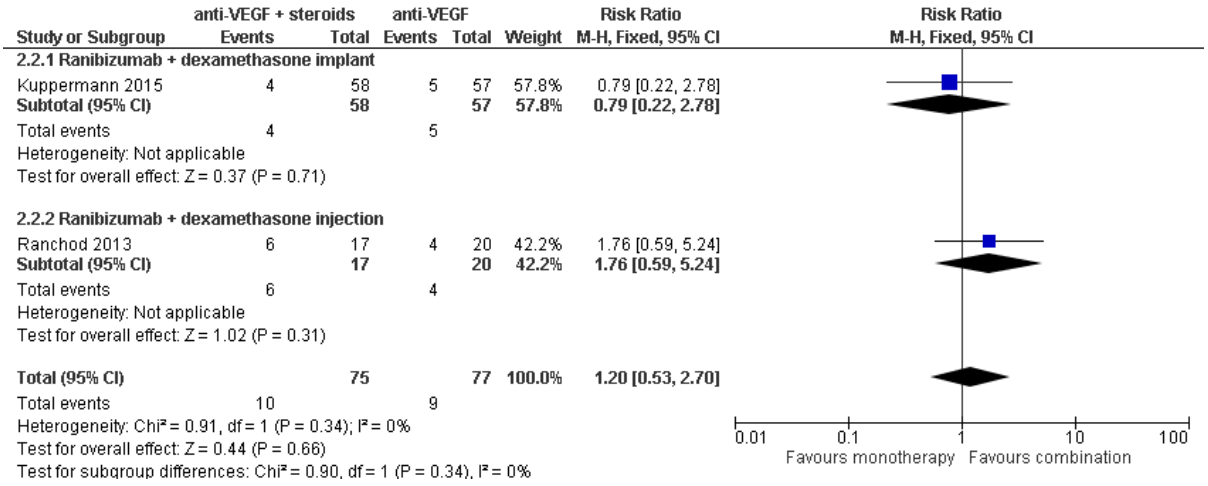
Meta-analysis: anti-VEGF + steroids vs anti-VEGF

Visual acuity

Letters (>3 month follow-up)



Letters gained (proportion 15 or more letters)



H.6.3.3 Anti-VEGF +PDT vs anti-VEGF steroid + PDT

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Anti-VEGF + PDT vs anti-VEGF steroids + PDT								
BCVA (ETDRS letters >3 months) – positive values favour triple therapy								
1 (Piri)*	RCT	Not serious	Not serious	Serious[1]	Serious[2]	84	MD 0.50 (-6.04, 7.04)	LOW
Reinjections (>3 months) – positive values favour triple therapy								
1 (Piri)	RCT	Not serious	Not serious	Serious[1]	Serious[2]	84	MD -0.40 (-0.83, 0.03)	LOW
Proportion needing retreatment (>3 months) – values greater than 1 favour triple therapy								
1 (Piri)	RCT	Not serious	Not serious	Serious[1]	Serious[2]	84	RR 0.84 (0.71, 0.98)	LOW

