HTA 15.09.10 Systematic review of treatment of dry age-related macular degeneration and Stargardt disease.

Supplementary file 4. Drug treatments

To save space, rows in tables for baseline characteristics have been removed if the studies provided no data.

Alprostadil

Augustin et al

Study details	**Participant details**
Augustin AJ, Diehm C, Grieger F, Bentz J. Alprostadil infusion in patients with dry age related macular degeneration: a randomized controlled clinical trial. Expert Opinion on Investigational Drugs 2013;22:803-12. *Country:* Germany and Austria *Design:* RCT *Number of centres:* 6 *Funding:* UCB Pharma SA *Trial ID:* not reported	*Number of Participants*: 36 (18 alprostadil, 18 placebo) *Number of eyes* not reported, assume 36 as refers to 'study eye' *Sample attrition/dropout*: 3 patients (2 alprostadil, 1 placebo) had no baseline measure and were excluded from full analysis. 12 had protocol deviations and were excluded from PPS (7 alprostadil, 5 placebo) *Sample crossovers:* not stated *Inclusion criteria:* adults over 50 years with dry AMD with hard drusen and possible early geographic atrophy limited to the perifoveal area in one eye, visual acuity within 0.2 to 0.7 logMAR (Early Treatment Diabetic Retinopathy Study charts) *Exclusion criteria:* neovascular AMD in at least one eye, detachment of the retinal pigment epithelium, AREDS III patients with large soft drusen, glaucoma, uveitis, diabetic retinopathy, medical history of retinal vein occlusion, retinal hemorrhage, vitrectomy, cataract surgery (last 12 months or during study), cardiac failure, myocardial infarction (past 6 months), inadequately controlled heart disease, cardiac arrhythmia, hypertension, indications of pulmonary oedema or pulmonary infiltration, chronic obstructive pulmonary disease, veno-occlusive lung disease, peripheral oedema, hepatic disease, malignant disease, known hypersensitivity to PGE1 or any component of study medication, intake of vasoactive medication (within 2 days of screening), intake of prostaglandins (past 3 months).

Intervention details	**Outcomes**
Intervention *1.* alprostadil *2.* Placebo *Dose details:* once daily(5 days per week) intravenous infusions (15 infusions over 3 weeks) of 60 µg/day alprostadil (in 100ml sodium chloride or 47.5mg lactose (placebo) in 100ml sodium chloride. Infusion took between 1.5 and 2 hours. *Dose modifications:* not stated *Concurrent treatment:* Treatments of diseases already present were continued, no further details. AREDS (reference given) medication, ophthalmologic dietary supplements, vasoactive	*Outcomes:* change from baseline in best corrected visual acuity (BCVA) at 3 months (primary outcome). Difference in BCVA immediately after treatment and at 6 months compared with baseline; differences in contrast sensitivity and colour vision immediately after as well as 3 and 6 months after the end of treatment; state of dry AMD and presence of neovascular AMD with binocular ophthalmoscopy, fundus photography and fluorescein angiography defined as Progression, Stabilization, or Amelioration (definitions provided below), laboratory measures, vital signs, adverse events. *Length of follow-up:* 6 months after end of 3

medication, prostaglandins, any other dry AMD treatment were prohibited. *Duration of treatment:* 3 weeks	week treatment phase

Participant characteristics, %			
(Safety set)	**Alprostadil, n=18**	**Placebo, n=18**	**P value**
Age, years mean (SD)	76.5 (8.3)	71.8 (7.8)	NR
Sex, % male	56	44	NR
Ethnic origin % White			
Classification			
Smoking history, %	11	0	
Alcohol, %	72	89	
Caffeine, %	83	83	
(Full analysis set)	**Alprostadil, n=16**	**Placebo, n=17**	**P value**
BCVA mean (SD), [median]	7,81 (1,28) [8,0]	7,29 (1,16) [7,0]	NR
Contrast sensitivity, (Pelli-Robson), study eye, mean (SD), [median]	1,153 (0,308) [1,2]	1,085 (0,329) [1,2]	NR
Colour vision (Panel D15) normal/pathologic, n	3/13	3/14	NR
lesion size			
previous treatments			
Key comorbidities			
Family history			
Comments			
Results All results are exploratory based on interim data as the study stopped early owing to poor recruitment Data extracted outcomes at interim time points as well as end of study as some differences in patterns seen, although unclear of significance of results between groups in some instances as not reported.			
	Alprostadil, n=16	**Placebo, n=17**	**P Value**
Change in BCVA, ETDRS lines at 3 months, mean (SD) [95% CI]	0.89 (0.537), [-0.21, 1.99]	-0.05 (0.578), [-1.24, 1.14]	0.122
Change in BCVA ETDRS lines immediately after treatment, mean (SD) [95% CI]	0.86 (0.615), [-0.41, 2.18]	-0.12 (0.630), [-1.42, 1.189]	NR
Change in BCVA ETDRS lines at 6 months mean (SD) [95% CI]	1.47 (0.569), [0.30, 2.64]	-0.04 (0.613), [-1.30, 1.22]	NR
Comments: reports similar patterns in the Per protocol analysis set, not reported here.			
Progression of dry AMD, recorded at least once	11/16 (68.8%)	12/17 (70.6%)	NR
Stabilisation or amelioration of dry AMD	5/16 (31.3%)	5/17 (29.4%)	NR
Progression = increase in either number or diameter of drusen, the development of hyperpigmentation or pigment epithelium detachment or starting geopgraphic atrophy. Stabilization = all measured parameters remained constant. Amelioriation = one or two test results showed improvement compared to baseline, but the other parameters had to remain constant.			
Development of neovascular AMD	0	0	
Contrast sensitivity of the study eye (Pelli Robson), mean (SD) [95% CI] after treatment	1.163 (0.331) [0.99; 1.34]	1.103 (0.304) [0.95; 1.26]	NR
Contrast sensitivity of the study eye (Pelli Robson), mean (SD) [95% CI] at 3 months	1.238 (0.282) [1.09; 1.39]	1.059 (0.293) [0.91; 1.21]	NR

Contrast sensitivity of the study eye (Pelli Robson), mean (SD) [95% CI] at 6 months	1.81 (0.299) [1.02; 1.34]	1.094 (0.224) [0.98; 1.21]	NR
Comments: Per protocol analysis set not reported here.			
Colour vision, change from baseline after treatment, n Normal – pathological: Unchanged: Pathological – normal:	 1 15 0	 0 13 4	 0.08
Colour vision, change from baseline at 3 months, n Normal – pathological: Unchanged: Pathological – normal:	 1 13 2	 0 14 3	 0.55
Colour vision, change from baseline at 6 months, n Normal – pathological: Unchanged: Pathological – normal:	 1 12 3	 0 15 2	 0.47
Comments: Per protocol analysis set not reported here.			
Adverse events			
Serious adverse events	0	0	
Any treatment emergent adverse events, patient % (n, events)	11.1 (4)	33.3 (9)	
Comments: One AE (phlebitis lasting over one day) in the alprostadil group had a probable or highly probable relation to the study medication. Ophthalmological AEs only reported in the placebo group (n= 3)			

BCVA: Best corrected visual acuity; CI: Confidence Interval; ETDRS: Early Treatment Diabetic Retinopathy Study; NR: not reported; SD: standard deviation

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States patients were randomised, no further details
Allocation concealment (selection bias)	Unclear	As above
Blinding participants and personnel (performance bias), Objective outcomes	Low	No description of blinding, placebo was administered in same volume of infusion but no other details, however, objective outcomes unlikely to be at risk of performance bias.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No description provided
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	Three analyses sets, safety set = all randomised who had at least one dose of medication; full analysis set = all randomised participants receiving at least one dose of medication and had baseline and post-baseline measurements at week 3 and/or 3 months. Per protocol set also analysed (all who did not show any protocol deviations). All data are exploratory as the study stopped prematurely. Study reports that 36 patients were randomised for the final analysis, unclear if any others were randomised as no flow

		chart provided. Of the 36 2 alprostadil and 1 placebo were not included in the full analysis set as no baseline data for the primary outcome were available.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Unclear	Laboratory values and vital signs reported as summary statement only that no major differences seen (although not relevant to the review)
Other biases	Low	No obvious other biases

Ladewig et al

Study details	**Participant details**
Ladewig MS, Ladewig K, Guner M, Heidrich H. Prostaglandin E<inf>1</inf> infusion therapy in dry age-related macular degeneration. Prostaglandins Leukotrienes and Essential Fatty Acids 2005;72:251-6. *Country:* Germany *Design:* Prospective cohort study (pilot study) *Number of centres:* one *Funding:* states financed independently *Trial ID:* Not reported	*Number of Participants*: Total 21 (treated 11, not treated 10) *Number of eyes:* Not reported *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* presence of dry form of AMD with ≥ 10 soft and/or hard drusen, atrophies and proliferations of the retinal pigment epithelium, early geographic atrophy and pigment epithelial detachment without indications of CNV. I think also, ETDRS acuity ≥0.2 and ≤0.8. *Exclusion criteria:* age < 50 years, other eye diseases, insufficiently treated heart failure or coronary heart disease, myocardial infarction within the past 6 months, clinical or radiological indications of pulmonary oedema or pulmonary infiltrations, serious chronic obstructive ventilation disorders, liver damage or liver disease, and anticipation of haemorrhagic complications (e.g., gastric ulcers, recent surgery).

