# **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: I	nterobserver agreement
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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 <sup>1</sup>	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 k statistic (SE): 0.58 (0.015), k weighted to give 75% credit for 1-step disagreement: 0.73(0.013).	MODERATE
Danis et al (2013) Retrospec tive cohort	AREDS 9-step severity scale	Serious <sup>1</sup>	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

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

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) Retrospec tive cohort	AREDS 4-step severity scale	Serious <sup>1</sup>	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 Retrospec tive cohort	CARMS	Serious <sup>1</sup>	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% Cl): 0.63 (0.53-0.74) Kappa, weighted (95% Cl): 0.78 (0.62-0.93) Agreement between 2 observers assessments of Age-Related Maculopathy.	MODERATE

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

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) Retrospec tive cohort	The Modified International Classification of ARM	Serious <sup>1</sup>	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) Retrospec tive cohort	The Modified International Classification of ARM	Serious <sup>1</sup>	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) Retrospec tive cohort	Harmonized Three Continent AMD Consortium Severity Scale	Serious <sup>1</sup>	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. Do	wngraded one lev	el for risk of bia	as due to lack of c	larity regarding ba	aseline character	ristics of included participar	its	

#### Agreement outcomes: Intraobserver Agreement

Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Danis et al (2013) Retrospec tive cohort	AREDS 9-step severity scale	Serious <sup>1</sup>	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) Retrospec tive cohort	AREDS 4-step severity scale	Serious <sup>1</sup>	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 Retrospec tive cohort	Clinical Age- Related Maculopathy Staging (CARMS) system	Serious <sup>1</sup>	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
Interobserv	ver agreement							
Classificati without RA		nly, 2) predomi	nantly classic, 3)	minimally clas	sic, 4) occult w	vithout PED (with or witho	ut RAP) and 5) vascularised	PED (with or
Cohen (2007) Prospectiv e cohort	CAMRS	Very serious <sup>1, 3, 4</sup>	N/A	Not serious	Serious <sup>2</sup>	207 patients with newly diagnosed exudative AMD	Lesion classification: Kappa: 0.59 Location of lesion: Kappa: 0.52	VERY LOW
(1) AMD wit		2) AMD with typ	oe 1 + 2 CNV; (3)	AMD with type	2 CNV only; (4)	Chorioretinal anastomos	is (RAP) (5) PCV, (using fund	dus phot, FA,
Coscas (2014) Prospectiv e cohort	CAMRS	Very Serious <sup>1, 3,</sup>	N/A	Not serious	Serious <sup>7</sup>	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 wi	th type 1 CNV; (2	2) AMD with typ	oe 1 + 2 CNV; (3)	AMD with type	2 CNV only; (4)	Chorioretinal anastomos	is (RAP) (5) PCV, (using fund	dus phot, FA)
Coscas (2014) Prospectiv	CAMRS	Very Serious <sup>1, 3,</sup>	N/A	Not serious	Serious <sup>7</sup>	99 consecutive Japanese eyes and 94 consecutive French	Crude agreement with final diagnosis: Range, Kyoto patients (n=	VERY LOW
e cohort						eyes with exudative AMD	99) AMD with type 1 CNV: 79.4 - 82.3%	

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)CARMSSerious1,6N/ASerious5Not serious374 treatment naïve patients with neovascular AMD in at least 1 eyeAgreement between and anatomic cla Kappa 0.65	
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Studies	Classification System	Risk of bias	Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
Prospectiv e cohort								
1) Classic o	only, 2) occult or	nly, 3) mixed, o	r 4) unable to det	ermine				
Friedman (2000) Retrospec itve cohort	CARMS	Very serious <sup>1, 3, 4, 6</sup>	N/A	Serious <sup>2</sup>	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	2) occult, or 3) m	nixed with class	ic component le	ss or equal/gre	ater than 50%			
Holz (2003) Prospectiv e cohort	CARMS	Very serious <sup>1, 3, 4</sup>	N/A	Serious <sup>2</sup>	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
Predomina	ntly classic, mir	nimally classic,	or occult					
Olsen (2004) Retrospec tive cohort	CAMRS	Very serious <sup>1, 4, 6</sup>	N/A	Serious <sup>2</sup>	Not serious	200 cases of nAMD from 2 centres	kappa agreement: 0.63	VERY LOW
1) Classic o	only 2) Occult or	nly 3) Classic ar	nd Occult (mixed	<50%/>50% cla	assic) 4) Discifo	orm scar 5) cannot detern	nine 6) Serous PED (present/	absent)
Maguire (2008) Retrospec tive cohort	CAMRS	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	282 eyes developed CNV or serous PED in CAPT trial	Agreement: 80-100% Weighted kappa: 0.75-100	LOW
Intraobserv	ver agreement							
classic, oc	cult, or mixed wi	th classic com	ponent less or ec	ual/greater tha	in 50%			
Holz (2003)	CAMRS	Very serious <sup>1, 3, 4</sup>	N/A	Serious <sup>2</sup>	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.						
<ol> <li>2. Downgrad</li> <li>3. Downgrad</li> <li>4. Downgrad</li> </ol>	ded one level for   ded one level for   ded one level for s	beople with PCV ack of clear pre- some participan	excluded or uncl -specified criteria	ear inclusion for diagnosis or ra investigation	unclear (e.g. ICG angiog	of included participants graphy) without a clear criter	ia RE who should receive the o	extra

- 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 clas	sification of late	dry AMD						
Brader (2011) Retrospec tive cohort	CAMRS	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	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
Intraobser	ver agreement							
classic, oc	cult, or mixed wi	ith classic cor	nponent less or (	equal/greater tha	an 50%			
Brader (2011) Retrospec tive cohort	CAMRS	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	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

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

Sti		Classification System		Inconsistency	Indirectness	Imprecision	Clinical population (n)	Effect	Quality
0	adioo	Oystem	NIUS	meeneleteney	manoothood	mproordioren			Quanty

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
	veloping neovas		meeneleiteiteitej			()	0.1100		Quanty
	verity Score								
Perlee et al (2013) Prospecti ve cohort study	Simple severity score	Very serious <sup>1,</sup> 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) Prospecti ve cohort study	Sandberg 4- point scale	Very Serious <sup>1,</sup> <sub>2, 3</sub>	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 dev	veloping geogra	ohic atrophy	,						
Simple Sev	verity Score								
Perlee et al (2013) Prospecti ve cohort study	Simple severity score	Very serious <sup>1,</sup> 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
	veloping advance	ed AMD							
Simple Sev	verity Score								
Klein et al (2011) Prospecti ve cohort study	Simple severity score	Very serious <sup>1,</sup> <sub>2, 3</sub>	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).

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

# 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?

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Low dose a	aspirin							
Christen (2001) Prospecti ve cohort	22,071	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious⁵	HR (95% CI)	0.77 (0.54, 1.11)	VERY LOW
Low dose a	aspirin							
Christen (2009) Prospecti ve cohort	39,876	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	1.03 (0.88, 1.21)	LOW
Ethnicity (r	isk of non-exudative	e AMD) – white as re	ference category					
van der Beek (2011) Prospecti ve cohort	1,772,962	Very serious <sup>1,2,3,4</sup>	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

#### Demographic and medical risk factors

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) Prospecti ve cohort	44,103	Very serious <sup>1,2,3,4</sup>	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 (k	m/day)							
Williams 2009 Prospecti ve cohort	41,708	Very serious <sup>1,2,3,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	0.90 (0.83, 0.97)	LOW
		performance times)						
Williams 2009 Prospecti ve cohort	41,708	Very serious <sup>1,2,3,4</sup>	N/A	Not serious	Serious⁵	HR (95% CI)	0.92 (0.60, 1.39)	VERY LOW

Stu	udies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
	1. E	vidence of bias from	sample selection						
	2. E	Evidence of bias from	study attrition						
	3. E	Evidence of bias from	outcome measureme	ent					
	4. E	Evidence of bias from	prognostic factor me	asurement					
	5. E	Downgraded one level	l for non-significant e	ffect					

#### Diet and nutrition

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Alcohol (<1	drink/week as refere	ence category)						
Ajani (1999) Prospecti ve cohort	21,041	Very serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	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 carot	tene, per standard d	eviation increase						
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	0.99 (0.94, 1.06)	LOW
Beta carote	ene, per standard de	viation increase						
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	1.00 (0.94, 1.06)	LOW
Beta crypto	xanthin, per standa	rd deviation increase	9					

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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Leeuwen (2005) Prospecti ve cohort	Participants of the Rotterdam study (2005)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	1.01 (0.92, 1.10)	LOW
Lutein/zea	xanthin, per standar	d deviation increase						
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	1.01 (0.93, 1.09)	LOW
Lycopene,	per standard deviat	ion increase						
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	1.01 (0.97, 1.04)	LOW
Vitamin A	(retinol equivalents)	, per standard deviat	tion increase					
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	0.95 (0.86, 1.05)	LOW
Vitamin C,	per standard deviat	ion increase						
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	1.02 (0.94, 1.10)	LOW
Vitamin E,	per standard deviat	ion increase						
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Not serious	HR (95% CI)	0.92 (0.84, 1.00)	MODERATE
Trace elem	nents Iron, per stand	lard deviation increa	se					

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	0.95 (0.86, 1.04)	LOW
Zinc, per st	andard deviation inc	crease						
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Not serious	HR (95% CI)	0.91 (0.83, 0.98)	MODERATE
Combined	intake of 4 predefine	ed antioxidant nutrie	nts (vitamins C and	d E, beta caroter	ne, and zinc) – m	edium intake as refe	rence category	
Leeuwen (2005) Prospecti ve cohort	4,170	Serious <sup>1</sup>	N/A	Not serious	Not serious	HR (95% CI)	Low: 1.20 (0.92, 1.56) High: 0.65 (0.46, 0.92)	MODERATE
stu inc	dy and/or had missi luded sample)	ing data, there was r	o meaningful com	parison between	those lost to foll	ow up or with missir	y people were lost to follo g data in the study and th	e rest of the

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 druse	Large drusen									
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 distinc	Soft distinct drusen vs hard distinct drusen									
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 are	а									
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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)

ventographic and medical fisk factors										
Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality		
Gender										
Klein (2008) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Female: 2.8 (1.6, 4.9)	MODERATE		
Increasing	education									
Klein (2008) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Serious⁵	Time-adjusted odds ratios (95% CI)	Increasing education 0.6 (0.4, 0.8)	LOW		
Obesity (BN	<i>/</i> II)									
Howard (2014)	2,641	Serious <sup>1,2</sup>	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		

#### Demographic and medical risk factors

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/m <sup>2</sup> ): 0.90 (0.75, 1.07) Female smoker BMI (per 2.5 kg/m <sup>2</sup> ): 1.07 (0.98, 1.17) Male smoker BMI (per 2.5 kg/m <sup>2</sup> ): 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 <sup>6</sup>	HR (95% CI)	Regular aspirin use: 0.86 (0.71, 1.05)	MODERATE
Age								
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 <sup>1,2</sup>	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) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Serious⁵	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)* Prospecti ve cohort	2,951	Very Serious <sup>1,2,3,4</sup>	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) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Serious⁵	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)* Prospecti ve cohort	2,914	Serious <sup>1,2</sup>	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)* Prospecti ve cohort	980	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Past: 1.0 (0.8, 1.4) Current: 2.2 (1.4, 3.3)	LOW
Diabetes hi	istory							
Klein (2008)	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>5</sup>	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 N	ЛІ							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	1.13 (0.60, 2.14)	VERY LOW
History of s	stroke							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	1.25 (0.46, 3.38)	VERY LOW
History of C	CVD							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	0.79 (0.46, 1.37)	VERY LOW
History of a	angina							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very Serious <sup>7</sup>	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 <sup>1,2,3</sup>	N/A	Not serious	Serious⁵	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.	<ol><li>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)</li></ol>								
3.	Evidence of bias from definition (e.g. hyperte						s measured, factors that rough	equire	
4.									
5.	Downgraded one level	for confidence interv	al crossing 1 line	of a defined min	imal important diff	erence			
6.	Downgraded one level	for non-significant ef	fect						

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 v	wine drinking							
Klein (2008) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	Time-adjusted odds ratios (95% CI)	Increased wine drinking 0.6 (0.3, 1.1)	LOW
Daily Alcoh	ol consumption, g	(none as reference	category)					
Boekhoor n (2008) Prospecti ve cohort	4,229	Serious <sup>1,2</sup>	N/A	Not serious	Serious⁴	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-carote	ene (quartile 1 as re	eference category)						
Chiu (2009) Prospecti ve cohort	2,924	Serious <sup>1</sup>	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)	
Docosahe	kaenoic acid (quart	ile 1 as reference ca	ategory)					
Chiu (2009) Prospecti ve cohort	2,924	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>4</sup>	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
Eicosapen	taenoic acid (quart	ile 1 as reference ca	itegory)					
Chiu (2009) Prospecti ve cohort	2,924	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>4</sup>	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 Glyca	emic Index (>81.5	as reference catego	ry)					
Chiu (2009)	2,924	Serious <sup>1</sup>	N/A	Not serious	Serious⁴	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. C	owngraded one leve	I for non-significant et	ffect					

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 su									
Chew (2009) Prospecti ve cohort	5,841	Very serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>5</sup>	HR (95% CI)	Right eye: 0.80 (0.61, 1.06) Left eye: 0.95 (0.71, 1.26)	VERY LOW	
Hyperpigm	entation (none as r	eference category)							
CAPT (2008) Prospecti ve cohort	1,052	Serious <sup>1</sup>	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	
Hyperpigm	entation								
Klein (2007)	3,917	Serious <sup>1,3</sup>	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 pig	ment epithelium de	pigmentation							
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,3</sup>	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 pig	Retinal pigment epithelium depigmentation								
CAPT (2008) Prospecti ve cohort	1,052	Serious <sup>1</sup>	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) Retrospec tive cohort	200	Very serious <sup>1,3,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	Pigmentary Changes: 5.75 (2.09, 15.84)	LOW
Pigmentary	abnormalities							
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,3</sup>	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 c	overed by drusen (	<10 as reference cat	egory)					
CAPT (2008) Prospecti ve cohort	1,052	Serious <sup>1</sup>	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 are	а							
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,3</sup>	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 druse	en							
Finger (2014) Retrospec tive cohort	200	Very serious <sup>1,3,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥125µm: 11.73 (1.47, 93.81)	LOW
Large druse	en							
Klein (2007)	3,917	Serious <sup>1,3</sup>	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	Soft distinct drusen vs hard distinct drusen										
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,3</sup>	N/A	Not serious	Very serious <sup>6</sup>	Time-adjusted odds ratios (95% CI)	1.2 (0.3, 5.7)	VERY LOW			
Soft indistin	nct vs soft distinct d	rusen or hard distinc	t drusen								
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,3</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	14.6 (6.8, 31.1)	MODERATE			
Reticular dr	rusen vs Soft distine	ct drusen									
Klein (2008) Prospecti ve cohort	3,917	Serious <sup>1,3</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	41.78 (9.43, 185.14)	MODERATE			
Reticular dr	rusen vs Soft indisti	inct drusen									
Klein (2008) Prospecti ve cohort	3,917	Serious <sup>1,3</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	6.23 (1.70, 22.73)	MODERATE			
Reticular pa	seudodrusen										
Finger (2014) Retrospec tive cohort	200	Very serious <sup>1,3,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	Reticular pseudodrusen: 4.93 (1.06, 22.93)	LOW			
Baseline vis	sual acuity (20/25-2	20/40 as reference ca	ategory)								
Grunwald (2014)	1,024	Serious <sup>3</sup>	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
Prospecti							20/100–20/160:	
ve cohort							1.70 (1.10, 2.62)	
							20/200–20/320:	
							2.65 (1.43, 4.93)	
Retinal ang	iomatous proliferation	on lesion						
Grunwald (2014)	1,024	Serious <sup>3</sup>	N/A	Not serious	Not serious	HR (95% CI)	1.69 (1.16, 2.47)	MODERATE
Prospecti ve cohort								
Geographic	atrophy in fellow e	ye						
Grunwald (2014)	1,024	Serious <sup>3</sup>	N/A	Not serious	Not serious	HR (95% CI)	2.07 (1.40, 3.08)	MODERATE
Prospecti ve cohort								

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 <sup>1</sup>	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:			
	veere ee reference	ootogon ()					1.98 (1.16, 3.39)			
CAPT	years as reference 1,052	Serious <sup>1</sup>	N/A	Not serious	Not serious	HR (95% CI)	60-69 years:	MODERATE		
(2008) Prospecti ve cohort	1,032	Sellous		Not senous	NUL SENUUS	TIK (95 % CI)	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 <sup>1,2</sup>	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 m	ellitus									
Hahn (2013) Retrospec tive cohort	6,621	Very Serious <sup>1,3,4,5</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	1.03 (0.97 1.09)	VERY LOW		
Long term u	use of aspirin									
Klein (2012) Prospecti ve cohort	4,926	Not serious	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Regular aspirin use: 1.65 (0.91, 2.99)	MODERATE		
Smoking										
Klein (2008) Prospecti ve cohort	2,119	Serious <sup>1,2</sup>	N/A	Not serious	Very Serious <sup>7</sup>	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 <sup>2</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	0.61 (0.07, 5.34)	VERY LOW		
History of C	VD									
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>2</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	1.31 (0.32, 5.27)	VERY LOW		
History of a	ngina									
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>2</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	1.53 (0.30, 7.85)	VERY LOW		
Exercise (s	edentary as referei	nce group)								
Knudtson (2006) Prospecti ve cohort	3,684	Very Serious <sup>1,2,3</sup>	N/A	Not serious	Very Serious <sup>7</sup>	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									
t	be inconsistency in measurement or definition)								
5. E	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 Alcol	hol consumption, g	(0 as reference categ	jory)						
Boekhoor n (2008) Prospecti ve cohort	4,229	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>4</sup>	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	g (quintile 1 as refer	ence category)							
Reynolds (2013) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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 <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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)	
Monounsat	urated Fat g (quintil	e 1 as reference cate	egory)					
Reynolds (2013) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	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 Polyu	nsaturated Fatty Ac	ids g (quintile 1 as re	eference category)					
Reynolds (2013) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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 fa	atty acids, Eicosape	ntaenoic Acid (EPA)	- quintile 1 as refe	erence category				
Reynolds (2013) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious⁴	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 f	atty acids, Docosa	hexaenoic Acid (DHA)	) (g) - quintile 1 as	reference categ	jory			
Reynolds (2013) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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 f	atty acids, DHA + I	EPA (g) - quintile 1 as	reference categor	у				
Reynolds (2013) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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 f	atty acids, Linoleni	c Acid (g) - quintile 1 a	as reference categ	Jory				
Reynolds (2013)	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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 F	atty Acids, Arachide	onic Acid (g) - quintile	e 1 as reference c	ategory						
Reynolds (2013) Prospecti ve cohort	4,165	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>4</sup>	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		
<ol> <li>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)</li> </ol>										
2. Evi dat	idence of bias from ta, there was no me	study attrition (for exa aningful comparison	ample, the paper i between those los	s not clear abou st to follow up or	t how many peop with missing dat	ble were lost to follow a in the study and th	w up in the study and/or have a study and/or have a study and/or have a study and/or have a study and a study and a study a stu	nple)		

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 d	lrusen							

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Macular photocoa gulation study group (1997) Prospecti ve cohort	670	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	2.1 (1.3, 3.5)	LOW
1 or more la	arge drusen							
Macular photocoa gulation study group (1997) Prospecti ve cohort	670	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	1.5 (1.0, 2.2)	VERY LOW
Large druse	en							
Bressler 1990 Prospecti ve cohort	127	Very serious <sup>1,2,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	Large drusen (≥50µm): 2.4 (1.1, 5.1)	LOW
Large Drus	en							
Finger (2014) Retrospec tive cohort	200	Very serious <sup>1,2,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥125µm: 1.96 (1.14, 3.36)	LOW
Large druse	en							
Klein (2007)	3,917	Serious <sup>1,2</sup>	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 <sup>1,2,4</sup>	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 are	Drusen area										
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 distinc	t drusen vs hard dis	tinct drusen									
Klein et al (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 <sup>1,2</sup>	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 <sup>1,2</sup>	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) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Very serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	2.82 (0.66, 12.01)	VERY LOW	
Reticular pseudodrusen									
Finger (2014) Retrospec tive cohort	200	Very serious <sup>1,2,4</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Reticular pseudodrusen: 1.19 (0.72, 1.94)	VERY LOW	
Confluent drusen									
Bressler 1990 Prospecti ve cohort	127	Very serious <sup>1,2,4</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	1.8 (0.8, 3.9)	VERY LOW	
Hyperpigmentation									
Macular photocoa gulation study group (1997)	670	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	2.0 (1.4, 2.9)	LOW	
Prospecti ve cohort									
Hyperpigmentation									
Bressler 1990 Prospecti ve cohort	127	Very serious <sup>1,2,4</sup>	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) Prospecti ve cohort	1,052	Serious <sup>2</sup>	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	
Hyperpigm	entation								
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 pigr	ment epithelium de	pigmentation							
Klein et al (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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	v changes								
Finger (2014) Retrospec tive cohort	200	Very serious <sup>1,2,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	Pigmentary Changes: 2.49 (1.51, 4.10)	LOW	
Pigmentary	abnormalities								
Klein et al (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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) Prospecti ve cohort	5,841	Very serious <sup>2,5</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Right eye 1.20 (0.82, 1.75) Left eye 1.07 (0.72, 1.58)	VERY LOW	

Studie	s Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality		
1.	<ol> <li>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)</li> </ol>									
2.							v up in the study and/or ha e rest of the included sam			
3.	Evidence of bias from definition (e.g. hyperte						s measured, factors that r lues)	equire		
4.	Evidence of bias from clear which confounde						nding factors were measur	ed, it is not		
5.		be no masking or co	onfirmation with m				asured and what investiga database codes where th			

- 6. Downgraded one level for non-significant effect
- 7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality			
Definite sys	Definite systemic hypertension										
Macular photocoa gulation study group (1997) Prospecti ve cohort	670	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	1.7 (1.2, 2.4)	LOW			
Hypertensio	on (normal as refere	ence category)									
CAPT (2008) Prospecti ve cohort	1,052	Serious <sup>2</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Suspect: 0.69 (0.45, 1.07) Definite: 1.23 (0.90, 1.68)	LOW			
Age (50-59	Age (50-59 years as reference category)										

## Demographic and medical risk factors

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
CAPT (2008) Prospecti ve cohort	1,052	Serious <sup>2</sup>	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) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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) Prospecti ve cohort	127	Very serious <sup>1,2,4</sup>	N/A	Not serious	Not serious	HR (95% CI)	Age, y, continuous: 1.08 (1.02, 1.14)	LOW
Smoking (n	ever as reference o	ategory)						
CAPT (2008) Prospecti ve cohort	1,052	Serious <sup>2</sup>	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) Retrospec tive cohort	326	Serious⁵	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) Prospecti ve cohort	2,119	Serious <sup>1,2</sup>	N/A	Not serious	Very Serious <sup>7</sup>	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) Prospecti ve cohort	6,621	Very serious <sup>2,3,4,5</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	1.11 (0.97, 1.27)	VERY LOW
Long term u	use of aspirin (no re	egular use as referen	ce category)					
Klein (2012) Prospecti ve cohort	4,926	Not serious	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Regular aspirin use: 1.07 (0.68, 1.67)	MODERATE
Aspirin use	r							
Wilson (2004) Retrospec tive cohort	326	Serious <sup>5</sup>	N/A	Not serious	Not serious	HR (95% CI)	0.63 (0.40, 0.98)	MODERATE
History of M	/1							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	1.56 (0.48, 5.08)	VERY LOW
History of C	VD							
Klein (2013)	1,700	Serious <sup>1</sup>	N/A	Not serious	Very Serious <sup>7</sup>	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 a	angina							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very Serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	0.92 (0.27, 3.13)	VERY LOW
Exercise								
Knudtson (2006) Prospecti ve cohort	3,684	Very Serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Sedentary: reference Active: 0.3 (0.1, 0.7)	LOW
Ethnicity (w	hite as reference c	ategory)						
van der Beek (2011) Prospecti ve cohort	1,772,962	Very Serious <sup>1,2,3,5</sup>	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 <sup>1,2,3,5</sup>	N/A	Not serious	Very Serious <sup>7</sup>	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, 2.00)	VERY LOW
							2.09) Korean: 0.97 (0.56, 1.66) Indian: 1.08 (0.71, 1.62) Pakistani: 0.45 (0.06, 3.21)	

- 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 Dov	wnaraded two level	s for confidence inter	val crossing 2 line	s of a defined m	inimal important c	lifference		

Diet and nutrition

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Alcohol us	e (<1 drink/week as	reference category)						
Ajani (1999) Prospecti ve cohort	21,041	Very serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>4</sup>	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 Alcol	nol consumption, g	(0 as reference categ	jory)					
Boekhoor n (2008) Prospecti ve cohort	4,229	Serious <sup>1,3</sup>	N/A	Not serious	Serious⁴	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)

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Large druse	en							
Finger (2014) Retrospec tive cohort	200	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥125µm: 2.08 (1.25, 3.49)	LOW
Large druse	en in the fellow ey	e (<250 µm in diamet	er in the fellow eye	as the referenc	e category)			
SST (2009) Prospecti ve cohort	370	Serious <sup>1,2</sup>	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 druse	en							
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 druse	en							
Klein (2011) Prospecti ve cohort	2,846	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	1.79 (1.50, 2.14)	LOW
Largest dru	sen size in non-a	dvanced eye (<63 µm	as reference cates	gory)				
Seddon (2011)* Prospecti ve cohort	2,937	Serious <sup>1</sup>	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) Prospecti ve cohort	370	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥250 µm in diameter: 1.73 (1.12, 2.66)	MODERATE
Size of dru	sen for those with	no advanced AMD in	n either eye (<63 µr	n in both eyes a	s reference categ	jory)		
Seddon (2011)* Prospecti ve cohort	2,937	Serious <sup>1</sup>	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) $\ge 250, <124: 28.0 (15.2, 51.6)$ $\ge 250, 125-249: 43.9 (26.1, 73.9)$ $\ge 250, \ge 250: 53.7$	MODERATE
Drusen are	2						(32.2, 89.4)	
Klein	2,846	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	Drusen area >16877	LOW
(2011)	2,040	very serious	IN/A	NOT SELIOUS	NOL SENOUS	TIK (95% CI)	$\mu m^2 vs \le 2596 \mu m^2$ :	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							32.3 (7.8, 133)	
Advanced A	AMD in one eye: lar	gest drusen size in n	on-advanced eye,	µm (<63 as refe	erence category)			
Seddon (2015)* Prospecti ve cohort	2,951	Very Serious <sup>1,2,4,5</sup>	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 advanc	ed AMD: largest dru	isen size in each eye	, μm (<63 μm in b	oth eyes as refe	erence category)			
Seddon (2015)* Prospecti ve cohort	2,951	Very Serious <sup>1,2,4,5</sup>	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) $250, \le 124$ : $31.0 (17.2, 55.9)$ 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 distinc	t drusen vs hard dis	stinct drusen								
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 indistir	Soft indistinct vs soft distinct drusen or hard distinct drusen									
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	17.5 (10.3, 29.8)	MODERATE		
Reticular dr	rusen vs Soft distine	ct drusen								
Klein (2008) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	28.29 (9.48, 84.44)	MODERATE		
Reticular dr	rusen vs Soft indisti	nct drusen								
Klein (2008) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	6.34 (2.28, 17.63)	MODERATE		
Reticular pe	seudodrusen									
Finger (2014) Retrospec tive cohort	200	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	1.20 (0.76, 1.89)	VERY LOW		
Pigmentary	changes									
Finger (2014)	200	Very serious <sup>1,2,3</sup>	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
Retrospec tive cohort								
Pigmentary	abnormalities							
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Pigmentary abnormalities present vs absent: 10.8 (6.5, 18.0)	MODERATE
Hyperpigme	entation							
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Increased pigment present vs absent: 9.8 (5.9, 16.3)	MODERATE
Hyperpigme	entation in a fellow	eye with CNV (no fo	cal hyperpigmenta	tion as reference	e category)			
SST (2009) Prospecti ve cohort	370	Serious <sup>1,2</sup>	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 pigr	ment epithelium de	pigmentation						
Klein (2007) Prospecti ve cohort	3,917	Serious <sup>1,2</sup>	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 pigr	ment epithelium de	pigmentation						
SST (2009) Prospecti ve cohort	370	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	HR (95% CI)	1.79 (1.14, 2.82)	MODERATE
Advanced a	age related macula	r degeneration in 1 e	eye					