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

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95% CI)	Quality
Ranibizumab to aflibercept vs continuing on ranibizumab								
Visual acuity (ETDRS letters) [change score] (Better indicated by higher values)								
1 (Mantel 2016)	RCT	Very serious[1]	N/A	Not serious	Not serious	21	MD -2.5 (-4.87 to -0.13)	LOW
Ranibizumab to bevacizumab vs bevacizumab to ranibizumab								
Best corrected visual acuity (logMAR) - 12 months (Better indicated by lower values)								
1 (Kucukerdonmez 2015)	Cohort study	Very serious[1]	N/A	Not serious	Not serious	87	MD 0.05 (-2.84 to 2.94)	LOW
Best corrected visual acuity (logMAR) - ≥ 12 months (Better indicated by lower values)								
1 (Kucukerdonmez 2015)	Cohort study	Very serious[1]	N/A	Not serious	Serious[2]	87	MD 0.16 (-0.88 to 1.20)	VERY LOW
Bevacizumab to ranibizumab								
Visual acuity (logMAR) - ≤ 3 months (Better indicated by lower values)								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95% CI)	Quality
1 (Moisseiev 2015)	Before–after study	Very serious[1]	N/A	Not serious	Serious[3]	110	MD- 0.02 (-0.11 to 0.07)	VERY LOW
Visual acuity (logMAR) – at least 4 months (Better indicated by lower values)								
1 (Moisseiev 2015)	Before–after study	Very serious[1]	N/A	Not serious	Serious[3]	110	MD -0.04 (-0.06 to 0.14)	VERY LOW
Bevacizumab to aflibercept								
Best corrected visual acuity (ETDRS) - ≥ 12 months (Better indicated by higher values)								
1 (Pinheiro-Costa 2015)	Observational study	Very serious[1]	N/A	Not serious	Serious[3]	39	MD -2.4 (-10.15 to 5.35)	VERY LOW
Bevacizumab and/or ranibizumab to aflibercept								
Best corrected visual acuity (logMAR) - After 1 injection (Better indicated by lower values)								
1 (Yonekawa 2013)	Observational study	Very serious[1]	N/A	Not serious	Serious[3]	102	MD 0.02 (-0.07 to 0.11)	VERY LOW
Best corrected visual acuity (logMAR) - > 3 months and <12 months (Better indicated by lower values)								
1 (Yonekawa 2013)	Observational study	Very serious[1]	N/A	Not serious	Serious[3]	102	MD -0.04 (-0.12 to 0.04)	VERY LOW
Best corrected visual acuity (logMAR) - ≥ 12 months (Better indicated by lower values)								
1 (Homer 2015)	Observational study	Very serious[1]	N/A	Not serious	Not serious	21	MD 0 (-0.17 to 0.17)	LOW
Best corrected visual acuity (ETDRS) - After 3 injections (Better indicated by higher values)								
1 (Gharbiya 2014)	Observational study	Very serious[1]	N/A	Not serious	Serious[3]	31	MD -0.2 (-5.95 to 5.55)	VERY LOW
Best corrected visual acuity (ETDRS) - > 3 months and <12 months (Better indicated by higher values)								
2 (Gharbiya 2014, Thorell 2014)	Observational studies	Very serious[1]	N/A	Not serious	Not serious	104	MD 0.44 (-2.59 l to 3.48)	LOW

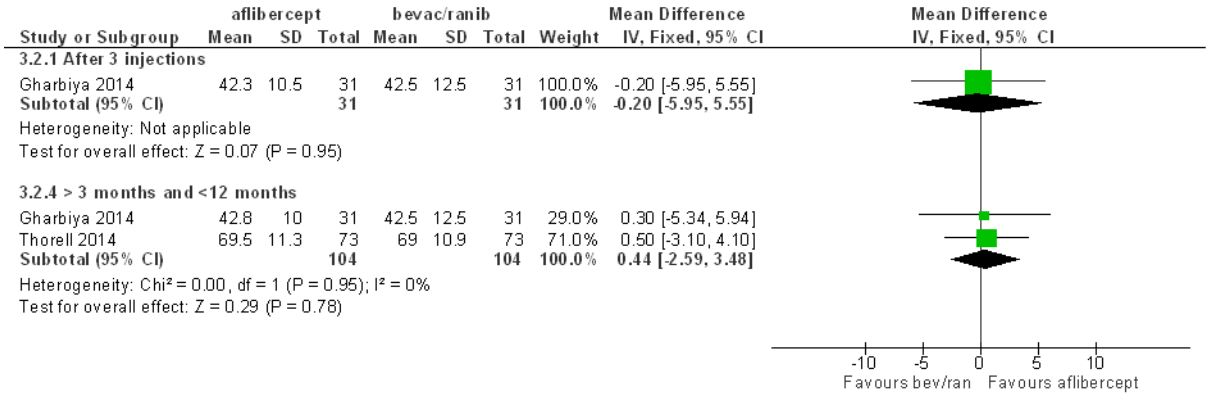
1. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

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

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 (ETDRS)