Intervention details	**Outcomes**
Intervention *1.* Prostaglandin E_1 (PGE_1) *2.* No treatment *Dose details:* intravenous infusion of PGE_1 (Prostavasin) 60µg, dissolved in 50 ml of sodium chloride once daily *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 21 days	*Outcomes (state if primary)* Visual acuity of the study eye (ETDRS chart) (primary outcome) Contrast vision Colour vision Visual field Drusen and atrophic areas Adverse events *Length of follow-up:* 6 months

Participant characteristics, %			
	PGE_1, n=11	**No treatment, n=10**	**P value**
Age, years mean (SD)	76 (4)	73 (6)	
Sex, % male	9.1	3	
Comments: states control participants showed a similar distribution of the forms of dry AMD. Of the treated groups 4 patients showed mainly hard drusen, 4 mainly geographic atrophy, 3 mainly soft confluent drusen			
Results			
	PGE_1, n=11	**No treatment, n=10**	**P Value**

Change in visual acuity at 6 months, % of patients:			
Improvement of 3 lines	9	NR	
Improvement of 1 line	27	NR	
No change	45	NR	
Decline by 1 line	18	NR	
An improvement in visual acuity of ≥ 1 line was found in 55% immediately after end of infusion therapy, and in 73% 2 months after end of medication.			
Mean change from baseline in visual acuity, ETDRS lines	0.4[a]	-0.8	
[a] Estimate from figure, scale not linear			
Change in contrast vision at 6 months, % of patients:			
Improvement of 1ine	18	NR	
Impairment of 1 line	18	NR	
An increase in contrast vision by ≥ one line was seen in 64% of patients immediately after the end of the infusion therapy and in 27% of patients 2 months after the infusion therapy			
Colour vision at 6 months	NR	NR	
States colour vision was markedly restricted in all patients enrolled in the study, and no substantial change was observed immediately after the infusion therapy and 6 months after the end of infusions.			
Visual field, depth of defect at 6 months	NR	NR	
States improvements seen immediately after end of infusions: decrease in the depth of defect in 64% of patients but at 6 months after the end of infusions, no substantial differences from the baseline findings were observed.			
Progression of the atrophies of retinal pigment epithelium were seen in those patients who had presented with atrophies before the therapy. No new atrophies were demonstrated in patients who had not had atrophies at the beginning of the study.			
Adverse events (drug-related)	0		

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			NR
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			CD time period of controls
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?			NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating: Poor

Recruitment period of control group, blinding of outcome assessors, not all outcomes reported)

*CD, cannot determine; NA, not applicable; NR, not reported

Dorzolomide

Remky et al

Study details	**Participant details**
Remky A, Weber A, Arend O, Sponsel WE. Topical dorzolamide increases pericentral visual function in age-related maculopathy: pilot study findings with short-wavelength automated perimetry. Acta Ophthalmologica Scandinavica 2005;83:154-60. *Country:* Germany *Design:* RCT (pilot) *Number of centres:* 1 *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: total 40: dorzolamide 20; placebo 20 *Number of eyes:* total 40: dorzolamide 20; placebo 20 *Sample attrition/dropout*: 2 participants withdrew after recruitment and were replaced by 2 others. 2 participants withdrew after receiving allocated intervention, unclear which groups these came from. *Sample crossovers:* none *Inclusion criteria:* AMD (any drusen, hyperpigmentation or small atrophic lesions) with visual acuity >0.4 (20/50). The eye with better visual acuity was selected, if equal, the eye with the lower refractive error was chosen. *Exclusion criteria:* any atrophic area greater than 200 µm in diameter on clinical examination, any exudative lesions or any history of eye disease that might have impact on retinal function, moderate and advanced nuclear opacities.

Intervention details	**Outcomes**
Intervention *1.* Dorzolamide 0.2% eye drop *2.* Placebo, artificial tear. *Dose details:* 3 times daily for 12 weeks *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 12 weeks	*Outcomes (state if primary)* Best corrected visual acuity, Shortwavelength automated perimetry mean and standard deviation sensitivity. *Length of follow-up:* 12 weeks (mean 96 (SD 9) days)

Participant characteristics, %			
	Dorzolamide, n=20	**Placebo, n=20**	**P value**
Age, years mean (SD)	70.6 (6.6)	70.1 (6.4)	P=0.80
Sex, % male	70	60	P=0.74
Classification Pseudophakic	1	1	
visual acuity, log MAR, mean (SD)	0.13 (0.10)	0.12 (0.13)	P=0.83
Metric acuity, mean (range)	0.74 (0.5-1.0)	0.76 (0.4-1.0)	
Shortwavelength automated perimetry (mean sensitivity) (SD) db	18.06 (5.9)	19.98 (5.43)	P=0.29
Shortwavelength automated perimetry (SD sensitivity) (SD) db	2.98 (1.38)	2.97 (1.23)	P=0.98
Results			

	Dorzolamide, n=20	Placebo, n=20	P Value
Visual acuity, mean LogMAR (SD)	0.14 (0.12)	0.14 (0.12)	NR
Comments: P-values reported within group but not between, although by observation not significant			
Shortwavelength automated perimetry (mean sensitivity) (SD) db	19.58 (4.51)	20.55 (5.82)	P=0.32
Comments			
Shortwavelength automated perimetry (SD sensitivity) (SD) db	2.96 (1.02)	2.88 (1.24)	NR
Comments States that based on estimating the remaining content of the bottles, there was judged to be good compliance.			
Adverse events, *severe* *mild conjunctival irritation*	 0 2	 0 1	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	No details
Allocation concealment (selection bias)	Unclear	No details
Blinding participants and personnel (performance bias), Objective outcomes	Low	Study drug was masked with bottles over-labelled with identification numbers only showing. Investigators and patients were masked to the actual content of the eyedrop bottle
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	At baseline two independent observers were masked to the identity of patients and any perimetry results assessed eye characteristics, unclear for endpoint assessment, as states BCVA was determined by an ophthalmologist.
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	Numbers and reasons provided but not clear which treatment group these were from. No numbers in analysis reported and unclear if ITT.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Unclear	Not enough detail to check.
Other biases	Unclear	Described as a pilot study, sample size reasonable but unlikely powered.

Eculizumab

Yehoshua et al

Study details	Participant details

Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, Gregori G, Penha FM, Moshfeghi AA, et al. Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: the COMPLETE study. Ophthalmology 2014;121:693-701. *Country:* USA *Design:* RCT *Number of centres:* one *Funding:* Commercial and non-commercial funding *Trial ID:* NCT00935883	*Number of Participants*: Total 30 1. Eculizumab n=20 (low dose 10, high dose 10) *2.* Placebo n=10 *Number of eyes:* Total 48 (30 study eyes, 18 fellow eyes) *Sample attrition/dropout*: 0 *Sample crossovers:* Not reported *Inclusion criteria:* age ≥50 years, total GA area of 1.25 to 18 mm^2, visual acuity of 20/63 or better (ETDRS letter score of at least 59). If both eyes were eligible, 1 eye was chosen as the study eye at the discretion of the investigator. Fellow eyes that met inclusion criteria were used for secondary outcome analysis. *Exclusion criteria:* GA contiguous with any peripapillary atrophy, any history of choroidal neovascularization in the study eye.

Intervention details	**Outcomes**
Intervention *1.* Eculizumab *2.* Placebo (saline infusion) *Dose details:* The first 10 patients received low dose eculizumab (600 mg via intravenous infusion for 4 weeks (induction) followed by 900 mg every 2 weeks until week 24 (maintenance)). The next 10 patients received high dose eculizumab (900 mg via intravenous infusion for 4 weeks (induction) followed by 1200 mg every 2 weeks until week 24 (maintenance) *Dose modifications:* Not reported *Concurrent treatment:* All patients received a meningococcal vaccine at least 15 days before the initiation of treatment *Duration of treatment:* 24 weeks	*Outcomes (state if primary)* Change in area of GA at 26 weeks (obtained using SD OCT sub-RPE slab images) (primary outcome) Change in area of GA (measured with autofluorescence and fluorescein angiographic imaging) Change from baseline in normal luminance and low luminance ETDRS visual acuity in both study and fellow eyes; conversion rate from dry AMD to wet AMD in both study and fellow eyes. Adverse events *Length of follow-up:* 12 months

ETDRS: Early Treatment Diabetic Retinopathy Study; GA: Geographic atrophy; RPE: retinal pigment epithelium; SD OCT spectral-domain optical coherence tomography

Participant characteristics, %			
	Eculizumab, n=20 eyes	**placebo, n=10 eyes**	**P value**
Age, years mean (SD)	79 (7)	81 (6)	
visual acuity, EDTRS letters, mean (SD)	71.3 (7.8)	78.6 (5.2)	P=0.012
Area of GA, mm^2, mean (SD) *Square route scale, mm, mean (SD)*	7.3 (4.8) 2.55 (0.94)	4.6 (3.6) 2.02 (0.74)	P=0.12 P=0.13
The mean visual acuity in the high-dose group was 67.8 (7.4) EDTRS letters, 7 letters fewer than in the low-dose group, which was 74.8 (6.7) EDTRS letters (P= 0.04).			
Results			
	Eculizumab, n=20 eyes	**placebo, n=10 eyes**	**P Value**
Mean change in GA at 26 weeks, mm (SD), primary outcome	0.19 (0.12)	0.18 (0.15)	P=0.96

