H.2.1 Strategies to slow the progression of age-related macular degeneration (AMD)

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

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

Statin for age-related macular degeneration

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

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

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

<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 acuity at 24 months											
1 (ARES2)	RCT	Not serious	N/A	Not serious	Very serious ¹	236	RR 1.14, (0.53, 2.45)	LOW			
Loss of 3 or more	lines of visual a	cuity at 36 months	3								
1 (ARES2)	RCT	Not serious	N/A	Not serious	Very serious ¹	230	RR 1.25, (0.69, 2.26)	LOW			
Incidence of CNV	at 24 months										

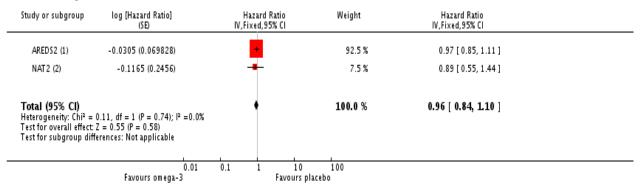
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Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality					
RCT	Not serious	N/A	Not serious	Very serious ¹	224	RR 1.06, (0.47,2.40)	LOW					
Incidence of CNV at 36 months												
RCT	Not serious	N/A	Not serious	Very serious ¹	195	RR 1.12, (0.53, 2.38)	LOW					
O over 5 years												
RCT	Not serious	Not serious	Not serious	Not serious	2343	HR 0.96 (0.84, 1.1)	HIGH					
RCT	Not serious	Not serious	Not serious	Not serious	2343	RR 1.01, (0.94 ,1.09)	HIGH					
RS letters; highe	er is better)											
RCT	Serious ³	N/A	Not serious	Not serious	79	MD 1.00 (-2.50 ,4.50)	MODERATE					
t F F	t 36 months RCT O over 5 years RCT RCT RS letters; higher	t 36 months RCT Not serious O over 5 years RCT Not serious RCT Not serious RS letters; higher is better) RCT Serious ³	t 36 months RCT Not serious N/A O over 5 years RCT Not serious Not serious RCT Not serious Not serious RS letters; higher is better) RCT Serious³ N/A	t 36 months RCT Not serious N/A Not serious O over 5 years RCT Not serious Not serious Not serious RCT Not serious Not serious Not serious RS letters; higher is better) RCT Serious ³ N/A Not serious	t 36 months RCT Not serious N/A Not serious Very serious¹ O over 5 years RCT Not serious Not serious Not serious Not serious RCT Not serious Not serious Not serious Not serious RCT Serious³ N/A Not serious Not serious	t 36 months RCT Not serious N/A Not serious Very serious¹ 195 O over 5 years RCT Not serious Not serious Not serious Not serious 2343 RCT Not serious Not serious Not serious Not serious 2343 RCT Not serious Not serious Not serious Not serious 2343	(0.47,2.40) (0.53, 2.38) (

^{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



⁽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

Laser treatment of drusen to prevent progression of advanced age-related macular degeneration									
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality	
		KISK UI DIAS	inconsistency	munectness	imprecision	Sample Size	Ellect (95%CI)	Quality	
Development of Cl					0 1	0.450	DD# 4.00		
11 (CAPT, DLS, Figueroa 1994, Little 1995, Olk 1999, PTAMD bilateral 2009, CNVPT, Fremensson 1995, Fremesson 2009, Laser to Drusen study 1995, PTAMD unilateral 2002)	RCT	Not serious	Not serious	Not serious	Serious ¹	2159 (3580 eyes)	RR* 1.03, (0.83, 1.27)	MODERATE	
Development of ge	eographic atroph	ıy							
2 (CNVPT, laser to Drusen study 1995)	RCT	Not serious	Not serious	Not serious	Very serious ²	148 (148 eyes)	RR* 1.27 (0.41, 3.94)	LOW	
Visual loss of 2-3+	lines of visual a	acuity at 3-year fo	llow-up						
9 (CAPT, DLS, Figueroa 1994, PTAMD bilateral 2009, CNVPT, Laser to Drusen Study 1995, Olk 1999, PTAMD unilateral 2002)	RCT	Serious ³	Not serious	Not serious	Not serious	2002 (3486 eyes)	RR* 0.99 (0.83, 1.18)	MODERATE	
Drusen reduction									

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Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
3 (CNVPT, PTAMD bilateral 2009, PTAMD unilateral 2002)	RCT	Not serious	Serious ⁴	Not serious	Not Serious	570 (944 eyes)	RR* 4.47 (1.64, 12.19)	MODERATE