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality		
Klein (2011) Prospecti ve cohort	2,846	Very serious <sup>1,2,3</sup>	N/A	Not serious	Not serious	HR (95% CI)	1.21 (1.02, 1.45)	MODERATE		
Advanced A	Advanced AMD in 1 eye									
Seddon (2011)* Prospecti ve cohort	2,937	Serious <sup>1</sup>	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 A	AMD in one eye									
Seddon (2015)* Prospecti ve cohort	2,951	Very Serious <sup>1,2,4,5</sup>	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 fello	w eye with CNV								
SST (2009) Prospecti ve cohort	370	Serious <sup>1,2</sup>	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 (2	011), Seddon (2013	3) and Seddon (2015	) all report the san	ne participants f	ros the ARED2 stu	vbu		

## Demographic and medical risk factors

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality		
Low dose a	aspirin									
Christen (2009) Prospecti ve cohort	39,876	Very serious <sup>1,2,3</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	0.90 (0.53, 1.52)	VERY LOW		
Long term use of aspirin										
Klein (2012) Prospecti ve cohort	4,926	Not serious	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Regular aspirin use: 1.21 (0.84, 1.74)	MODERATE		
Obesity (BN	VII)									
Howard (2014) Prospecti ve cohort	2,641	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	HR (95% CI)	Female, non-smoker BMI (per 2.5 kg/m <sup>2</sup> ): 1.31 (1.15, 1.50) Male, non-smoker BMI (per 2.5 kg/m <sup>2</sup> ): 0.86 (0.61, 1.20) Female smoker BMI (per 2.5 kg/m <sup>2</sup> ): 0.99 (0.81, 1.21)	MODERATE		
Obesity (BN	VI)									
Lechante ur (2012)	108	Serious <sup>1,2</sup>	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 (BN	/II) - <25 as referen	ce category								
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	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 (BN	Obesity (BMI) - <25 as reference category									
Seddon (2011)* Prospecti ve cohort	2,937	Serious <sup>1</sup>	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 (BN	/II) - <25 as referen	ce category								
Seddon (2013)* Prospecti ve cohort	2,914	Serious <sup>1,2</sup>	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 (BN	/II) - <25 as referen	ce category								
Seddon (2015)* Prospecti ve cohort	2,951	Very serious <sup>1,2,3,4</sup>	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 smo	oker									
Klein (2011) Prospecti ve cohort	2,846	Very serious <sup>1,2,5</sup>	N/A	Not serious	Not serious	HR (95% CI)	1.78 (1.37, 2.31)	LOW		
Smoking										
Seddon (2003)	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>6</sup>	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 (p	oack years) – 0 to 1	as reference categor	У					
Lechante ur (2012) Prospecti ve cohort	108	Serious <sup>1,2</sup>	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 <sup>1</sup>	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 Hist	ory of AMD							
Klein (2011) Prospecti ve cohort	2,846	Very serious <sup>1,2,5</sup>	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 <sup>1,2</sup>	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 a	s reference catego	ry)						
Lechante ur (2012) Prospecti ve cohort	108	Serious <sup>1,2</sup>	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 a	s reference catego	ry)						
Seddon (2011)*	2,937	Serious <sup>1</sup>	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	s reference categor	у)						
Seddon (2013)* Prospecti ve cohort	2,914	Serious <sup>1,2</sup>	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	s reference categor	y)						
Seddon (2013)* Prospecti ve cohort	980	Serious <sup>1,2</sup>	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	s reference categor	y)						
Seddon (2015)* Prospecti ve cohort	2,951	Very serious <sup>1,2,3,4</sup>	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 M	11							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	1.04 (0.36, 3.02)	VERY LOW
History of C	VD							
Klein (2013) Prospecti ve cohort	1,700	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>7</sup>	Time-adjusted odds ratios (95% CI)	1.33 (0.59, 3.01)	VERY LOW
History of a	ngina							
Klein (2013)	1,700	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>7</sup>	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										
Cardiovasc	ular disease									
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	1.21 (0.73, 2.02)	LOW		
Gender (ma	Gender (male as reference category)									
Lechante ur (2012) Prospecti ve cohort	108	Serious <sup>1,2</sup>	N/A	Not serious	Not serious	HR (95% CI)	Female: 2.6 (1.4, 5.0)	MODERATE		
Gender (fer	male as reference c	ategory)								
Seddon (2011)* Prospecti ve cohort	2,937	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Male: 1.0 (0.9, 1.2)	LOW		
Gender (fer	male as reference c	ategory)								
Seddon (2013)* Prospecti ve cohort	2,914	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Male: 1.0 (0.8, 1.1)	LOW		
Gender (fer	male as reference c	ategory)								
Seddon (2013)* Prospecti ve cohort	980	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	Male: 1.0 (0.8, 1.2)	LOW		
Gender (fer	male as reference c	ategory)								
Seddon (2015)*	2,951	Very serious <sup>1,2,3,4</sup>	N/A	Not serious	Serious <sup>6</sup>	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	
Prospecti ve cohort									
Education (	(≤ high school as re	ference category)							
Lechante ur (2012) Prospecti ve cohort	108	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	> high school: 0.6 (0.4, 1.1)	LOW	
Education (	(≤ high school as re	ference category)							
Seddon (2011)* Prospecti ve cohort	2,937	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	> high school: 0.9 (0.8, 1.0)	LOW	
Education (	(≤ high school as re	ference category)							
Seddon (2013)* Prospecti ve cohort	2,914	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	> high school: 0.9 (0.8, 1.0)	LOW	
Education (	(≤ high school as re	ference category)							
Seddon (2013)* Prospecti ve cohort	980	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>6</sup>	HR (95% CI)	> high school: 0.8 (0.6, 1.0)	LOW	
Education (high school as reference category)									
Seddon (2015)* Prospecti ve cohort	2,951	Very serious <sup>1,2,3,4</sup>	N/A	Not serious	Serious <sup>6</sup>	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)

Studie	s Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality	
3.	<ol> <li>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)</li> </ol>								
4.	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.		m confounding factor n ders were adjusted for					ding factors were measu	red, it is not	
6.	Downgraded one le	vel for non-significant e	ffect						
7.	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 Alcoh	ol consumption, g (	0 as reference cated	jory)						
Boekhoor n (2008) Prospecti ve cohort	4,229	Serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	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 glyo	caemic index (quint	ile 1 as reference ca	tegory)						
Chiu (2007) Prospecti ve cohort	3,977	Serious <sup>1,2</sup>	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 <sup>1</sup>	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
Prospecti ve cohort							75.2–78.6: 0.77 (0.63, 0.94) 75.2: 0.76 (0.60, 0.96)	
Beta-carote	ene (quartile 1 as	reference category)						
Chiu (2009) Prospecti ve cohort	2,924	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	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
Docosahex	aenoic acid (quar	tile 1 as reference ca	ategory)					
Chiu (2009) Prospecti ve cohort	2,924	Serious <sup>1</sup>	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
Eicosapent	taenoic acid (quar	tile 1 as reference ca	ategory)					
Chiu (2009) Prospecti ve cohort	2,924	Serious <sup>1</sup>	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

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	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 refere	nce category)						
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	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 f	fat (quartile 1 as ref	erence category)						
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	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 fa	at (quartile 1 as refe	erence category)						
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	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
Monounsat	urated fat (quartile	1 as reference categ	ory)					
Seddon (2003)	261 ical Guidelines 20	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	2nd quartile:	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							1.27 (0.65, 2.45) 3rd quartile: 2.13 (1.03, 4.43) 4th quartile: 2.21 (0.90, 5.47)	
Polyunsatu	rated fat (quartile 1	as reference categor	y)					
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	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
Transunsat	turated fat (quartile	1 as reference catego	ory)					
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	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 servi	ings of fish a week	(<1 as reference cate	egory)					
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	1: 1.30 (0.78, 2.16) ≥2: 0.88 (0.49, 1.60)	LOW
High-fat da	iry (quartile 1 as ref	erence category)						
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	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 (quar	tile 1 as reference o	category)						
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	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 (quar	tile 1 as reference ca	tegory)					
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	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 pe	r week (<1 as referer	ice category)					
Seddon (2003) Prospecti ve cohort	261	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	1: 0.69 (0.40, 1.17) ≥2: 0.60 (0.32, 1.02)	LOW
Taking anti	oxidants (clinical tri	al)						
Seddon (2011)* Prospecti ve cohort	2,937	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	HR (95% CI)	0.9 (0.8, 1.0)	LOW
1. Ev	idence of bias from	study sample (for ex	ample, the paper is	s not clear abou	t how many peop	e were eligible for t	he study and were not inc	luded, 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 (2	2011), Seddon (2013	3) and Seddon (2015	) all report the sar	ne participants fi	ros the ARED2 stu	udy		

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

#### 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 progressio	n							
1 (Guymer 2013)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	114	RR 0.78 (0.50, 1.02)	LOW
Adverse outcom	nes							
1 (Guymer 2013)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	114	RR 0.64 (0.39, 0.92)	LOW
		or incomplete outco		• •	•	•		

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

<u> </u>	•		<u> </u>	<u> </u>	<u>U</u>	U		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Loss of 3 or more	lines of visual a	cuity at 24 months	6					
1 (ARES2)	RCT	Not serious	N/A	Not serious	Very serious <sup>1</sup>	236	RR 1.14, (0.53, 2.45)	LOW
Loss of 3 or more	lines of visual a	cuity at 36 months	5					
1 (ARES2)	RCT	Not serious	N/A	Not serious	Very serious <sup>1</sup>	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 <sup>1</sup>	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 <sup>1</sup>	195	RR 1.12, (0.53 , 2.38)	LOW
Progression of Al	MD 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 (ET	DRS letters; high	ner is better)						
1 (Ute E K 2015)	RCT	Serious <sup>3</sup>	N/A	Not serious	Not serious	79	MD 1.00 (-2.50 ,4.50)	MODERATE
1. Downgra	ded two levels fo	or confidence inter	val crossing 2 line	s of a defined m	inimal important o	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

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

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI	
AREDS2 (1)	-0.0305 (0.069828)	+	92.5 %	0.97 [0.85, 1.11]	
NAT2 (2)	-0.1165 (0.2456)	-	7.5 %	0.89 [ 0.55, 1.44 ]	
Test for overall effect:	0.11, df = 1 (P = 0.74); l <sup>2</sup> =0.0% Z = 0.55 (P = 0.58) ferences: Not applicable		<b>100.0</b> %	0.96 [ 0.84, 1.10 ]	
	0.01 Favours omega-3	0.1 1 1 Favour	0 100 s placebo		

(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	•	levent progrees						
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Development of C	NV							
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 <sup>1</sup>	2159 (3580 eyes)	RR* 1.03, (0.83, 1.27)	MODERATE
Development of ge	eographic atroph	ıy						
2 (CNVPT, laser to Drusen study 1995)	RCT	Not serious	Not serious	Not serious	Very serious <sup>2</sup>	148 (148 eyes)	RR* 1.27 (0.41, 3.94)	LOW
Visual loss of 2-3+	- lines of visual a	acuity at 3-year fol	llow-up					
9 (CAPT, DLS, Figueroa 1994, PTAMD bilateral 2009, CNVPT, Laser to Drusen Study 1995, Olk 1999, PTAMD unilateral 2002)	RCT	Serious <sup>3</sup>	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 <sup>4</sup>	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)								
2. Downgrad 3. Downgrad	ded two levels fo ded one level for ded one level for	r confidence inter risk of bias due to heterogeneity (i <sup>2</sup>	,	es of a defined m	ninimal important o	difference		

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

## **Development of CNV<sup>1</sup>**

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration Comparison: 1 Photocoagulation versus control Outcome: 1 Development of choroidal neovascularisation (CNV)

50/1008 7/103 1/30 5/27 3/65 20/220 1453 = 0.46); l <sup>2</sup> =0.0% 13/47		22.6 % 7.9 % 0.9 % 3.6 % 3.1 % 14.9 % <b>53.0</b> %	0.81 [0.53, 1.24] 1.81 [0.68, 4.80] 0.32 [0.01, 8.24] 0.55 [0.12, 2.58] 2.21 [0.42, 11.66] 1.22 [0.65, 2.28] 0.99 [0.72, 1.36]
1/30 5/27 3/65 20/220 <b>1453</b> = 0.46);   <sup>2</sup> = 0.0%		0.9 % 3.6 % 3.1 % 14.9 % 5 <b>3.0</b> %	0.32 [0.01, 8.24] 0.55 [0.12, 2.58] 2.21 [0.42, 11.66] 1.22 [0.65, 2.28] <b>0.99 [0.72, 1.36</b> ]
5/27 3/65 20/220 <b>1453</b> = 0.46);   <sup>2</sup> =0.0%		3.6 % 3.1 % 14.9 % 5 <b>3.0</b> %	0.55 [0.12, 2.58] 2.21 [0.42, 11.66] 1.22 [0.65, 2.28] <b>0.99 [0.72, 1.36</b> ]
3/65 20/220 <b>1453</b> = 0.46); I <sup>2</sup> =0.0%		3.1 % 14.9 % 53.0 %	2.21 [ 0.42, 11.66 ] 1.22 [ 0.65, 2.28 ] <b>0.99 [ 0.72, 1.36</b> ]
20/220 <b>1453</b> = 0.46); l <sup>2</sup> =0.0%		14.9% 5 <b>3.0</b> %	1.22 [0.65, 2.28] 0.99 [0.72, 1.36]
<b>1453</b> = 0.46); i <sup>2</sup> =0.0%	•	53.0 %	0.99 [ 0.72, 1.36 ]
= 0.46); l <sup>2</sup> =0.0%	<b>•</b>		
13/47	_		
		8.7 %	0.92 [ 0.37, 2.31 ]
15/85		12.5 %	1.97 [ 0.96, 4.03 ]
5/19 +	+	1.0 %	0.08 [ 0.00, 1.48 ]
5/68		5.6 %	1.47 [ 0.44, 4.88 ]
11/42		6.4 %	0.50 [ 0.16, 1.51 ]
7/26	—— <b>—</b> —	4.4 %	0.52 [ 0.13, 2.05 ]
9/71		8.5 %	1.79 [ 0.71, 4.53 ]
<b>358</b> (P = 0.12);   <sup>2</sup> =41%	•	47.0 %	1.04 [ 0.60, 1.79 ]
<b>1811</b> I) ! (P = 0.23);   <sup>2</sup> =21% (P = 0.88),   <sup>2</sup> =0.0%	•	100.0 %	107 [ 0.79, 1.46 ]
	l) (P = 0.23); l <sup>2</sup> =21%	)) (P = 0.23);   <sup>2</sup> = 21% (P = 0.88),   <sup>2</sup> = 0.0%	)) (P = 0.23); $l^2 = 21\%$ (P = 0.88), $l^2 = 0.0\%$

#### **Development of geographic atrophy**

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration Comparison: 1 Photocoagulation versus control Outcome: 3 Development of geographic atrophy

Study or subgroup	Photocoagulation n/N	Control n/N			dds Ratio ixed,95% Cl		Weight	Odds Ratio M - H, Fixed, 95% Cl
CNVPT	5/32	3/34		_	-	-	56.3 %	1.91 [0.42, 8.76]
Laser to Drusen Stu	dy 1995 1/40	2/42	-	•			43.7 %	0.51 [0.04, 5.89]
		<b>76</b> =0.0%		-			100.0 %	1.30 [ 0.38, 4.51 ]
	Fav	ours experimenta	0.01	0.1	1 Favo	10 ours control	100	

<sup>&</sup>lt;sup>1</sup> Meta-analysis were extracted form the Cochrane review, and odds ratios were reported in Cochrane review. Internal Clinical Guidelines, 2017

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

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration Comparison: 1 Photocoagulation versus control Outcome: 4 Visual loss of 2 to 3+ lines

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI	
1 Bilateral studies CAPT	-0.2691125 (0.1748489)		36.1 %	0.76[0.54,1.08]	
DLS	-0.573346 (0.67029815) -		2.5 %	0.56 [0.15, 2.10]	
Figueroa 1994 -	0.3254224 (0.99673272)		1.1 %	0.72 [0.10, 5.09]	
PTAMD bilateral	200918162 (0.16900101)		38.6 %	1.20 [0.86, 1.67]	
Subtotal (95% Cl Heterogeneity: Tau <sup>2</sup> Test for overall effec	<b>)</b> = 0.03; Chi <sup>2</sup> = 4.13, df = 3 (P = 0 tt: Z = 0.47 (P = 0.64)	.25); l <sup>2</sup> =27%	<b>78.3</b> %	0.93 [ 0.67, 1.28 ]	
2 Unilateral studies CNVPT	-0.2772899 (0.5531024)		3.6 %	0.76 [ 0.26, 2.24 ]	
DLS	0.4986213 (0.4032875)		6.8 %	1.65 [ 0.75, 3.63 ]	
Laser to Drusen	Stoldly955979454-6 (0.7104946)		2.2 %	0.82 [ 0.20, 3.31 ]	
0lk 1999	-0.238411 (0.5902647)		3.2 %	0.79 [0.25, 2.51]	
PTAMD unilatera	1 200 BZ46934 (0.4297128)		6.0 %	1.45 [ 0.63, 3.38 ]	
	<b>)</b> = 0.0; Chi <sup>2</sup> = 2.29, df = 4 (P = 0.6 :t: Z = 0.70 (P = 0.48)	58); I <sup>2</sup> =0.0%	21.7 %	117 [ 0.75, 1.82 ]	
Test for overall effect	= 0.0; Chi <sup>2</sup> = 7.13, df = 8 (P = 0.5 :t: Z = 0.10 (P = 0.92) lifferences: Chi <sup>2</sup> = 0.71, df = 1 (P =		100.0 %	0.99 [ 0.81, 1.22 ]	
	0.1 Favours photocoagulation	0.2 0.5 1 2 5 Favours c			

#### **Drusen reduction**

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration Comparison: 1 Photocoagulation versus control Outcome: 7 Drusen reduction

itudy or subgroup	Photocoagulation n/N	Control n/N	Odds Ratio IV,Fixed,95% Cl	Weight	Odds Ratio IV,Fixed,95% CI
CNVPT	25/30	14/31		10.1 %	6.07 [1.84, 20.01]
PTAMD bilateral 2009	177/375	34/374		86.5 %	8.94 [ 5.95, 13.43 ]
PTAMD unilateral 2002	40/79	1/55		3.5 %	55.38 [7.30, 420.27]
Fotal (95% CI) Fotal events: 242 (Photocc Heterogeneity: Chi <sup>2</sup> = 3.50 Fest for overall effect: Z = Fest for subgroup differen	), df = 2 (P = 0.17);   <sup>2</sup> 11.48 (P < 0.00001)	460 ol) =43%	•	100.0 %	9.16 [ 6.28, 13.37 ]
		0.01	0.1 1 10	100	

## 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 <sup>1</sup>	2140	RR* 0.77 (0.67 ,0.89)	MODERATE			
Progression to La	te AMD (wet act	ive)									
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious <sup>1</sup>	1206	RR* 0.67 (0.53, 0.85)	MODERATE			
Progression to La	te AMD (geogra	phic atrophy)									
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious <sup>1</sup>	1206	RR* 0.76 (0.53 ,1.10)	MODERATE			
Progression to vis	ual loss (loss of	3 or more lines or	n logMAR chart)								
1 (ARED 2001)	RCT	Not serious	N/A	Not serious	Serious <sup>1</sup>	1807	RR* 0.83 (0.70,0.97)	MODERATE			
Quality of lifeasse	ssed with chang	e in NEI-VFQ sco	re (higher scores	indicate better C	QoL)						
1 (CARMIS 2011)	RCT	Serious <sup>2</sup>	N/A	Not serious	Serious <sup>1</sup>	110	MD=12.30 (4.24, 20.36)	LOW			
Visual acuity (log	Visual acuity (logMAR score) (lower values indicate better vision)										
4 (AMDSG 1996, CARMA 2013, Bartlett 2007, Veterans LAST study 2004)	RCT	Serious <sup>2</sup>	Not serious	Not serious	Serious <sup>1</sup>	979	SMD=0.01 <sup>2</sup> (-0.12,0.13)	LOW			

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality				
1. Downgrad	1. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference											

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)

			Multivitamin			Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Total	l Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
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 = Test for overall effect:	)%				0.2 0.5 1 2 5 Favours multivitamin Favours placebo		

#### 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

Multivitamin		Placebo				Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	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]	<b>-</b>
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: Chi <sup>2</sup> = 0.45, df =	1 (P = 0.:	50); l² :	= 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]	<b>•</b>
Heterogeneity: Chi <sup>2</sup> = 1.61, df =	2 (P = 0	45); l² :	= 0%						
Test for overall effect: Z = 0.87 (I	P = 0.38)								
									l
Total (95% CI)			495			484	100.0%	0.01 [-0.12, 0.13]	•
Heterogeneity: Chi <sup>2</sup> = 3.23, df =	4 (P = 0.)	52); l² :	= 0%					-	
Test for overall effect: Z = 0.09 (I	P = 0.93)								Favours placebo Favours multivitamin
Test for subgroup differences: (	Chi <b>²</b> = 1.1	7, df =	1 (P=	0.28), P	²= 14.4	4%			

Ecotnotes (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

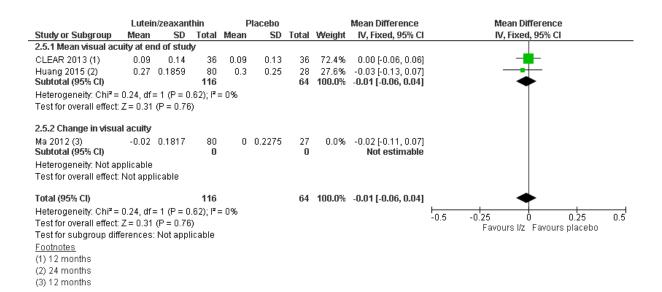
#### Lutein/zeaxanthin

	-											
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 <sup>1</sup>	Serious <sup>2</sup>	6891	RR 0.94 (0.87, 1.01)	LOW				
Progression to La	te AMD (wet act	tive)										
1 (AREDS2 2013)	RCT	Not serious	N/A	Serious <sup>1</sup>	Serious <sup>2</sup>	6891	RR 0.92 (0.84,1.02)	LOW				
Progression to La	ite AMD (geogra	phic atrophy)										
1 (AREDS2 2013)	RCT	Not serious	N/A	Serious <sup>1</sup>	Serious <sup>2</sup>	6891	RR 0.92 (0.80 ,1.05)	LOW				
Quality of lifeasse	essed with chang	e in NEI-VFQ sco	ore (higher scores	better)								
1 (Huang 2015)	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	108	MD 1.48 (-5.53 , 8.49)	MODERATE				
Visual acuity (log	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 <sup>3</sup> (-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											

<sup>&</sup>lt;sup>3</sup> -0.01 logMAR= + 0.5 letters, 95%Cl -2 to 3 letters Internal Clinical Guidelines, 2017

# Meta-analysis: Lutein and zeaxanthin

# Distance visual acuity mean (logMAR)



# Zinc supplement

Enic Supplement								
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Progression to La	te AMD (wet act	ive or geographic	atrophy)					
3 (AREDS 2001, Holz 1993, Stur 1996)	RCT	Not serious <sup>1</sup>	Not serious	Not Serious	Serious <sup>2</sup>	3776	RR* 0.87 (0.77, 0.98)	MODERATE
Progression to La	te AMD (wet act	ive)						
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	3640	RR* 0.80 (0.67, 0.94)	MODEATE
Progression to La	te AMD (geogra	phic atrophy)						
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	3640	RR* 0.85 (0.66, 1.09)	MODERATE
Distance visual a	cuity (logMAR) (l	ower values bette	r)					
2 (Stur 1996, Newsome 1998)	RCT	Not serious	Serious <sup>3</sup>	Not serious	Serious <sup>2</sup>	155	MD -0.09 <sup>4</sup> (-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<sup>2</sup>>50%)

\*Converted from odds ratios reported in included Cochrane review

<sup>&</sup>lt;sup>4</sup> -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			Weight	Odds Ratio IV, Fixed, 95% Cl	Odds Ratio IV, Fixed, 95% Cl
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 = Test for overall effect		~	53%				0.5 0.7 1 1.5 2 Favours zinc Favours placebo

<u>Footnotes</u>

(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**

	i	Zinc		Р	lacebo		9	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.5.1 Mean visual ac	uity at er	nd of s	tudy						
Stur 1996 (1) Subtotal (95% CI)	0.05	0.12	37 <b>37</b>	0.03	0.14	41 41	50.3% <b>50.3</b> %	0.15 [-0.29, 0.60] <b>0.15 [-0.29, 0.60]</b>	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z= 0.67	(P=0	1.51)						
3.5.2 Change in visua	al acuity								
Newsome 1988 (2) Subtotal (95% Cl)	4.1	6.2	40 40	7.1	10.95	37 37	49.7% <b>49.7</b> %	-0.34 [-0.79, 0.11] - <b>0.34 [-0.79, 0.11]</b>	
Heterogeneity: Not ap Test for overall effect:	•		1.14)						_
Total (95% CI)			77			78	100.0%	-0.09 [-0.57, 0.39]	•
Heterogeneity: Tau <sup>2</sup> =	0.07; CI	hi <b>²</b> = 2.	29. df=	= 1 (P =	0.13); P	= 56%			
Test for overall effect:	Z = 0.38	(P = 0	.71)						-2 -1 0 1 2
Test for subgroup diff				df = 1 (F	<sup>o</sup> = 0.13	), l² = 5	6.3%		Favours placebo Favours zinc
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