Mean change in GA at 52 weeks, mm (SD)	0.37 (0.21)	0.37 (0.22)	P=0.93
Also reports results for study and fellow eyes combined (data not extracted), no statistically significant difference between treatment and placebo.			
Change in ETDRS visual acuity at 26 weeks[a], mean (SD)	2.5 (4.1)	-2.6 (7.2)	P=0.019
Change in ETDRS, % *≤ -15* *-6 to -14* *Within +/- 5* *5 to 14* *≥15*	 0 0 80 15 5	 10 0 90 0 0	
Change in ETDRS visual acuity at 52 weeks	0.7 (7.2)	2.9 (7.0)	P=0.43
Change in ETDRS, % *≤ -15* *-6 to -14* *Within +/- 5* *5 to 14* *≥15*	 5 10 70 10 5	 10 0 90 0 0	
[a]States the significance of this difference was largely the result of a single placebo eye that lost 22 letters of visual acuity when this eye's GA affected the fovea			
Adverse events	0	0	
Compares high dose and low dose subgroups (data not extracted), no statistically significant difference. Also reports the correlation between genotype, geographic atrophy area at baseline and disease progression and states that genetic analysis found there was no evidence of an effect of the number of at-risk alleles at a particular locus on the enlargement rate of GA and there was no evidence of an interaction between the total number of alleles on the enlargement rate of GA.			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Randomization schedules were stratified with the use of a permuted-block strategy to insure balance.
Allocation concealment (selection bias)	Unclear	Not reported
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Described as ‘double masked’, no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Described as ‘double masked’, and 2 independent graders, no further details
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	Low	States none
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	High	Change from baseline in normal luminance and low luminance ETDRS visual acuity, conversion rate from dry AMD to wet AMD not reported
Other biases	Low	No other bias noted, study was powered

Emixustat

Dugal et al

Study details	**Participant details**
Dugel PU, Novack RL, Csaky KG, Richmond PP, Birch DG, Kubota R. Phase ii, randomized, placebo-controlled, 90-day study of emixustat hydrochloride in geographic atrophy associated with dry age-related macular degeneration. Retina 2015;35:1173-83. *Country: USA* *Design:* RCT *Number of centres:* 12 *Funding:* Acucela Inc. (drug sponsor) *Trial ID:*ClinicalTrials.gov (NCT01002950)	*Number of Participants*: total 72: Emixustat 2mg qAM (n=12) ; Emixustat 5mg qAM (n=12) ; Emixustat 5mg qPM (n=12) ; Emixustat 7mg qAM (n=12) ; Emixustat 10mg qAM (n=6) ; Placebo (n=18) *Number of eyes:* one study eye – defined by it being either: (i) only eye, (ii) if both eyes qualified, then worse eye by largest lesion of GA; (iii) if both eyes qualified and same size lesion of GA and all inclusion criteria met, then right eye. *Sample attrition/dropout*: Overall: N=29 (Emixustat n=23; placebo n=6) due to ocular adverse events; Participant discontinuation: adverse events: N=8 (Emixustat n=8; placebo n=0); Sponsor discontinuation: 7mg and 10mg qAM doses discontinued due to adverse events: N=21 (Emixustat n=15; placebo n=6). *Sample crossovers:* None stated. *Inclusion criteria:* Adults, clinical diagnosis of GA, as defined by well-demarcated areas of partial or complete RPE depigmentation or loss that was confirmed by a central reading centre; best corrected visual acuity equal to or better than 20/400 in study eye. *Exclusion criteria:* GA in either eye associated with ocular disease other than AMD; known congenital/inherited colour vision abnormalities; active exudative AMD or current treatment for exudative AMD in study eye; cataract or other intraocular surgery within 3 months; or laser-assisted in situ keratomileusis surgery, glaucoma filtration surgery, or corneal transplant within 6 months of study entry in either eye; or active ocular disease or clinically significant ocular abnormalities in either eye that would interfere with study evaluation. (Note: 12 participants (10 emixustat, 2 placebo) exempt from inclusion criteria due to medication changes before study dosing.)

Intervention details	**Outcomes**
Intervention *1.* Emixustat (oral, once daily) *2.* Placebo *Dose details:* *1.* Emixustat 2mg once every morning (qAM) *2.* Emixustat 5mg qAM *3.* Emixustat 5mg once every evening (qPM) 4. Emixustat 7mg qAM *5.* Emixustat 10mg qAM *Dose modifications:* None stated *Concurrent treatment:* None stated *Duration of treatment:* 90 days	*Outcomes (state if primary)* Modulation of visual cycle (Time course of recovery of rod sensitivity (rod b-wave amplitude) after exposure to a bleaching light using electroretinography following International Society for Clinical Eletrophysiology of Vision methodology. Values were normalised to a common scale by transforming each postbleach b-wave amplitude to the percentage of the prebleach amplitude at baseline. Rate of recovery after bleach (over 30-minute period at 10 minute intervals) was then calculated from the transformed rod b-wave amplitude data, and a mean slope value (%/minute +/- SD) for each cohort obtained. Outcome measured at baseline and days 14, 60, 90 and study exit (7-14 days discontinuation of drug) and also at days 7 and 30 for Emixustat 5mg qAM) Safety Measures (Adverse events; Clinical laboratory tests; Vital signs and physical examinations)

	Changes in ophthalmologic findings (BCVA; Slit-lamp examination; Intraocular pressure; Dilated ophthalmoscopy) Routine safety monitoring (OCT images) Compliance (pill count and diary cards) *Length of follow-up:* 90 days (7-mg and 10-mg emixustat groups received median exposure 25 days compared to 90 days for other groups)

Participant characteristics, %								
	Emixustat							
	2mg qAM, n=12	**5mg qAM, n=12**	**5mg qPM, n=12**	**7mg qAM, n=12**	**10mg qAM, n=6**	**All, n=54**	**Placebo, n=18**	**P value**
Age, years median (range)	78 (55-88)	75.5 (60-89)	82.0 (67-91)	79.0 (65-95)	77.0 (73-85)	78.5 (55-95)	82.0 (55-87)	NR
Sex, % male	16.7	33.3	33.3	41.7	33.3	31.5	44.4	NR
Ethnic origin % White	91.7	83.3	91.7	100	100	92.6	94.4	NR
Study eye right, %	50.0	58.3	58.3	58.3	33.3	53.7	50.0	NR
Study eye left, %	50.0	41.7	41.7	41.7	66.7	46.3	50.0	NR
BCVA, median (range) letter score	68.0 (33-83)	74.0 (34-85)	58.5 (30-84)	52.5 (19-74)	60.0 (18-85)	63.0 (18-85)	65.0 (40-79)	NR
BCVA, median (range) approximate Snellen equivalent	20/44 (20/219-20/22)	20/33 (20/209-20/20)	20/68 (20/250-20/21)	20/89 (20/418-20/33)	20/63 (20/438-20/20)	20/55 (20/438-20/20)	20/50 (20/160-20/26)	NR
lesion size median (range), mm²	9.61 (0.84-28.77	7.38 (2.24-14.34)	11.77 (0.68-31.01)	9.37 (4.79-23.42	7.47 (5.36-25.56)	8.98 (0.68-31.01)	8.23 (0.16-23.13)	NR
Results								
Pharmacodynamic recovery: Slope of rod ERG recovery function in the 5-mg qAM groups at each visit relative to baseline								
	Day 7 (N=9)	Day 14 (N=11)	Day 30 (N=8)	Day 60 (N=10)	Day 90 (N=10)	P value		
Slope at Day 0	2.66	2.55	2.70	2.51	2.51	NR		
Slope at Follow-up[a]	1.17	0.99	1.23	0.92	1.17	NR		
Degree of suppression,[b] *%*	56.0	61.2	54.4	63.3	53.4	NR		
[a] Percent recovery per minute; [b] Slope at Day 0 – slope at follow-up)/(slope at Day 0 x100); obtained during the 30 minute recovery period. Rod recovery rates and cone amplitudes comparable across all treatment groups (assessed baseline, day 14, and study exit (7-20 days post treatment). On Day 14 dose dependent relationship, suppression relative to placebo ranged from 34% in 2-mg group to 90% in 10-mg group, returning to baseline levels after study exit. Differences for 5-mg qAM[*], 5-mg qPM[*], 7mg q-AM[#] and 10-mg qAM[#] were statistically significant compared to baseline ([*] $p \leq 0.05$, [#] $p \leq 0.001$). No detectable effect on cone receptor function.								
Mean (SD) GA lesion size change from baseline at Day 90 for study eye								
	Emixustat[a]							
	2-mg qAM (N=12)	5-mg qAM (N=12)	5-mg qPM (N=12)	Placebo (N=18)				
Colour photography (mean (SD), n) Total area, mm²	0.2 (0.5) 11	0.3 (0.5) 10	0.1 (0.5) 8	0.4 (0.7) 9				
Fundus autofluorescence photography (mean (SD), n) Total area, mm²	-0.1 (1.4) 11	0.0 (0.2) 4	0.0 (1.0) 8	0.2 (0.4) 8				