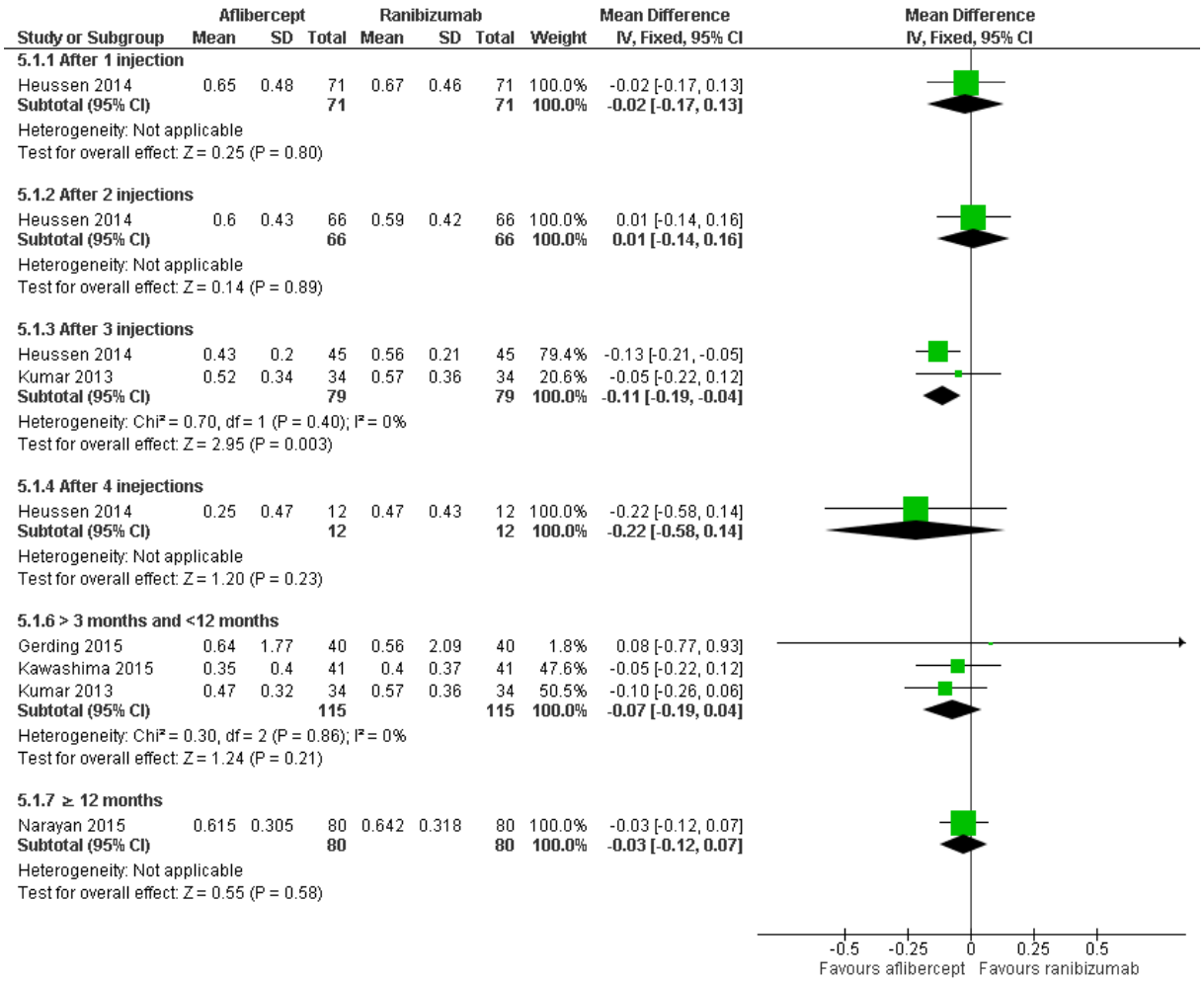
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Ranibizumab to aflibercept								
Best corrected visual acuity (logMAR) - After 1 injection (Better indicated by lower values)								
1 (Heussen 2014)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	71	MD -0.02 (-0.17 l to 0.13)	VERY LOW
Best corrected visual acuity (logMAR) - After 2 injections (Better indicated by lower values)								
1 (Heussen 2014)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	66	MD 0.01 (-0.14 to 0.16)	VERY LOW
Best corrected visual acuity (logMAR) - After 3 injections (Better indicated by lower values)								
2 (Kumar 2013, Heussen 2014)	Observational studies	Very serious[1]	N/A	Not serious	Serious[2]	79	MD -0.11 (-0.19 to - 0.04)	VERY LOW
Best corrected visual acuity (logMAR) - After 4 injections (Better indicated by lower values)								
1 (Heussen 2014)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	12	MD -0.22 (-0.58 to 0.14)	VERY LOW
Best corrected visual acuity (logMAR) - > 3 months and <12 months (Better indicated by lower values)								
3 (Gerding 2015, Kawshima 2015, Kumar 2013)	Observational studies	Very serious[1]	N/A	Not serious	Serious[2]	115	MD -0.07 (-0.19 to 0.04)	VERY LOW
Best corrected visual acuity (logMAR) - ≥ 12 months (Better indicated by lower values)								
1 (Narayan 2015)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	80	MD -0.03 (-0.12 to 0.07)	VERY LOW
Best corrected visual acuity (ETDRS) - > 3 months and <12 months (Better indicated by higher values)								
2 (Chang 2015, Sarao 2016)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	141	MD 4.45 (0.96 to 7.94)	VERY LOW