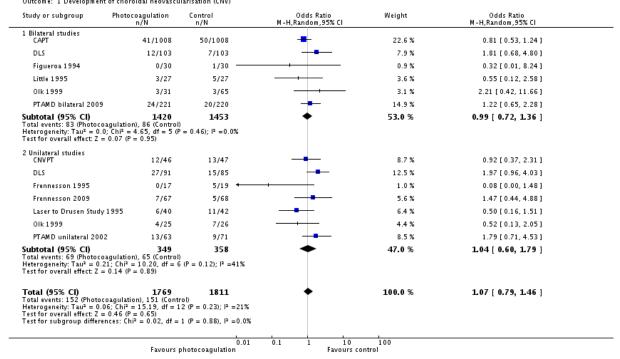
- 1. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
- 2. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
- 3. Downgraded one level for risk of bias due to visual acuity examiners were masked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

^{*}Converted from odds ratios reported in included Cochrane review

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

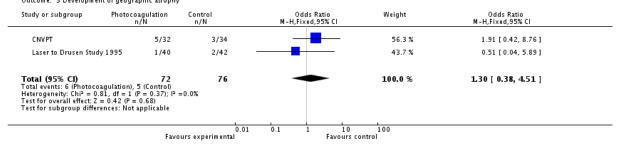
Development of CNV¹

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)



Development of geographic atrophy

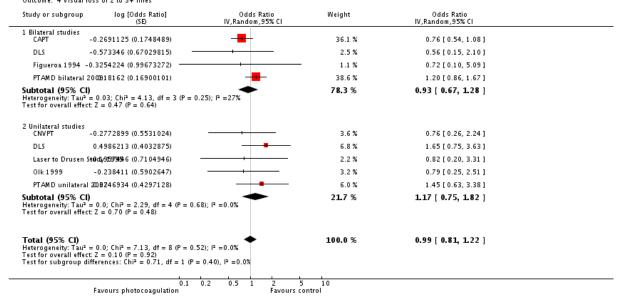
Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration Comparison: 1 Photocoagulation versus control Outcome: 3 Development of geographic atrophy



¹ Meta-analysis were extracted form the Cochrane review, and odds ratios were reported in Cochrane review. © NICE 2018. All rights reserved. See Notice of rights.

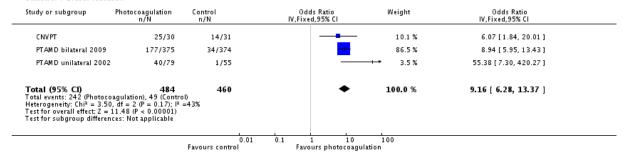
Visual acuity (loss of at least 2 lines)

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



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



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

Multivitamin supplement

maitritaiiii oap	la contraction											
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, CARMA 2013, CARMIS 2011)	RCT	Not serious	Not serious	Not serious	Serious ¹	2140	RR* 0.77 (0.67 ,0.89)	MODERATE				
Progression to La	Progression to Late AMD (wet active)											
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious ¹	1206	RR* 0.67 (0.53, 0.85)	MODERATE				
Progression to La	Progression to Late AMD (geographic atrophy)											
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious ¹	1206	RR* 0.76 (0.53 ,1.10)	MODERATE				
Progression to vis	ual loss (loss of	3 or more lines or	n logMAR chart)									
1 (AREDS 2001)	RCT	Not serious	N/A	Not serious	Serious ¹	1807	RR* 0.83 (0.70,0.97)	MODERATE				
Quality of lifeasse	ssed with chang	e in NEI-VFQ sco	ore (higher scores	indicate better C	QoL)							
1 (CARMIS 2011)	RCT	Serious ²	N/A	Not serious	Serious ¹	110	MD=12.30 (4.24, 20.36)	LOW				
Visual acuity (logN	MAR score) (low	er values indicate	better vision)									
4 (AMDSG 1996, CARMA 2013, Bartlett 2007, Veterans	RCT	Serious ²	Not serious	Not serious	Serious ¹	979	SMD=0.01 ² (-0.12,0.13)	LOW				

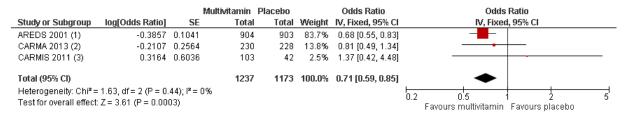
² 0.01 logMAR= - 0.5 letters, 95%CI -6.5 to 6 letters © NICE 2018. All rights reserved. See Notice of rights.