Fluorescein angiography (mean (SD), n) Total area, mm²		0.2 (0.6) 12	0.5 (0.5) 10	0.2 (0.6) 9	0.4 (0.5) 12			
[a] Lesion data were not analysed for the 7-mg qAM and 10-mg qAM cohorts.								
Visual Acuity (decrease of ≥15 letters)								
	2mg qAM, n=12	**5mg qAM, n=12**	**5mg qPM, n=12**	**7mg qAM, n=12**	**10mg qAM, n=6**	**All, n=54**	**Placebo, n=18**	**P value**
	0	0	1	1	0	2	0	NR
Comments Best corrected visual acuity: Subject 1 (7-mg) – left eye – baseline 78 letters, Day14 62 letters, posttreatment 69 letters; Right eye – baseline 51 letters, 55-56 letters subsequent visits. Subject 2 (5-mgqPM) – right eye – baseline 53 letters, Day 14 9 letters, posttreatment 57 letters; Left eye – baseline 66 letters, during treatment ≥61 letters, posttreatment 64 letters								
Serious Adverse Events								
	2mg qAM, n=12	**5mg qAM, n=12**	**5mg qPM, n=12**	**7mg qAM, n=12**	**10mg qAM, n=6**	**All, n=54**	**Placebo, n=18**	**P value**
	1	1	1	0	0	0	0	NR
2-mg: Hospitalised for exacerbation of chronic obstructive pulmonary disease (n=1) 5-mg qAM and qPM: chromatopsia (n=2)								
Systemic (nonocular) adverse events (mild to moderate) : n (%) [patients]								
	All, n=54	**Placebo, n=18**	**P value**					
All	57%	67%	NR					
Headache	5 (9%)	1 (6%)	NR					
Urinary tract infection	4 (7%)	0	NR					
Dizziness	3 (6%)	1 (6%)	NR					
Nausea	3 (6%)	1 (6%)	NR					
Comments: states non-ocular adverse events were observed in all dose cohorts; no dose related patterns States most AEs were mild, moderate events were typically isolated (1 participant each) except 3 emixustat participants had UTS, and 2 had ligament sprain (not reported if any other ligament sprains). Also states AEs were considered to be treatment related for 1 participant for each group.								
Ocular adverse events: n (%) [patients]								
	Emixustat							
	2mg qAM, n=12	**5mg qAM, n=12**	**5mg qPM, n=12**	**7mg qAM[a], n=12**	**10mg qAM[a], n=6**	**All, n=54**	**Placebo, n=18**	**P value**
At least one ocular AE						93%	28%	
Chromatopsia[b]	4 (33.3)	8 (66.7)	5 (41.7)	9 (75.0)	5 (83.3)	31 (57.4)	3 (16.7)	NR
Night blindness (delayed dark adaptation	3 (25.0)	6 (50.0)	6 (50.0)	6 (50.0)	5 (83.3)	26 (48.1)	1 (5.6)	NR
Visual impairment	1 (8.3)	5 (41.7)	4 (33.3)	2 (16.7)	2 (33.3)	14 (25.9)	1 (5.6)	NR
Blurred vision	2 (16.7)	2 (16.7)	3 (25.0)	1 (8.3)	0	8 (14.8)	1 (5.6)	NR
Visual field defect	1 (8.3)	2 (33.3)	0	1 (8.3)	2 (33.3)	8 (14.8)	0	NR
Reduced visual acuity	1 (8.3)	0	2 (16.7)	2 (16.7)	1 (16.7)	6 (11.1)	0	NR
Photopsia	1 (8.3)	1 (8.3)	1 (8.3)	1 (8.3)	1 (16.7)	5 (9.3)	1 (5.6)	NR
Vitreous detachment	0	2 (16.7)	1 (8.3)	0	0	3 (5.6)	0	NR
Photophobia	0	1 (8.3)	1 (8.3)	0	0	2 (3.7)	0	NR
Discontinuation due to ocular adverse events (mild or moderate) [patients]	0	2	3	2	1	8	0	NR

[a] 7-mg and 10-mg groups were prematurely discontinued by the sponsor. Patients receiving 5-mg emixustat the proportion of participants with treatment-emergent ocular adverse events was identical for qAM and qPM groups, however the number of events was lower in qPM group (53 events qAM vs. 30 events qPM), particularly chromatopsia (incidence 67% qAM vs. 42% qPM), moderate severity ocular adverse events (incidence: 25% qAM vs. 8% qPM; number: 5 events qAM vs. 1 event qPM). [b]Treatment related events: Chromatopsia - 30 subjects in emixustat and 3 subjects in placebo groups. Time to resolution of adverse events (available data): (i) Chromatopsia (n=53 events) - 29 (54.7%) resolved before end of dosing and 24 (45.3%) resolved at or after the end of dosing; (ii) Delayed dark adaptation (n=26 events) 6 (23.1%) resolved before end of dosing and 20 (76.9%) resolved at or after the end of dosing; (iii) visual impairment (n=31 events) 24 (77.4%) resolved before end of dosing and 7 (22.6%) resolved at or after the end of dosing. Moderate-severity ocular events in 26% of emixustat vs. 0 placebo. Most ocular events were considered related to study drug.
Other Outcomes No clinically relevant findings reported in safety assessment of clinical laboratory tests, vital signs, physical examinations, electrocardiograms, slit lamp biomocroscopy, intraocular pressure, dilated ophthalmoscopy and optical coherence tomography. Compliance (percentage of expected doses received for time on study) was >90% for all but 6 subjects, which included 4 participants with low calculated compliance because of missing data

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Dose cohorts were sequentially enrolled and subjects were randomly assigned….[using] Computer-generated randomisation code….
Allocation concealment (selection bias)	Unclear	Computer-generated randomisation code was kept under lock and key, and no investigators or subjects were inadvertently unmasked.
Blinding participants and personnel (performance bias), Objective outcomes	Low	The study was double masked within each cohort to avoid bias, and emixustat and placebo tablets were identical in appearance. Computer-generated randomisation code was kept under lock and key, and no investigators or subjects were inadvertently unmasked.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	As above, however, it is unclear if assessors were classified as investigators and were blinded. Some outcomes may be influenced by assessors judgement.
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias)	High	Eight subjects, all of whom received emixustat, discontinued study drug; all discontinuations were due to adverse event(s)….the 7-mg and 10-mg dose cohorts were discontinued by the sponsor early because of initial estimates of frequency and severity of adverse events, which led to discontinuation of an additional 15 emixustat subjects (28%) and 6 placebo subjects (33%). Numbers and reasons provided, imbalance between groups
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	High	Not all outcome data is fully reported with summary statements rather than point estimates and measures of variability. Pharmacokinetics stated as an outcome in the NCT record but not reported.
Other biases	None	

Fenretinide

Mata et al

Study details	**Participant details**
Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ. Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. Retina 2013;33:498-507. *Country:* USA *Design:* RCT *Number of centres:* 30 *Funding:* commercial funding *Trial ID:* NCT00429936	*Number of Participants*: total 246; fenretinide 100mg: 80; fenretinide 300mg 84; placebo 82 *Number of eyes* not reported (but refers to study eye and fellow eye) *Sample attrition/dropout*: total 68; fenretinide 100mg: 28 (12 withdrew consent, 2 lost to follow-up; 14 adverse event); fenretinide 300mg 26 (8 withdrew consent, 1 protocol violation, 17 adverse event); placebo 14 (8 withdrew consent, 1 protocol violation, 5 adverse events). *Sample crossovers:* assume none *Inclusion criteria:* 50-89 years, geographic atrophy (secondary to dry AMD) within 500 µm of fovea, total atrophic area 1-8 disk areas (2.54–20.32 mm^2) not characterized as either focal or patchy by FAF photography and best-corrected visual acuity of 20/20 to 20/100. *Exclusion criteria:* active choroidal neovascularization (CNV) in the study eye.

Intervention details	**Outcomes**
Intervention *1.* Fenretinide 100mg *2.* Fenretinide 300mg *3.* Placebo *Dose details:* oral fenretinide at either 100mg or 300mg after evening meal. No details of the placebo. *Dose modifications:* not reported *Concurrent treatment:* also took vitamins without beta carotene. *Duration of treatment:* not reported (assume 2 years)	*Outcomes (state if primary)* change in aggregate lesion size growth (primary outcome) BCVA Contrast sensitivity Onset of CNV Night vision questionnaire (validated) – delayed dark adaptation (DDA) Adverse events Serum RBP concentrations (not extracted) *Length of follow-up 25 months*

Participant characteristics, %				
	Fenretinide 100, n=80	**Fenretinide 300, n=84**	**Placebo, n=82**	**P value**
Age, years median (range)	79.5 (58-89)	79 (53-90)	80 (55-89)	
Sex, % male	35	46.4	36.6	
Ethnic origin *% White*	100	98.8	98.8	
BCVA, mean	68.59	68.12	66.57	
lesion size by colour fundus photography, median (SD) mm^2	8.10 (4.78)	9.06 (5.03)	8.17 (4.5)	
lesion size by fundus autofluorescent photography, median (SD) mm^2	8.33 (5.10)	9.02 (5.26)	8.55 (4.84)	
Comments: states reported baselines were similar between groups, no p-values provided.				
Results				
	Fenretinide 100, n=80	**Fenretinide 300, n=84**	**Placebo, n=82**	**P Value**

Visual Acuity change from baseline (mean letters lost) at 25 months[a]	-11.0	-10.0	-8.0	
[a]estimated from figure				
Mean % change in DDA grade	28	38	16	
Comments: reports mean DDA at 24 months in a figure but mean change values in the text, therefore extracted the data presented rather than estimate from a small figure.				
Incidence of CNV onset in study or fellow eye, %				
No CNV event	91.3	90.4	81.7	
≥1 CNV event	8.8	9.6	18.3	
States analysis of time to first CNV event, in either the study or fellow eye, showed a reduced incidence of CNV events in the fenretinide treatment groups during the second year of the study. There was no dose dependency. There was a 2.2-fold increased risk for a CNV event in patients within the placebo group compared with patients in the combined fenretinide arms ("95% CI, P = 0.0,606", not clear if this value is CI or P value).				
Adverse events				
Adverse events leading to withdrawal, %	17.5	20.2	6.1	
Specific adverse events leading to withdrawal, %				
Cardiac disorders	2.5	0	1.2	
Eye disorders (see below)	3.8	9.6	0	
Gastrointestinal	3.8	1.2	2.4	
Investigations	2.5	1.2	0	
Neoplasms	0	2.4	2.4	
Nervous system	3.8	2.4	0	
Respiratory	0	1.2	1.2	
Skin and subcutaneous	3.8	2.4	0	
Vascular	1.3	0	1.2	
Eye disorders leading to study withdrawal, n				
Night blindness	1	3	NR	
Visual disturbance	0	4	NR	
Reduced visual acuity	1	3	NR	
Dry eye	1	0	NR	
Macular degeneration	1	1	NR	
Adverse events not leading to withdrawal, %				
Cataract	11.3	13.3	12.2	
CNV	8.8	9.6	18.3	
Conjunctivitis	1.3	4.8	0	
Dry eye	6.3	3.6	3.7	
Lacrimation increased	3.8	7.2	1.2	
Night blindness	36.3	37.3	29.3	
Retinal haemorrhage	12.5	7.2	7.3	
Vision blurred	6.3	8.4	2.4	
Visual acuity reduced	66.3	71.1	69.5	
Visual disturbance	18.8	26.5	7.3	
Comments: not discussion of any significance testing between treatment groups on these outcomes. Of specific adverse events leading to withdrawal, states, only disorders of skin/subcutaneous and eye were determined to be drug related States that nonocular AEs (blood chemistries, etc.) were not significantly different among the treatment groups.				
Subgroups				
Comments: reports correlation between lesion growth rate and retinal binding protein levels, not extracted. Reports CNV incidence in patients with fellow eye CNV history, not extracted.				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement