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

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

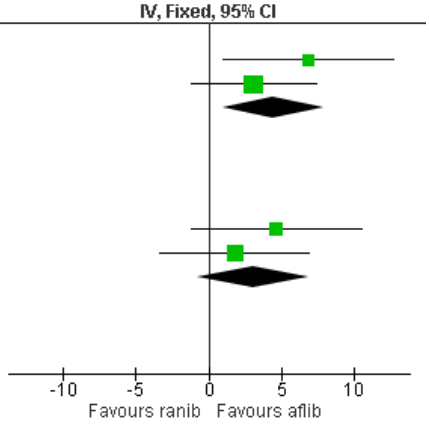
Meta-analysis (forest plots) for ranibizumab to aflibercept

Best corrected visual acuity (logMAR)



Best corrected visual acuity (letter)

Study or Subgroup	Aflibercept Mean	SD	Total	Ranibizumab Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.2.1 > 3 months and <12 months								
Chang 2015	67.4	13.27	49	60.5	16.2	49	35.5%	6.90 [1.04, 12.76]
Sarao 2016	55.9	11.64	92	52.8	17.8	92	64.5%	3.10 [-1.25, 7.45]
Subtotal (95% CI)			**141**			**141**	**100.0%**	**4.45 [0.96, 7.94]**
Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4%								
Test for overall effect: Z = 2.50 (P = 0.01)								
5.2.5 ≥ 12 months								
Chang 2015	65.2	13.35	49	60.5	16.2	49	43.3%	4.70 [-1.18, 10.58]
Sarao 2016	54.6	17.74	92	52.8	17.8	92	56.7%	1.80 [-3.34, 6.94]
Subtotal (95% CI)			**141**			**141**	**100.0%**	**3.06 [-0.81, 6.92]**
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%								
Test for overall effect: Z = 1.55 (P = 0.12)								



Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%

Bevacizumab to bevacizumab + triamcinolone acetonide

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95% CI)	Quality
Bevacizumab to bevacizumab + triamcinolone acetonide								
Best corrected visual acuity (logMAR) - ≤ 3 months (Better indicated by lower values)								
1 (Tao 2010)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	31	MD -0.11 (-0.3 to 0.08)	VERY LOW
Best corrected visual acuity (logMAR) - > 3 months and <12 months (Better indicated by lower values)								
1 (Tao 2010)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	31	MD -0.07 (-0.26 to 0.12)	VERY LOW
1 (Tao 2010)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	31	MD -0.02 (-0.21 to 0.17)	VERY LOW

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?

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Visual acuity (ETDRS letter) change from baseline to CNV event (higher values indicate better vision)								
1 (Chew E Y 2014)	RCT	Serious[1]	N/A	Not serious	Serious[2]	81	MD=5.20 (-1.48, 11.88)	LOW
Visual acuity (ETDRS letter) at CNV event (higher values indicate better vision)								
1 (Chew E Y 2014)	RCT	Serious[1]	N/A	Not serious	Serious[2]	81	MD=4.2 (-2.69, 11.09)	LOW
Percentage of participants maintaining 20/40 or better visual acuity								
1 (Chew E Y 2014)	RCT	Serious[1]	N/A	Not serious	Serious[2]	81	RR=1.31 (0.94, 1.81)	LOW
CNV detection rate								
1 (Chew E Y 2014)	RCT	Serious[1]	N/A	Not serious	Serious[2]	1520	RR=1.63 (1.06, 2.52)	LOW
Frequency of self-monitoring (VMS journal vs usual care control group)								
1 (Bittner A K 2014)	RCT	Very serious[3,4]	N/A	Not serious	Serious[2]	198	RR[5]=1.61 (1.25, 1.82)	VERY LOW
No confidence in self-monitoring (VMS journal vs usual care control group)								
1 (Bittner A K 2014)	RCT	Very serious[3,4]	N/A	Not serious	Not serious	198	RR[5]=0.31 (0.12, 0.69)	LOW

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)

H.7.3 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)?

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Neovascularisation (fluid)											
SD-Optical coherence tomography vs FA											
2 studies (Giani, Khurana,)	Retrospective	152 eyes (149 people)	92.3% (83.9, 96.5%)	35.8% (25.3, 47.8%)	LR+	1.37 (1.15, 1.63)	Serious[1]	Not serious	Not serious	Not serious	MODERATE
					LR-	0.22 (0.10, 0.50)	Serious[1]	Not serious	Not serious	Serious[2]	LOW
TD-Optical coherence tomography vs FA											
3 studies (Eter, Khurana, van velthoven)	2 x Retrospective 1 x Prospective (van velthoven)	149 eyes (146 people)	69.6% (59.7, 78.0%)	63.1% (48.2, 75.9%)	**LR+**	1.58 (1.04, 2.39)	Serious[1]	Not serious	Not serious	Serious[2]	LOW
					LR-	0.48 (0.33, 0.70)	Serious[1]	Not serious	Not serious	Serious[2]	LOW
TD-Optical coherence tomography vs FA (analysis unit: sets of OCT and FA)											
2 (Henschel, Salinas-Alaman)	Prospective	237 sets of OCT and FA (66 people), up to 12 months follow-up	95.9% (91.1, 98.1%)	51.8% (41.4, 62.1%)	**LR+**	1.85 (1.51, 2.28)	Serious[3]	Not serious	Not serious	Serious[2]	LOW
					LR-	0.08 (0.03, 0.17)	Serious[3]	Not serious	Not serious	Not serious	MODERATE
OCT-A vs multimodal imaging (FA, ICG, OCT)											
1 (Coscas)	Retrospective	80 eyes (73 people)	96.6% (90.6, 99.6%)	86.4% (69.6, 97.0%)	**LR+**	7.08 (2.47, 20.29)	Serious[1]	N/A	Not serious	Not serious	MODERATE