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

# 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%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Blurred vision	on										
1	Prospective	1,683	83%	26%	LR+	1.12 (1.07, 1.18)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
(Hesselund)	cohort	1,003	(80, 86%)	(24, 29%)	LR-	0.05	Very serious <sup>1</sup>		Serious <sup>2</sup>	Not serious	VERY LOW
Central dark	spot										
1	Prospective	1,683	46%	68%	LR+	1.45 (1.28, 1.64)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
(Hesselund)	cohort	1,005	(42, 50%)	(65, 71%)	LR-	0.70	Very serious <sup>1</sup>		Serious <sup>2</sup>	Not serious	VERY LOW
Metamorpho	osia										
1	Prospective	4 000	51%	60%	LR+	1.27 (1.13, 1.41)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
(Hesselund)		1,683	(47, 55%)	(57, 63%)	LR-	0.80 (0.75, 0.91)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
Micropsia											
1	Prospective	1 602	10%	89%	LR+	0.88 (0.65, 1.20)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
(Hesselund)		1,683	(8, 113%)	(87, 91%)		1.01 (0.98, 1.05)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
Dyschromat	topsia										

design	size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prospective	4 600	18%	89%	LR+	1.62 (1.27, 2.05)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Serious <sup>3</sup>	VERY LOW
cohort	1,683	(15, 22%)	(87, 90%)	LR-	0.92 (0.88, 0.96)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
et										
Prospective	4 000	36%	73%	LR+	1.31 (1.13, 1.51)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
cohort	1,683	(32, 40%)	(70, 75%)	LR-	0.88 (0.82, 0.95)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
of symptoms										
Prospective	4 600	62%	46%	LR+	1.15 (1.05, 1.25)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
cohort	1,083	(58, 66%)	(43, 49%)	LR-	0.83 (0.73, 0.94)	Very serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	VERY LOW
	cohort et Prospective cohort f symptoms Prospective cohort	cohort1,683Prospective cohort1,683f symptoms1Prospective cohort1,683	cohort       1,683       (15, 22%)         et       (15, 22%)         Prospective cohort       1,683       36% (32, 40%)         f symptoms       (32, 40%)         Prospective cohort       1,683       62% (58, 66%)	cohort       1,683       (15, 22%)       (87, 90%)         et	$\begin{array}{c} \mbox{Prospective} \\ \mbox{cohort} \end{array} & \begin{array}{c} 1,683 \\ 1,683 \end{array} & \begin{array}{c} 18\% \\ (15,22\%) \end{array} & \begin{array}{c} 89\% \\ (87,90\%) \end{array} & \begin{array}{c} \mbox{IR-} \\ \mbox{lR-} \\ \mbox{obst} \end{array} \\ \\ \mbox{et} \end{array} \\ \\ \mbox{et} \end{array} \\ \begin{array}{c} \mbox{Prospective} \\ \mbox{cohort} \end{array} & \begin{array}{c} 1,683 \end{array} & \begin{array}{c} 36\% \\ (32,40\%) \end{array} & \begin{array}{c} 73\% \\ (70,75\%) \end{array} & \begin{array}{c} \mbox{IR-} \\ \mbox{IR-} \\ \mbox{IR-} \\ \mbox{f symptoms} \end{array} \\ \\ \mbox{Prospective} \\ \mbox{cohort} \end{array} & \begin{array}{c} 1,683 \end{array} & \begin{array}{c} 62\% \\ (58,66\%) \end{array} & \begin{array}{c} 46\% \\ (43,49\%) \end{array} & \begin{array}{c} \mbox{IR-} \\ \mbox{IR-} \\ \mbox{IR-} \\ \mbox{IR-} \end{array} \\ \end{array} $	Prospective cohort $1,683$ $18\%$ (15,22%) $89\%$ (87,90%) $IR+$ $(1.27, 2.05)$ $IR IR+$ $0.92$ $(0.88, 0.96)$ et       Image: Sigma set         Prospective cohort $1,683$ $36\%$ $(32,40\%)$ $73\%$ $(70,75\%)$ $IR+$ $1.31$ $(1.13, 1.51)$ $IR+$ $0.88$ $(0.82, 0.95)$ f symptoms $IR+$ $I.15$ $(1.05, 1.25)$	$ \begin{array}{c} \mbox{Prospective}\\ \mbox{cohort} \end{array} & 1,683 & 18\%\\ (15,22\%) & (87,90\%) \\ \mbox{isc} (127,2.05) \\ \mbox{isc} (92,09\%) \\ \mbox{isc} (127,2.05) \\ \mbox{isc} (92,09\%) \\ \mbox{isc} (127,2.05) \\ \mbox{isc} (127,2.05)$	$ \begin{array}{c} \mbox{Prospective cohort} \\ \mbox{Prospective cohort} \\ \mbox{1,683} \\ \mbox{1,683} \\ \mbox{15,22\%} \\ \mbox{15,22\%} \\ \mbox{15,22\%} \\ \mbox{16,22\%} \\ $	$ \begin{array}{c} \mbox{Prospective}\\ \mbox{cohort} \end{array} & 1,683 \end{array} & \frac{18\%}{(15,22\%)} & \frac{89\%}{(87,90\%)} & \frac{\mbox{LR}}{\mbox{LR}} & \frac{0.92}{(0.88,0.96)} & \frac{\mbox{Very}}{\mbox{serious}} & N/A & \mbox{Serious}^2 \end{array} \\ \hline \mbox{t} & t & t & t & t & t & t & t & t & t &$	$ \begin{array}{c} \mbox{Prospective}\\ \mbox{cohort} \end{array} & \begin{array}{c} \mbox{1} & \mbox{8} & \mbo$

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

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

# 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%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Diagnostic	c tools for use	in detecti	ng drusen								
Fundus ph	hotograph (gra	ding crite	ria) 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 <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	VERY LOW
					LR-	0.51 (0.16, 1.58)	Very serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	VERY LOW
Diagnostic	c tools for use	in detecti	ng age-relate	d macular dege	neratio	on					
				tograph to detec large drusen in				ration(the prese	nce of ≥10 sma	ıll (≤63µm) haı	rd druse and
1 (Mokwa 2013)	Retrospective case-control	eyes (66	89.3% (81.5, 95.2)	75.6% (62.2, 86.8)	LR+	3.65 (2.17, 6.14)	Very serious <sup>4</sup>	N/A	Not serious	Not serious	LOW
		people)			LR-	0.14 (0.07, 0.28)	Very serious <sup>4</sup>	N/A	Not serious	Not serious	LOW
				oh to detect age- ge drusen inside				(the presence of	≥10 small (≤63	sµm) hard drus	se and
1 (Mokwa 2013)	Retrospective case-control	eyes (66	92.0% (84.9, 97.0)	82.2% (69.9, 91.8)	LR+	5.18 (2.75, 9.73)	Very serious <sup>4</sup>	N/A	Serious⁵	Not serious	VERY LOW
		people)			LR-	0.10 (0.04, 0.21)	Very serious <sup>4</sup>	N/A	Serious <sup>5</sup>	Not serious	VERY LOW

No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Diagnostic	tools for use	in detecti	ng dry age-re	lated macular d	egene	ration					
Fundus ph	notography vs	clinical as	ssessment to	detect geograp	hic atr	ophy					
1 (Pirbhai 2004)	Prospective case series	223 eyes (118	66.0% (51.5, 78.0)	86.9% (81.1, 91.2)	LR+	(3.27, 7.78)	Serious <sup>4</sup>	N/A	Serious <sup>5</sup>	Not serious	LOW
		people)			LR-	0.39 (0.26, 0.59)	Serious <sup>4</sup>	N/A	Serious <sup>5</sup>	Serious <sup>3</sup>	VERY LOW
Diagnostic	tools for use	in detecti	ng pigment e	pithelial detachr	nent(F	PED)					
Fundus ph	notography vs	clinical as	ssessment to	detect pigment	epithe	elial detachme	ent(PED)				
1 (Pirbhai 2004)	Prospective case series	223 eyes	40.0% (21.44, 61.6)	94.1% (90.5, 96.9)	LR+	6.77 (3.14, 14.58)	Serious <sup>4</sup>	N/A	Serious <sup>5</sup>	Not serious	LOW
		(118 people)			LR-	0.64 (0.45, 0.91)	Serious <sup>4</sup>	N/A	Serious⁵	Serious <sup>3</sup>	VERY LOW
Fundus ph	notograph (gra	ding crite	ria) to detect	pigment epithel	ial det	achment (PEI	D)				
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 <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	VERY LOW
					LR-	0.51 (0.24, 1.07)	Very serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	VERY LOW
Diagnostic	tools for use	in detecti	ng neovascu	lar age-related n	nacula	r degeneratio	n/choroida	al neovascularat	ion		
Optical coh	erence tomogra	aphy vs flu	iorescein angi	ography to detect	choro	idal neovascul	arisation (s	ee figure 1, meta	analysis)		
4 (Talks	Retrospective	476/130	93.5% (72.2, 98.8)	89.2% (74.8, 95.8)	LR+	6.72 (3.19, 14.14)	Serious <sup>4</sup>	Serious <sup>6</sup>	Not serious	Not serious	LOW
2007; Wilde 2015; Mathew 2014; Mokwa 2013)		/120 eyes (759 people)			LR-	0.08 (0.02, 0.30)	Serious <sup>4</sup>	Serious <sup>6</sup>	Not serious	Not serious	LOW

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No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	
3 (Do 2012;	Prospective cohort	295 eyes:	84.4% (49.0, 96.8)	75.0% (48.6, 90.5)	LR+	3.27 (1.27, 8.43)	Serious <sup>7</sup>	Serious <sup>6</sup>	Not serious	Serious <sup>3</sup>	VERY LOW	
Padnick 2012; Sandhu 2005)		87/77/1 31 eyes (282 people)			LR-	0.21 (0.05, 0.96)	Serious <sup>7</sup>	Serious <sup>6</sup>	Not serious	Serious <sup>3</sup>	VERY LOW	
<b>Optical co</b>	herence tomog	graphy ar	ngiography vs	fluorescein ang	giogra	phy to detect	choroidal	neovascularisati	ion			
1 (De Carlo	Retrospective	(24	50.0% (20, 80%)	90.9% (70, 97.9%)	LR+	5.50 (1.24, 24.5)	Serious <sup>4</sup>	N/A	Not serious	Serious <sup>3</sup>	LOW	
2015)		people)			LR-	0.55 (0.27, 1.11)	Serious <sup>4</sup>	N/A	Not serious	Serious <sup>3</sup>	LOW	
Optical co	herence tomog	graphy ar	ngiography vs	fluorescein ang	giogra		neovascul	ar AMD				
1 (Gong 2016)	Retrospective	ctive 86 eyes (53	86 eyes (53	86.5% (76.1-	79.4% (64.5-91.0%)	LR+	4.20 (2.15,8.20)	Serious <sup>8</sup>	N/A	Not serious	Not serious	MODERATE
		people)			LR-	0.17 (0.08, 0.35)	Serious <sup>8</sup>	N/A	Not serious	Not serious	MODERATE	
	rous pigment							ar degeneration , retinal macroan				
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 <sup>4,8</sup>	N/A	Not serious	Serious <sup>3</sup>	VERY LOW	
					LR-	0.07 (0.03, 0.14)	Very serious <sup>4,8</sup>	N/A	Not serious	Not serious	LOW	
Fundus ph	notography vs	Fluoresc	ein angiograp	by to detect neo	ovasci	ılar age-relate	ed macular	degeneration –	cohort study			
1 (Maberley	Prospective cross	74 eyes (40	97.0% (89.1, 99.9)	86.6% (74.8, 95.1)	LR+	7.23 (3.31, 15.77)	Serious <sup>9</sup>	N/A	Not serious	Not serious	MODERATE	
2005)	sectional	people)			LR-	0.03 (0.01, 0.24)	Serious <sup>9</sup>	N/A	Not serious	Not serious	MODERATE	

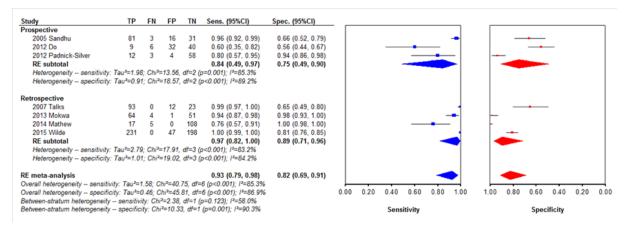
No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Fundus ph	notography vs	Fluoresco	ein angiograp	ohy to detect neo	ovascu	ılar age-relate	ed macular	degeneration -	case-control s	tudy	
1 (Mokwa 2013)	Retrospective case control	eyes (66	77.9% (67.4, 86.9)	98.1% (93.0, 100)	LR+	40.53 (5.79, 283,49)	Very serious <sup>4</sup>	N/A	Not serious	Not serious	LOW
		people)			LR-	0.22 (0.14, 0.35)	Very serious <sup>4</sup>	N/A	Not serious	Not serious	LOW
Fundus ph	notography + c	linical inf	ormation vs	Fluorescein ang	iograp	hy to detect r	neovascula	ar age-related ma	acular degener	ation	
1 (Maberley		74 eyes (40	98.5% (92.7, 100)	76.2% (62.4, 87.6)	LR+	4.14 (2.41, 7.12)	Serious <sup>9</sup>	N/A	Not serious	Not serious	MODERATE
2005)	sectional	people)			LR-	0.02 (0.00, 0.30)	Serious <sup>9</sup>	N/A	Not serious	Not serious	MODERATE
Fundus ph	notography vs	clinical a	ssessment to	detect neovasc	ular ag	ge-related ma	cular dege	eneration			
1 (Pirbhai 2004)	Prospective case series	223 eyes	82.1% (43.3, 89.5)	79.1% (72.0, 85.5)	LR+	3.94 (2.81, 5.53)	Serious <sup>4</sup>	N/A	Not serious	Not serious	MODERATE
		(118 people)			LR-	0.23 (0.14, 0.36)	Serious <sup>4</sup>	N/A	Not serious	Not serious	MODERATE
Fundus ph	notograph (gra	ding crite	ria) to detect	CNV							
1 (Lim 2002)	Prospective cross	33 eyes (17	64.0% (44.7, 81.2)	87.5% (59.0, 99.6)	LR+	5.12 (0.80, 32.78)	Very serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	VERY LOW
	sectional	people)			LR-	0.41 (0.23, 0.74)	Very serious <sup>1,2</sup>	N/A	Not serious	Serious <sup>3</sup>	VERY LOW
Fundus au	utofluoresence	vs fluore	scein angiog	raphy 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 <sup>1,8</sup>	N/A	Not serious	Not serious	LOW
					LR-	0.12 (0.03, 0.46)	Very serious <sup>1,8</sup>	N/A	Not serious	Not serious	LOW

No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Indocyanir	ne green angio	ography v	s fluorescein	angiography to	detect	t choroidal ne	ovasculari	isation (see figu	re 2, meta anal	ysis)	
2 (Cachulo 2011;	Prospective cohort; retrospective	52/58 eyes (104	58.4% (46.2, 69.7)	82.8% (70.0, 90.8)	LR+	3.25 (1.64, 6.45)	Very serious <sup>4,8</sup>	Not serious	Not serious	Serious <sup>3</sup>	VERY LOW
Sallet 1996)	cross sectional	people)			LR-	0.49 (0.36, 0.66)	Very serious <sup>4,8</sup>	Not serious	Not serious	Serious <sup>3</sup>	VERY LOW
Diagnostic	tools for use	in detecti	ng polypoida	l choroidal vasc	ulopa	thy (PCV)					
Optical co	herence tomog	graphy vs	Indocyanine	green angiogra	phy to	detect polyp	oidal chore	oidal vasculopat	hy (PCV)		
1 (De Salvo	Retrospective case-control	(44	94.6% (85.5, 99.3)	92.9% (75.3, 99.8)	LR+	13.24 (2.00, 87.68)	Very serious⁴	N/A	Not serious	Not serious	LOW
2014)		people)			LR-	0.06 (0.02, 0.23)	Very serious⁴	N/A	Not serious	Not serious	LOW
Optical col	herence tomog	graphy an	igiography (C	CT-A) vs Indocy	vanine	green angiog	raphy to d	letect polypoidal	choroidal vas	culopathy (PC	CV)
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 <sup>1</sup>	N/A	Not serious	Serious	LOW
					LR-	0.73 (0.55, 0.98)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERATE
				angiography vs I vasculopathy (		ocal scanning	laser oph	thalmoscope-ba	sed ilndocyani	ne green angi	iography
1 (Cheung et al.	Retrospective comparative	241 eyes	78.6% (71.2, 85.2)	87.3% (80.5, 92.8)		6.18 (3.76. 10.16)	Very serious <sup>4,2</sup>	N/A	Not serious	Not serious	LOW
2015)		(230 people)			LR-	0.24 (0.18, 0.34)	Very serious <sup>4,2</sup>	N/A	Not serious	Not serious	LOW
Fundus ph	notography vs	clinical a	ssessment to	detect choroida	l neov	ascular mem	brane				
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 <sup>4</sup>	N/A	Not serious	Not serious	MODERATE

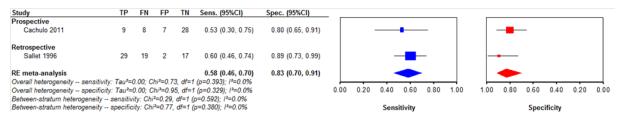
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No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
		(118 people)			LR-	0.13 (0.07, 0.22)	Serious <sup>4</sup>	N/A	Not serious	Not serious	MODERATE
1.	Downgraded	wngraded one level for inadequate or unclear blinding between index test and reference standard;									
2.	Downgraded	owngraded one level for exclusion criteria not reported;									
3.	Downgraded	owngraded one level for confidence interval cross 1 line of defined minimal important difference;									
4.	Downgraded	Downgraded two levels for case-control study design; downgraded one level for case series, retrospective study;									
5.	Downgraded	one level f	or reference te	est was not consi	stent w	rith protocol ref	ference test	t (OCT);			
6.	Downgraded	one level f	or heterogene	ity (i2>50%);							
7.	Downgraded	Downgraded one level for time interval between index test and reference standard unclear;									
8.	Downgraded	Downgraded one level for selection bias (pre-defined study population or patients being treated with anti-VGF);									
9.	Downgraded	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



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

# 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?

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality			
Diagnosis agre	ement between o	optometrist and o	ohthalmologist								
Rapid access re	eferral form (hist	ory finding (reduc	tion in vision, di	stortion, centra	al scotoma)						
1 (Muen 2011)	Prospective cohort	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	54 (referrals)	57.4% (n=31) (44.2 to 70.6%)	VERY LOW			
Rapid access re	eferral form (acc	uracy in detecting	Exudative AMD	)							
1 (Muen 2011)	Prospective cohort	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	54 (referrals)	37.0% (n=20) (24.1 to 50.0%)	VERY LOW			
Vignette (no. of	correctly classi	fied nAMD)									
1 (Reeves 2016)	RCT	Serious <sup>3</sup>	N/A	Not serious	Not serious	2016 images	RR 1.01 (0.99 to 1.04)	MODERATE			
Vignette (no. of	correctly classi	fied as reactivated	i)								
1 (Reeves 2016)											
Vignette (no. of	error occurred t	hat classified as r	eactivated)								

## Models of care

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Number of								
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
1 (Reeves 2016)	RCT	Serious <sup>3</sup>	N/A	Not serious	Very serious <sup>4</sup>	994 images	RR 1.09 (0.77 to 1.54)	VERY LOW
Vignette (no. o	f correctly classi	fied as quiescent	/suspicious)					
1( Reeves 2016)	RCT	Serious <sup>3</sup>	N/A	Not serious	Not serious	1022 images	RR 1.09 (1.06 to 1.11)	MODERATE
Number of pati	ients referred							
Routine eye ex	amination (patie	nts with no symp	toms being refer	ed for AMD)				
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious <sup>7</sup>	N/A	Serious <sup>6</sup>	Not serious	1084	2.7% (n=30) (1.7 to 3.7%)	VERY LOW
Routine eye ex	amination (patie	nts with symptom	ns being referred	for AMD)				
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious <sup>7</sup>	N/A	Serious <sup>6</sup>	Not serious	2992	5.1% (n=153) (4.3 to 6.0%)	VERY LOW
Routine eye ex	amination (numb	per of patients wit	hout symptoms	vs no. of patien	ts with symptom	ns being referred	for AMD)	
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious <sup>7</sup>	N/A	Serious <sup>6</sup>	Not serious	4,076	RR 0.54 (0.37 to 0.80)	VERY LOW
Teleretinal scr	eening							
1 (Chasan 2014)	Retrospective cohort	Serious <sup>7</sup>	N/A	Serious <sup>6</sup>	Not serious	1935	24.0% (n=465) (22.1 to 25.9%)	VERY LOW
Electronically	referrals resulting	g in a hospital ap	pointment (with v	s without attac	hed images)			
1 (Goudie 2014)	Retrospective cohort	Serious <sup>7</sup>	N/A	Serious <sup>6</sup>	Not serious	1152 (referrals)	RR 0.73 (0.73 to 0.79)	VERY LOW
Anti-VEGF inje	ction administra	tion						
% of injection	cycles were unin	terrupted injectio	n (by retinal spec	ialist)				
1 (Engman 2011)	Chart review	Serious <sup>7</sup>	N/A	Not serious	Not serious	175 injection cycles	76.5% (70.2 to 82.8%)	VERY LOW

Risk of bias         pllow-up         f 15 ETDRS letters         ve       Serious <sup>8</sup> 5 letters         ve       Serious <sup>8</sup> ts, ETDRS letters (h ve         ve       Serious <sup>8</sup> orovision (after vs be of 15 letter or more	N/A N/A igher values better) N/A	Not serious Not serious	Imprecision Serious <sup>5</sup> Very serious <sup>4</sup> Serious <sup>5</sup>	Sample size 62 people (72 eyes) 62 people (72 eyes) 62 people (72 eyes)	Effect (95%CI) RR 9.00 (1.17 to 68.92) RR 0.43 (0.12 to 1.59) MD 1.20 (-4.00 to 6.40)	Quality VERY LOW VERY LOW VERY LOW
15 ETDRS letters         ve       Serious <sup>8</sup> 5 letters         ve       Serious <sup>8</sup> ts, ETDRS letters (h         ve       Serious <sup>8</sup> provision (after vs be         of 15 letter or more	N/A igher values better) N/A	Not serious	Very serious <sup>4</sup>	eyes) 62 people (72 eyes) 62 people (72	(1.17 to 68.92) RR 0.43 (0.12 to 1.59) MD 1.20	VERY LOW
15 ETDRS letters         ve       Serious <sup>8</sup> 5 letters         ve       Serious <sup>8</sup> ts, ETDRS letters (h         ve       Serious <sup>8</sup> provision (after vs be         of 15 letter or more	N/A igher values better) N/A	Not serious	Very serious <sup>4</sup>	eyes) 62 people (72 eyes) 62 people (72	(1.17 to 68.92) RR 0.43 (0.12 to 1.59) MD 1.20	VERY LOW
ve Serious <sup>8</sup> 5 letters ve Serious <sup>8</sup> ts, ETDRS letters (h ve Serious <sup>8</sup> provision (after vs be of 15 letter or more	N/A igher values better) N/A	Not serious	Very serious <sup>4</sup>	eyes) 62 people (72 eyes) 62 people (72	(1.17 to 68.92) RR 0.43 (0.12 to 1.59) MD 1.20	VERY LOW
5 letters ve Serious <sup>8</sup> ts, ETDRS letters (h ve Serious <sup>8</sup> provision (after vs be of 15 letter or more	N/A igher values better) N/A	Not serious	Very serious <sup>4</sup>	eyes) 62 people (72 eyes) 62 people (72	(1.17 to 68.92) RR 0.43 (0.12 to 1.59) MD 1.20	VERY LOW
ve Serious <sup>8</sup> ts, ETDRS letters (h ve Serious <sup>8</sup> provision (after vs be of 15 letter or more	<b>igher values better)</b> N/A		-	eyes) 62 people (72	(0.12 to 1.59) MD 1.20	
ts, ETDRS letters (h ve Serious <sup>8</sup> provision (after vs be of 15 letter or more	<b>igher values better)</b> N/A		-	eyes) 62 people (72	(0.12 to 1.59) MD 1.20	
ve Serious <sup>8</sup> provision (after vs be of 15 letter or more	N/A		Serious <sup>5</sup>	• • •		VERY LOW
provision (after vs be of 15 letter or more		Not serious	Serious <sup>5</sup>	• • •		VERY LOW
of 15 letter or more	efore)					
dy Serious <sup>7,8</sup>	N/A	Not serious	Serious <sup>5</sup>	113	RR 3.53 (1.05 to 11.85)	VERY LOW
sion						
dy Serious <sup>7,8</sup>	N/A	Not serious	Serious <sup>5</sup>	113	RR 1.11 (0.94 to 1.45)	VERY LOW
usual care						
o (12 months) (ETDI	RS letters; higher so	ores indicate b	etter vision)			
Serious <sup>10</sup>	N/A	Not serious	Serious <sup>5</sup>	169	MD -4.80 letters (-11.31 to 1.71)	LOW
vs usual care						
AR; lower scores in	dicate better vision)					
ve Serious <sup>8</sup>	n/a	Not serious	Very serious <sup>11</sup>	360	MD -0.05	VERY LOW
	o (12 months) (ETDI Serious <sup>10</sup> x vs usual care AR; lower scores ine	o (12 months) (ETDRS letters; higher so         Serious <sup>10</sup> N/A         x vs usual care         AR; lower scores indicate better vision)         ve       Serious <sup>8</sup> n/a	o (12 months) (ETDRS letters; higher scores indicate b         Serious <sup>10</sup> N/A         N/A       Not serious         a vs usual care         AR; lower scores indicate better vision)         ve       Serious <sup>8</sup> n/a       Not serious	o (12 months) (ETDRS letters; higher scores indicate better vision)         Serious <sup>10</sup> N/A       Not serious       Serious <sup>5</sup> Serious usual care       Serious scores indicate better vision)       Serious <sup>8</sup> n/a       Not serious         Ve       Serious <sup>8</sup> n/a       Not serious       Very serious <sup>11</sup>	o (12 months) (ETDRS letters; higher scores indicate better vision)         Serious <sup>10</sup> N/A       Not serious       Serious <sup>5</sup> 169         x vs usual care         AR; lower scores indicate better vision)         ve       Serious <sup>8</sup> n/a       Not serious       Very serious <sup>11</sup> 360	Serious <sup>10</sup> N/A       Not serious       Serious <sup>5</sup> 169       MD -4.80 letters (-11.31 to 1.71)         x vs usual care       AR; lower scores indicate better vision)

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Improvement i	n service provisi	ion (after vs before	e)					
% of patients I	peing referred to	1 <sup>st</sup> assessment wi	thin 1 week					
1 (Ghazala 2013)	Audit study	Serious <sup>7</sup>	n/a	Not serious	Not serious	120	RR 2.14 (1.33 to 3.45)	VERY LOW
Teleophthalmo	ology vs routine			·	·			
Time from refe	erral to diagnosis	(diagnostic image	e), days					
1 (Li 2015)	RCT	Serious <sup>12</sup>	N/A	Not serious	Serious <sup>13</sup>	106	MD 4.5 (-2.80 to 11.80)	LOW
Time from refe	erral to treatment	, days						
1 (Li 2015)	RCT	Serious <sup>12</sup>	N/A	Not serious	Serious <sup>13</sup>	106	MD 8.7 (-5.29 to 22.69)	LOW
Time to recurr	ence, days							
1 (Li 2015)	RCT	Serious <sup>12</sup>	N/A	Not serious	Serious <sup>13</sup>	63	MD -4.2 (-47.77 to 39.15)	LOW
Recurrence to	treatment, days							
1 (Li 2015)	RCT	Serious <sup>12</sup>	N/A	Not serious	Not serious	63	MD 13.5 (9.0 to 18.2)	MODERATE
Teleconsultati	on network vs us	sual care (time from	m first visit to tre	atment), days				
1 (Azzolini 2013)	Prospective cohort	Serious <sup>8</sup>	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 cond	litions included in th	e study not AMD	specific				
7. Downgraded	one level for retro	spective study desi	gn					
8. Downgraded	one level for study	y design (audit stud	y; before-after)					
9. Downgraded	one level for Injec	tion by nurse practi	tioners, no head-	to-head compari	son			
10.Downgraded	one level for risk	of bias due to open	label study					
11. Downgraded	two levels for 95	%CI of the effect ca	nnot be estimate	d				
12. Downgraded	l one level for risk	of bias due to mas	king of study part	icipants being ui	nclear			
13. Downgraded	l one level for non	n-significant effect e	stimate (mean dif	ference 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 a	nd visual acuity							
Visual acuity se	core change (longe	est vs shortest tin	ne to treatment)	-	-		-	
1 (Arias 2009)	Retrospective cohort	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	100	Correlation r 0.3534 (p=0.0004)	VERY LOW
Visual acuity c	hange treatment ar	nd baseline, BCV	A decimal (highe	er values better	)			
1 (Rauch 2012) (symptoms duration <1m)	Case series	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	22	MD 0.09 (-0.03 to 0.21)	VERY LOW
1 (Rauch 2012) (symptoms duration 1-6m)	Case series	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	17	MD 0.07 (-0.04 to 0.18)	VERY LOW
1 (Rauch 2012) (symptoms duration >6m)	Case series	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Not serious	6	MD 0.06 (-0.05 to 0.19)	VERY LOW

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Number of								
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
VA change bet	ween diagnosis an	d treatment (long	er vs shorter trea	atment waiting	time) (ETDRS le	tters; higher sco	ores indicate bette	er vision)
1 (Real 2013)	Case series	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Serious <sup>3</sup>	78	MD -7.55 <sup>5</sup> (-12.94 to - 2.16)	VERY LOW
1 (Rasmussen 2015)	Case series	Serious <sup>1</sup>	N/A	Serious <sup>2</sup>	Serious <sup>3</sup>	1185	MD -4.24 <sup>6</sup> (- 5.93 to -2.55)	VERY LOW
% of people ha	d a gain of more th	an 2 lines (10 lett	ers)					
Longer (>21 w)	vs shorter (<7 w) o	delay from sympto	om to treatment					
1 (Lim 2012)	Case series	Serious <sup>4</sup>	N/A	Serious <sup>2</sup>	Serious <sup>3</sup>	109	RR 0.53 (0.29 to 1.00)	VERY LOW
Longer (>3w) v	s shorter (<1w) del	ay from diagnosi	s to treatment					
1 (Lim 2012)	Case series	Serious⁴	N/A	Serious <sup>2</sup>	Serious <sup>5</sup>	134	RR 0.77 (0.41 to 1.43)	VERY LOW
% of people ha	d a loss of more th	an 2 lines (10 lett	ers)					
Longer (>21w)	vs shorter (7w) del	ay from symptom	to treatment					
1 (Lim 2012)	Case series	Serious <sup>4</sup>	N/A	Serious <sup>2</sup>	Serious⁵	109	RR 1.19 (0.43 to 3.31)	VERY LOW
Longer (>3w) v	s shorter (<1w) del	ay from diagnosi	s to treatment					
1 (Lim 2012)	Case series	Serious <sup>4</sup>	N/A	Serious <sup>2</sup>	Serious⁵	134	RR 0.84 (0.34 to 2.10)	VERY LOW
Vison loss duri	ng latency (ETDRS	letters; higher s	cores indicate be	etter vision)				
1 (Muether 2013)	Non-randomised trial	Serious <sup>6</sup>	N/A	Serious <sup>2</sup>	Not serious	83	MD -1.79 (-3.71 to 0.13)	VERY LOW
Vision loss witl	h time delay (betwe	en initial referral	and assessment	and treatment				

<sup>5</sup> 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. <sup>6</sup> 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. Internal Clinical Guidelines, 2017 90

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
1 (Oliver- Fermandez 2005)	Case series	Serious <sup>8</sup>	N/A	Serious <sup>2</sup>	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 f	irst treatment, days	5						
People with vis	sual loss vs no visu	al loss						
1 (Muether 2011)	Non-randomised trial	Serious <sup>6</sup>	N/A	Serious <sup>2</sup>	Not serious	69	MD 7.6 (1.07 to 14.13)	VERY LOW
People had a lo	oss of more than 1	line vs no visual	loss more than 1	line				
1 (Muether 2011)	Non-randomised trial	Serious <sup>6</sup>	N/A	Serious <sup>2</sup>	Serious <sup>7</sup>	69	MD 11.0 (-0.27 to 22.27)	VERY LOW
Time days in re	ecurrent treatment,	days						
People with vis	sual loss vs no visu	al loss						
1 (Muether 2011)	Non-randomised trial	Serious <sup>6</sup>	N/A	Serious <sup>2</sup>	Serious <sup>7</sup>	21	MD 5.4 (-3.54 to 14.34)	VERY LOW
People had a lo	oss of more than 1	line vs no visual	loss more than 1	line				
1 (Muether 2011)	Non-randomised trial	Serious <sup>6</sup>	N/A	Serious <sup>2</sup>	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 retrosp	ective study desigr	ı					
2. Downgraded	one level for no head	d-to-head compari	sons and outcome	es differed from	primary interest-fo	or instance.		
3. Downgraded	3. Downgraded one level for confidence interval crossing 1 lines of a defined minimal important difference							
4. Downgraded	one level for self-rep	orted time delay (	questionnaire colle	ected information	n)			
5. Downgraded	two levels for confide	ence interval cross	ing 2 lines of a de	efined minimal in	nportant differenc	е		
6. Downgraded	one level for study d	esign (intervention	al case series/no	n-randomised tri	ial)			
7. Downgraded	7. Downgraded one level for non-significant effect estimate (mean difference crosses 0)							
8. Downgraded	one level for study p	opulation (selected	from a review of	letters from refe	erring 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 qu	ality of life (NE	I-VFQ-25) (highe	r values better)					
Chronic model o	of care vs usual	care						
Markun 2015	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	169	MD 2.10 (-0.96 to 5.16)	LOW
1.Downgraded on 2. Downgraded or	•	•	ossing 1 line of a d	efined minimal i	mportant difference	e.		