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
LAST study 2004)								

- 1. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference
- 2. Downgraded for risk of bias (randomisation and allocation; blinding; incomplete outcome) *Converted from odds ratios reported in included Cochrane review

Meta-analysis: Multivitamin antioxidant vitamin or mineral supplement

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



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

	Mult	tivitam	iin	PI	acebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.5.1 Mean visual acuity at end	l of study	У							
AMDSG 1996 (1)	0.33	0.41	35	0.29	0.24	24	5.9%	0.11 [-0.41, 0.63]	
CARMA 2013 (2)	79.7	8.9	243	80.4	9.8	250	50.7%	-0.07 [-0.25, 0.10]	-
Kaiser 1995 (3)	-0.67	0.2	9	-0.6	0.22	11	0.0%	-0.32 [-1.20, 0.57]	
Subtotal (95% CI)			278			274	56.5%	-0.06 [-0.22, 0.11]	•
Heterogeneity: Chi² = 0.45, df =	1 (P = 0.	50); 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]	*
Heterogeneity: Chi2 = 1.61, df =	2 (P = 0.	45); l²	= 0%						
Test for overall effect: $Z = 0.87$ (P = 0.38)							
Total (95% CI)			495			484	100.0%	0.01 [-0.12, 0.13]	+
Heterogeneity: Chi ² = 3.23, df =	4 (P = 0.	52); l²	= 0%					_	
Test for overall effect: Z = 0.09 (P = 0.93)							Favours placebo Favours multivitamin
Test for subgroup differences:	Chi² = 1.1	17. df=	1 (P =	0.28), F	z = 14.	4%			ravours praceso - ravours munivitamm

- Test for subgroup differences: Chi² = 1.17, df = 1 (P = 0.28), I^2 = 14.4%
- <u>Footnotes</u>
- (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

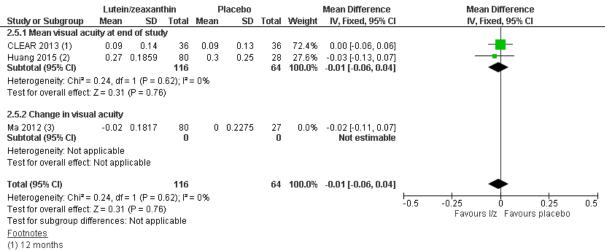
Lutein/zeaxanthin

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Progression to La	ite AMD (wet act	tive or geographic	atrophy)					
1 (AREDS2 2013)	RCT	Not serious	N/A	Serious ¹	Serious ²	6891	RR 0.94 (0.87, 1.01)	LOW
Progression to La	ite AMD (wet act	tive)						
1 (AREDS2 2013)	RCT	Not serious	N/A	Serious ¹	Serious ²	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 ¹	Serious ²	6891	RR 0.92 (0.80 ,1.05)	LOW
Quality of lifeasse	essed with chang	ge in NEI-VFQ sco	ore (higher scores	better)				
1 (Huang 2015)	RCT	Not serious	N/A	Not serious	Serious ²	108	MD 1.48 (-5.53, 8.49)	MODERATE
Visual acuity (logI	MAR score) (low	ver values better)						
2 (CLEAR 2013, Huang 2015)	RCT	Not serious	Not serious	Not serious	Not Serious	180	MD -0.01 ³ (-0.06, 0.04)	HIGH
_			everyone in trial toor		•		stimate of effect	

³ -0.01 logMAR= + 0.5 letters, 95%CI -2 to 3 letters © NICE 2018. All rights reserved. See Notice of rights.

Meta-analysis: Lutein and zeaxanthin

Distance visual acuity mean (logMAR)



^{(2) 24} months

^{(3) 12} months

Zinc supplement

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

- 1. Although there were risk of bias due to incomplete outcome date and selective reporting in Holz 1993 and Stur 1996, AREDS contributed to 98% of weight in pooled results, so not downgraded.
- 2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.
- 3. Downgraded one level for heterogeneity (i²>50%)

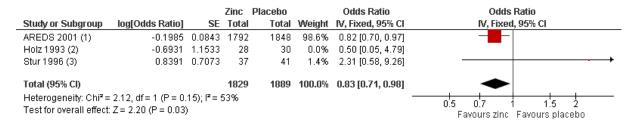
^{*}Converted from odds ratios reported in included Cochrane review

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

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Meta-analysis: Zinc supplements

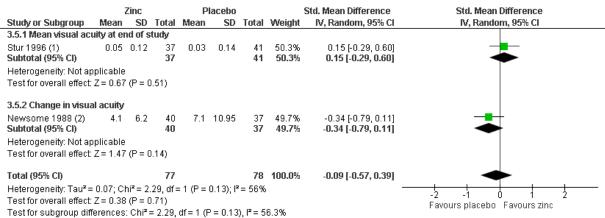
Progression to late AMD (wet active) or late AMD (geographic atrophy)



<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



<u>Footnotes</u>

- (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