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					LR-	0.04 (0.01, 0.16)	Serious[1]	N/A	Not serious	Not serious	MODERATE
Neovascular AMD activities (PED)											
SD-Optical coherence tomography vs FA											
1 (Giani)	Retrospective	93 eyes (93 people))	38.5% (25.8, 51.9%)	68.3% (53.5, 81.4%)	**LR+**	1.21 (0.69, 2.14)	Serious[1]	N/A	Not serious	Serious[2]	LOW
					LR-	0.90 (0.67, 1.22)	Serious[1]	N/A	Not serious	Not serious	MODERATE
TD-Optical coherence tomography vs FA											
1 (Van de Moere))	Retrospective	121 eyes (121 people)	6.3% (2.0, 13.0%)	99.0% (95.2, 100.0%)	**LR+**	6.59 (0.36, 119.77)	Serious[1]	N/A	Not serious	Very serious[4]	VERY LOW
					LR-	0.95 (0.89, 1.01)	Serious[1]	N/A	Not serious	Not serious	MODERATE
Neovascular AMD activities (intraretinal fluid)											
SD-Optical coherence tomography vs FA											
1 ((Khurana)	Retrospective	59 eyes (56 people)	65.5% (47.6, 81.4%)	63.3% (45.7, 79.3%)	**LR+**	1.79 (1.04, 3.06)	Serious[1]	N/A	Not serious	Serious[2]	LOW
					LR-	0.54 (0.31, 0.96)	Serious[1]	N/A	Not serious	Serious[2]	LOW
TD-Optical coherence tomography vs FA											
2 Khurana, van de moere)	Retrospective	180 eyes (177 people)	67.6% (56.3, 77.1%)	59.9% (48.6, 70.2%)	**LR+**	+ 1.71 (1.28, 2.27)	Serious[1]	Not serious	Not serious	Serious[2]	LOW
					LR-	0.65 (0.48, 0.88)	Serious[1]	Not serious	Not serious	Serious[2]	LOW
TD-Optical coherence tomography vs FA (analysis unit: sets of OCT and FA)											

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Henschel)	Prospective	14 people (61 pairs of OCT and FA during 12 weeks after PDT treatment)	90.3% (77.9, 97.9%)	40.0% (23.5, 57.7%)	**LR+**	1.51 (1.10, 2.06)	Serious[3]	N/A	Not serious	Serious[2]	LOW
					LR-	0.24 (0.08, 0.77)	Serious[3]	N/A	Not serious	Serious[2]	LOW
Neovascular AMD activities (subretinal fluid)											
SD-Optical coherence tomography vs FA											
1 (Khurana)	Retrospective	59 eyes (56 people)	69.0% (51.3, 84.1%)	76.7% (60.3, 89.7%)	**LR+**	2.96 (1.48, 5.91)	Serious[1]	N/A	Not serious	Serious[2]	LOW
					LR-	0.41 (0.23, 0.72)	Serious[1]	N/A	Not serious	Serious[2]	LOW
TD-Optical coherence tomography vs FA											
2 (Khurana, van de moere)	Retrospective	180 eyes (177 people)	47.5% (37.9, 57.3%)	83.9% (74.3, 90.4%)	**LR+**	2.96 (1.73, 5.09)	Serious[1]	Not serious	Not serious	Serious[2]	LOW
					LR-	0.63 (0.51, 0.77)	Serious[1]	Not serious	Not serious	Not serious	MODERATE
TD-Optical coherence tomography vs FA (analysis unit: sets of OCT and FA)											
1 study (Henschel)	Prospective	14 people (61 pairs of OCT and FA during 12 weeks after PDT treatment)	71.0% (54.1, 85.3%)	73.3% (56.5, 87.3%)	**LR+**	2.66 (1.41, 5.02)	Serious[3]	N/A	Not serious	Serious[2]	LOW
					LR-	0.40 (0.22, 0.72)	Serious[3]	N/A	Not serious	Serious[2]	LOW
Neovascular AMD activities (retinal cystoid abnormalities)											