Random sequence generation (selection bias)	Unclear	States randomly assigned with a 1:1:1 ratio, but no further details
Allocation concealment (selection bias)	Unclear	No discussion of concealment of allocation
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	States was double-masked, no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Low	Says baseline FAF images were evaluated by masked readers at baseline and that retinal images were evaluated by masked readers
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	States efficacy analysis was on intention-to-treat basis defined as all randomised who received at least one dose and had at least 2 follow-up visits. The primary outcome was evaluated only for those completing at least 18 months treatment. There was differential drop out between groups (reasons were provided).
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	High	Outcomes stated in report and clinical trial record were reported, but primary outcome (lesion growth) not reported for all patients
Other biases	Low	No other apparent biases

Glatiramer acetate

Landa et al

Study details	**Participant details**
Landa G, Rosen RB, Patel A, Lima VC, Tai KW, Perez VR, et al. Qualitative spectral OCT/SLO analysis of drusen change in dry age-related macular degeneration patients treated with Copaxone. Journal of Ocular Pharmacology & Therapeutics 2011;27:77-82. Related publication of an earlier pilot study, Landa G, Butovsky O, Shoshani J, Schwartz M, Pollack A. Weekly vaccination with Copaxone (glatiramer acetate) as a potential therapy for dry age-related macular degeneration. Current Eye Research 2008;33:1011-3.reported here as few relevant outcomes and unclear if overlapping participants as states is ongoing. *Country:* USA *Design:* CCT (pilot described as an RCT) *Number of centres:* one *Funding:* not reported	*Number of Participants*: main analysis total 14; glatiramer acetate 7; placebo 7. Pilot study total 6; glatiramer acetate 4; placebo 2. *Number of eyes* main analysis total 26; glatiramer acetate 14; placebo 12. Pilot study total 12; glatiramer acetate 8; placebo 4. *Sample attrition/dropout*: not reported *Sample crossovers:* assume none *Inclusion criteria:* Dry AMD For the pilot study this was those aged over 50 years with bilateral intermediate dry AMD *Exclusion criteria:* not reported in main publication. In the pilot study states excluded those with evidence of past or present exudative AMD in any eye.

Trial ID: not reported	
Intervention details	**Outcomes**
Intervention *1.* glatiramer acetate *2.* placebo (sham injections) *Dose details:* weekly subcutaneous injections (pilot study states 20mg) *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 12 weeks	*Outcomes (state if primary)* Drusen changes (primary outcome) Pilot study: total drusen area (primary outcome) *Length of follow-up:* 12 weeks

Participant characteristics, %			
	glatiramer acetate, n=7	**Placebo, n=7**	**P value**
Age, years mean (SD)			
Number of drusen *Number with convex shape* *Number with concave shape*	172 108 64	139 103 36	
Results			
	glatiramer acetate, n=7	**Placebo, n=7**	**P Value**
% drusen disappeared or shrank at 12 weeks	19.2	6.5	0.13
% convex drusen disappeared or shrank at 12 weeks	27.8	6.8	0.008
% concave drusen disappeared or shrank at 12 weeks	4.7	5.6	0.89
Comments: also reports change in drusen by internal reflectivity (low, medium, high); homogeneous and nonhomogeneous and presence of core; and by overlying foci on hyperreflectivity (present or absent) – not data extracted.			
Pilot study	**glatiramer acetate, n=4**	**Placebo, n=2**	
Change in drusen area, arbitrary units	Baseline: 48130 12 weeks: 16205	Baseline: 32294 12 weeks: 32781	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	No discussion in the main publication, the pilot study states was randomised
Allocation concealment (selection bias)	Unclear	No discussion of concealment of allocation
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Pilot study states ‘double blind’
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not described; pilot described as double bind but no details reported
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	No details of any drop outs or the analysis set provided
Incomplete outcome data (attrition	N/A	

bias), Subjective outcomes		
Selective reporting (reporting bias)	High	Text states other tests were undertaken but no results were reported
Other biases	Low	No other biases

L-Dopa

Brilliant et al

Study details	**Participant details**
Brilliant MH, Vaziri K, Connor TB, Jr., Schwartz SG, Carroll JJ, McCarty CA, et al. Mining Retrospective Data for Virtual Prospective Drug Repurposing: L-DOPA and Age-related Macular Degeneration. American Journal of Medicine 2016;129:292-8. *Country:* USA *Design:* Retrospective cohort study *Number of centres:* not applicable *Funding:* non-commercial grants *Trial ID:* not reported	*Number of Participants*: data from 3 registries. Marshfield Epidemiologic Study Area (approximately 17,500); Marshfield Clinic Personalized Medicine Research Project (PMRP, approximately 20,000); Truven MarketScan databases (15,215,458) *Number of eyes* not reported *Sample attrition/dropout*: not applicable *Sample crossovers:* not applicable *Inclusion criteria:* data on those with long-term nearly complete electronic health records in the Marshfield Epidemiologic Study Area and those with an ophthalmology record from the Truven MarketScan databases. *Exclusion criteria:* not stated

Intervention details	**Outcomes**
Intervention *1.* exposure to L-DOPA *2.* no exposure to L-DOPA *Dose details:* data on exposure captured by L-DOPA prescriptions *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* not reported	*Outcomes (state if primary)* incidence of AMD (any) Incidence of neovascular AMD (not extracted) incidence of AMD + Parkinson's disease (not extracted) *Length of follow-up:* not reported

Participant characteristics, %				
	Marshfield Clinic, n=20,000	**Marshfield Epidemiology study, n=17500**	**TruvenMarket Scan, n=15,215,458**	**P value**
Age, years mean (SD)	L-DOPA treatment 67.1 AMD diagnosis without L-DOPA 71.2 AMD with L-DOPA 79.3	L-DOPA treatment 67.2 AMD diagnosis without L-DOPA 71.3	L-DOPA treatment 68 AMD diagnosis without L-DOPA 71.4 AMD with L-DOPA 79.3	
Comments: ages presented may not be baselines. States in patients taking L-DOPA who did develop AMD, the age of onset was significantly delayed ($p<0.01$).				
Results				

	Marshfield cohorts, n=37,500	TruvenMarket Scan, n=15,215,458	P Value
PMRP, n=20,000: *AMD present* *AMD present and prescribed L-DOPA*	 1142/20,000 (5.7%) 39/20,000 (0.2%)		
Marshfield Epidemiologic Study Area, n=17,500 *AMD present and prescribed L-DOPA*	 20/17,500 (0.1%)		
Comments: state that after stratification for age, AMD and L-DOPA prescription occur more frequently together than expected. The expectation was to see L-DOPA prescription prior to a diagnosis of AMD, and authors state that as L-DOPA is most often taken after a diagnosis this is suggestive of a protective effect of L-DOPA on AMD. AMD occurred significantly later in patients with an L-DOPA prescription (79.3 years versus 71.2-71.3 years). States 79.4 years in the abstract. Truven MarketScan cohort: controlling for age and gender, patients with a prescription history of L-DOPA were significantly less likely to have a diagnosis of AMD (OR 0.78; CI, 0.76-0.80; P <0.001).			

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?	x		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?			N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			N/A
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?			N/A
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?			N/A
13. Was loss to follow-up after baseline 20% or less?			N/A
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Good

*CD, cannot determine; NA, not applicable; NR, not reported

NT-501

Zhang et al

Study details	Participant details
Zhang K, Hopkins JJ, Heier JS, Birch DG, Halperin LS, Albini TA, et al. Ciliary neurotrophic factor delivered by encapsulated cell	*Number of Participants*: Total n=51; *1.* High dose intraocular NT-501 n=27 *2.* Low dose intraocular NT-501 n=12

intraocular implants for treatment of geographic atrophy in age-related macular degeneration. Proc Natl Acad Sci USA 2011;108:6241-5. *Country:* USA *Design:* RCT (pilot) *Number of centres:* 8 *Funding:* some funding from Neurotech USA (manufacturer) Trial ID: NCT00277134 (duplicate of record NCT00447954)	3. Sham n=12 *Number of eyes:* 51 (one eye per participant) *Sample attrition/dropout*: 0 *Sample crossovers*: not stated *Inclusion criteria:* age ≥ 50 years, BCVA of 20/50–20/200 (Snellen equivalent, EDTRS) and presence of category 3 or 4:00 AMD geographic atrophy (defined by AREDS). *Exclusion criteria:* None stated.