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

# 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 m	onths (better ind	dicated by lower v	alues)					
1 (Rovner 2007)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	206	RR 0.74 (0.44, 1.24)	LOW
Mean difference in	n Hamilton Depre	ession Rating Sco	ore (6 months) (be	tter indicated by	lower values)			
1 (Rovner 2007)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	206	MD 0.01 (-1.14, 1.16)	LOW
No. of lost activitie	es at 6 months (t	petter indicated by	v lower values)					
1 (Rovner 2007)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	206	RR 0.66 (0.45, 0.98)	LOW
Mean difference in	n NEI VFQ-17 so	core at 6 months (	better indicated by	higher values)				
1 (Rovner 2007)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	206	MD 1.48 (-1.05, 4.01)	LOW
1. Downgrad	led one level for	single-masked de	esign					

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 F	unction at 6 m	onths (better indic	ated by lower valu	ies)				
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 0.03	VERY LOW

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Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
							(-0.21, 0.27)	
Activities Inventor	ry at 6 month	s (better indicated	by lower values)					
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 0.01 (-0.29, 0.31)	VERY LOW
NEI-VFQ total sco	ore at 6 mont	ths (better indicated	by higher values)					
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Very serious <sup>3</sup>	141	MD 1.60 (-2.71, 5.91)	VERY LOW
NEI-VFQ QoL So	cial Function	ing at 6 months (be	etter indicated by h	igher values)				
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 2.53 (-4.19, 9.25)	VERY LOW
NEI-VFQ QoL Me	ental Health (	better indicated by	higher values)					
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 5.50 (-1.14, 12.14)	VERY LOW
NEI-VFQ QoL Ro	le Functionir	ng at 6 months (bet	ter indicated by hig	her values)				
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD -0.70 (-6.17, 4.77)	VERY LOW
NEI-VFQ QoL De	pendency at	6 months (better in	dicated by higher	values)				
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 6.10 (-1.55, 13.75)	VERY LOW
Control strategies	: selective p	rimary control at 6 r	nonths (better indi	cated by higher v	values)			
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Not serious	141	MD -1.00 (-1.79, -0.21)	LOW
Control strategies	: compensat	ory primary control	at 6 months (bette	r indicated by hig	gher values)			
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 0.20 (-1.40, 1.80)	VERY LOW
Control strategies	: selective se	econdary control at	6 months (better in	ndicated by highe	er values)			
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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	compensator	y secondary contr	ol at 6 months (be	etter indicated by	higher values)			
1 (Rovner 2013)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 1.20 (-0.02, 2.42)	VERY LOW
2. Downgrad	ded one level f	or non-significant	result		hose included and inimal important dif		llow up	

# Psychosocial intervention programme vs usual care

Number of studies	Design	Risk of bias	Inconsisten cy	Indirectness	Imprecision	Sample size	Effect size (95% Cl)	Quality
Mean difference	Positive affect (	PANAS) score at	7-9 weeks follow	w up (better indicat	ed by lower value	s)		
1 (Birk 2004)	Non- randomised trial	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	22	MD -0.12 (-0.58, 0.34)	VERY LOW
Mean difference	negative affect	(PANAS) score at	t 7-9 weeks (bet	ter indicated by hig	her values)			
1 (Birk 2004)	Non- randomised trial	Very serious <sup>1</sup>	N/A	Not serious	Not serious	22	MD 0.53 (0.13, 0.93)	LOW
Mean difference	geriatric depres	sion scale (GDS)	score at 7-9 we	eks (better indicate	ed by higher value	s)		
1 (Birk 2004)	Non- randomised trial	Very serious <sup>1</sup>	N/A	Not serious	Not serious	22	MD 1.45 (0.31, 2.59)	LOW
Mean difference	activities of dail	y living score at 7	-9 weeks (better	indicated by highe	er values)			
1 (Birk 2004)	Non- randomised trial	Very serious <sup>1</sup>	N/A	Not serious	Not serious	22	MD 6.10 (1.18, 11.02)	LOW
Mean difference	perceived autor	nomy at 7-9 week	s (better indicate	ed by lower values				

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

Number of studies	Design	Risk of bias	Inconsisten cy	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
1 (Birk 2004)	Non- randomised trial	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	20	MD -1.80 (-3.62, 0.02)	VERY LOW
Mean difference a	ctive problem	orientation score a	at 7-9 weeks (be	etter indicated by low	ver values)			
1 (Birk 2004)	Non- randomised trial	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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% Cl)	Quality
Mean difference tota	I profile of mod	od states (POMS	score at 6 montl	ns (better indicated	by lower values)			
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	214	MD -11.78 (-18.43, -5.13)	LOW
Mean difference NEI	-VFQ-25 total	score at 6 month	ns (better indicated	d by higher values)				
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	213	MD 2.63 (0.23, 5.03)	LOW
Mean difference AMI	D self-efficacy	scale total score	at 6 months (bett	ter indicated by high	ner values)			
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Not serious	213	MD 5.64 (2.11, 9.17)	MODERATE
Mean difference in P	OMS total sco	re at 6 months a	mong those with	depression at basel	ine (better indicat	ed by lower valu	es)	
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Not serious	51	MD -26.24 (-42.40, -10.08)	MODERATE
Mean difference in to	otal NEI-VFQ-2	5 at 6 months a	mong those with c	lepression at baseli	ne (better indicate	ed by higher valu	ies)	
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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 P	OMS total so	core at 6 months a	among those witho	out depression at t	baseline (better ind	dicated by lower	values)	
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	162	MD 2.67 (-3.76, 9.10)	LOW
Mean difference in to	otal NEI-VFQ	-25 at 6 months a	mong those witho	ut depression at b	aseline (better inc	licated by higher	values)	
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	161	MD -0.83 (-3.29, 1.63)	LOW
Mean difference in A	MD self-effic	acy score at 6 mc	onths amongst tho	se with depression	n at baseline (bette	er indicated by hi	gher values)	
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Not serious	66	MD 9.87 (2.31, 17.43)	MODERATE
Mean difference in A	MD self-effic	acy score at 6 mc	onths amongst tho	se without depres	sion at baseline (b	etter indicated by	y higher values)	
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	161	MD 1.42 (-2.22, 5.06)	LOW
Mean difference in g	eriatric depre	ession scale total	score at 6-months	amongst those w	ith a diagnosis of	depression at bas	seline (better indicate	ed by lower values
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	32	MD -1.82 (-4.40, 0.56)	LOW
Mean difference Duk	e Social Sup	port Index-11 sco	ore at 6 months an	nong those with de	epression at basel	ine (better indicat	ted by higher values)	)
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	32	MD 5.72 (-3.37, 14.81)	LOW
Mean difference life	orientation te	st at 6-months an	nongst those with	depression at bas	eline (better indica	ated by higher val	lues)	
1 (Brody 2002)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	32	MD -0.87 (-3.72, 1.98)	LOW

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% Cl)	Quality
Mean difference total	profile of mo	od states (POMS	) score at 6 month	s (better indicated	oy lower values)			
1 (Rovner 2014)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	188	RR 0.59 (0.29, 1.17)	VERY LOW
1. Downgraded	two levels fo	r single masked; o	differences in base	eline characteristics	between those w	ho did and did n	not complete follow-u	р

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 depend	lence , 28 months	s follow-up (health e	ducation program	ne vs individu	ual programme)		
1 (Eklund 2008)	RCT	Very serious <sup>1,6</sup>	N/A	Not serious	Serious <sup>2</sup>	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 restr	iction score	(enhanced low v	vision rehabilitatio	on by a rehabilitatio	n officer vs conven	tional low vis	ion rehabilitation	)	
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Not serious <sup>4</sup>	124	MD 0.04 (-0.02, 0.11)	HIGH	
Self rated restr	iction score	, enhanced low v	ision rehabilitatio	on by community ca	re worker vs conve	ntional low vi	sion rehabilitatio	on	
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious <sup>3</sup>	130	MD -0.00 (-0.06, 0.06)	MODERATE	
Melbourne low	vision activ	ities of daily livin	ig index, at 3 mor	ths follow-up (prisr	n spectacle vs plac	ebo)			
Melbourne low	vision activ	ities of daily livin	ig, part 1 (perform	nance of ADL depen	dent on vision), cu	stom prisms	vs placebo (high	er values better)	
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious <sup>3</sup>	150	MD -0.72 (-2.30, 0.87)	MODERATE	
Melbourne low	vision activ	ities of daily livin	ig, part 1 (perform	nance of ADL depen	dent on vision), sta	andard prisms	s vs placebo (hig	her values better)	
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious <sup>3</sup>	155	MD 0.45 (-1.11, 2.01)	MODERATE	
Melbourne low	vision activ	ities of daily livin	ig, part 2 (self ass	essment of ADL pe	rformance), custon	n prisms vs pl	lacebo (higher va	alues better)	
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious <sup>3</sup>	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 activ	vities of daily livir	ng, part 2 (self ass	sessment of ADL pe	erformance), standa	rd prisms vs	placebo (higher	values better)
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious <sup>3</sup>	155	MD -0.07 (-0.59, 0.45)	MODERATE
Melbourne low	vision activ	vities of daily livir	ng index (part 2), 8	8 weeks (eccentric v	viewing vs control)	(higher value	s better)	
1 (Vukicevic 2009)	RCT	Serious⁵	N/A	Not serious	Not serious	48	MD 6.25 (3.72, 8.78)	MODERATE
-		-	study participants r interval cross 1 line	not reported. e of a defined minima	Il important difference	е.		

- 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 secu	Perceived security in the performance of daily activities, 28 months follow-up (health education programme vs individual programme)									
1 (Eklund 2004)	RCTs	Very serious <sup>1,3</sup>	N/A	Not serious	Not serious	131	MD <sup>2</sup> 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						Sample	Effect	
RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	size		Quality
• •	•	of people with V vidual programn	. ,	easure the distan	ce visual acuity at	a test distanc	e of 5m, 28 month	ns follow-up
1 (Eklund 2008)	RCT	Very serious <sup>1,3</sup>	N/A	Not serious	Very serious <sup>2</sup>	131	RR 0.97 (0.52, 1.83)	VERY LOW
Visual acuity	logMAR at 1	year (prisms co	rrection vs contro	ol) (lower values i	indicate better visio	on)		
1 (Parodi 2004)	RCT	Serious <sup>1</sup>	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) (lowe	r values indicate b	etter 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	d prism spectacle	e vs placebo) (low	ver 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 viewin	g vs control) (low	ver values indicate	better vision)		
1 (Vukicevic 2009)	RCT	Serious <sup>4</sup>	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	
	•	onths follow-up abilitation by reh	abilitation office	r or community wor	ker vs convention	al low vision	rehabilitation)		
Vision specific QoL)	c quality of I	ife score (enhan	ced low vision re	habilitation vs conv	entional low visio	n rehabilitatio	on) (higher score	s indicate poorer	
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious <sup>1</sup>	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 <sup>1</sup>	130	MD -0.05 (-0.29, 0.18)	MODERATE	
NEI-VFQ-25 at	3 months								
NEI-VFQ-25, c	ustom prisn	ns vs placebo (hi	gher scores indi	cate better QoL)					
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	150	MD 1.25 (-1.98, 4.47)	MODERATE	
NEI-VFQ-25, st	andard pris	ms vs placebo (	higher scores inc	licate better QoL)					
1 (Smith 2005)	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	155	MD 0.29 (-2.90, 3.49)	MODERATE	

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			
l (Eklund 2008)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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 <sup>1,4</sup>	N/A	Not serious	Serious <sup>2</sup>	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 indicate better		hanced low visi	on rehabilitation I	by rehabilitation o	fficer vs conventio	onal low visio	n rehabilitation) (I	higher values			
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	124	MD -6.05 (-10.2, -1.91)	MODERATE			
SF-36, physical better HRQoL)	l (enhance	d low vision reha	abilitation by com	munity worker vs	conventional low	vision rehabi	litation) (higher va	alues indicate			
1 (Reeves 2004)	RCT	Not serious	N/A	Not serious	Serious <sup>3</sup>	130	MD -2.27 (-6.29, 1.76)	MODERATE			
SF-36, mental h indicate better	•	anced low visio	n rehabilitation by	rehabilitation off	icer vs conventior	al low vision	rehabilitation) (hi	gher values			
1 (Deeuse	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	124	MD -4.04	MODERATE			
1 (Reeves 2004)							(-7.44, -0.65)				
2004)		d low vision reha	abilitation by com	munity worker vs	conventional low	vision rehabi	( , , ,	alues indicate			

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, a	t 3-months	(prism spectacl	e vs control) (hig	her scores indicate	better reading)						
1 (Smith 2005)	RCTs	Not serious	N/A	Not serious	Serious <sup>1</sup>	250	MD 6.50 (-7.84, 20.84)	MODERATE			
1. Downgra	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.

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 <sup>1</sup>
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	$\oplus \oplus \oplus \oplus$

#### H.6.1.1 Photodynamic therapy versus placebo

# Macular Degeneration

Appendix H: Grade tables and meta-analysis results

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 <sup>1</sup>
Adverse effects: visual disturbance	270 per 1000	170 per 1000	RR 1.56 1.21 to 2.01	1075 (3 studies)	$\oplus \oplus \oplus \ominus$ Moderate <sup>1</sup>
Adverse effects: injection site	120 per 1000	60 per 1000	RR 1.36 0.50 to 3.71	1075 (3 studies)	$\begin{array}{c} \oplus \ominus \ominus \ominus \\ \text{Very low}^2 \end{array}$
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 <sup>3</sup>
Adverse effects: allergic reactions	17 per 1000	19 per 1000	RR 0.94 (0.35 to 2.51)	948 (2 studies)	⊕⊕⊝⊝ Low⁴
Adverse effects: photosensitivity reactions	24 per 1000	3 per 1000	RR 2.73 (0.08 to 97.96)	948 (2 studies)	$\begin{array}{c} \bigoplus \ominus \ominus \ominus \\ \text{Very low}^2 \end{array}$

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)

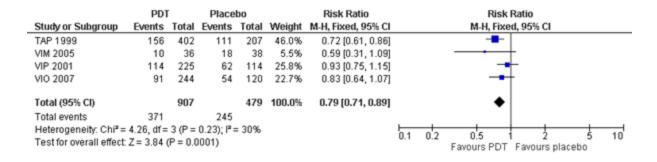
3. Not downgraded for imprecision: confidence interval wide however do not include 1 (no effect)

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)

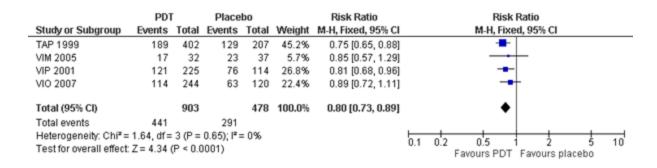
	PD1	r	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
TAP 1999	59	402	49	207	47.6%	0.62 [0.44, 0.87]	
VIM 2005	3	36	6	38	4.3%	0.53 [0.14, 1.95]	
VIP 2001	37	166	30	92	28.4%	0.68 [0.45, 1.03]	
VIO 2007	39	244	20	120	19.7%	0.96 [0.59, 1.57]	<b>_</b>
Total (95% CI)		848		457	100.0%	0.70 [0.56, 0.88]	◆
Total events	138		105				
Heterogeneity: Chi# = 2.25, df = 3 (P = 0.52); I# = 0%							
Test for overall effect	: Z = 3.07	(P = 0.0	0.1 0.2 0.5 1 2 5 10 Favours PDT Favours placebo				

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

	PD1	Г	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
TAP 1999	24	402	5	207	68.3%	2.47 [0.96, 6.38]	<b>⊢_∎</b>
VIP 2001	5	166	2	92	26.6%	1.39 [0.27, 7.00]	
VIM 2005	1	36	0	38	5.0%	3.16 [0.13, 75.20]	
Total (95% CI)		604		337	100.0%	2.22 [1.01, 4.88]	◆
Total events	30		7				
Heterogeneity: Chi <sup>2</sup> =	0.42, df=	2 (P =	0.81); l² :	= 0%			0.01 0.1 1 10 100
Test for overall effect:	Z=1.98	(P = 0.0	)5)				Favours placebo Favours PDT

#### Two years

# Visual acuity (loss of 3 or more line ETDRS)



#### Visual acuity (loss of 6 or more lines ETDRS)

	Treatm	nent	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	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: Chi <sup>2</sup> =	4.35, df=	3 (P =	0.23); I <sup>2</sup> =	: 31%			0.1 0.2 0.5 1 2 5 10
Test for overall effect	Z= 4.64	(P < 0.0	0001)				0.1 0.2 0.5 1 2 5 10 Favours treatment Favours placebo

#### Visual acuity (gain of 3 or more lines ETDRS)

	PD1	r	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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: Chi <sup>2</sup> =	0.38, df=	2 (P =	0.83); I <sup>z</sup> :	= 0%			0.01 0.1 1 10 100
Test for overall effect:	Z= 2.80	(P = 0.0	105)				Favours placebo Favours PDT

#### Adverse effects

## Acute severe visual acuity decrease

	PDT	1	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
VIM 2005	1	87	1	40	50.9%	0.46 [0.03, 7.17]	
TAP 1999	3	402	0	207	24.5%	3.61 [0.19, 69.61]	
VIP 2001	10	225	0	114	24.6%	10.69 [0.63, 180.74]	
Total (95% CI)		714		361	100.0%	3.75 [0.87, 16.12]	-
Total events	14		1				
Heterogeneity: Chi <sup>2</sup> =	2.77, df=	2 (P =	0.25); I <sup>2</sup> :	= 28%			0.001 0.1 1 10 1000
Test for overall effect	Z=1.78	(P = 0.0	)8)				Favours PDT Favours placebo

## Infusion-related back pain

	PDT	1	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
TAP 1999	10	402	0	207	19.6%	10.84 [0.64, 184.05]	
VIP 2001	5	225	0	114	19.7%	5.60 [0.31, 100.35]	
VIM 2005	9	87	1	40	40.8%	4.14 [0.54, 31.56]	
VIO 2007	25	244	0	120	19.9%	25.19 [1.55, 410.23]	—— <b>→</b>
Total (95% CI)		958		481	100.0%	9.93 [2.82, 35.02]	
Total events	49		1				
Heterogeneity: Chi <sup>2</sup> =	1.30, df=	3 (P =	0.73); I <sup>2</sup> =	= 0%			0.02 0.1 1 10 50
Test for overall effect	Z= 3.57 (	(P = 0.0	0004)				0.02 0.1 1 10 50 Favours PDT Favours placebo

### Visual disturbance

	PD1	ſ	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
TAP 1999	89	402	32	207	51.4%	1.43 [0.99, 2.07]	
VIP 2001	94	225	26	114	42.0%	1.83 [1.26, 2.66]	<b></b>
VIM 2005	7	87	4	40	6.7%	0.80 [0.25, 2.59]	
Total (95% CI)		714		361	100.0%	1.56 [1.21, 2.01]	◆
Total events	190		62				
Heterogeneity: Chi <sup>2</sup> =	2.16, df=	2 (P =	0.34); I <sup>2</sup> =	= 7%			0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z= 3.42	(P = 0.0	006)				Favours PDT Favours placebo

# Injection site

	PD1	r	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
TAP 1999	64	402	12	207	41.2%	2.75 [1.52, 4.97]	
VIP 2001	18	225	6	114	34.8%	1.52 [0.62, 3.72]	
VIM 2005	3	87	4	40	24.1%	0.34 [0.08, 1.47]	•
Total (95% CI)		714		361	100.0%	1.36 [0.50, 3.71]	
Total events	85		22				
Heterogeneity: Tau <sup>2</sup> =	0.55; Ch	i² = 7.0	7, df = 2 (	P = 0.0	3); I <sup>2</sup> = 72	2%	
Test for overall effect.	Z = 0.59	(P = 0.5	55)				Favours PDT Favours placebo

# Allergic reactions

	PDT		Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
TAP 1999	8	402	3	207	49.9%	1.37 [0.37, 5.12]		
VIP 2001	3	225	3	114	50.1%	0.51 [0.10, 2.47]	_	
Total (95% CI)		627		321	100.0%	0.94 [0.35, 2.51]		
Total events	11		6					
Heterogeneity: Chi <sup>2</sup> =	0.90, df=	1 (P =	0.34); I <sup>2</sup> =	= 0%			5	0.2 0.5 1 2 5 10
Test for overall effect:	Z=0.13	(P = 0.9	30)				0.1	Favours PDT Favours placebo

# Photosensitivity reactions

	PDT		Place	bo		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rando	om, 95% Cl	
TAP 1999	14	402	0	207	49.7%	14.97 [0.90, 249.66]		-		<b>→</b>
VIP 2001	1	225	1	114	50.3%	0.51 [0.03, 8.03]	_	-		
Total (95% CI)		627		321	100.0%	2.73 [0.08, 97.96]				
Total events	15		1							
Heterogeneity: Tau² = Test for overall effect:				P = 0.0	17); I² = 70	9%	0.02	0.1 Favours PDT	10 Favours placebo	50

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

### Macular Degeneration

Appendix H: Grade tables and meta-analysis results

						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 <sup>3</sup>	
Serious ocular adverse events at one year	169 per 1000	91 per 1000	RR 1.86 (0.73 to 4.74)	131 (1 study)	$\begin{array}{c} \oplus \oplus \ominus \ominus \\ Low^3 \end{array}$	
*The basis for the assumed risl	k is based on the assumed ris	sk in the comparison group a	nd the relative effect of th	e intervention (and its 9	5%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)

	Bevacizumab Control		ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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	1 (P = 0	.44); I <sup>2</sup> = (	0%			0.02 0.1 1 10 50
Test for overall effect	Z= 3.61 (F	P = 0.00	03)				Favors control Favors bevacizumab

#### Footnotes

Control group in the ABC study received standard therapy including pegaptanib injections, verteporfin PDT, or sham injection
 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)

	Bevacizu	mab	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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: Chi <sup>2</sup> =	1.15, df = 1	(P = 0.1)	28); I <sup>2</sup> = 1	13%			0.5 0.7 1 1.5 2
Test for overall effect	Z = 3.44 (P	= 0.00	06)				Favors control Favors bevacizumab

Footnotes

Control group in the ABC study received standard therapy including pegaptanib injections, verteporfin PDT, or sham injection
 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 <sup>1</sup>	
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)	$\oplus \oplus \ominus \ominus Low^2$	

# Macular Degeneration

Appendix H: Grade tables and meta-analysis results

Stroke or cerebral infarction	< 10 per 1000	< 10 per 1000	RR 1.04 (0.09, 11.38)	603 (2 studies)	$\oplus \oplus \ominus \ominus Low^2$	
Treatment-emergent hypertension	60 per 1000	80 per 1000	RR 0.67 (0.36, 1.24)	603 (2 studies)	$\oplus \oplus \oplus \ominus$ Moderate <sup>3</sup>	
Non-ocular hemorrhage	60 per 1000	30 per 1000	RR 1.90 (0.78, 4.62)	603 (2 studies)	$\oplus \oplus \ominus \ominus Low^2$	
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)	$\oplus \oplus \oplus \oplus$ 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 <sup>3</sup>	
Cataract	100 per 1000	70 per 1000	RR 1.48 (0.83, 2.66)		$\oplus \oplus \oplus \ominus$ Moderate <sup>3</sup>	
			rison group and the	e relative effect of the	intervention (and its 95%	CI)

#### One year

#### Visual acuity (loss of fewer than 15 letters)

	Ranibizu	ımab	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
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: Tau <sup>2</sup> =	= 0.00; Chi <sup>a</sup>	= 4.04	df = 3 (P	= 0.26	); I <sup>2</sup> = 269	6	0.5 0.7 1 1.5 2
Test for overall effect	Z = 9.00 (	P < 0.00	0001)				0.5 0.7 1 1.5 2 Favors control Favors ranibizumab

**Footnotes** 

(1) Control group in the ANCHOR study received sham injections plus active verteportin 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)

	Ranibizu	mab	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
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: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 6.33,	df = 2 (P	= 0.04	); I <sup>2</sup> = 689	6	0.5 0.7 1 1.5 2
Test for overall effect:	Z = 3.43 (F	P = 0.00	06)				0.5 0.7 1 1.5 2 Favors control Favors ranibizumab

<u>Footnotes</u>

(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)

	Ran	Ranibizumab Control						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	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: Chi <sup>a</sup> = Test for overall effect:				)%					-20 -10 0 10 20 Favors control Favors ranibizumab		

Footnotes

(1) Control group in the ANCHOR study received sharm injections plus active verteportin 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