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
SD-Optical coherence tomography vs FA											
1 (Khurana)	Retrospective	59 eyes (56 people)	58.6% (40.6, 75.5%)	56.7% (38.9, 73.6%)	**LR+**	1.35 (0.81, 2.26)	Serious[1]	N/A	Not serious	Serious[2]	LOW
					LR-	0.73 (0.43, 1.25)	Serious[1]	N/A	Not serious	Serious[2]	LOW
TD-Optical coherence tomography vs FA											
1 (Khurana)	Retrospective	59 eyes (56 people)	73.3% (56.5, 87.3%)	55.6% (32.9, 77.0%)	**LR+**	1.29 (0.60, 2.81)	Serious[1]	N/A	Not serious	Serious[2]	LOW
					LR-	0.89 (0.64, 1.26)	Serious[1]	N/A	Not serious	Not serious	MODERTE
Neovascular AMD activities (cystoid macular oedema)											
TD-Optical coherence tomography vs FA											
1 (van de moere)	Retrospective	121 eyes (121 people)	22.9% (13.9, 33.3%)	98.0% (92.9, 99.9%)	LR+	11.66 (1.60, 85.1)	Serious[1]	N/A	Not serious	Serious[2]	LOW
					LR-	0.79 (0.69, 0.90)	Serious[1]	N/A	Not serious	Not serious	MODERATE
Neovascular AMD activities (cystoid spaces)											
TD-Optical coherence tomography vs FA											
1 (Eter)	Retrospective	60 eyes (60 people)	80% (66.7, 88.9%)	80% (45.9, 95.0%)	**LR+**	4.00 (1.15 to 13.92)	Serious[1]	N/A	Not serious	Serious[2]	LOW
					LR-	0.25 (0.13 to 0.47)	Serious[1]	N/A	Not serious	Not serious	MODERATE
SD-Optical coherence tomography vs FA											
1 (Giani)	Retrospective	93 eyes (93 people)	51.9% (38.5, 65.0%)	43.9% (29.7, 59.2%)	**LR+**	0.93 (0.64 to 1.35)	Serious[1]	N/A	Not serious	Not serious	MODERATE

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	LRs	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					LR-	1.09 (0.70 to 1.71)	Serious[1]	N/A	Not serious	Not serious	MODERATE

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 mininmal 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?