Intervention details	**Outcomes**
Intervention *1.* High dose intraocular NT-501 *2.* Low dose intraocular NT-501 (intended as placebo) 3. Sham *Dose details:* High dose: 20 ng per day Low dose: 5 ng per day *Dose modifications:* None *Concurrent treatment:* not reported *Duration of treatment:* 12 months	*Outcomes (state if primary)* Change in BCVA at 12 months after implant (primary outcome) Retinal thickness and morphology GA lesion size Central vision visual field sensitivity *Length of follow-up:* 12 months

Participant characteristics				
	High dose NT-501, n=27	**Low dose NT-501, n=12**	**Sham 2, n=12**	**P Value**
Age, years, mean (SD)	74.9 (7.5)	78.3 (5.6)	74.5 (6.0)	
Sex, % male	37.0	58.3	58.3	
Ethnic origin, % *White*	100	100	100	
Smoking history				
visual acuity *BCVA, mean SD*	53.5 (9.0)	49.9 (10.2)	55.3 (7.3)	
lesion size *Area of GA lesion, mm^2, mean (SD)*	7.23 (5.29)	11.41 (7.56)	9.84 (8.41)	Overall = 0.506; High vs. Sham = 0.3078; Low vs. Sham = 0.3202; High vs. Low = 0.8320
Total macular volume, mean (SD)	6.01 (0.56)	5.79 (0.47)	6.29 (0.51)	Overall = 0.175; High vs. Sham = 0.298; Low vs. Sham = 0.064; High vs. Low = 0.268
Visual field sensitivity, dB	1407.8 (487.5)	1217.2 (390.3)	1504.9 (336.7)	
Results				
	High dose NT-501, n=27	**Low dose NT-501 / Sham 2, n=24**		**P Value**

Change in BCVA, grouped according to baseline:				
20/200 or better	−0.2 ± 8.4 (n = 27)	−1.0 ± 13.5 (n = 24)		0.8087
20/100 or better	0.1 ± 6.7 (n = 19)	−4.4 ± 12.9 (n = 15)		0.1966
20/80 or better	1.5 ± 5.6 (n = 12)	−6.0 ± 14.0 (n = 12)		0.0998
20/63 or better	0.8 ± 5.4 (n = 10)	−9.7 ± 13.0 (n = 9)		0.0313
Visual acuity stabilization, % losing < 3 lines (15 letters) of visual acuity	96.3	83 (estimated from graph)	75	0.078 high vs sham
Subgroup with baseline BCVA 20/63 or better, %	100 (n=10)	55.6 (n=9)		0.033
Change in total macular volume, mm3, mean (SD)	0.48 ± 0.22	0.22 ± 0.24	−0.07 ± 0.15	<0.001
Comments				
Change in cystoid macular oedema at month 12[a] *% Yes*	n=25 40	n=9 33.3	n=11 63.6	Not reported
Comments [a] Only eyes without CME at baseline were included in this analysis				
Change in area of geographic atrophy, mm2, mean (SD)	2.03 ± 1.04	2.19 ± 1.87	2.42 ± 1.95	0.788
Comments				
Change in Humphrey visual field sensitivity, dB, mean (SD)	59.1 ± 373.1	−136.0 ± 279.3	75.0 ± 135.9	0.893
Adverse events				
IOP increase	2 (7.4%)	2 (16.7%)	3 (25%)	
Eye hemorrhage	2 (7.4%)	1 (8.3%)	1 (8.3%)	
Photopsia	2 (7.4%)	1 (8.3%)	0 (0.0%)	
Miosis	1 (3.7%)	1 (8.3%)	0 (0.0%)	
Cataract	1 (3.7%)	0 (0.0%)	0 (0.0%)	
CNV	0 (0.0%)	0 (0.0%)	1 (8.3%)	
Wound leaks or erosion	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Endophthalmitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Implant extrusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Retinal detachment	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	No details
Allocation concealment (selection bias)	Unclear	No details
Blinding participants and personnel (performance bias), Objective outcomes	Low	'The physician who performed the implant surgery was not masked for the implant or sham but was masked to the dose of implant. Other personnel at each study site (except for those assisting with implant), patients … were masked to the patient treatment assignment'
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Low	'The acuity testers were masked to the treatment assignment.' 'Personnel at the reading centers were masked to the patient treatment assignment.'
Blinding outcome assessors	N/A	

(detection bias), Subjective outcomes		
Incomplete outcome data (attrition bias), Objective outcomes	Low	'No patients dropped out of the study'
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	High	Clinical trials record checked. Outcomes assessed at 18 months but not reported. QoL not reported
Other biases	Low	No other source of bias

OT-551

Wong et al

Study details	**Participant details**
Wong WT, Kam W, Cunningham D, Harrington M, Hammel K, Meyerle CB, et al. Treatment of geographic atrophy by the topical administration of OT-551: results of a phase II clinical trial. Investigative Ophthalmology & Visual Science 2010;51:6131-9. *Country:* USA *Design:* RCT (phase II, pilot) *Number of centres:* one *Funding:* non-commercial funding *Trial ID:* NCT00306488	*Number of Participants*: total 11 *Number of eyes* total 22; 11 OT-551; 11 no treatment (one eye from each participant randomly assigned to each arm) *Sample attrition/dropout*: 1 lost to follow-up at 3 months *Sample crossovers:* none *Inclusion criteria:* bilateral GA, ≥ 60 years, area of GA in each eye that was not contiguous with areas of peripapillary atrophy and absence of evidence or history or exudative forms of AMD, adequate media clarity, good subjective tolerance and displayed no signs of an allergic response. *Exclusion criteria:* either eye with: history of other ocular disease, chronic ocular medication use for diseases that may affect study outcome, pseudovitelliform macular degeneration, vitreoretinal traction maculopathy, previous laser, photodynamic therapy, intravitral injections, other AMD treatments, ocular herpes simplex virus, cataract removal in previous 3 months.

Intervention details	**Outcomes**
Intervention *1.* OT-551 (a lipophilic, disubstituted hydroxylamine) *2.* No treatment (observation) *Dose details:* 0.45%, eye drop with 40 µL, three times daily. *Dose modifications:* not reported *Concurrent treatment:* asked to refrain from using any medication into the no treatment eye. *Duration of treatment:* 2 years	*Outcomes (state if primary)* BCVA (ETDRS) (primary outcome) Changes in GA area Progression to neovascular AMD Drusen area Contrast sensitivity Microperimetry measurements (not extracted) Safety *Length of follow-up:* 104 weeks (2 years + one month stated elsewhere)

Participant characteristics, %			
	All participants, n=10		**P value**
Age, years mean (SD)	76.8 (8.27)		
Sex, % male	40		

Ethnic origin *% White*	100		
	OT-551, n=10 (eyes)	**No treatment, n=10 (eyes)**	
BCVA, letters, mean (SD)	46.1 (20.8)	57.1 (12.0)	p>0.05
CS, mean (SD)	0.9 (0.339)	1.04 (0.18)	p>0.05
Area of GA, mm^2, mean (SD) by fundus photography	6.87 (3.35)	6.80 (3.28)	p>0.05
Area of GA, mm^2, mean (SD) by autofluorescence imaging	7.15 (3.16)	7.01 (3.47)	p>0.05
Mean (SD) total drusen area, mm^2	0.454 (0.476)	0.415 (0.445)	p>0.05
Results			
	OT-551, n=10 (eyes)	**No treatment, n=10 (eyes)**	**P Value**
BCVA letters change at 104 weeks, mean (SD)	0.2 (13.3)	-11.3 (7.6)	0.0259
At 52 weeks the Ot-551 eyes had an approximate gain of 4, otherwise pattern was similar for the OT-551 treated group. The no-treatment eyes deteriorated at each assessment			
Loss of BCVA, 104 weeks, % *≥ 5 letters* *≥ 10 letters* *≥ 15 letters*	 30 30 10	 90 60 30	
Comments: ≥ 5 letters and ≥ 10 letters, proportions taken from a figure			
Progression to neovascular AMD, %	0	0	
Comments			
CS, change at 104 weeks, mean (SD)	-0.075 (0.33)	-0.15 (0.27)	0.6059
Comments			
Increase in GA area at 104 weeks, mm^2, fundus photos mean (SD)	2.46 (1.25)	2.47 (0.73)	0.9502
% increase in GA area, fundus photos[a]	58	41	0.4306
Increase in GA area at 104 weeks, mm2, autofluorescence image	2.17 (0.83)	2.24 (0.91)	0.7712
% increase in GA area, autofluorescence image[a]	42	38	0.7742
Comments: states there was excellent agreement between the areas of GA, as quantified by the two imaging modalities. [a]estimated from a figure			
Total drusen area at 104 weeks, by fundus photos[b]	0.32	0.39	0.5391
Change in total drusen area, mm^2[b] *fundus photos*	-0.15	-0.05	0.0948
% change in drusen area[b] *fundus photos*	-43	-12	0.1373
[b]estimated from figure			
Adverse events (11 participants) Mild/Grade 1[a] Moderate/Grade 2[a]	N events 32 4		
Serious adverse events	0	0	

Ocular events, total	9 (events)	6 (events)	
Small sub/intra-retinal bleed	4	1	
Raised intraocular pressure	0	2	
Blurry vision	1	1	
Increase in cataract	1	0	
Decreased visual acuity	1	1	
Sore eye	1	0	
Dry skin on eyelid	1	1	
Comments: states the study drug was withheld for a period in 4 participants (for hip injury, blurry vision and thrush, sore eye and decreased visual acuity, shingles). [a] Categories reported, not extracted. States that all 10 remaining participants reported compliance with the application of the treatment			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States random, no further details
Allocation concealment (selection bias)	Unclear	No description
Blinding participants and personnel (performance bias), Objective outcomes	High	Open label study
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Change in GA area and drusen were assessed by masked investigators.
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	low	One participant (one eye from each group) dropped out and was only included in the safety analysis.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes stated in trial report were presented
Other biases	Low	No other apparent bias.