Study or Subgroup	Mean		Total		Control SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
15.1 Overall vision-re NCHOR 2006 (1) MRINA 2006 (2)	7.008	15.2556 13.3286	276 478		15.0693 14.0958	142 238	44.6% 55.4%	4.81 (1.74, 7.87) 8.20 (6.05, 10.35)	
ubtotal (95% Cl) eterogeneity: Tau* = 3 est for overall effect Z				0.08);	I#= 68%	380	100.0%	6.69 [3.38, 9.99]	+
15.2 Near vision activ VCHOR 2006		22.2793	276	37	18.0831	142	48.6%	4.16 (0.19, 8.13)	
ARINA 2006 ubtotal (95% CI) eterogeneity: Tau# = 3	9.9021	19.2392	478 754	-2.6	18.0113	238 380	51.4% 100.0%	12.50 [9.64, 15.37] 8.45 [0.28, 16.62]	-
est for overall effect. Z									
15.3 Distance vision NCHOR 2006 ARINA 2006	7.8605	21.1335 18.0418	276 478		20.4942 18.0113	142 238	47.1% 52.9%	6.16 [1.97, 10.35] 12.75 [9.95, 15.55]	
ubtotal (95% CI) eterogeneity: Tau* = 1 est for overall effect Z	8.40; Chi	*= 6.56, df	754				100.0%	9.65 [3.20, 16.09]	-
15.4 Dependency	- 2.00 0	- 0.000							
NCHOR 2006 ARINA 2006 Abtotal (95% CI)		26.1869 22.4207	276 478 754		23.5081 24.2761	142 238 380	35.6% 64.4% 100.0%	9.65 (4.71, 14.60) 9.91 (6.23, 13.59) 9.82 (6.86, 12.77)	
leterogeneity: Tau <sup>a</sup> = 0 est for overall effect. Z				0.94);	I*= 0%				
.15.5 Driving ability									_
INCHOR 2006 MARINA 2006 Subtotal (95% CI)	3.4205 -1.2464	30.316 28.2651	244 478 722		24.8952 28.1916	120 238 358	35.9% 64.1% 100.0%	7.52 [1.66, 13.38] 11.15 [6.77, 15.54] 9.85 [6.34, 13.36]	
leterogeneity: Tau* = 0 est for overall effect: Z			= 1 (P =	0.33);	I*= 0%		1	2000 [0024] 10020]	
NCHOR 2006	-3.5598	20.5098	276	-7	22.9053	142	34.8%	3.44 [-1.04, 7.92]	
MRINA 2006 Aubtotal (95% CI) leterogeneity: Tau <sup>a</sup> = 0 'est for overall effect Z	00; Chi#		478 754 1 (P =		21.1437 P=0%	238 380	65.2% 100.0%	3.04 [-0.23, 6.32] 3.18 [0.54, 5.82]	+
15.7 Role difficulties	= 2.36 (P	= 0.02)							
NCHOR 2006 MARINA 2006		26.4393 26.7134	276 478		27.7275 25.8423	142 238	45.5% 54.5%	3.51 [-2.01, 9.04] 9.90 [5.84, 13.96]	+•
Aubtotal (95% CI) Reterogeneity: Tau* = 1 Test for overall effect Z	4.28; Chi	*= 3.33, df	754				100.0%	6.99 [0.76, 13.23]	
2.15.8 Mental health									
	14.8562 12.5523	24.9365 22.4514	276 478 754		18.6859 21.9268	142 238 380	39.5% 60.5% 100.0%	7.16 [2.90, 11.41] 9.25 [5.82, 12.69] 8.42 [5.75, 11.10]	
feterogeneity: Tau <sup>a</sup> = 0 fest for overall effect. Z			1 (P =	0.45);	I*= 0%	366	TO DO DO T	over for of 1 mol	•
15.9 General vision	10.5051	21.2766	276	2.0	10 6060	142	22.6%	6 61 12 62 10 60	
ARINA 2006 ARINA 2006 Aubtotal (95% CI)		18.4326	276 478 754		18.6859 18.0113	142 238 380	33.5% 66.5% 100.0%	6.61 [2.63, 10.58] 9.00 [6.18, 11.82] 8.20 [5.90, 10.50]	
leterogeneity: Tau* = 0 est for overall effect: Z			= 1 (P =	0.34);	I#= 0%			,	
15.10 Social function NCHOR 2006		22.3886	276	-0.5	24.1109	142	31.2%	6.87 [2.10, 11.63]	
AARINA 2006 Subtotal (95% CI)		21.1773	478 754		20.3606	238 380	68.8% 100.0%	8.55 [5.34, 11.76] 8.03 [5.36, 10.69]	
leberogeneity: Tau <sup>s</sup> = 0 est for overall effect: Z				0.57);	P = 0%				
NCHOR 2006	1.3564	20.9439	273	-1.4	22.5747	138	31.6%	2.76 [-1.76, 7.27]	
ARINA 2006 aubtotal (95% CI)	0.4987	20	478 751	-1.9	19.5775		68.4% 100.0%	2.40 [-0.67, 5.46] 2.51 [-0.02, 5.05]	-
leterogeneity: Tau* = 0 'est for overall effect: Z			(0- =	3.30%	- = 0.36				
.15.12 Peripheral visi NCHOR 2006		26.0514	275	3.3	25.3164	142	44.5%	2.44 [-2.73, 7.62]	
ARINA 2006 Aubtotal (95% CI)	3.7008	24.6948	478 753	-3.7	26.6254	238	55.5% 100.0%	7.40 [3.36, 11.44] 5.20 [0.37, 10.03]	-
leterogeneity: Tau <sup>#</sup> = 6 'est for overall effect: Z			= 1 (P =	0.14);	I <sup>#</sup> = 54%				
2.15.13 Ocular pain NCHOR 2006	2 601 4	14 0305	276		16,0600	143	20.04	-2.30 [-5.33, 0.74]	
ARINA 2006 MARINA 2006 Subtotal (95% CD		14.8265 16.8752	276 478 754		15.0693 14.8789	238	38.9% 61.1% 100.0%	-2.30 [-5.33, 0.74] -1.45 [-3.87, 0.97] -1.78 [-3.67, 0.11]	1
leterogeneity: Tau* = 0 est for overall effect Z				0.67);	I#= 0%	500	And Article 18	-not stor, and	•
									-20 -10 0 10
									-20 -10 0 10 Favors control Favors control

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

#### Two years

#### Visual acuity (gain of 15 letters or more ETDRS)

	Ranibizu	mab	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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: Chi <sup>2</sup> =	2.84, df =	2 (P = 0	.24); I <sup>2</sup> =	30%			0.05 0.2 1 5 20
Test for overall effect	Z = 8.39 (F	< 0.00	001)				Favors control Favors ranibizumab

Footnotes

(1) Control group in the ANCHOR study received sham injections plus active verteportin 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)

	Ranibizu	ımab	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
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]	<b>_</b>
Total (95% CI)		878		444	100.0%	1.62 [1.32, 1.98]	-
Total events	783		246				
Heterogeneity: Tau <sup>2</sup> =	0.02; Chi <sup>a</sup>	= 9.02	df = 2 (P	= 0.01	); I <sup>z</sup> = 789	6	
Test for overall effect:	Z= 4.69 (	P < 0.00	001)		-		0.5 0.7 1 1.5 2 Favors control Favors ranibizumab

Footnotes

(1) Control group in the ANCHOR study received sharm injections plus active verteportin 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)

	Ranibizu	mab	Contr	ol		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	d, 95% Cl
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: Chi <sup>2</sup> =		-		28%			0.5 0.7 1	1.5 2
Test for overall effect:	Z = 7.78 (F	< 0.00	001)					Favors ranibizumab

Footnotes

(1) Control group in the ANCHOR study received sham injections plus active verteportin photodynamic therapy

(2) Control group in the MARINA study received sham injections

## Mean change in visual acuity (number of letters)

	Ranibizumab Control						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	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: Chi <sup>a</sup> = Test for overall effect				-20 -10 0 10 20 Favors control Favors ranibizumab					

Footnotes

Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
 Control group in the MARINA study received sham injections
 Control group in the PIER study received sham injections

# Quality of life score

## Macular Degeneration

# Appendix H: Grade tables and meta-analysis results

Study or Subgroup 2.16.1 Overall vision r	Ranibiz Mean related quality	SD T	fotal		Control SD	Total	Weight	Mean Difference IV, Random, 95% CI			n Difference ndom, 95% (	3
ANCHOR 2006 (1) MARINA 2006 (2) Subtotal (95% CI) Heterogeneity: Tau* =	5.4029 21. 4.6494 1	2708 5.296	276 478 754	-6.5	16.8776 14.8789	142 238 380	46.2% 53.8% 100.0%	5.70 [1.96, 9.44] 11.15 [9.81, 13.48] 8.63 [3.31, 13.95]				-
Test for overall effect 2				- 0.02)	,r=03%							
2.16.2 Near vision act NCHOR 2006	Miles 7.4475 24	9245	276	0.2	22.9053	142	47.9%	7.25 (2.47, 12.03)				
ARINA 2008 Subtotal (95% CI)	8.7506 22		478		21.9268	238		15.45 [12.00, 18.90] 11.52 [3.49, 19.55]				-
leterogeneity: Tau <sup>a</sup> = fest for overall effect 2			:1(P	= 0.006	5); I# = 87%							
2.16.3 Distance vision												
NCHOR 2006 MARINA 2006	5.9525 23. 5.8494 21.		276 478		22.9053 19.5775	142 238		7.05 [2.40, 11.71] 14.25 [11.10, 17.40]				
ubtotal (95% CI) leterogeneity: Tau* = : 'est for overall effect 2			754 = 1 (P =	= 0.01)	; I*= 84%	380	100.0%	10.86 [3.82, 17.90]				
.16.4 Dependency	L = 0.01 (r = 0											
WCHOR 2006	4.6116 28 4.2573 26		276		28.3303 25.8423	142 238	46.5%	6.81 [1.04, 12.58] 14.76 [10.71, 18.80]				<u> </u>
ubtotal (95% CI) leterogeneity: Tau <sup>a</sup> = :			754								-	
est for overall effect 2	Z = 2.79 (P = 0	.005)										
NCHOR 2006	2 35		244		30.4275		32.6%				-	
ARINA 2006 aubtotal (95% CI)	-2.1523 30		722		32.1071	238 358		14.95 [10.05, 19.85] 13.53 [9.51, 17.55]				-
eterogeneity: Tau*= est for overall effect 2				0.32);	I*= 0%							
16.6 General health NCHOR 2006	-5.0058 22	7957	276	.7.2	22.9053	142	35.7%	2.19 [-2.43, 6.82]				
ARINA 2005 abtotal (95% CD)	-6.2021 22		478		21.9268	238	64.3% 100.0%	2.80 [-0.65, 6.25] 2.58 [-0.18, 5.35]				
eterogeneity: Tau <sup>a</sup> = 1 est for overall effect 2				0.84);	P = 0%	300	100.0 1	run for of sead			-	
16.7 Role difficulties												
NCHOR 2006 IARINA 2006	5.7159 31. 6.2021 29.		276 478		29.5358 28.1916	142	46.6% 53.4%	5.02 [-1.10, 11.13] 13.30 [8.87, 17.73]				_
ubtotal (95% CI) leterogeneity: Tau* = : lest for overall effect 2			754 = 1 (P =	= 0.03)	; IP = 78%	380	100.0%	9.44 [1.34, 17.54]				
.16.8 Mental health												
NCHOR 2006 MRINA 2005	12.1109 26. 12.2515 2		276 478	5.4 -0.7	24.1109 23.493	142 238	46.1% 53.9%	6.71 [1.69, 11.74] 12.95 [9.26, 16.65]				<b></b>
ubtotal (95% CI) leterogeneity: Tau <sup>a</sup> =			754				100.0%	10.07 [3.98, 16.17]				
est for overall effect 2												
16.9 General vision NCHOR 2006	10.9518	22.27	276	3.8	21.097	142	42.3%	7.15 [2.80, 11.50]				
ARINA 2006 Aubtotal (95% CI)	9.1025 19	2233	478 754	-2.3	18.0113	238 380	57.7% 100.0%	11.40 [8.54, 14.27] 9.61 [5.49, 13.72]				-
leterogeneity: Tau* = est for overall effect 2				0.11);	P= 61%							
.16.10 Social functio	-		230		22.5204							
NCHOR 2006 MRINA 2005	4.2547 1.649 23		478		23.5081 23.493	238	46.6%	4.65 [-0.27, 9.58] 11.15 [7.49, 14.80]				
ubtotal (95% CI) leterogeneity: Tau# = est for overall effect 2		4.31, dfi	754 1 (P	= 0.04)	; P= 77%	380	100.0%	8.12 [1.77, 14.47]				
.16.11 Color vision	2-2.51 (F = 0											
NCHOR 2006 MARINA 2006	-0.4963 21. -0.4586 22		273 478		24.951 21.9268	138 238	33.3% 66.7%	3.80 [-1.07, 8.68] 6.64 [3.20, 10.08]				_
lubtotal (95% CI)			751				100.0%	5.70 [2.89, 8.51]				-
leterogeneity: Tau <sup>a</sup> = est for overall effect 2			1.04 2	J. 35);	- = 0.%							
.16.12 Peripheral vis NCHOR 2006	ion 2.2793 27.	9811	275	-1.4	27.1247	142	43.2%	3.68 [-1.87, 9.23]			+-	_
ARINA 2005 aubtotal (95% CI)	2.0469 25		478 753		25.0592	238	56.8% 100.0%	9.15 [5.25, 13.05] 6.79 [1.48, 12.09]				
eterogeneity: Tau <sup>e</sup> = est for overall effect.2			1 (P =	0.11);	P = 60%							
.16.13 Ocular pain												
NCHOR 2006 ARINA 2006	1.6964 15. 1.9477 16.		276		18.0831 15.662	142 238	66.7%	-0.80 [-4.31, 2.70] -1.25 [-3.73, 1.23]				
ubtotal (95% Cl) leterogeneity: Tau* =			754 1 (P =	0.84);	l*= 0%	380	100.0%	-1.10 [-3.13, 0.92]			1	
est for overall effect 2	z = 1.07 (P = 0	.290								_		_
									-20	-10 Favors cor	0 itrol Favors	10 ranibizumab
ootnotes.												

Ecotodes (1) Control group in the ANCHOR study received sharn injections plus active verteportin photodynamic therapy (2) Control group in the MARINA study received sharn 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% Cl 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 <sup>1</sup>	
Gastrointestinal disorders	10 per 1000	20 per 1000	RR 1.85 (1.01, 3.40)	3038 (5 studies)	$\oplus \oplus \oplus \ominus$ Moderate <sup>1</sup>	
Myocardial infarction	<10 per 1000	<10 per 1000	RR 0.51 (0.22 to 1.19)	3038 (5 studies)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	
Stroke or cerebral infarction	<10 per 1000	<10 per 1000	RR 0.65 (0.25 to 1.67)	3038 (5 studies)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	
Venous thrombotic event	<10 per 10000	<10 per 1000	RR 2.04 (0.61 to 6.75)	2721 (4 studies)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	

Appendix H: Grade tables and meta-analysis results

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)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	
Severe uveitis	< 10 per 1000	<10 per 1000	RR 4.14 (0.46 to 36.97)	1795 (2 studies)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	
Endophthalmitis	<10 per 1000	<10 per 1000	RR 1.68 (0.40 to 7.00)	2111 (3 studies)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	
Retinal pigment epithelial tear	<10 per 1000	<10 per 1000	RR 1.37 (0.31 to 6.12)	2236 (3 studies)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	
cataract	<10 per 1000	<10 per 1000	RR 0.51 (0.05 to 5.62	2280 (3 studies)	$\oplus \oplus \ominus \ominus$ Low <sup>2</sup>	

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 <sup>1</sup>	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)

	Bevacizi	umab	Ranibizu	ımab		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	_ <b>+</b> •
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]	<b>_</b>
MANTA 2013	36	154	35	163	8.6%	1.09 [0.72, 1.64]	<b>_</b>
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: Chi <sup>2</sup> =	9.31, df=	7 (P = 0.	23); <b>I²</b> = 2	5%			
Test for overall effect:	Z=0.71 (F	P = 0.48	)				0.1 0.2 0.5 1 2 5 10 Favors ranibizumab Favors bevacizumab
Footpotoo							

Footnotes (1) follow-up was 18 months

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

	Bevacizu	ımab	Ranibizu	mab		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	4
Total events	1299		1355				
Heterogeneity: Chi <sup>2</sup> =	4.86, df = 8	6 (P = 0.	56); I <sup>2</sup> = 0	%			0.5 0.7 1 1.5
Test for overall effect:	Z=0.27 (F	P = 0.79)					0.5 0.7 1 1.5 Favors ranibizumab Favors bevacizumab

Footnotes (1) follow-up was 18 months

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

	Bev	acizumab	I	Rai	nibizumab	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
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]	<b>_</b>
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 = 0.7	0); I <sup>z</sup> =	0%					
Test for overall effect:	Z = 0.95 (	P = 0.34)	~						-10 -5 Ó Ś 10 Favors ranibizumab Favors bevacizumab

# Quality of life (no problem in quality of life)

Chuch an Culturation	Bevacizu		Ranibizu		Risk Ratio	Risk Ratio
Study or Subgroup	Events	TOCAL	Events	Total	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
4.11.1 Mobility						
IVAN 2013	155	262	173	286	0.98 [0.85, 1.12]	
4.11.2 Self care						
IVAN 2013	217	262	246	286	0.96 [0.90, 1.04]	-+-
4.11.3 Usual activities	;					
IVAN 2013	178	262	199	286	0.98 [0.87, 1.09]	+
4.11.4 Pain/discomfor	t					
IVAN 2013	158	262	168	285	1.02 [0.89, 1.17]	<b>+</b>
4.11.5 Anxiety/depres	sion					
IVAN 2013	188	262	214	286	0.96 [0.87, 1.06]	-+-
						0.5 0.7 1 1.5 2 Favors ranibizumab Favors bevacizumab
						Favors fambizuman Favors pevacizuman

## Number of injections

	Bevac	cizum	ab	Ranik	oizum	ab		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Biswas 2011	4.3	0	50	5.6	0	54		Not estimable	
CATT 2011	7.7	3.5	300	6.9	3	298	25.9%	0.80 [0.28, 1.32]	
GEFAL 2013	6.8	2.7	191	6.5	2.4	183	26.5%	0.30 [-0.22, 0.82]	- <b>+</b>
LUCAS 2015	8.9	2.6	184	8	2.3	187	28.3%	0.90 [0.40, 1.40]	
MANTA 2013	6.1	2.8	154	5.8	2.7	163	19.3%	0.30 [-0.31, 0.91]	-+ <b>-</b>
Total (95% Cl)			829			831	100.0%	0.60 [0.33, 0.87]	•
Heterogeneity: Chi <sup>2</sup> =	4.18, df=	= 3 (P	= 0.24)	; <b>I<sup>2</sup> = 2</b> 89	ж				
Test for overall effect:	Z= 4.42	(P < 0	.00001	)					-4 -2 U 2 4 Favours ranibizumab Favours bevacicumab

## Two years

Visual acuity (gain of 15 letters or more)

## Macular Degeneration

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

	Bevacizu	ımab	Ranibizu	ımab		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
4.2.1 Participants in	n groups as	randon	nized at b	aseline					
CATT 2011	144	502	162	528	72.2%	0.93 [0.77, 1.13]			
IVAN 2013	41	249	63	268	27.8%	0.70 [0.49, 1.00]			
Subtotal (95% CI)		751		796	100.0%	0.87 [0.74, 1.03]		•	
Total events	185		225						
Heterogeneity: Chi2:	= 2.01, df = 1	1 (P = 0	.16); I <sup>2</sup> = 5	0%					
Test for overall effect	t: Z = 1.64 (F	P = 0.10	)						
4.2.2 Participants re	emaining in	same (	jroups aft	ег ге-га	andomiza	tion			
CATT 2011	112	380	125	398	66.8%	0.94 [0.76, 1.16]			
IVAN 2013	41	249	63	268	33.2%	0.70 [0.49, 1.00]			
Subtotal (95% CI)		629		666	100.0%	0.86 [0.72, 1.03]		◆	
Total events	153		188						
Heterogeneity: Chi <sup>2</sup> :	= 1.94, df = 1	1 (P = 0	.16); I <sup>2</sup> = 4	9%					
Test for overall effect	t: Z = 1.63 (F	P = 0.10	)						
							0.05		20
							0.05	0.2 1 5 Favors ranibizumab Favors bevacizumab	20
								Favors rannuzunnau - Favors Devacizunnau	

## Visual acuity (loss of fewer than 15 letters)

	Bevacizu	ımab	Ranibizu	mab		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
4.4.1 Participants in	groups as	randon	nized at ba	aseline				
CATT 2011	447	502	488	528	66.8%	0.96 [0.93, 1.00]		<b>—</b>
IVAN 2013	226	249	245	268	33.2%	0.99 [0.94, 1.05]		
Subtotal (95% CI)		751		796	100.0%	0.97 [0.94, 1.00]		◆
Total events	673		733					
Heterogeneity: Chi <sup>2</sup> =	= 0.78, df = 1	1 (P = 0	.38); I <sup>z</sup> = 0 <sup>4</sup>	%				
Test for overall effect	t: Z = 1.68 (F	P = 0.09	)					
4.4.2 Participants re	emaining in	same (	proups aft	ег ге-га	andomiza	tion		
CATT 2011	341	380	370	398	60.5%	0.97 [0.92, 1.01]		-
IVAN 2013	226	249	245	268	39.5%	0.99 [0.94, 1.05]		
Subtotal (95% CI)		629		666	<b>100.0</b> %	0.98 [0.94, 1.01]		•
Total events	567		615					
Heterogeneity: Chi2=	= 0.63, df = 1	1 (P = 0	.43); I² = 0 <sup>4</sup>	%				
Test for overall effect	t: Z = 1.40 (F	P = 0.16	)					
								0.7 1 1.5 3
							0.0	
							0.5	U.7 1 1.5 2 Favors ranibizumab Favors bevacizumab

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

	Bev	acizumab	1	Rar	nibizuma	b		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
CATT 2011	5.9505	17.1539	380	7.407	15.063	398	53.9%	-1.46 [-3.73, 0.82]	
IVAN 2013	4.1	13.5	249	4.9	15	268	46.1%	-0.80 [-3.26, 1.66]	
Total (95% Cl)			629			666	100.0%	-1.15 [-2.82, 0.51]	•
Heterogeneity: Chi² = Test for overall effect			~	0%					-10 -5 0 5 10 Favors ranibizumab Favors bevacizumab

# Quality of life (no problem in quality of life)

## Macular Degeneration

# Appendix H: Grade tables and meta-analysis results

	Bevacizu	ımab	Ranibizu	ımab	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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 activitie	s					
IVAN 2013	179	247	197	267	0.98 [0.88, 1.09]	<b>+</b>
4.12.4 Pain/discomfo	ort					
IVAN 2013	145	247	154	267	1.02 [0.88, 1.18]	
4.12.5 Anxiety/depre	ssion					
IVAN 2013	203	247	220	267	1.00 [0.92, 1.08]	-+-
						Favors ranibizumab Favors bevacizumab

Appendix H: Grade tables and meta-analysis results

## 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)	$\oplus \oplus \oplus \ominus$ Moderate <sup>1</sup>	
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)	$\oplus \oplus \oplus \ominus$ Moderate <sup>1</sup>	

\*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 mo follow –up	ore than 5 ETDRS I	etters and having	g clinical impro	vement (more t	han 6-points) i	n the NEI-VFQ25	at 52-weeks
2 (VIEW 1, VIEW2)	Not serious	Serious <sup>1</sup>	Not serious	Not serious	1193	RR 0.97 (0.86, 1.10)	MODERATE
NEI-VFQ-25 subscale score char	nges from baseline	e to week 52 (hig	her scores indi	cate 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 <sup>2</sup>	1193	MD 0.08 (-2.43, 2.58)	MODERATE
Mental health	Not serious	Not serious	Not serious	Serious <sup>2</sup>	1193	MD 0.14 (-2.41, 2.70)	MODERATE
Role difficulities	Not serious	Not serious	Not serious	Serious <sup>2</sup>	1193	MD 1.09 (-2.04, 4.23)	MODERATE
Dependency	Not serious	Not serious	Not serious	Serious <sup>2</sup>	1193	MD -1.29 (-4.00, 1.43)	MODERATE
Social funictioning	Not serious	Not serious	Not serious	Serious <sup>2</sup>	1193	MD 0.18 (-2.35, 2.70)	MODERATE
Driving	Not serious	Not serious	Not serious	Serious <sup>2</sup>	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

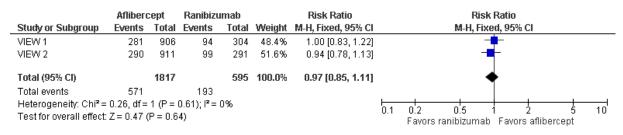
Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Ocular pain	Not serious	Not serious	Not serious	Not serious	1193	MD -0.94 (-3.21, 1.32)	HIGH
Peripheral vision	Not serious	Not serious	Not serious	Not serious	1193	MD 0.86 (-3.73, 2.00)	HIGH
General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



#### Loss of ≥15 letters of BCVA

	Aflibero	:ept	Ranibizu	ımab		Risk Ratio			Risk Ra	tio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl			M-H, Fixed,	95% Cl		
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% Cl)		1817		595	100.0%	0.89 [0.61, 1.30]			-			
Total events	92		34									
Heterogeneity: Chi <sup>2</sup> =	0.13, df=	1 (P =	0.71); I <sup>z</sup> =	0%			0.1	0.2	0.5 1	<u> </u>	<u></u>	10
Test for overall effect:	: Z = 0.61 (	P = 0.5	4)				0.1	0.2	ors aflibercept F:	∠ avors ranib	izumab	10

#### Mean change in BCVA in ETDRS letters

	Af	libercept		Rani	bizum	ab		Mean Difference		Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, Fixed	I, 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]			<u> </u>		
Total (95% Cl)			1817			595	100.0%	-0.15 [-1.47, 1.17]					
Heterogeneity: Chi² = Test for overall effect				0%					-10	-5 Favors ranibizumab	) Favors afli	5 bercept	10

## Arterial thrombotic events

	Afliber	cept	Ranibizu	ımab		Risk Ratio		Risk Ratio	
Study or Subgroup			Events		<u> </u>	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
1.8.1 Any Antiplatelet	t Trialists	' Collab	oration a	rterial tl	romboly	tic event			
VIEW 1	15	911	5	304	49.7%	1.00 [0.37, 2.73]		<b>_</b>	
VIEW 2	17	913	5	291	50.3%	1.08 [0.40, 2.91]			
Subtotal (95% Cl)		1824		595	100.0%	1.04 [0.52, 2.11]		<b>•</b>	
Total events	32		10						
Heterogeneity: Chi <sup>2</sup> =	0.01, df=	1 (P = I	0.91); I <sup>z</sup> =	0%					
Test for overall effect:	Z=0.12	(P = 0.9	1)						
1.8.2 Vascular death									
VIEW 1	5	911	1	304	49.7%	1.67 [0.20, 14.23]		<b>_</b>	
VIEW 2	4	913	1	291	50.3%	1.27 [0.14, 11.36]			
Subtotal (95% CI)		1824			100.0%	1.47 [0.32, 6.78]			
Total events	9		2						
Heterogeneity: Chi <sup>2</sup> =	0.03. df=	1 (P = 1	-	0%					
Test for overall effect:									
			·						
1.8.3 Non-fatal myoc	ardial infa	arction						_	
VIEW 1	6	911	4	304	66.4%	0.50 [0.14, 1.76]			
VIEW 2	9	913	2	291	33.6%	1.43 [0.31, 6.60]			
Subtotal (95% Cl)		1824		595	100.0%	0.81 [0.32, 2.09]		-	
Total events	15		6						
Heterogeneity: Chi <sup>2</sup> =	1.10, df=	1 (P = I	0.29); I <sup>z</sup> =	9%					
Test for overall effect:	Z=0.43	(P = 0.6	7)						
1.8.4 Non-fatal strok	e								
VIEW 1	4	911	0	304	19.8%	3.01 [0.16, 55.74]			
VIEW 2	4	913	2	291	80.2%	0.64 [0.12, 3.46]		<b></b>	
Subtotal (95% Cl)		1824		595	100.0%	1.11 [0.27, 4.50]			
Total events	8		2						
Heterogeneity: Chi <sup>2</sup> =	0.86, df=	1 (P = )	0.35); I <sup>2</sup> =	0%					
Test for overall effect:		•							
							<del></del>	<u></u>	10
							0.01	0.1 1 10 Favors aflibercept Favors ranibizumab	10