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%CI)	Quality
Barriers to appointment attendance and uptake of treatment								
Burden of periodic follow-up visits (3 studies)								
1 (Boulanger-Scemama 2015)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	20 lost to follow-up and no longer receiving care	15% (n=3) (5%, 36%)	VERY LOW
1 (Varano Monic 2015)	Observational study	Very serious[1]	N/A	Not serious	Not serious	910 treated for wet AMD	8.6% (n=78) (7%, 10.7%)	LOW
1 (Vaze 2014)	Observational study	Very serious[1]	N/A	Serious[3]	Not serious	248 began anti-VEGF treatment	0.8% (n=2) (0.2%, 2.9%)	VERY LOW
Travel problem (4 studies)								
1 (Boulanger-Scemama 2015)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	58 lost to follow-up	51.7% (n=30) (39.2%, 64.1%)	VERY LOW
1 (Droege 2013)	Observational study	Very serious[1]	N/A	Serious[3]	Serious[2]	19 stopped visits and interviewed	26.3% (n=5) (11.8%, 48.8%)	VERY LOW
1 (Nunes 2010)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	19 answered phone questionnaire	5.3% (n=1) (0.9%, 24.6%)	VERY LOW
1 (Vaze 2014)	Observational study	Very serious[1]	N/A	Serious[3]	Not serious	248 began anti-VEGF treatment	10.9%(n=27) (7.6%, 15.2%)	VERY LOW
Comorbidities (5 studies)								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%CI)	Quality
1 (Boulanger-Scemama 2015)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	58 lost to follow-up	1.7% (n=1) (0.3%, 9.1%)	VERY LOW
1 (Droege 2013)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	19 stopped visits and interviewed	15.8% (n=3) (5.5%, 37.6%)	VERY LOW
1 (Nunes 2010)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	19 answered phone questionnaire	15.8% (n=3) (5.5%, 37.6%)	VERY LOW
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date	23.5% (n=24) (16.3%, 32.6%)	LOW
1 (Vaze A 2014)	Observational study	Very serious[1]	Not serious	Serious[3]	Not serious	248 began anti-VEGF	4.4% (n=11) (2.5%, 7.8%)	VERY LOW
Treatment related emotion (pain/discomfort/fear/dissatisfaction with treatment benefit) (4 studies)								
1 (Boulanger-Scemama 2015)	Observational study	Very serious[1]	Not serious	Not serious	Serious[2]	20 lost to follow-up and no longer receiving care	50% (n=10) (29.9%, 70.1%)	VERY LOW
1 (Droege 2013)	Observational study	Very serious[1]	Not serious	Not serious	Serious[2]	19 stopped visits and interviewed	36.8% (n=7) (19.1%, 59.0%)	VERY LOW
1 (Varano 2015)	Observational study	Very serious[1]	Not serious	Not serious	Not serious	910 treated for wet AMD	3.0% (n=27) (2.0%, 4.3%)	LOW
1 (Vaze A 2014)	Observational study	Very serious[1]	Not serious	Serious[3]	Not serious	248 began anti-VEGF	1.2% (n=3) (0.4%, 3.5%)	VERY LOW
Lack of information (2 studies)								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%CI)	Quality
1 (Mitchell 2002)	Observational study	Serious[1]	Not serious	Serious[5]	Not serious	604 completed and answered the question	43.4% (n=262) (39.5%, 47.4%)	LOW
1 (Nunes 2010)	Observational study	Very serious[1]	Not Serious	Not serious	Serious[2]	19 answered phone questionnaire	26.3% (n=5) (11.8%, 48.8%)	VERY LOW
Specialist's attitudes (dismissive, patronising, brusque, unfeeling, uninterested in patients, using jargon) (1 study)								
1 (Mitchell 2002)	Observational study	Serious[1]	N/A	Serious[5]	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 serious[1]	N/A	Not serious	Serious[2]	19 answered phone questionnaire	42.1%(n=8) (23.1%, 63.7%)	VERY LOW
1 (Vaze 2014)	Observational study	Very serious[1]	N/A	Serious[3]	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 serious[1]	N/A	Not serious	Serious[2]	19 answered phone questionnaire	10.5% (n=2) (2.9%, 31.3%)	VERY LOW
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	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)								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%CI)	Quality
1 (Varano 2015)	Observational study	Very serious[1]	N/A	Not serious	Not serious	910 treated for wet AMD	23.5% (n=214) (20.9%, 26.4%)	LOW
1)Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date	21.6% (n=22) (14.7%, 30.5%)	LOW
Financial burden (4 studies)								
1 (Boulanger-Scemama 2015)	Observational study	Very serious[1]	N/A	Not serious	Serious[2]	58 lost to follow-up	8.6% (n=5) (3.7%, 18.6%)	VERY LOW
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date	25.5% (n=26) (18.0%, 34.7%)	LOW
1 (Varano 2015)	Observational study	Very serious[1]	N/A	Not serious	Not serious	910 treated for wet AMD	5.0% (n=45) (3.7%, 6.5%)	LOW
1 (Vaze 2014)	Observational study	Very serious[1]	N/A	Serious[3]	Not serious	248 began anti-VEGF	0.8% (n=2) (0.2%, 2.9%)	VERY LOW
Long wait time (1 study)								
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	102 failed to reschedule a missed or patient-cancelled	52.0% (n=53) (42.3%, 61.4%)	LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%CI)	Quality
						appointment within 1 month of the desired follow-up date		
Facilitators to appointment attendance and uptake of treatment (1 study)								
Pre-appointment reminder (by phone, text, email)								
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	240 participants answered the question	81.7% (n=153) (70.6%, 93.9%)	LOW
Parking vouchers								
1 study (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	240 participants answered the question	47.9% (n=115) (41.7%, 54.2%)	LOW
Transportation service to and from the clinic								
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	240 participants answered the question	44.6% (n=107) (38.4%, 50.9%)	LOW
Mobile eye care van								
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	240 participants answered the question	32.1% (n=77) (26.5%, 38.2%)	LOW
Networking with other patients with the same eye diseases								
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	240 participants answered the question	41.3% (n=99) (35.2%, 47.5%)	LOW
More education on eye disease/the importance of follow-up								
1 (Thompson 2015)	Observational study	Serious[1]	N/A	Serious[4]	Not serious	240 participants answered the question	70.8% (n=170) (64.8, 76.2%)	LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%CI)	Quality
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) ; 4. Downgraded one level for 86 of a total of 240 participants had AMD; 5. Downgraded one level for participants were member of macular society and not all had AMD								