Prednisolone

Vojniković et al

Study details	**Participant details**
Vojnikovic B, Kovacevic D, Njiric S, Coklo M. Long term results of age-related macular degeneration therapy with prednisolone acetate--special refer to peripheral visual field changes. Collegium Antropologicum 2008;32:351-3 *Country:* Croatia *Design:* Prospective cohort study *Number of centres:* Not reported	*Number of Participants*: Total 475 (prednisolone 400, control 75) *Number of eyes* Not reported *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* Dry AMD, no further details *Exclusion criteria:* Not reported

Funding: Not reported *Trial ID:* Not reported	

Intervention details	**Outcomes**
Intervention *1.* Prednisolone acetate *2.* Control *Dose details:* *1.* Prednisolone acetate 5 mg in parabulbar injections, 5 daily doses 2. multivitamin therapy (Lutein, Beta carotene, Vitamin E) in ordinary doses *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 5 days for intervention, assume 6 months for control	*Outcomes (state if primary)* Visual acuity, visual field, intraocular pressure, biomicroscopic and fundus examination *Length of follow-up:* 6 months

Participant characteristics, %			
	All patients, n=475		
Age, years range	39-80		
Results			
	Prednisolone, n=400	**Control, n=75**	**P Value**
Peripheral visual field	Improvement of 10 to 25%	No significant improvement	
Comments			
Central visual field	Improvement of 5 to 20%	Improvement of 0.5 to 1% in 43 patients	
Comments			

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?		x	
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			CD
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		x	
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		x	
12. Were the outcome assessors blinded to the exposure status of participants?		x	

13. Was loss to follow-up after baseline 20% or less?			CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating: Poor
Selection of patients, selective reporting of outcomes, limited data reported, outcome assessment, blinding, attrition, confounding

*CD, cannot determine; NA, not applicable; NR, not reported

Ranibizumab

Gallego-Pinazo et al

Study details	**Participant details**
Gallego-Pinazo R, Marina A, Suelves C, Frances-Munoz E, Millan JM, Arevalo JF, et al. Intravitreal ranibizumab for symptomatic drusenoid pigment epithelial detachment without choroidal neovascularization in age-related macular degeneration. Clin Ophthalmol 2011;5:161-5 *Country:* Spain *Design:* Before and after study *Number of centres:*1 *Funding:* NR *Trial ID:* NR	*Number of Participants*: 6 patients *Number of eyes*: 6 eyes (1 per patient) *Sample attrition/dropout*: none *Sample crossovers:* NA *Inclusion criteria:* ≥50 years of age, study eye had Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) lower than 20/30; drusenoid pigment epithelial detachment from age-related macular degeneration (defined clinically and tomographically. Clinically as a focal area of at least 1/2 disc diameter of confluent soft drusen under the centre of the macula with faint hypofluoresecence which increased progressively but stabilized in later phases, with no leakage, tomographically defined as a focal elevation of the retinal pigment epithelium contour associated with fluid beneath the elevation but without coexistent shadowing; and presence of metamorphosia). *Exclusion criteria:* angiographic evidence of choroidal neovascularization; prior treatment with photodynamic therapy, intravitreal corticosteroids, or vascular endothelial growth factor inhibitors (at any time); peribulbar steroid injection (within the previous six months) or pars plana vitrectomy (at any time); history of uncontrolled glaucoma; retinal vascular disorder potentially related to macular oedema; and intraocular pressure of 25 mmHg or more.

Intervention details	**Outcomes**
Intervention *1.* intravitreal ranibizumab *Dose details:* a single intravitreal injection of 0.5 mg/0.05 mL of ranibizumab (Lucentis®, Genentech, South San Francisco, CA). *Dose modifications: None* *Concurrent treatment:* topical gentamycin ointment following injection *Duration of treatment:* Patients were treated at baseline and	*Outcomes (state if primary)* ETDRS BCVA Central macular thickness Measurement of intraocular pressure (not reported) Symptoms, including metamorphopsia Presence of choroidal neovascularization (not reported) Number of treatments/re-treatments *Length of follow-up:*12 months (mean 66.7, SD 10.3, weeks)

followed up monthly. Retreatment based on persistence or recurrence of focal elevation of the retinal pigment epithelium contour on optical coherence tomography, persistence or recurrence of intraretinal fluid on optical coherence tomography, or loss of ≥ five ETDRS letters compared with the prior examination. Mean number of re-treatments was 2.	

ETDRS: Early Treatment Diabetic Retinopathy Study; NA: not applicable; NR: not reported

Participant characteristics, %			
	Intervention 1, n=6	**Intervention 2, n=**	**P value**
Age, years mean (SD)	69 (2.9)		
Sex, % male	33.3		
Ethnic origin *% White*	NR		
Classification, drusenoid pigment epithelial detachment, %	100		
visual acuity (decimal ETDRS equivalent)	0.40 (0.15)		
Central macular thickness (µm), mean (SD)	287.83 (23.25)		
Results			
	Intervention 1, n=6	**Intervention 2, n=**	**P Value**
BCVA, mean (decimal ETDRS equivalent)	0.58 (0.3)		0.046[1]
Comments: 33.3% of patients gained between 19 to 21 letters of BCVA at the end of follow-up. No patient experienced loss of BCVA during the study period. [1]There was a statistically significant difference between baseline and final BCVA after intravitreal ranibizumab.			
Central macular thickness (µm), mean (SD)	273.50 (12.74)		NR
Comments: The median decrease in central macular thickness from baseline at the end of follow-up was 21 µm (*P* = 0.18). Only one (16.6%) eye showed a minimal increase in central macular thickness of 2 µm; the other five (83.3%) patients showed a mean decrease in central macular thickness of 17.6 ± 13.2 µm. All these changes were not statistically significant.			
Cases of metamorphosia	0		
Comments: All cases of metamorphosia disappeared.			
Treatments, Median (range)	3 (1 to 5)		
Adverse events	NR		
Comments			

Before-After (Pre-Post) Studies With No Control Group

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	x		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?	x		
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and	x		

assessed consistently across all study participants?			
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	x		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Sirolimus

Petrou et al

Study details	**Participant details**
Petrou PA, Cunningham D, Shimel K, Harrington M, Hammel K, Cukras CA, et al. Intravitreal sirolimus for the treatment of geographic atrophy: results of a phase I/II clinical trial. Investigative Ophthalmology & Visual Science 2015;56:330-8. *Country:* USA *Design:* RCT *Number of centres:* one *Funding:* non-commercial grants (and investigational product donated by commercial company) *Trial ID:* NCT01445548	*Number of Participants*: total 6 *Number of eyes* 12: one eye chosen randomly for the intervention group (n=6) and no treatment group (n=6) *Sample attrition/dropout*: one participant dropped out (adverse events); one participant had treatment discontinued (adverse events) *Sample crossovers:* none *Inclusion criteria:* ≥56 years; bilateral GA; GA in each eye of area ≥ one-half disc area (approximately 1 mm^2); ≥1 large drusen (≥125 µm) in each eye; BCVA 20/20 - 20/400 in each eye; absence of evidence or history of exudative AMD *Exclusion criteria:* history of other ocular disease, intravitral injection within 4 months or expectation of ocular surgery, lens removal or laser capsulotomy in previous 1 month, chronic ocular medication use for diseases that may affect study outcome, previous laser, photodynamic therapy, ocular herpes simplex virus, vitrectomy, history of cancer or receiving chemotherapy, other medical conditions that would preclude participation, ocular or systemic medications toxic to the eye, taking named medication (reported but not extracted)

Intervention details	**Outcomes**
Intervention *1.* Sirolimus *2.* No treatment (observation) *Dose details:* 22 µg/lL (2%) solution in PEG 400 and 4% ethanol, 0.3ml injected as a 440 µg intravitreous injection in a 20 µL volume following anaesthetic. Given every 2 months. *Dose modifications:* not reported *Concurrent treatment:* not reported	*Outcomes (state if primary)* Adverse events (primary outcome) Changes in GA area on colour fundus photography (primary outcome) BCVA (ETDRS) Change in drusen area (not stated in publication but stated in trial record) Changes in GA area on autofluorescence on fundus photography and on confocal scanning ophthalmoscope (not data extracted) Microperimetry measures (not data extracted) Central retinal subfield thickness and macular

Duration of treatment: 12 months (aim was for 24 months).	volume (not data extracted) *Length of follow-up:* 1 year

Participant characteristics, %			
	Participants, n=6		**P value**
Age, years mean (SD)	74.33 (8.45)		
Sex, % male	66.7		
Ethnic origin *% White*	83.3		
	Sirolimus, n=6 (eyes)	**No treatment, n=6 (eyes)**	
BCVA, mean (SD)	52.7 (14.5)	39.2 (20.0)	p>0.05
Total GA area, mm^2, mean (SD) by fundus photography	13.95 (3.74)	13.45 (3.92)	p>0.05
Results			
	Sirolimus, n=5 (eyes)	**No treatment, n=5 (eyes)**	**P Value**
Rate of change in area of GA mm2 / month at 12 months, mean (SD)	0.19 (0.08)[a]	0.13 (0.06)[a]	NR
Change in GA area, mm^2, mean (SD), by fundus photography at 12 months[b]	2.26 (0.94)[a]	1.53 (0.75)[a]	0.15
Change in BCVA at 12 months, mean (SD)	-15.6 (7.23)[a]	0 (13.47)[a]	0.013
Change in drusen area, mm^2, mean (SD), by fundus photography at 12 months	N=3 0.02 (0.19) [a]	N=3 0.29 (0.78) [a]	NR
Proportion of eyes with ≥10 letters vision loss at 12 months	80[c]	20[c]	NR
Proportion of eyes with ≥15 letters vision loss at 12 months	60[c]	20[c]	NR
[a]from trial record. [b]trial record also reports relative change in area, not extracted [c]estimated from figure			
Development of neovascular changes	0	0	
Comments			
	All participants (n=6)		
Total adverse events, n of events	49		
Severe / Grade 3 adverse events, no of events	3		
Mild or Moderate / Grade 1 or 2 adverse events, n of events	46		
Serious adverse events	3		
Comments: adverse event by category provided but not extracted. States that all systemic adverse events (n=45) were judged as unrelated to the investigational product.			
Ocular adverse events, n of events	4		
Comments: 2 were judged as possibly related to the investigational product and two related to the injection procedure (details of specific events were reported but not extracted)			
Subgroups			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Says eyes were randomised, no further details
Allocation concealment (selection	Unclear	No details

bias)		
Blinding participants and personnel (performance bias), Objective outcomes	High	Is open label trial
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Change in GA area (primary outcome) was assessed by masked investigators. Unclear for other outcomes
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	low	1 participant withdrew and was not included in the analysis, 1 other discontinued but was included in the analysis, but an eye was withdrawn from each group for each of these participant
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Intraocular pressure is noted as being measured but it isn't stated as an outcome and all other stated outcomes are reported
Other biases	Unclear	Study stopped early.