# Serious systemic events

## Macular Degeneration

# Appendix H: Grade tables and meta-analysis results

	Aflibero	cept	Ranibizu	mab		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
1.9.1 Any serious sy	stemic ad	verse e	event						
VIEW 1	141	911	57	304	68.4%	0.83 [0.62, 1.09]			
VIEW 2	111	913	26	291	31.6%	1.36 [0.91, 2.04]		<b>}</b> ■	
Subtotal (95% Cl)		1824		595	100.0%	0.99 [0.79, 1.25]		•	
Total events	252		83						
Heterogeneity: Chi <sup>2</sup> =	4.00, df=	1 (P =	0.05); I² = 1	75%					
Test for overall effect	Z = 0.05 (	(P = 0.9	6)						
1.9.2 Congestive hea	art failure	event							
VIEW 1	6	911	2	304	66.4%	1.00 [0.20, 4.93]			
VIEW 2	1	913	1	291	33.6%	0.32 [0.02, 5.08]			
Subtotal (95% Cl)		1824		595	100.0%	0.77 [0.20, 2.97]			
Total events	7		3						
Heterogeneity: Chi <sup>z</sup> =	:0.49, df=	1 (P =	0.48); I² = I	0%					
Test for overall effect	Z = 0.38 (	(P = 0.7	1)						
1.9.3 Non-ocular her	norrhagic	event							
VIEW 1	7	911	1	304	66.4%	2.34 [0.29, 18.91]		<b></b>	
VIEW 2	3	913	0	291	33.6%	2.24 [0.12, 43.17]			_
Subtotal (95% Cl)		1824		595	100.0%	2.30 [0.42, 12.70]			
Total events	10		1						
Heterogeneity: Chi <sup>2</sup> =	0.00, df=	1 (P =	0.98); l² = l	0%					
Test for overall effect	Z = 0.96 (	(P = 0.3	4)						
							0.01		10
							0.01	Favors aflibercept Favors ranibizumab	

Test for subgroup differences: Chi<sup>2</sup> = 1.06, df = 2 (P = 0.59), l<sup>2</sup> = 0%

#### Serious ocular events

	Aflibero	•	Ranibizu			Risk Ratio	Risk Ratio
			Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.10.1 Any serious ocu	ilar adve	erse ev	ent				
VIEW 1	16	911	10	304	52.4%	0.53 [0.24, 1.16]	
VIEW 2	20	913	9	291	47.6%	0.71 [0.33, 1.54]	
Subtotal (95% Cl)		1824		595	100.0%	0.62 [0.36, 1.07]	◆
Total events	36		19				
Heterogeneity: Chi <sup>2</sup> = 0	.25, df=	1 (P =	0.61); I <sup>z</sup> = I	0%			
Test for overall effect: Z	:= 1.73 (	P = 0.0	8)				
1.10.2 Visual acuity re	duced						
VIEW 1	3	911	2	304	66.4%	0.50 [0.08, 2.98]	
VIEW 2	7	913	1	291	33.6%	2.23 [0.28, 18.06]	
Subtotal (95% CI)		1824		595	100.0%	1.08 [0.30, 3.93]	
Total events	10		3				
Heterogeneity: Chi <sup>z</sup> = 1	.18, df=	1 (P =	0.28); I <b>ž</b> = 1	15%			
Test for overall effect: Z	:= 0.12 (	P = 0.9	1)				
1.10.3 Retinal hemorrh	nage						
VIEW 1	2	911	2	304	66.4%	0.33 [0.05, 2.36]	
VIEW 2	4	913	1	291	33.6%	1.27 [0.14, 11.36]	
Subtotal (95% CI)		1824		595	100.0%	0.65 [0.16, 2.60]	
Total events	6		3				
Heterogeneity: Chi <sup>2</sup> = 0	.81, df=	1 (P =	0.37); l² = l	0%			
Test for overall effect: Z	.= 0.61 (	P = 0.5	4)				
	Ì						
							0.01 0.1 1 10 1

Test for subgroup differences: Chi<sup>2</sup> = 0.62, df = 2 (P = 0.73), l<sup>2</sup> = 0%

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

	Aflibero	:ept	Ranibizu	ımab		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
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 = Test for overall effect	•			P = 0.15)	; I² = 52%	)	0.1 0.2 0.5 1 2 5 10 Favours Ranibizumab Favours Aflibercept

Mean change in NEI-VFQ subscale score

## Macular Degeneration

# Appendix H: Grade tables and meta-analysis results

udy or Subgroup	Aflibercept Mean SD	t Total I		zumab SD Total	Weight	Mean Difference IV, Fixed, 95% Cl	Mean Difference IV, Fixed, 95% Cl
<b>13.1 General vision</b> EW 1 EW 2	10.1 19 9.1 17	293 306	9.5 1 9.5 1	18.1 291	46.3% 53.7%	0.60 [-2.44, 3.64] -0.40 [-3.22, 2.42]	_ <b>_</b>
ibtotal (95% Cl) eterogeneity: Chi² = st for overall effect: .			= 0%	594	100.0%	0.06 [-2.00, 2.13]	•
13.2 Near activities							_
EW 1 EW 2	6.1 22.2 7 21.03	293 306	7.2 2 7.2 2	21.1 291	53.6%	-1.10 [-4.74, 2.54] -0.20 [-3.58, 3.18]	
l <b>btotal (95% Cl)</b> eterogeneity: Chi <sup>2</sup> = st for overall effect: .			= 0%	594	100.0%	-0.62 [-3.09, 1.86]	•
13.3 Distance activi							
EW 1 EW 2	6.2 21.8 4.3 21.8	293 306	2.5 2		48.3% 51.7%	3.70 [0.10, 7.30] -3.30 [-6.78, 0.18]	
ibtotal (95% Cl) eterogeneity: Chi <sup>2</sup> =	7 49 df - 1 (P -	599	IZ- 97%		100.0%	0.08 [-2.43, 2.58]	<b></b>
st for overall effect:			1 - 07 %	,			
1 <b>3.4 Mental health</b> EW 1	40.4 04.4	202	0.0.7		47.70	0.0010.000	
EW 2	10.1 24.1 10.4 22	293 306	9.8 2 10.4	22 291	47.7% 52.3%	0.30 [-3.39, 3.99] 0.00 [-3.53, 3.53]	
lbtotal (95% CI) eterogeneity: Chi² = st for overall effect: .			= 0%	594	100.0%	0.14 [-2.41, 2.70]	-
3.5 Role difficulitie							
EW 1 EW 2	7.1 26.7 7.8 24.1	293 306	5.8 2 6.9 2		48.5% 51.5%	1.30 [-3.21, 5.81] 0.90 [-3.47, 5.27]	
ibtotal (95% Cl) eterogeneity: Chi² =	0.02, df = 1 (P =	<b>599</b> 0.90); I <sup>2</sup>			100.0%	1.09 [-2.04, 4.23]	+
st for overall effect:	Z = 0.68 (P = 0.4	19)					
13.6 Dependency EW 1	3.4 22.9	293	5.4 2	22.6 303	55.4%	-2.00 [-5.65, 1.65]	_ <b>_</b>
W 2 btotal (95% Cl)	4.1 25.2	306 599	4.5 2	25.5 291	44.6%	-0.40 [-4.47, 3.67] -1.29 [-4.00, 1.43]	
terogeneity: Chi² = st for overall effect: .		0.57); l²	= 0%				
13.7 Social function	-	202	2	20 202	66 6N	0 40 / 0 70 0 001	
EW 1 EW 2	2.6 22.1 1 24	293 306	3 0.1 2		44.5%	-0.40 [-3.79, 2.99] 0.90 [-2.89, 4.69]	
btotal (95% CI) terogeneity: Chi² = st for overall effect: .			= 0%	594	100.0%	0.18 [-2.35, 2.70]	-
3.8 Driving							
W 1 W 2	2.2 24.4 1 24	293 306	0.1 0.1 2	22 303 23.2 291	50.7% 49.3%	2.10 [-1.63, 5.83] 0.90 [-2.89, 4.69]	
btotal (95% Cl)		599			49.5% 100.0%	1.51 [-1.15, 4.17]	-
erogeneity: Chi² = t for overall effect: .			= 0%				
<b>3.9 Colour vision</b> № 1	0.6 22.3	293	1.9 1	19.1 303	47.3%	-1.30 [-4.64, 2.04]	
EW 2 btotal (95% CI)	0.4 21.2	306 599	3.1 1	18.2 291	52.7%	-2.70 [-5.86, 0.46] -2.04 [-4.33, 0.26]	
terogeneity: Chi² = st for overall effect: .		0.55); I <sup>z</sup>	= 0%	594	100.071	-2.04 [-4.33, 0.20]	•
3.10 Ocular pain	1.2	202	4.0		EE 004	0401044.000	
EW 1 EW 2	1.2 20 3.1 19.4	293 306	1.3 1 5.1 2	22.7 291	44.4%	-0.10 [-3.14, 2.94] -2.00 [-5.40, 1.40]	
ibtotal (95% Cl) eterogeneity: Chi² = st for overall effect: .			= 0%	594	100.0%	-0.94 [-3.21, 1.32]	-
3.11 Peripheral vis		,					
	4.4 23.9 2.5 25.7	293 306	5.5 2 3.1 2			-1.10 [-5.05, 2.85] -0.60 [-4.77, 3.57]	
btotal (95% Cl)		599				-0.86 [-3.73, 2.00]	-
eterogeneity: Chi² = st for overall effect: .			= 0%				
<b>13.12 General healt</b> EW 1	h -4.9 22.1	293	-3.6 2	20.4 303	16 E 00.	-130 L473 3431	
EW 2	-4.9 22.1 1.5 19	306	-3.6 2	20.6 291	53.5%	-1.30 [-4.72, 2.12] 0.70 [-2.48, 3.88]	<u> </u>
i <b>btotal (95% Cl)</b> eterogeneity: Chi <sup>2</sup> = st for overall effect: .			= 0%	594	100.0%	-0.23 [-2.56, 2.10]	-
							-20 -10 0 10 20

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#### H.6.1.6 Treatment frequency: PRN vs routine injection

readment nequency. That vo to							
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, EI-Mollayess 2012, IVAN 2012, Chan 2015)	Serious <sup>1</sup>	Not serious	Not serious	serious <sup>3</sup>	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 <sup>1,2</sup>	Not serious	Not serious	Not serious	2755	RR 0.99 (0.97, 1.01)	MODERATE
Mean change in BCVA in ETDRS	letters at one yea	r (higher values	indicate better	vision)			
4 studies (CATT 2011, HARBOUR 2013, , EI-Mollayess 2012, IVAN 2012)	Serious <sup>1</sup>	Not serious	Not serious	Not serious	2874	MD -1.45 (-2.45, -0.45)	MODERATE
Mean number of injections at on	e year						
2 studies (CATT 2011, , HARBOUR 2013)	Serious <sup>1</sup>	Serious <sup>4</sup>	Not serious	Not serious	2202	MD -4.22 (-4.72, -3.73)	LOW
Adverse events (serious system	ic events at one ye	ear)					
2 studies (CATT 2011, HARBOUR 2013,)	Serious <sup>1</sup>	Serious⁴	Not serious	Serious <sup>5</sup>	2280	RR 1.07 (0.70, 1.63)	VERY LOW
Adverse events (serious ocular e	events at one year	)					
2 studies (CATT 2011, HARBOUR 2013,)	Serious <sup>1</sup>	Serious⁴	Not serious	not serious	2280	RR 0.31 (0.13, 0.78)	LOW
A Decomposite de la secol	C					all and a survey of the first	Constant for the state

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										

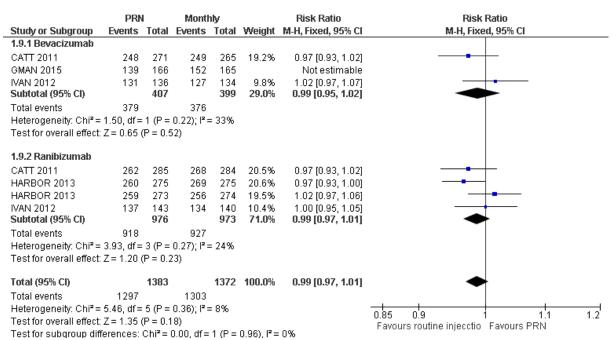
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#### **PRN vs routine injections**

#### Gain of 15 or more letters ETDRS

	PRM	I	Monti	hly		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.2.1 Ranibizumab							
CATT 2011	71	285	97	284	21.4%	0.73 [0.56, 0.94]	<b>_</b>
Chan 2015	3	7	2	6	0.5%	1.29 [0.31, 5.31]	· · · · · · · · · · · · · · · · · · ·
HARBOR 2013	90	273	99	274	21.8%	0.91 [0.72, 1.15]	
HARBOR 2013	83	275	95	275	20.9%	0.87 [0.69, 1.11]	
IVAN 2012	29	143	36	140	8.0%	0.79 [0.51, 1.21]	
Subtotal (95% CI)		983		979	72.6%	0.84 [0.73, 0.95]	◆
Total events	276		329				
Heterogeneity: Chi <sup>2</sup> =	2.17, df=	4 (P =	0.70); l² :	= 0%			
Test for overall effect:	Z = 2.64 (	(P = 0.0	008)				
1.2.2 Bevacizumab							
CATT 2011	76	271	83	265	18.5%	0.90 [0.69, 1.16]	
El-Mollayess 2012	24	60	21	60	4.6%	1.14 [0.72, 1.82]	
GMAN 2015	22	166	40	165		Not estimable	
IVAN 2012	25	136	19	134	4.2%	1.30 [0.75, 2.24]	
Subtotal (95% CI)		467		459	27.4%	1.00 [0.81, 1.23]	
Total events	125		123				
Heterogeneity: Chi <sup>2</sup> =	1.87, df=	2 (P =	0.39); l² :	= 0%			
Test for overall effect:	Z = 0.01 (	(P = 0.9	39)				
Total (95% Cl)		1450		4430	100.0%	0.88 [0.79, 0.99]	
Total events	401	1430	450	1430	100.070	0.00 [0.75, 0.55]	
		7 (D -	452	- 001			
Heterogeneity: Chi <sup>2</sup> =				- 0%			0.5 0.7 1 1.5 2
Test for overall effect:		•		4.00	0.4.03 17	40.00	Favors monthly injections Favors PRN injections
Test for subgroup diff	erences:	Uni⁼=	1.97, df =	1 (P =	U.16), I* =	49.3%	

#### Loss of fewer than15 letters ETDRS



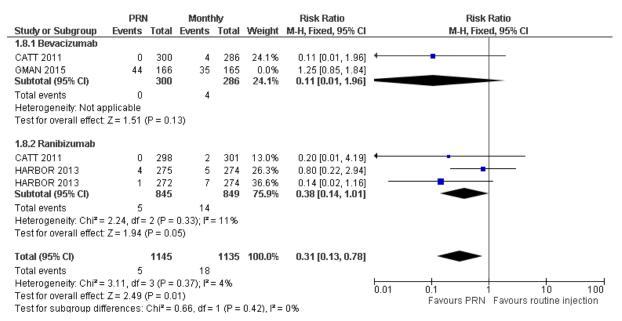
# Mean change in BCVA of EDTRS letters

		PRN		N	lonthly			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
1.1.1 Ranibizumab									
CATT 2011	6.8	13.1	285	8.5	14.1	284	20.0%	-1.70 [-3.94, 0.54]	
HARBOR 2013	8.2	13.3	275	10.1	13.3	275	20.2%	-1.90 [-4.12, 0.32]	
HARBOR 2013	8.6	13.8	273	9.2	14.6	274	17.6%	-0.60 [-2.98, 1.78]	
IVAN 2012	5.1	10.4	143	7.8	14.2	140	11.8%	-2.70 [-5.60, 0.20]	
Subtotal (95% CI)			976			973	69.7%	-1.65 [-2.85, -0.45]	◆
Heterogeneity: Chi <sup>2</sup> =	1.30, df	= 3 (P =	: 0.73);	I <b>²</b> = 0%					
Test for overall effect	Z = 2.70	) (P = 0.	007)						
1.1.2 Bevacizumab									
CATT 2011	5.9	15.7	271	8	15.8	265	14.0%	-2.10 [-4.77, 0.57]	
El-Mollayess 2012	9.2	10.45	59	11	14.72	60	4.8%	-1.80 [-6.38, 2.78]	
GMAN 2015	52.8	19.4	166	57.2	17.6	165	0.0%	-4.40 [-8.39, -0.41]	
IVAN 2012	5.1	11.4	136	4.4	13.2	134	11.5%	0.70 [-2.24, 3.64]	•
Subtotal (95% CI)			466			459	30.3%	-0.99 [-2.80, 0.83]	
Heterogeneity: Chi <sup>2</sup> =	2.05, df	= 2 (P =	: 0.36);	I² = 3%					
Test for overall effect:	Z=1.07	(P = 0.	29)						
Total (95% CI)			1442			1432	100.0%	-1.45 [-2.45, -0.45]	•
Heterogeneity: Chi <sup>2</sup> =	3.71. df	= 6 (P =	: 0.72):	I <sup>2</sup> = 0%					
Test for overall effect:									-10 -5 0 5 10
Test for subaroup dif			,	lf = 1 (P	= 0.55)	2 = 0.9	6		Favors monthly injections Favors PRN injections
restion subdroup an	rerences	. Chi=	0.35,0	0 – 1 (P	- 0.55),	1 - 09	0		

# Serious systemic events

	PRM	1	Month	ily		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.7.1 Ranibizumab							
CATT 2011	29	298	21	301	23.3%	1.39 [0.81, 2.39]	- <b>-</b>
HARBOR 2013	31	272	28	274	25.1%	1.12 [0.69, 1.81]	
HARBOR 2013	20	275	36	274	23.9%	0.55 [0.33, 0.93]	
IVAN 2012	24	302	18	308		Not estimable	
Subtotal (95% CI)		845		849	72.3%	0.95 [0.56, 1.62]	<b>•</b>
Total events	80		85				
Heterogeneity: Tau <sup>2</sup> =	0.16; Ch	i² = 6.5	2, df = 2 (	P = 0.0	4); l <sup>2</sup> = 69	1%	
Test for overall effect:	Z = 0.18	(P = 0.8	35)				
1.7.2 Bevacizumab							
CATT 2011	50	300	33	286	27.7%	1.44 [0.96, 2.17]	<b>⊢</b> ∎
GMAN 2015	28	166	20	165		Not estimable	
Subtotal (95% Cl)		300		286	27.7%	1.44 [0.96, 2.17]	◆
Total events	50		33				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.76	(P = 0.0	)8)				
Total (95% CI)		1145		1135	100.0%	1.07 [0.70, 1.63]	★
Total events	130		118				
Heterogeneity: Tau <sup>2</sup> =	0.12; Ch	i² = 9.1	5, df = 3 (	P = 0.0	3); l² = 67	'%	
Test for overall effect:	•						0.01 0.1 1 10 100
Test for subgroup diff							Favours PRN Favours routine injection

#### Serious ocular events



#### Number of injections

	I	PRN		Мо	onthly	/		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.5.1 Ranibizumab									
CATT 2011	6.9	3	285	11.7	1.5	284	25.2%	-4.80 [-5.19, -4.41]	+
HARBOR 2013	7.7	2.7	275	11.3	1.8	275	25.3%	-3.60 [-3.98, -3.22]	+
HARBOR 2013	6.9	2.4	273	11.2	2.1	274	25.4%	-4.30 [-4.68, -3.92]	+
Subtotal (95% Cl)			833			833	75.9%	-4.23 [-4.91, -3.56]	◆
Heterogeneity: Tau <sup>2</sup> =	= 0.32; C	hi² =	18.72,	df = 2 (F	° < 0.	0001);	l² = 89%		
Test for overall effect:	Z=12.2	24 (P	< 0.000	001)					
1.5.2 Bevacizumab									
CATT 2011	7.7	3.5	271	11.9	1.2	265	24.1%	-4.20 [-4.64, -3.76]	
El-Mollayess 2012	3.8	0	60	9.5	0	60		Not estimable	
GMAN 2015	9.1	0	166	10.8	0	165		Not estimable	
Subtotal (95% CI)			331			325	24.1%	-4.20 [-4.64, -3.76]	◆
Heterogeneity: Not ap	oplicable								
Test for overall effect	Z=18.6	6 (P	< 0.000	001)					
Total (95% CI)			1164			1158	100.0%	-4.22 [-4.72, -3.73]	◆
Heterogeneity: Tau <sup>2</sup> =	= 0.21; C	hi² =	18.73,	df = 3 (F	<sup>o</sup> = 0.	0003);	l² = 84%		
Test for overall effect:									-4 -2 0 2 4
					-				Favors PRN injections Favors monthly injections

Test for subgroup differences: Chi<sup>2</sup> = 0.01, df = 1 (P = 0.94), l<sup>2</sup> = 0%

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

reatinent nequency: =e week											
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 <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	231	RR 0.55 (0.34 to 0.88)	LOW				
Loss of <15 letters at one year											
1 study (GMAN 2015)	Serious <sup>1</sup>	N/A	Not serious	Not serious	231	RR 0.91 (0.84 to 0.99)	MODERATE				
Mean change in BCVA in ETDR	S letters at one ye	ar(higher values i	ndicate better v	vision)							
1 study (GMAN 2015)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	231	MD -4.40 (-8.39 to -0.41)	LOW				
Adverse events (serious system	nic events at one y	ear)									
1 study (GMAN 2015)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	231	RR 1.39 (0.82 to 2.37)	LOW				
Adverse events (serious ocular	<sup>,</sup> events at one yea	r)									
1 study (GMAN 2015)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	231	RR 1.25 (0.85 to 1.84)	LOW				
Routine injections (interval 6 w	eeks or less vs mo	re than 6 weeks)									
Gain of ≥15 letters at one year											
4 studies (Lushchyk 2013, NATTB 2012, VIEW 2012, EXCITE)	Serious <sup>3</sup>	Not serious	Not serious	Serious <sup>2</sup>	1276	RR 1.28 (1.08, 1.52)	LOW				
Loss of <15 letters at one year											
3 studies (Lushchyk 2013, NATTB 2012, EXCITE)	Serious <sup>3</sup>	Serious <sup>4</sup>	Not serious	not serious	671	RR 0.99 (0.92, 1.06)	LOW				
Mean change in BCVA in ETDR	S letters at one ye	ar (higher scores	indicate better	vision)							

Appendix H: Grade tables and meta-analysis results

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 <sup>3</sup>	Serious <sup>4</sup>	Not serious	Not serious	1276	MD 1.87 (0.36, 3.39)	LOW					
Adverse events (serious systemi	Adverse events (serious systemic events at one year)											
2 studies (Lushchyk 2013, VIEW 2012)	Serious⁵	Not serious	Not serious	Serious <sup>2</sup>	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 <sup>3</sup>	Not serious	Not serious	Serious <sup>2</sup>	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

	6 weeks o	r less	more than 6 y	weeks		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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: Chi <sup>2</sup> =	= 3.65, df = 3 (	(P = 0.30)	); I² = 18%				
Test for overall effect	: Z = 2.86 (P =	= 0.004)					0.05 0.2 1 5 20 Favours >6 weeks Favours 6 weeks or less

## Loss of fewer than 15 letters of visual acuity

	6 weeks or	less	more than 6 v	weeks		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
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; Chi <b>²</b> =	7.77, df	= 2 (P = 0.02); I	l² = 74%			0.1	
Test for overall effect:	Z = 0.32 (P =	0.75)					0.1	Favours >6weeks Favours 6 weeks or less

## Mean visual change in BCVA (EDTRS letters)

	6 wee	eks or l	or less more than 6 weeks				Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
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]	<b>_</b>
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: Chi <sup>2</sup> =	: 17.72, c	lf = 3 (P	= 0.000	)5); l² = 8	3%				
Test for overall effect	: Z = 2.43	) (P = 0.	02)						-20 -10 0 10 20 Favours >6 weeks Favours 6 weeks or less

## Serious systemic events

	6 weeks or	less	more than 6 v	veeks		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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: Chi <sup>2</sup> =	0.10, df = 1 (l)	P = 0.75	); I² = 0%				
Test for overall effect:	Z=1.42 (P=	0.16)					0.01 0.1 1 10 100 Favours 6 weeks or less Favours ≻6 weeks

## Serious ocular events

	6 weeks o	r less	more than 6 v	veeks		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
EXCITE 2010	62	115	91	238	77.2%	1.41 [1.12, 1.78]	
Lushchyk 2013	8	127	5	64	8.7%	0.81 [0.27, 2.37]	
NATTB 2012	17	91	9	94	11.5%	1.95 [0.92, 4.15]	<b>—</b> •—
VIEW 2012	4	304	2	303	2.6%	1.99 [0.37, 10.80]	
Total (95% CI)		637		699	100.0%	1.44 [1.15, 1.79]	◆
Total events	91		107				
Heterogeneity: Chi <sup>2</sup> =	: 1.91, df = 3 (	(P = 0.59	l); I² = 0%				
Test for overall effect	Z = 3.17 (P =	= 0.002)					0.01 0.1 1 10 100 Favours 6 weeks or less Favours >6 weeks

# 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 <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	60	RR 0.83 (0.43, 1.63)	VERY LOW
Gain of ≥10 letters at one year							
1 study (BeMoc 2013)	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	99	RR 0.93 (0.38, 2.25)	VERY LOW
Mean change in BCVA in ETDRS	letters at one yea	r (higher scores	indicate better	vision)			
2 studies (Barikian 2015, BeMoc 2013)	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>3</sup>	189	MD 1.20 (-2.51, 4.91)	LOW
Mean number of injections at on	e year						
2 studies (Barikian 2015, BeMoc 2013)	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>3</sup>	189	MD -0.30 (-1.92, 1.32)	LOW
Quality of life measures at one y	ear (VFQ-25) (high	er values indicat	e better QoL)				
1 studiy (BeMoc 2013)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>4</sup>	99	MD -0.06	LOW
PRN with 4 week vs 12 weeks loa	ading phase						
Gain of ≥15 letters at one year							
1 study (CLEART-IT 2011)	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	126	RR 0.94 (0.51, 1.72)	VERY LOW
Loss of <15 letter at one year							
1 study (CLEART-IT 2011)	Serious <sup>1</sup>	N/A	Not serious	Not serious	126	RR 1.05 (0.94, 1.18)	MODERATE

Appendix H: Grade tables and meta-analysis results

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Mean change in BCVA (ETDRS le	tters)						
1 study (CLEART-IT 2011)	Serious <sup>1</sup>	N/A	Not serious	Serious⁵	126	MD 3.41 (-0.16, 6.98)	LOW
<ol> <li>Downgraded for risk of bias due to randomisation, allocation concealment, masking of participants, and selective report were unclear</li> <li>Downgrade two levesl for imprecision due to 95%Cl of the effect crossing 2 lines of a defined minimal important difference</li> <li>Downgraded one level for imprecision as one of studies (BeMoc 2013) had no SD reported to estimate effect</li> </ol>							

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)

	no loa	ding P	RN	load	ing PF	N.		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Barikian 2015	8.3	6.7	30	8	10.4	30	100.0%	0.30 [-4.13, 4.73]	
BeMOc 2013	0.86	0	49	2.08	0	50		Not estimable	Т
Total (95% CI)			79			80	100.0%	0.30 [-4.13, 4.73]	+
Heterogeneity: Not a	pplicable								-20 -10 0 10 20
Test for overall effect	: Z = 0.13	(P = 0.	.89)						Favours loading PRN Favours no loading PRN

#### 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 <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	60	RR 1.67 (0.52, 5.39)	VERY LOW
Mean change in BCVA in ETDRS	letters at one year	· (higher scores i	indicate better	vision)			
1 study (TREX-AMD 2015)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	60	MD 2.70 (-4.38, 9.78)	LOW
Mean number of injections at one	year						
1 study (TREX-AMD 2015)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>4</sup>	60	MD -2.90	LOW
Adverse events (serious systemic	events at one ye	ar)					
1 study (TREX-AMD 2015)	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	60	RR 5.63 (0.33, 97.10)	VERY LOW
Adverse events (serious ocular ev	vents at one year)						
1 study (TREX-AMD 2015)	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	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 <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	67	RR 1.48 (0.72, 3.05)	VERY LOW
Mean change in BCVA in ETDRS	letters at one yea	r (higher scores	indicate better	vision)			
1 study (Elden 2015)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	67	MD 4.50 (-3.78, 12.78)	LOW
Mean number of injections at on	e year						
1 study (Eldem 2015)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>4</sup>	67	MD 1.1	LOW
Adverse events (serious system	ic events at one ye	ear)					
1 study (Eldem 2015)	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	67	RR 1.71 (0.44, 6.66)	VERY LOW
Adverse events (ocular events a	t one year)						
1 study (Eldem 2015)	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>2</sup>	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

Appendix H: Grade tables and meta-analysis results

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	
Mean cha	nge in BCVA	at 12 montl	ns						
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 <sup>1</sup>	MODERATE	
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious <sup>1</sup>	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 <sup>2</sup>	Not serious	Not serious	Not serious	MODERATE	
					Anti-VEGF frequency – PRN with and without loading phase	Serious <sup>3</sup>	Not serious	Not serious	Not serious
			Anti-VEGF frequency – different frequencies of routine treatment	Serious <sup>4</sup>	Not serious	Not serious	Not serious	MODERATE	
			Anti-VEGF frequency – treat-and-extend compared with routine or PRN	Serious <sup>2</sup>	Not serious	Not serious	Serious <sup>1</sup>	LOW	
			Anti-VEGF frequency – PRN-and-extend compared with routine or PRN	Serious <sup>3</sup>	Not serious	Not serious	Serious <sup>1</sup>	LOW	
Mean cha	nge in BCVA	A at 24 montl	ns						
10	RCT	7,041	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH	

Appendix H: Grade tables and meta-analysis results

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 <sup>1</sup>	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 <sup>6</sup>	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious <sup>3</sup>	Not serious	Not serious	Not serious	MODERATE
Categoric	al change in	BCVA <sup>7</sup> (cha	nge in ETDRS letters) at 12m	onths				
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 <sup>1</sup>	MODERATE
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious <sup>1</sup>	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 <sup>3</sup>	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious <sup>3</sup>	Not serious	Not serious	Not serious	MODERATE

<sup>7</sup> The estimated effects=z score \* 13.7 (standard deviation) at 12 months; and z score \*15.1(standard deviation) at 24 months

Appendix H: Grade tables and meta-analysis results

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			Anti-VEGF frequency – different frequencies of routine treatment	Serious <sup>4</sup>	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – treat-and-extend compared with routine or PRN	Serious <sup>2</sup>	Not serious	Not serious	Serious <sup>1</sup>	LOW
			Anti-VEGF frequency – PRN-and-extend compared with routine or PRN	Serious <sup>3</sup>	Not serious	Not serious	Serious <sup>1</sup>	LOW
Categoric	al change in	BCVA (char	nge in ETDRS letters) at 24 m	onths				
10		CT 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 <sup>1</sup>	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 <sup>6</sup>	Not serious	Not serious	MODEATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious <sup>3</sup>	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).