CERQual tables

Review finding	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
Barriers to appointment attendance and uptake of treatment			
Patients' psychological issues (anxiety, fear and distressing)			
Patients may decline treatment due to emotion such as anxiety, fear and distressing. Patients described these emotions, when they prepared for treatment, or were relative newness of the treatment, or experienced disease progression.	Burton Amy E, Shaw Rachel, and Gibson Jonathan. 2013. British Journal of Visual Impairment 31:178-188 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.
Communication with healthcare professionals			
Patients described a sense of confusion when having to interact with a variety of healthcare professionals during their treatments and commented on problems with hospital appointment letters which gave little information about what each appointment was for and what the participant should expect plus many struggled to read letters. A wide variety of information deficits after diagnosis was evident. A lack of knowledge about the purpose of medical processes and procedures was highlighted. Patients were unsure about when their treatment cycle and there were examples of patients attempting to make their own judgement about the need for treatment.	Burton Amy E, Shaw Rachel, and Gibson Jonathan. 2013. British Journal of Visual Impairment 31:178-188 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			
The invasiveness of the treatment and often painful recovery were significant issues for patients.	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

Review finding	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
The physical difficulties participants experienced with frequent and on-going treatment were often compounded by anxiety and fear.			were recruited through a nonprobability, convenience sampling). Coherence could not be assessed as only 1 study. Adequate data with minor concern about relevance.
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.	Burton Amy E, Shaw Rachel, and Gibson Jonathan. 2013. British Journal of Visual Impairment 31:178-188	Moderate confidence	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. 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.	Burton A E, Shaw R L, and Gibson J M. 2013. BMJ Open	Moderate confidence	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
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	Burton Amy E, Shaw Rachel, and Gibson Jonathan. 2013. British Journal of Visual Impairment 31:178-188	Moderate confidence	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	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
regarding treatment and management of their condition.			
Treatment outcome (vision acuity)			
Patients expressed a clear willingness to endure their treatments if they continued to gain or maintain their vision.	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, convenience sampling). Coherence could not be assessed as only 1 study. Adequate data with minor concern about relevance.

H.8.2 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?

Review finding	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
Theme 1: Information required and when			
Timing: Before diagnosis			
Information about types of AMD and risk factors/causes			
• Patients and carers want increased public awareness of the causes and symptoms of AMD (Burton, Vukicevic). • This could provide a context for diagnosis, could help people seek advice earlier (Burton). • This could help improve public interaction with people with AMD (more understanding of the challenges facing the visually impaired) (Vukicevic).	Burton (2013) Vukicevic (2016)	Moderate confidence	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.
At the opticians- detection of possible AMD			
• 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.	Burton (2013)	Moderate confidence	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.
Timing: At or following diagnosis			
• 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	Burton (2013)	Moderate confidence	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.
Information about types of AMD and frequency of diagnosis			

Review finding	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
• Patients were confused about the different names and types of AMD (Dahlin Ivanoff) • Patients were unware 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 vison (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.
Information about treatment regimens			

Review finding	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
• Patients often had unrealistic expectations of treatment outcomes and this was not helped by inaccurate information from neighbours/family members (Burton). • 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). • Patients did not understand why glasses were not able to correct their vision problems (Dahlin Ivanoff). • Patients were often unaware of the purpose of hospital visits and medical procedures (Burton). • 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). • Information about abnormal outcomes and when to seek help would also be useful (McCloud). • Good communication regarding changes in treatment regimens was linked to better patient experience (McCloud).	Burton (2013) Dahlin Ivanoff (1996) McCloud (2015)	Moderate confidence	This review finding is rated as moderate because there were three studies 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.
Other non-NHS support services/ financial help			
• Patients were unaware of support groups or unlikely to attend them for fear of associating with depressed people. • Patients were not necessarily aware of sources of financial help (e.g. attendance allowance) or the advantages associated with being registered as partially sighted.	Burton (2013)	Moderate confidence	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.
Monitoring of symptoms- when to seek help?			
• 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	Burton (2013)	Moderate confidence	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.

Review finding	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
and emergency if their vision changed as they did not associate A and E with this type of care.			
Theme 2: Format of information			
• 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. • 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. • Patients reported finding the language use by medical staff to be confusing and inaccessible.	Burton (2013)	Moderate confidence	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.
Theme 3: Additional sources of information			
• 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. • Support groups could be useful sources of information, but patients were not necessarily aware of them. • Public presentations were raised as a useful source of information, but required pro-active patients.	Burton (2013)	Moderate confidence	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.
Theme 4: Caregiver perspectives and needs			
• Carers need sufficient information to allow them to understand the condition and the physical/emotional effects on the person's wellbeing. • 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.	Vukicevic (2016)	High confidence	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.

Review finding	Contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
• They lack information about support services and respite care options.			
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).	Dahlin Ivanoff (1996) McCloud (2015)	Moderate confidence	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.