Appendix H: Grade tables and meta-analysis results

No. of	Study	Sample						
studies	design	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<sup>2</sup>>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	t 1 year (visual a	acuity $\geq 6/12$ vs	VA<6/12 to VA>6	6/96) (ETDRS le	tters; higher sco	ores indicate be	tter vision)	
2 (Writing committee for the UK AMD EMR user group 2014, Ying 2013)	Cohort study	Serious <sup>1</sup>	Serious <sup>3</sup>	Not serious	Not serious	11,914	MD 16.52 (13.41, 19.64)	LOW
Visual acuity at	t 1 year (visual a	acuity ≤6/96 vs \	VA<6/12 to VA>6	/96) (ETDRS let	tters; higher sco	res indicate bet	tter vision)	
1 (Writing committee for the UK AMD EMR user group 2014)	Cohort study	Serious <sup>1</sup>	N/A	Not serious	Not serious	8,888	MD -17.23 (-22.36, -12.10)	MODERATE
Change in visu	al acuity at 1 ye	ar (visual acuity	y ≥ 6/12 vs VA<6/	/12 to VA>6/96)	(ETDRS letters;	higher scores	indicate better vis	sion)
3 (Writing committee for the UK AMD EMR user group 2014, William 2011, Ying 2013)	Cohort study	Serious <sup>1</sup>	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)

Appendix H: Grade tables and meta-analysis results

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 <sup>1</sup>	N/A	Not serious	Not serious	8888	MD 13.99 (10.39, 17.59)	MODERATE
Change in visu scores indicate		onths (visual ac	cuity <6/96 vs VA	≥6/96) (Fang 20	013, vision thres	hold up to≥60 le	etters) (ETDRS le	tters; higher
2 (Fang 2013, Writing committee for the UK AMD EMR user group 2014)	Cohort study	Serious <sup>1</sup>	Not serious	Not serious	Not serious	9032	MD 7.77 (5.44, 10.10)	MODERATE
Change in visu	al acuity at 5 ye	ars (visual acui	ty ≥ 6/12 vs VA <	<6/12 to VA≥6/6	0) (ETDRS letter	s; higher score	s indicate better v	/ision)
1 (Zhu 2015)	Case series	Very serious <sup>2</sup>	N/A	Not serious	Not serious	186	MD -11.75 (-18.98, -4.52)	LOW
Percentage of	people who lost	15 letters or m	ore at 1 year (vis	ual acuity ≥6/1	2 vs VA <6/12to V	VA >6/100 (23 le	etter)	
2 (Buckle 2014, El- Mollagyess 2013)	Prospective cohorts	Serious <sup>1</sup>	Serious <sup>3</sup>	Not serious	Very serious <sup>4</sup>	1389	RR 0.41 (0.04, 3.94)	VERY LOW
Percentage of	people who lost	t less than 15 le	tters at 1 year (vi	sual acuity ≥6/	12 vs VA <6/12to	VA ≥6/196)		
1 (William 2011)	Prospective cohort	Very serious <sup>2</sup>	N/A	Not serious	Not serious	615	RR 10.01 (0.95, 1.08)	LOW
Percentage of	people who gaiı	ned 15 letters o	r more at 1 year (	visual acuity≥6	6/12 vs VA<6/12 )	)		
4 (El- Mollagyess	Prospective and	Serious <sup>1</sup>	Not serious	Not serious	Not serious	2310	RR 0.16 (0.12, 0.22)	MODERATE

Appendix H:	Grade	tables	and	meta-	-analysis	s results
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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 <sup>2</sup>	Not serious	Not serious	Serious <sup>5</sup>	239	RR 1.44 (1.02, 2.01)	VERY LOW					
1. Downgr	aded one level fo	or non-randomise	ed study design bu	ut large sample	size included in th	e analysis.							
2. Downgr	aded two levels f	for non-randomis	ed study design.										
3. Downgr													
4. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference													
5. Downgr	aded one level fo	or confidence inte	erval crossing 1 lir	ne of a defined n	ninimal 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

	VA bet	ter than	6/12	VA>6/96 to <6/12				Mean Difference	Mean Dif	ference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Randoi	n, 95% Cl
Writing committee for the UK AMD EMR user Grou2014	71.83	55.42	2332	53.53	70.67	8477	44.5%	18.30 [15.59, 21.01]		
Ying 2013	77.7	13.9	397	62.6	14.4	708	55.5%	15.10 [13.37, 16.83]		+
Total (95% CI)			2729			9185	100.0%	16.52 [13.41, 19.64]		•
Heterogeneity: Tau <sup>2</sup> = 3.78; Chi <sup>2</sup> = 3.81, df = 1 (P = 0.05); I Test for overall effect: Z = 10.39 (P < 0.00001)	<b>²</b> =74%								-20 -10 C VA6/12 and >6/96	10 20 VA better than 6/12

#### Change in visual acuity

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

Study or Subgroup	VA bet Mean	ter than SD		VA >6 Mean	/96 to < SD		Weight	Mean Difference IV, Fixed, 95% Cl	Mean Difference IV. Fixed, 95% Cl
Study of Subgroup	Inean	30	TULAI	wear	30	TULAI			
William 2011	-0.5	4.79	88	6.43	16.84	527	31.5%	-6.93 [-8.68, -5.18]	
Writing committee for the UK AMD EMR user Grou2014	-3.39	36.27	2332	3.11	33.33	8477	36.2%	-6.50 [-8.13, -4.87]	
Ying 2013	3.7	13.9	397	9.3	14.4	708	32.3%	-5.60 [-7.33, -3.87]	
Total (95% CI)			2817			9712	100.0%	-6.34 [-7.33, -5.36]	•
Heterogeneity: Chi <sup>2</sup> = 1.17, df = 2 (P = 0.56); l <sup>2</sup> = 0%									-10 -5 0 5 10
Test for overall effect: Z = 12.65 (P < 0.00001)									VA>6/96 to <6/12 VA better than 6/12

### Change in visual acuity at 6 months

	VA wo	se than	6/96	VA >6	/96 to <	6/12		Mean Difference		Mea	n Diffe	erence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, Fi	ixed, !	95% CI		
Fang 2013	13.8	27.6	23	8.3	33.2	121	3.4%	5.50 [-7.24, 18.24]						
Writing committee for the UK AMD EMR user Grou2014	11.4	23.32	411	3.54	35.74	8477	96.6%	7.86 [5.48, 10.24]				-	-	
Total (95% CI)			434			8598	100.0%	7.78 [5.44, 10.12]				•		
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); l² = 0% Test for overall effect: Z = 6.52 (P < 0.00001)									-20	-10 VA>6/96 to <6.	/12 \	1 /A <6/96	0	20

#### Change in visual acuity at 6 months

	VA wo	se than	6/96	VA >6	/96 to <	6/12		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Fang 2013	13.8	27.6	23	8.3	33.2	121	3.4%	5.50 [-7.24, 18.24]	
Writing committee for the UK AMD EMR user Grou2014	11.4	23.32	411	3.54	35.74	8477	96.6%	7.86 [5.48, 10.24]	- <mark>■</mark> -
Total (95% CI)			434			8598	100.0%	7.78 [5.44, 10.12]	•
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); l² = 0% Test for overall effect: Z = 6.52 (P < 0.00001)									-20 -10 0 10 20 VA>6/96 to <6/12 VA <6/96

#### 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

	VA better tha	n 6/12	VA >6/96 to	<6/12		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
El-Mollagyess 2013	0	30	17	60	3.8%	0.06 [0.00, 0.90]	<b>←</b>			
Regillo 2015	7	62	162	438	12.9%	0.31 [0.15, 0.62]				
William 2011	1	88	153	527	14.1%	0.04 [0.01, 0.28]	<b>←</b>			
Ying 2013	28	397	299	708	69.2%	0.17 [0.12, 0.24]				
Total (95% CI)		577		1733	100.0%	0.16 [0.12, 0.22]		•		
Total events	36		631							
Heterogeneity: Chi <sup>2</sup> =	5.66, df = 3 (P =	: 0.13); I <sup>z</sup>	= 47%				L	<u>.</u>		
Test for overall effect:							0.01 C VA >	).1 ∘6/96 to 6/12	1 10 VA better than 6	100 <sup>°</sup> 3/12

	VA <6/	120	VA 6/120 or b	etter		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Fang 2013	10	23	36	121	41.2%	1.46 [0.85, 2.51]	+ <b>-</b>	
Vogel 2016	17	30	26	65	58.8%	1.42 [0.92, 2.18]	+∎-	
Total (95% CI)		53		186	100.0%	1.44 [1.02, 2.01]	◆	
Total events	27		62					
Heterogeneity: Chi² = Test for overall effect			~				L L L L 0.01 0.1 1 10 Favours VA 6/120or better Favours VA≺6/120	100

# 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	s anti-VEGF							
BCVA (ETDRS letter	rs ≤3 month	s) - positive valu	es favour combir	nation				
1 (Lazic)*	RCT	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	106	MD -7.25 (-19.82, 5.31)	LOW
BCVA (ETDRS letter	rs >3 month	s) - positive valu	es favour combii	nation				
11 (Datseris; Bashshur; Hatz; Kaiser; Krebs; Larsen; Semeraro*; Weingessel; Williams: Gomi; Koh)	RCT	Not serious <sup>3</sup>	Not serious	Not serious	Not serious	1025	MD -0.54 (-1.29, 0.21)	HIGH
BCVA (proportion g	ain ≥15 lette	ers, >3 months) -	values greater t	han 1 favour com	oination			
9 (Datseris; Bashshur; Hatz; Kaiser; Larsen; Vallance; Williams: Gomi; Koh)	RCT	Not serious <sup>3</sup>	Not serious	Not serious	Serious <sup>2</sup>	923	RR 0.76 (0.63, 0.92)	MODERATE
Reinjections (>3 mo	onths) - posit	tive values favou	r monotherapy					
5 (Datseris; Bashshur; Larsen; Gomi; Koh)	RCT	Serious <sup>4</sup>	Serious <sup>5</sup>	Not serious	Not serious	488	MD -1.43 (-2.42, -0.45)	LOW
Total number of inje	ections (>3 n	nonths) - positive	e values favour n	nonotherapy				

Appendix H: Grade tables and meta-analysis results

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 <sup>4</sup>	Serious <sup>5</sup>	Not serious	Not serious	474	MD -0.94 (-1.76, -0.12)	LOW				
<b>Proportion needing</b>	retreatment	: (>3 months) - va	alues greater tha	n 1 favour combin	ation							
1 (Hatz)	RCT	Serious <sup>6</sup>	N/A	Not serious	Serious <sup>2</sup>	40	RR 0.69 (0.42, 1.13)	LOW				
Proportion having o	ocular adver	se events - value	es greater than 1	favour combination	on							
5 (Lazic; Bashshur; Hatz; Kaiser; Larsen)	RCT	Not serious <sup>3</sup>	Not serious	Not serious	Not serious	762	RR 1.03 (0.88, 1.21)	HIGH				
Proportion having r	non-ocular a	dverse events - v	alues greater the	an 1 favour combi	nation							
1 (Larsen)	RCT	Not serious	N/A	Not serious	Serious <sup>2</sup>	255	RR 1.03 (0.82, 1.29)	MODERATE				
-	<ol> <li>Downgraded one level for study design (open label, single blinded)</li> <li>Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.</li> </ol>											

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<sup>2</sup>>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

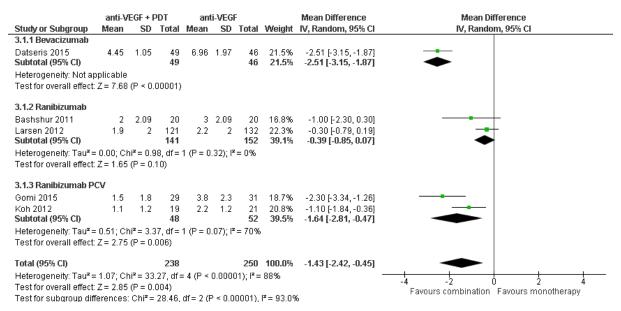
## Letters (>3 month follow-up)

		VEGF + PD			ti-VEGF			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
1.3.1 Bevacizumab									i l
Datseris 2015 Subtotal (95% CI)	8.37	12.39	49 49	8.64	14.32	46 46	1.9% <b>1.9</b> %	-0.27 [-5.67, 5.13] - <b>0.27 [-5.67, 5.13]</b>	-
Heterogeneity: Not ap	plicable								
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]	+ <b>-</b> -
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% Cl)			456			375	29.6%	-0.28 [-1.65, 1.10]	<b></b>
Heterogeneity: Chi <sup>2</sup> =	15.00, df	= 7 (P = 0.	04); I <sup>z</sup> =	: 53%					
Test for overall effect:	Z = 0.39	(P = 0.69)							
1.3.3 Ranibizumab P	cv								
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]	<u> </u>
Subtotal (95% Cl)			49			50	68.5%	-0.66 [-1.57, 0.24]	•
Heterogeneity: Chi <sup>2</sup> =	0.41, df=	1 (P = 0.5	2); I <sup>z</sup> =	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: Chi <sup>2</sup> =	15.63, df	= 10 (P = 1	0.11); I <sup>≥</sup>	= 36%				-	-20 -10 0 10 20
Test for overall effect:	Z=1.42	(P = 0.16)	~						-20 -10 Ó 10 20 Favours monotherapy Favours combination
Test for subaroup diff			2. df = 2	(P = 0.)	89), I <sup>2</sup> =	0%			Favours monounerapy Favours complitation

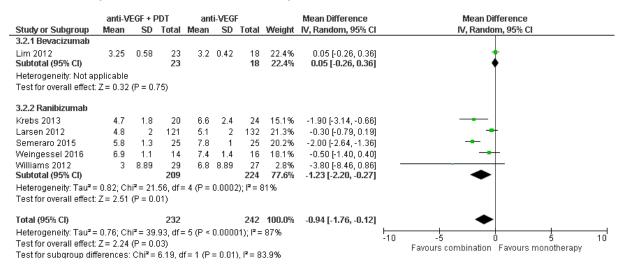
## Letters gained (proportion 15 or more letters)

	anti-VEGF +		anti-VE			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.4.1 Bevacizumab							
Datseris 2015 Subtotal (95% Cl)	21	49 49	20	46 46	13.1% <b>13.1</b> %	0.99 [0.62, 1.56] <b>0.99 [0.62, 1.56]</b>	<b></b>
Total events	21		20				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	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]	
_arsen 2012	22	121	34	132	20.7%	0.71 [0.44, 1.14]	
/allance 2010	1	9	1	9	0.6%	1.00 [0.07, 13.64]	
Villiams 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	•	•	i); i² = 0%				
Test for overall effect: 2	Z= 2.91 (P=	: 0.004)					
1.4.3 Ranibizumab PC	v						
Gomi 2015	13	29	15	31	9.2%	0.93 [0.54, 1.60]	
<oh 2012<="" td=""><td>4</td><td>19</td><td>7</td><td>21</td><td>4.2%</td><td>0.63 [0.22, 1.82]</td><td></td></oh>	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 = (	• •	•	!); I² = 0%				
Test for overall effect: 2	Z= 0.73 (P=	: 0.47)					
		504		419	100.0%	0.76 [0.63, 0.92]	•
Fotal (95% CI)							
Fotal (95% CI) Total events	136		145				
1 1		P = 0.90					
Total events	3.53, df = 8 (	•					0.01 0.1 1 10 1 Favours monotherapy Favours combination

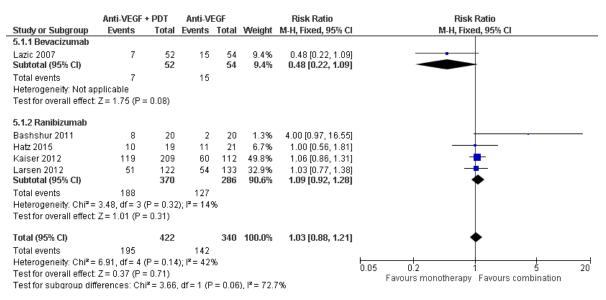
#### Number of injections: reinjections



#### Number of injections: total number of injections



#### **Ocular adverse events**



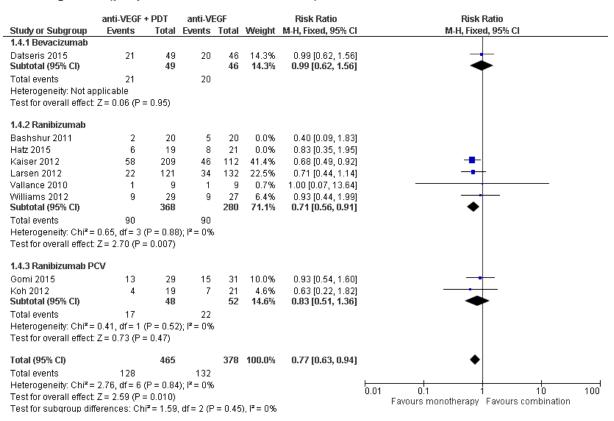
#### Meta-analysis (excluded study population with previous treatment history)

#### Visual acuity

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

	anti-	VEGF + PD	т	an	ti-VEGF	:		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
1.3.1 Bevacizumab									
Datseris 2015 Subtotal (95% CI)	8.37	12.39	49 49	8.64	14.32	46 46	2.4% 2.4%	-0.27 [-5.67, 5.13] - <b>0.27 [-5.67, 5.13]</b>	
Heterogeneity: Not ap	oplicable								
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	0.0%	-9.20 [-17.31, -1.09]	
Hatz 2015	9	2.8	19	7.5	2.9	21	0.0%	1.50 [-0.27, 3.27]	
Kaiser 2012	4.8478	15.5995	209	8.1	15.1	112	5.6%	-3.25 [-6.76, 0.25]	
Krebs 2013	46.89	28.3	19	57.09	24.61	22	0.3%	-10.20 [-26.56, 6.16]	
Larsen 2012	2.5	14.8	121	4.4	15.9	132	4.8%	-1.90 [-5.68, 1.88]	
Semeraro 2015	24.5	7	25	24	14	25	1.8%	0.50 [-5.64, 6.64]	
Weingessel 2016	57.2	24.4	14	58.7	17.6	16	0.3%	-1.50 [-16.92, 13.92]	
Williams 2012	2.6	18.53	29	9.9	23.88	27	0.5%	-7.30 [-18.55, 3.95]	
Subtotal (95% CI)			417			334	13.3%	-2.51 [-4.78, -0.24]	$\bullet$
Heterogeneity: Chi <sup>2</sup> =	2.76, df=	5 (P = 0.7	4); I² =	0%					
Test for overall effect:	Z = 2.17	(P = 0.03)							
1.3.3 Ranibizumab P									
Gomi 2015	8.1	1.8	31	8.8	1.8	29	83.0%	-0.70 [-1.61, 0.21]	<b>–</b>
Koh 2012	10.9	10.9	18	9.2	12.4	21	1.3%	1.70 [-5.61, 9.01]	
Subtotal (95% CI)			49			50	84.3%	-0.66 [-1.57, 0.24]	•
Heterogeneity: Chi <sup>2</sup> =	0.41, df=	: 1 (P = 0.5	2); I <sup>z</sup> =	0%					
Test for overall effect:	Z=1.44	(P = 0.15)							
Total (95% CI)			515			430	100.0%	-0.90 [-1.73, -0.07]	•
Heterogeneity: Chi <sup>2</sup> =			1); l² =	0%					-20 -10 0 10 20
Test for overall effect:		· /							Favours monotherapy Favours combination
Test for subgroup dif	ferences:	Chi <sup>2</sup> = 2.24	4. df = 2	2 (P = 0.3	33), I² =	10.9%			· · · · · · · · · · · · · · · · · · ·

#### Letters gained (proportion 15 or more letters)



#### Total number of injections

	anti-V	EGF + F	DT	ant	i-VEG	-		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.2.1 Bevacizumab									
Lim 2012 Subtotal (95% CI)	3.25	0.58	23 0	3.2	0.42	18 0	0.0%	0.05 [-0.26, 0.36] Not estimable	
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Not app	licable							
3.2.2 Ranibizumab									
Krebs 2013	4.7	1.8	20	6.6	2.4	24	19.7%	-1.90 [-3.14, -0.66]	_ <b></b>
Larsen 2012	4.8	2	121	5.1	2	132	27.2%	-0.30 [-0.79, 0.19]	
Semeraro 2015	5.8	1.3	25	7.8	1	25	25.9%	-2.00 [-2.64, -1.36]	
Weingessel 2016	6.9	1.1	14	7.4	1.4	16	23.4%	-0.50 [-1.40, 0.40]	
Williams 2012 Subtotal (95% CI)	3	8.89	29 <b>209</b>	6.8	8.89	27 <b>224</b>	3.7% <b>100.0</b> %	-3.80 [-8.46, 0.86] - <b>1.23 [-2.20, -0.27]</b>	
Heterogeneity: Tau <sup>2</sup> =				= 4 (P =	0.0002	2); <b>I2</b> = 8	81%		
Test for overall effect:	2 - 2.91	(==0.	51)						
Total (95% CI)			209			224	100.0%	-1.23 [-2.20, -0.27]	•
Heterogeneity: Tau² =	= 0.82; Cł	ni <b>≈</b> = 21	56, df=	= 4 (P =	0.0002	2); <b> </b> ² = 8	31%		
Test for overall effect:	Z = 2.51	(P = 0.	D1)						Favours combination Favours monotherapy
Test for subgroup diff	ferences	: Not ap	plicabl	е					·

# Proportion of people had ocular adverse events

	Anti-VEGF		Anti-VI			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
5.1.1 Bevacizumab							
Lazic 2007	7	52	15	54	10.2%	0.48 [0.22, 1.09]	
Subtotal (95% Cl)		52		54	10.2%	0.48 [0.22, 1.09]	
Total events	7		15				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.75 (P =	0.08)					
5.1.2 Ranibizumab							
Bashshur 2011	8	20	2	20	0.0%	4.00 [0.97, 16.55]	
Hatz 2015	10	19	11	21	0.0%	1.00 [0.56, 1.81]	
Kaiser 2012	119	209	60	112	54.1%	1.06 [0.86, 1.31]	-
Larsen 2012	51	122	54	133	35.8%	1.03 [0.77, 1.38]	- <b>+</b> -
Subtotal (95% CI)		331		245	89.8%	1.05 [0.88, 1.25]	◆
Total events	170		114				
Heterogeneity: Chi <sup>2</sup> =	0.03, df = 1 (	P = 0.86	i); I² = 0%				
Test for overall effect:	Z = 0.55 (P =	0.58)					
Total (95% CI)		383		299	100.0%	0.99 [0.84, 1.17]	•
Total events	177		129				
Heterogeneity: Chi <sup>2</sup> =	3.47, df = 2 (	P = 0.18	); <b>I</b> ² = 429	%			
Test for overall effect:							0.05 0.2 1 5 20
Test for subaroup diff	•		df = 1/P	- 0.07	18 - 70 (	104	Favours monotherapy Favours combination

Appendix H: Grade tables and meta-analysis results

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

		01			1					
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 <sup>1</sup>	Not serious	Serious <sup>2</sup>	Not serious	267	MD 0.82 (-1.91, 3.55)	MODERATE		
<b>BCVA</b> (proportion	gain ≥15 letter,	, >3 months	s) - values greater	than 1 favour co	ombination					
2 (Kuppermann; Ranchod)	RCT	Serious <sup>3</sup>	Not serious	Serious <sup>2</sup>	Very serious <sup>4</sup>	152	RR 1.20 (0.53, 2.70)	VERY LOW		
Total number of in	njections (>3 mo	onths) - pos	sitive values favou	ur combination						
1 (Ranchod)	RCT	Serious <sup>3</sup>	N/A	Serious <sup>2</sup>	Serious⁵	37	MD -0.50 (-1.30, 0.30)	VERY LOW		
Proportion needing	ig retreatment (	>3 months)	- values greater t	than 1 favour co	mbination					
1 (Ahmadieh)	RCT	Serious <sup>3</sup>	N/A	Serious <sup>2</sup>	Serious <sup>6</sup>	115	RR 0.65 (0.42, 1.00)	VERY LOW		
Proportion having	ocular adverse	e events - v	alues greater than	n 1 favour combi	nation					
1 (Kuppermann)	RCT	Serious <sup>3</sup>	N/A	Serious <sup>2</sup>	Serious <sup>6</sup>	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.

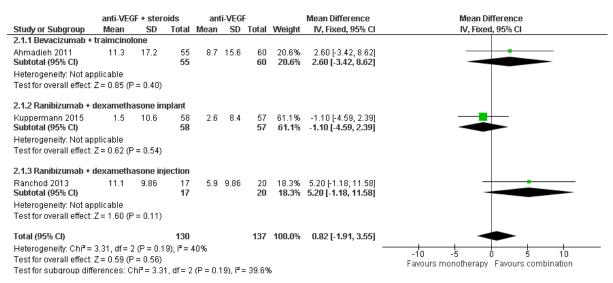
6. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.

\*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)

	anti-VEGF + ste	eroids	anti-VE	GF		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
2.2.1 Ranibizumab +	dexamethasone	e implant					
Kuppermann 2015 Subtotal (95% CI)	4	58 58	5	57 57	57.8% <b>57.8</b> %	0.79 [0.22, 2.78] <b>0.79 [0.22, 2.78]</b>	
Total events	4		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.37 (P = 0.7	'1)					
2.2.2 Ranibizumab +	dexamethasone	injection	n				
Ranchod 2013 Subtotal (95% CI)	6	17 17	4	20 <b>20</b>	42.2% <b>42.2</b> %	1.76 [0.59, 5.24] <b>1.76 [0.59, 5.24]</b>	
Total events Heterogeneity: Not ap	6 Indicable		4				
Test for overall effect:		1)					
Total (95% CI)		75		77	100.0%	1.20 [0.53, 2.70]	-
Total events	10		9				
Heterogeneity: Chi <sup>2</sup> =	0.91, df = 1 (P =	0.34); l² =	= 0%				
Test for overall effect:	Z = 0.44 (P = 0.6)	i6)					Favours monotherapy Favours combination
Test for subgroup diff	erences: Chi² = I	0.90, df=	1 (P = 0.	34), I² =	= 0%		r aroure menerally r arours combination

### 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 + PE	DT vs anti-VEG	F steroids + PDT	•					
<b>BCVA (ETDRS</b>	letters >3 mon	ths) – positive va	lues favour triple	therapy				
1 (Piri)*	RCT	Not serious	Not serious	Serious <sup>1</sup>	Serious <sup>2</sup>	84	MD 0.50 (-6.04, 7.04)	LOW
Reinjections (>	3 months) – po	sitive values fav	our triple therapy					
1 (Piri)	RCT	Not serious	Not serious	Serious <sup>1</sup>	Serious <sup>2</sup>	84	MD -0.40 (-0.83, 0.03)	LOW
Proportion need	ing retreatment	(>3 months) - val	ues greater than 1	favour triple ther	ару			
1 (Piri)	RCT	Not serious	Not serious	Serious <sup>1</sup>	Serious <sup>2</sup>	84	RR 0.84 (0.71, 0.98)	LOW
•			ct status of study p rossing 1 line of a c	•	mportant difference	<del>)</del> .		

\*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 b	oy higher values)	I			
1 (Mantel 2016)	RCT	Very serious <sup>1</sup>	N/A	Not serious	Not serious	21	MD -2.5 (-4.87 to -0.13)	LOW
Ranibizumab	to bevacizumab	vs bevacizuma	b to ranibizumab					
Best correcte	d visual acuity (le	ogMAR) - 12 m	onths (Better indic	ated by lower va	lues)			
1 (Kucukerdon mez 2015)	Cohort study	Very serious <sup>1</sup>	N/A	Not serious	Not serious	87	MD 0.05 (-2.84 to 2.94)	LOW
Best correcte	d visual acuity (le	ogMAR) - ≥ 12 i	months (Better ind	licated by lower	values)			
1 (Kucukerdon mez 2015)	Cohort study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	87	MD 0.16 (-0.88 to 1.20)	VERY LOW
Bevacizumab	to ranibizumab							
Visual acuity	(logMAR) - ≤ 3 m	onths (Better ir	ndicated by lower	values)				

Appendix H: Grade tables and meta-analysis results

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95% CI)	Quality
1 (Moisseiev 2015)	Before–after study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	110	MD- 0.02 (-0.11 to 0.07 )	VERY LOW
Visual acuity	(logMAR) – at lea	ast 4 months (E	etter indicated by	lower values)				
1 (Moisseiev 2015)	Before–after study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	110	MD -0.04 (-0.06 to 0.14)	VERY LOW
Bevacizumab	to aflibercept							
Best correcte	d visual acuity (I	ETDRS) - ≥ 12 n	nonths (Better ind	icated by higher	values)			
1 (Pinheiro- Costa 2015)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	39	MD -2.4 (-10.15 to 5.35)	VERY LOW
Bevacizumab	and/or ranibizur	nab to afliberce	ept					
Best correcte	d visual acuity (I	ogMAR) - After	1 injection (Bette	r indicated by lo	wer values)			
1 (Yonekawa 2013)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	102	MD 0.02 (-0.07 to 0.11)	VERY LOW
Best correcte	d visual acuity (I	ogMAR) - > 3 m	onths and <12 mo	onths (Better ind	licated by lower	values)		
1 (Yonekawa 2013)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	102	MD -0.04 (-0.12 to 0.04)	VERY LOW
Best correcte	d visual acuity (I	ogMAR) - ≥ 12	months (Better ind	dicated by lower	values)			
1 (Homer 2015)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Not serious	21	MD 0 (-0.17 to 0.17)	LOW
Best correcte	d visual acuity (I	ETDRS) - After	3 injections (Bette	r indicated by h	igher values)			
1 (Gharbiya 2014)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>3</sup>	31	MD -0.2 (-5.95 to 5.55)	VERY LOW
Best correcte	d visual acuity (I	ETDRS) - > 3 m	onths and <12 mo	nths (Better indi	cated by higher	values)		
2 (Gharbiya 2014, Thorell 2014)	Observational studies	Very serious <sup>1</sup>	N/A	Not serious	Not serious	104	MD 0.44 (-2.59 I to 3.48)	LOW

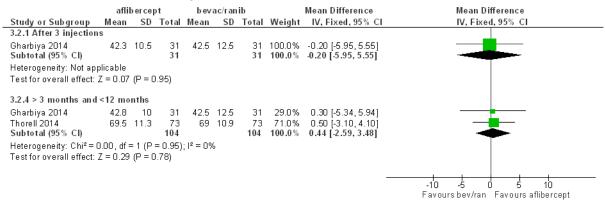
1. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Appendix H: Grade tables and meta-analysis results

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95% CI)	Quality
2. Downg	raded one level for	or non-significan	t effect.					
3. Downg	raded by 1 incren	nent if the confid	ence interval cross	ed 1 MID or by 2 i	ncrements if the o	confidence inte	rval crossed both MIDs	6

### Meta-analysis (forest plots) for bevacizumab and/or ranibizumab to aflibercept

#### Best corrected visual acuity (ETDRS)



Number of						Sample	Effect size (95%	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	size	CI)	Quality
Ranibizumab	to aflibercept							
Best correcte	d visual acuity (l	logMAR) - After	1 injection (Bette	r indicated by lo	wer values)			
1 (Heussen 2014)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	71	MD -0.02 (-0.17 I to 0.13)	VERY LOW
Best correcte	d visual acuity (I	logMAR) - After	2 injections (Bett	er indicated by I	ower values)			
1 (Heussen 2014)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	66	MD 0.01 (-0.14 to 0.16)	VERY LOW
Best correcte	d visual acuity (I	logMAR) - After	3 injections (Bett	er indicated by I	ower values)			
2 (Kumar 2013, Heussen 2014)	Observational studies	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	79	MD -0.11 (-0.19 to - 0.04)	VERY LOW
Best correcte	d visual acuity (I	logMAR) - After	4 injections (Bett	er indicated by I	ower values)			
1 (Heussen 2014)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	12	MD -0.22 (-0.58 to 0.14)	VERY LOW
Best correcte	d visual acuity (I	logMAR) - > 3 m	onths and <12 mo	onths (Better ind	icated by lower	values)		
3 (Gerding 2015, Kawshima 2015, Kumar 2013)	Observational studies	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	115	MD -0.07 (-0.19 to 0.04)	VERY LOW
Best correcte	d visual acuity (I	logMAR) - ≥ 12 i	months (Better ind	dicated by lower	values)			
1 (Narayan 2015)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	80	MD -0.03 (-0.12 to 0.07)	VERY LOW
Best correcte	d visual acuity (I	ETDRS) - > 3 m	onths and <12 mo	nths (Better indi	cated by higher	values)		
2 (Chang 2015, Sarao 2016)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 4.45 (0.96 to 7.94)	VERY LOW

Appendix H: Grade tables and meta-analysis results

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Best correcte	d visual acuity (E	ETDRS) - ≥ 12 m	onths (Better indi	cated by lower v	alues)			
2 (Chang 2015, Sarao 2016)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	141	MD 3.06 ( -0.86 to 6.92)	VERY LOW
Ranibizumab	to pegaptanib							
Best correcte	d visual acuity (I	ogMAR) - ≥ 12 ו	nonths (Better ind	licated by lower	values)			
1 (Shiragami 2014)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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)

tudu or Eubarous		-	t		ibizuma		Mean Difference		Mean Difference		
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% C		
.1.1 After 1 injection											
leussen 2014 Jubtotal (95% CI)	0.65	0.48	71 71	0.67	0.46	71 71	100.0% <b>100.0</b> %	-0.02 [-0.17, 0.13] - <b>0.02 [-0.17, 0.13]</b>			
leterogeneity: Not ap	plicable										
est for overall effect:	Z = 0.25	(P = 0.8	80)								
.1.2 After 2 injection	IS										
leussen 2014 J <b>ubtotal (95% CI)</b>	0.6	0.43	66 <b>66</b>	0.59	0.42	66 <b>66</b>	100.0% <b>100.0</b> %	0.01 [-0.14, 0.16] <b>0.01 [-0.14, 0.16]</b>			
leterogeneity: Not ap est for overall effect:		(P = 0.)	89)								
.1.3 After 3 injectio	ıs										
leussen 2014	0.43	0.2	45	0.56	0.21	45	79.4%	-0.13 [-0.21, -0.05]			
(umar 2013 Subtotal (95% CI)	0.52	0.34	34 79	0.57	0.36	34 79	20.6%	-0.05 [-0.22, 0.12] - <b>0.11 [-0.19, -0.04]</b>	•		
leterogeneity: Chi² = est for overall effect:				I <sup>2</sup> = 0%							
.1.4 After 4 inejectio	ons										
leussen 2014 Jubtotal (95% CI)	0.25	0.47	12 <b>12</b>	0.47	0.43		100.0% <b>100.0</b> %	-0.22 [-0.58, 0.14] - <b>0.22 [-0.58, 0.14]</b>			
leterogeneity: Not ap est for overall effect:		(P = 0.1	23)								
.1.6 > 3 months and	<12 moi	nths									
erding 2015	0.64	1.77	40	0.56	2.09	40	1.8%	0.08 [-0.77, 0.93]			
awashima 2015	0.35	0.4	41	0.4	0.37	41	47.6%	-0.05 [-0.22, 0.12]			
(umar 2013 Subtotal (95% CI)	0.47	0.32	34 115	0.57	0.36	34 115	50.5% <b>100.0</b> %	-0.10 [-0.26, 0.06] - <b>0.07 [-0.19, 0.04]</b>			
leterogeneity: Chi² = 'est for overall effect:				I² = 0%							
.1.7 ≥ 12 months											
larayan 2015 J <b>ubtotal (95% CI)</b>	0.615	0.305	80 <b>80</b>	0.642	0.318	80 <b>80</b>	100.0% <b>100.0</b> %	-0.03 [-0.12, 0.07] - <b>0.03 [-0.12, 0.07]</b>			
leterogeneity: Not ap est for overall effect:	•	(P = 0.:	58)								
								-	-0.5 -0.25 0 0.		
									Favours aflibercept Favou		

Best corrected visual acuity (letter)

	Afl	ibercep	t	Rani	bizum	ab		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
5.2.1 > 3 months and	d <12 ma	onths							
Chang 2015	67.4	13.27	49	60.5	16.2	49	35.5%	6.90 [1.04, 12.76]	<b>-</b>
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: Chi <sup>2</sup> =	= 1.04, df	= 1 (P =	0.31);	l² = 4 %					
Test for overall effect	t: 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: Chi <sup>2</sup> =	= 0.53, df	= 1 (P =	0.47);	I <sup>2</sup> = 0%					
Test for overall effect	t Z = 1.55	5 (P = 0.	12)						
Test for subaroun di	fforoncoc	: Chiž =	0.27 d	f = 1/P	- 0.60	$1 \mathbf{P} = 0$	96		Favours ranib Favours aflib

Test for subaroup differences:  $Chi^2 = 0.27$ , df = 1 (P = 0.60),  $l^2 = 0\%$ 

#### 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	Observational	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	31	MD -0.11	VERY LOW	
(Tao 2010)	study						(-0.3 to 0.08)		
Best corrected visual acuity (logMAR) - > 3 months and <12 months (Better indicated by lower values)									
1	Observational	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	31	MD -0.07	VERY LOW	
(Tao 2010)	study						(-0.26 to 0.12)		
1	Observational	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	31	MD -0.02	VERY LOW	
(Tao 2010)	study						(-0.21 to 0.17)		
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									

 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 <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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 <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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 <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	81	RR=1.31 (0.94, 1.81)	LOW	
CNV detection rate									
1 (Chew E Y 2014)	RCT	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	1520	RR=1.63 (1.06, 2.52)	LOW	
Frequency of	of self-monitoring	g (VMS journal v	vs usual care con	ntrol group)					
1 (Bittner A K 2014)	RCT	Very serious <sup>3,4</sup>	N/A	Not serious	Serious <sup>2</sup>	198	RR⁵=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 <sup>3,4</sup>	N/A	Not serious	Not serious	198	RR⁵=0.31 (0.12, 0.69)	LOW	
K 2014)		serious <sup>3,4</sup>	Ive to early stopp		1101 301005	190			

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)?

				U 1							
No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Neovascul	Neovascularisation (fluid)										
SD-Optica	SD-Optical coherence tomography vs FA										
2 studies	2 studies (Giani, Retrospective Khurana,)	152 eyes (149 people)	92.3% (83.9, 96.5%)	(25.3,	LR+	1.37 (1.15, 1.63)	Serious <sup>1</sup>	Not serious	Not serious	Not serious	MODERATE
<b>`</b>					LR-	0.22 (0.10, 0.50)	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	LOW
<b>TD-Optical</b>	TD-Optical coherence tomography vs FA										
3 studies (Eter,	2 x Retrospective	ive (146	69.6% (59.7, 78.0%)	63.1% (48.2, 75.9%)	LR+	1.58 (1.04, 2.39)	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	LOW
Khurana, van velthoven)	1, 1 x Prospective				LR-	0.48 (0.33, 0.70)	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	LOW
<b>TD-Optical</b>	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-	LR+	1.85 (1.51, 2.28)	Serious <sup>3</sup>	Not serious	Not serious	Serious <sup>2</sup>	LOW
					LR-	0.08 (0.03, 0.17)	Serious <sup>3</sup>	Not serious	Not serious	Not serious	MODERATE
OCT-A vs	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 <sup>1</sup>	N/A	Not serious	Not serious	MODERATE

No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					LR-	0.04 (0.01, 0.16)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERATE
Neovascu	lar AMD activitie	s (PED)									
SD-Optica	I coherence tom	ography v	vs FA								
1 (Giani)	Retrospective	93 eyes	38.5% (25.8,	68.3%	LR+	1.21 (0.69, 2.14)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
	(93 people))	51.9%)	(53.5, 81.4%)	LR-	0.90 (0.67, 1.22)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERATE	
<b>TD-Optica</b>	I coherence tom	ography v	's FA								
1 (Van de Retrospective Moere))	rospective 121 eyes (121	(121 0.370	121 (2.0, 13.0%) people)	99.0% (95.2,	LR+	6.59 (0.36, 119.77)	Serious <sup>1</sup>	N/A	Not serious	Very serious <sup>4</sup>	VERY LOW
				100.0%)	LR-	0.95 (0.89, 1.01)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERATE
Neovascu	lar AMD activitie	s (intrareti	nal fluid)								
SD-Optica	I coherence tom	ography v	rs FA								
1 ((Khurana	Retrospective	59 eyes (56	65.5%	63.3%	LR+	1.79 (1.04, 3.06)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
)		(56 people)	(47.6, 81.4%)	(45.7, 79.3%)	LR-	0.54 (0.31, 0.96)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
<b>TD-Optica</b>	I coherence tom	ography v	's 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 <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	LOW
					LR-	0.65 (0.48, 0.88)	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	LOW
<b>TD-Optica</b>	I coherence tom	ography v	s FA (analysis	s unit: sets of	ОСТ а	nd FA)					

### Macular Degeneration

No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality		
1 (Henschel	Prospective	14 people (61 pairs			LR+	1.51 (1.10, 2.06)	Serious <sup>3</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW		
)	and FA during 7 weeks after PE treatme ) vascular AMD activities (subre	of OCT and FA during 12 weeks after PDT treatment )	90.3% (77.9, 97.9%)	40.0% (23.5, 57.7%)	LR-	0.24 (0.08, 0.77)	Serious <sup>3</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW		
Neovascular AMD activities (subretinal fluid)													
SD-Optica	l coherence tom	ography v	s FA										
1 (Khurana)	Retrospective	59 eyes	69.0% (51.3,			76.7%	LR+	2.96 (1.48, 5.91)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
		<b>,</b> ,	(60.3, 89.7%)	LR-	0.41 (0.23, 0.72)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW			
<b>TD-Optical</b>	coherence tom	ography v	s FA										
2 (Khurana,	Retrospective	180 eyes	180 eyes (177	47.5%	83.9%	LR+	2.96 (1.73, 5.09)	Serious <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	LOW	
van de moere)		people)	(37.9, 57.3%)	(74.3, 90.4%)	LR-	0.63 (0.51, 0.77)	Serious <sup>1</sup>	Not serious	Not serious	Not serious	MODERATE		
<b>TD-Optical</b>	coherence tom	ography v	s FA (analysis	s unit: sets of	OCT a	nd FA)							
1 study (Henschel	Prospective	14 people (61 pairs			LR+	2.66 (1.41, 5.02)	Serious <sup>3</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW		
)	of an du we afi	of OCT and FA during 12	85.3%)	73.3% (56.5, 87.3%)	LR-	0.40 (0.22, 0.72)	Serious <sup>3</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW		
Neovascul	Neovascular AMD activities (retinal cystoid abnormalities)												

No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
SD-Optica	I coherence tom	ography v	vs FA								
1 (Khurana)	Retrospective	59 eyes (56	58.6%	56.7%	LR+	1.35 (0.81, 2.26)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
		people)	(40.6, 75.5%)	(38.9, 73.6%)	LR-	0.73 (0.43, 1.25)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
TD-Optical coherence tomography vs FA											
1 (Khurana)	urana) Retrospective 59 eye	59 eyes		55.6%	LR+	1.29 (0.60, 2.81)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
		(56 people)	(56.5, 87.3%)	(32.9, 77.0%)	LR-	0.89 (0.64, 1.26)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERTE
Neovascu	ar AMD activitie	s (cystoid	macular oede	ma)							
<b>TD-Optica</b>	I coherence tom	ography v	's FA								
1 (van de moere)	Retrospective	ctive 121 eyes (121	22.9%	98.0%	LR+	11.66 (1.60, 85.1)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
		people)	(13.9, 33.3%)	(92.9, 99.9%)	LR-	0.79 (0.69, 0.90)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERATE
Neovascu	ar AMD activitie	s (cystoid	spaces)								
<b>TD-Optica</b>	I coherence tom	ography v	's FA								
1 (Eter)	Retrospective	60 eyes (60	80%	80%	LR+	4.00 (1.15 to 13.92)	Serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	LOW
		(60 people)	(66.7, 88.9%)	(45.9, 95.0%)	LR-	0.25 (0.13 to 0.47)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERATE
SD-Optica	I coherence tom	ography v	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 <sup>1</sup>	N/A	Not serious	Not serious	MODERATE

No. of studies	Study design	Sample size	Sensitivity (95%Cl)	Specificity (95%Cl)	LRs	Effect size (95%Cl)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					LR-	1.09 (0.70 to 1.71)	Serious <sup>1</sup>	N/A	Not serious	Not serious	MODERATE
1. 2. 3.	<ol> <li>Downgraded for study design (retrospective study)</li> <li>Downgraded for imprecision because 95%CI of the positive likelihood ratio crossing 1 line of defined minimal importance difference</li> <li>Downgraded for overall results of diagnostic accuracy based on sets of OCT and FA with no individual time point result</li> </ol>										

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%Cl)	Quality		
Barriers to appoi	ntment attendan	ce and uptake of	f treatment							
Burden of period	Burden of periodic follow-up visits (3 studies)									
1 (Boulanger- Scemama 2015)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	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 <sup>1</sup>	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 <sup>1</sup>	N/A	Serious <sup>3</sup>	Not serious	248 began anti- VEGF treatment	0.8% (n=2) (0.2%, 2.9%)	VERY LOW		
Travel problem (4	4 studies)									
1 (Boulanger- Scemama 2015)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	58 lost to follow- up	51.7% (n=30) (39.2%, 64.1%)	VERY LOW		
1 (Droege 2013)	Observational study	Very serious <sup>1</sup>	N/A	Serious <sup>3</sup>	Serious <sup>2</sup>	19 stopped visits and interviewed	26.3% (n=5) (11.8%, 48.8%)	VERY LOW		
1 (Nunes 2010)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	19 answered phone questionnaire	5.3% (n=1) (0.9%, 24.6%)	VERY LOW		
1 (Vaze 2014)	Observational study	Very serious <sup>1</sup>	N/A	Serious <sup>3</sup>	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%Cl)	Quality
1 (Boulanger- Scemama 2015)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	58 lost to follow- up	1.7% (n=1) (0.3%, 9.1%)	VERY LOW
1 (Droege 2013)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	19 stopped visits and interviewed	15.8% (n=3) (5.5%, 37.6%)	VERY LOW
1 (Nunes 2010)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	19 answered phone questionnaire	15.8% (n=3) (5.5%, 37.6%)	VERY LOW
1 (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious <sup>4</sup>	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 <sup>1</sup>	Not serious	Serious <sup>3</sup>	Not serious	248 began anti- VEGF	4.4% (n=11) (2.5%, 7.8%)	VERY LOW
Treatment relate	d emotion (pain/	discomfort/fear/	dissatisfaction wi	ith treatment be	enefit) (4 studies)	)		
1 (Boulanger- Scemama 2015)	Observational study	Very serious <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	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 <sup>1</sup>	Not serious	Not serious	Serious <sup>2</sup>	19 stopped visits and interviewed	36.8% (n=7) (19.1%, 59.0%)	VERY LOW
1 (Varano 2015)	Observational study	Very serious <sup>1</sup>	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 <sup>1</sup>	Not serious	Serious <sup>3</sup>	Not serious	248 began anti- VEGF	1.2% (n=3) (0.4%, 3.5%)	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%Cl)	Quality
1 (Mitchell 2002)	Observational study	Serious <sup>1</sup>	Not serious	Serious⁵	Not serious	604 completed and answered the question	43.4% (n=262) (39.5%, 47.4%)	LOW
1 (Nunes 2010)	Observational study	Very serious <sup>1</sup>	Not Serious	Not serious	Serious <sup>2</sup>	19 answered phone questionnaire	26.3% (n=5) (11.8%, 48.8%)	VERY LOW
Specialist's attitu	udes (dismissive	, patronising, br	usque, unfeeling,	, uninterested in	n patients, using	jargon) (1 study)		
1 (Mitchell 2002)	Observational study	Serious <sup>1</sup>	N/A	Serious⁵	Not serious	604 completed and answered the question	43.5%(n=263) (39.6%, 47.5%)	LOW
Poor visual resu	lts (2 studies)							
1 (Nunes 2010)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	19 answered phone questionnaire	42.1%(n=8) (23.1%, 63.7%)	VERY LOW
1 (Vaze 2014)	Observational study	Very serious <sup>1</sup>	N/A	Serious <sup>3</sup>	Not serious	248 began anti- VEGF	2.4% (n=6) (1.1%, 5.2%)	VERY LOW
Difficulty in re-so	cheduling (2 stud	lies)						
1 (Nunes 2010)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	19 answered phone questionnaire	10.5% (n=2) (2.9%, 31.3%)	VERY LOW
1 (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious⁴	Not serious	102 failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up date	37.3% (n=38) (28.5%, 46.9%)	LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	% (n) reported (95%Cl)	Quality
1 (Varano 2015)	Observational study	Very serious <sup>1</sup>	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 <sup>1</sup>	N/A	Serious <sup>4</sup>	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	n (4 studies)							
1 (Boulanger- Scemama 2015)	Observational study	Very serious <sup>1</sup>	N/A	Not serious	Serious <sup>2</sup>	58 lost to follow- up	8.6% (n=5) (3.7%, 18.6%)	VERY LOW
1 (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious <sup>4</sup>	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 <sup>1</sup>	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 <sup>1</sup>	N/A	Serious <sup>3</sup>	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 <sup>1</sup>	N/A	Serious <sup>4</sup>	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%Cl)	Quality
	20030					appointment within 1 month of the desired follow-up date		
Facilitators to a	ppointment atten	dance and uptak	e of treatment (1	study)				
Pre-appointmen	it reminder (by ph	none, text, email)						
1 (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious <sup>4</sup>	Not serious	240 participants answered the question	81.7% (n=153) (70.6%, 93.9%)	LOW
Parking vouche	rs							
1 study (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious <sup>4</sup>	Not serious	240 participants answered the question	47.9% (n=115) (41.7%, 54.2%)	LOW
Transportation	service to and fro	om the clinic						
1 (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious <sup>4</sup>	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 <sup>1</sup>	N/A	Serious <sup>4</sup>	Not serious	240 participants answered the question	32.1% (n=77) (26.5%, 38.2%)	LOW
Networking with	n other patients w	vith the same eye	diseases					
1 (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious <sup>4</sup>	Not serious	240 participants answered the question	41.3% (n=99) (35.2%, 47.5%)	LOW
More education	on eye disease/t	he importance of	f follow-up					
1 (Thompson 2015)	Observational study	Serious <sup>1</sup>	N/A	Serious⁴	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%Cl)	Quality	
1. Downgraded one level for study design; downgraded two levels for retrospective design;									
2. Downgraded or	ne level for wide 9	5%CI;							
3. Downgraded or	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 or	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 or	f 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	e 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.	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
Patients highlighted the need to self-advocate; they were expected to identify advancing vision loss and seek appropriate support as and when it was necessary.			
Relationship with healthcare providers			
Some patients described building relationship with healthcare professionals (i.e. nurses) as a way to manage the distress treatment caused. Patients preferred appointments that exemplified balanced relationships, mutual respect, and professional friendship and that left them feeling empowered about decisions they could make	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

10

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					
<ul> <li>Patients and carers want increased public awareness of the causes and symptoms of AMD (Burton, Vukicevic).</li> </ul>	Burton (2013) Vukicevic	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		
<ul> <li>This could provide a context for diagnosis, could help people seek advice earlier (Burton).</li> </ul>	(2016)		no serious problems with relevance and fairly adequate data from UK and Australia.		
<ul> <li>This could help improve public interaction with people with AMD (more understanding of the challenges facing the visually impaired) (Vukicevic).</li> </ul>					
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	
<ul> <li>Patients were confused about the different names and types of AMD (Dahlin Ivanoff)</li> <li>Patients were unware that AMD was so common (Burton, Dahlin Ivanoff)).</li> </ul>	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				
<ul> <li>Patients often lacked a clear understanding of the potential causes and risk factors associated with AMD (Burton, Crossland, Dahlin Ivanoff).</li> <li>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).</li> <li>Patients often linked AMD to wear and tear and ageing (Crossland, McCloud).</li> <li>The role of genetic susceptibility in developing AMD was not widely understood (Crossland).</li> </ul>	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				
<ul> <li>Patients were suffering unnecessarily due to inaccurate/insufficient information about disease progression, leaving them to worry about going completely blind (Burton, McCloud, Dahlin Ivanoff).</li> <li>Patients discussed a need for accurate information to help them plan for the future and avoid unrealistic expectations (Burton, Dahlin Ivanoff,</li> <li>Patients reported giving up favourite pastimes to help preserve their vison (Burton).</li> </ul>	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				

		Confidence	
Review finding	Contributing studies	in the evidence	Explanation of confidence in the evidence assessment
<ul> <li>Patients often had unrealistic expectations of treatment outcomes and this was not helped by inaccurate information from neighbours/family members (Burton).</li> <li>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).</li> <li>Patients did not understand why glasses were not able to correct their vision problems (Dahlin Ivanoff).</li> <li>Patients were often unaware of the purpose of hospital visits and medical procedures (Burton).</li> <li>An understanding of the processes involved in treatment and the short -term side effects allowed patients to plan their posttreatment activities to cope with these problems (McCloud).</li> <li>Information about abnormal outcomes and when to seek help would also be useful (McCloud).</li> <li>Good communication regarding changes in treatment regimens was linked to better patient experience (McCloud).</li> </ul>	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			
<ul> <li>Patients were unaware of support groups or unlikely to attend them for fear of associating with depressed people.</li> <li>Patients were not necessarily aware of sources of financial help (e.g. attendance allowance) or the advantages associated with being registered as partially sighted.</li> </ul>	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.	Studies	evidence		
Theme 2: Format of information				
<ul> <li>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.</li> <li>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.</li> </ul>	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.	
<ul> <li>Patients reported finding the language use by medical staff to be confusing and inaccessible.</li> </ul>				
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.	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.	
<ul> <li>Support groups could be useful sources of information, but patients were not necessarily aware of them.</li> </ul>				
<ul> <li>Public presentations were raised as a useful source of information, but required pro-active patients.</li> </ul>				
Theme 4: Caregiver perspectives and needs				
<ul> <li>Carers need sufficient information to allow them to understand the condition and the physical/emotional effects on the person's wellbeing.</li> <li>Caregivers raised the point that since AMD has a genetic</li> </ul>	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.	
component it is important that all family members of AMD sufferers are aware of their increased risk and have regular eye tests.	107			

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