Wong et al

Study details	**Participant details**
Wong WT, Dresner S, Forooghian F, Glaser T, Doss L, Zhou M, et al. Treatment of geographic atrophy with subconjunctival sirolimus: results of a phase I/II clinical trial. Investigative Ophthalmology & Visual Science 2013;54:2941-50 *Country:* USA *Design:* RCT *Number of centres:* one *Funding:* non-commercial (and study drug donated by commercial entity) *Trial ID:* NCT00766649	*Number of Participants*: total 11 *Number of eyes* one eye chosen randomly for the intervention group (n=11) and no treatment group (n=11) *Sample attrition/dropout*: 3 did not complete 24 months follow-up (2 withdrew for relocation and inability to travel; 1 died); all unrelated to study drug. *Sample crossovers:* none *Inclusion criteria:* ≥55 years, bilateral GA, GA in each eye of area ≥ one-half disc area (approximately 1 mm2); ≥1 large drusen (≥125 μm) in each eye; BCVA 20/20 - 20/400 in each eye; absence of evidence or history of exudative AMD *Exclusion criteria:* history of other ocular disease, topical treatment for advanced AMD within 1 one month, intravitral injection within 4 months or expectation of ocular surgery, lens removal in last 3 months or laser capsulotomy in previous 1 month, chronic ocular medication use for diseases that may affect study outcome, previous laser, photodynamic therapy, ocular herpes simplex virus, vitrectomy, history of cancer or receiving chemotherapy, other medical conditions that would preclude participation, ocular or systemic medications toxic to the eye, taking named medication (reported but not extracted)

Intervention details	**Outcomes**
Intervention *1.* Sirolimus *2.* No treatment	*Outcomes (state if primary)* Area of GA change by colour fundus photography (primary outcome) BCVA Retinal subfield thickness (not extracted)

Dose details: 2% solution in PEG 400 and 4% ethanol, injected into the subconjunctival space (20 µL volume with 440 µg sirolimus), administered at baseline and every 3 months. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 24 months	Area of drusen Retinal sensitivity (not extracted) Area of GA change by modified fundus camera and by confocal scanning ophthalmoscope (not extracted) *Length of follow-up:* 24 months for efficacy, 27 months for safety

Participant characteristics, %			
	All participants, n=8		**P value**
Age, years mean (SD)	77.88 (8.15)[a]		
Sex, % male	62.5[a]		
Ethnic origin *% White*	100		
	Sirolimus, n=8 (eyes)	**No treatment, n=8 (eyes)**	**P Value**
BCVA, mean (SD) letters	62.4 (12.7)	55.1 (20.6)	
Total area of GA, mm^2, mean (SD) by fundus photography	6.96 (4.15)	7.29 (4.98)	
Total area of drusen, mm^2, mean (SD)	0.643 (0.607)	0.661 (0.928)	
Comments [a]trial record reports 78.4 (7.1) years, and 45% male for all 11 participants.			
Results			
	Sirolimus, n=8 (eyes)	**No treatment, n=8 (eyes)**	**P Value**
Rate of change in area of GA mm^2 / month at 24 months, mean (SD)[b]	0.102 (0.049)	0.087 (0.034)	NR
Change in GA area, mm2, mean (SD), by fundus photography at 24 months[b]	2.46 (1.18)	2.08 (0.83)	0.17
Percentage increase in GA area at 24 months[c]	55	39	0.41
Change in drusen area, mm^2, mean (SD), by fundus photography at 24 months[b]	0.04 (0.58)	0.08 (0.36)	0.81
Comments [b]values from trial record, p-values from the publication [c]estimated from figure, p-value from publication			
Change in BCVA letters at 24 months, mean (SD)	-21.0 (21.5)	-3.0 (8.1)	0.03 (95% CI 0.9, 25)
Proportion of eyes with ≥5 letters vision loss at 24 months[d]	88	52	
Proportion of eyes with ≥10 letters vision loss at 24 months[d]	50	12.5	
Number of eyes with a 15 letter loss in visual acuity	4		
Development of exudative neovascular AMD	0	0	
[d]estimated from figures			
Adverse events	**Sirolimus, n=11 (participants)**		
Mild/grade 1, n of events	61[e]		
Life-threatening / grade 4, n of events	1[f]		
[e]5 were possibly related to study medication [f]death (unrelated to study medication)			

	Sirolimus, n=11 (eyes)	No treatment, n=11 (eyes)	P Value
Ocular adverse events (all mild/grade 1)	7	2	
Comments: provides reasons, not extracted.			
Compliance: all participants received scheduled study injections at all the specified time points.			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Used a computer generated algorithm
Allocation concealment (selection bias)	Unclear	Not described
Blinding participants and personnel (performance bias), Objective outcomes	High	Is an open label trial
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Total area of GA (primary outcome) was assessed by masked readers offsite. Unclear for other outcomes
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	low	Analysis of efficacy was from those completing the study, analysis of adverse events was the intention to treat population, but eyes from each participant were withdrawn from each group for reasons unrelated to study drug
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes reported as stated
Other biases	Low	No other apparent biases.

Statins

Maguire et al

Study details	Participant details
Maguire MG, Ying GS, McCannel CA, Liu C, Dai Y, Complications of Age-related Macular Degeneration Prevention Trial Research G. Statin use and the incidence of advanced age-related macular degeneration in the Complications of Age-related Macular Degeneration Prevention Trial. Ophthalmology 2009;116:2381-5. *Country:* USA *Design:* Cross-sectional study (embedded within an RCT) *Number of centres:* 22 *Funding:* non-commercial grants	*Number of Participants*: 744 (of 764 in the trial). 296 had used statins, 187 started during commencement of the trial, 29 stopped using statins. *Number of eyes* 1477 *Sample attrition/dropout*: Not applicable *Sample crossovers:* Not applicable *Inclusion criteria:* for original trial: ≥10 drusen ≥125 μm in diameter, visual acuity ≥20/40; no evidence of CNV, serous pigment epithelial detachment, GA within 500 μm of the foveal centre or >1 macular photocoagulation study disc area in size, or other ocular conditions likely to compromise visual acuity or contraindicate application of laser treatment; ≥50 years old; free of conditions that would likely preclude 5 years of follow-up. For this study, participants at the end of the trial were interviewed

Trial ID: none	*Exclusion criteria:* no further criteria stated

Intervention details	**Outcomes**
Intervention *1.* Statins *Dose details:* no details *Dose modifications:* no details *Concurrent treatment:* no details but the focus of the trial was on laser treatment. *Duration of treatment:* starting year and ending year of statin use were recorded but not details provided	*Outcomes (state if primary)* Presence of endpoint geographic atropy (total of >1 Macular Photocoagulation Study disc area of atrophy when all areas of GA were combined). Presence of CNV (expansion or persistence of hyperfluorescence in the late phase of the fluorescein angiogram) Presence of advanced AMD (CNV, end point GA, or serous detachment of the RPE) *Length of follow-up:* between 5-6 years

CNV: choroidal neovascularization; GA: Geographic atrophy; RPE: retinal pigment epithelium

Participant characteristics, %			
	All patients, n=744		**P value**
Age, years mean (SD)	70 (7.4)		
Sex, % male	36.6		
Ethnic origin *% White*	99.5		
Percent of global area covered by drusen (>63 µ), % eyes (n=1477) *<10* *10-24* *≥25* *Cannot grade/determine/missing*	 64.9 27.9 6.0 1.4		
Focal hyperpigmentation, % eyes (n=1477) *None/questionable* *<250 µ* *≥ 250 µ* *Cannot grade/determine/missing*	 29.1 55.4 14 1.6		
Depigmentation of the retinal pigment epithelium, % eyes (n=1477) *None* *Any* *Cannot grade/determine/missing*	 93.9 4.9 1.2		
Smoking history, % *Never* *Quit* *Current*	 46.1 48.7 5.2		
visual acuity	Not reported		
lesion size	Not applicable		
previous treatments	Not reported		
Hypertension, % *Normal* *Suspect* *Definite* *Unknown*	 35.5 18.3 45.7 0.5		
Results			

	All patients, n=744 All eyes, n=1477	Adjusted risk ratios (95% CI) associated with statin use[a]	P Value
Endpoint GA, n/N(%) *Eyes* *patients*	 114/1468[b] (7.7) 80/743[b] (10.8)	 0.80 (0.46–1.39) 0.75 (0.43–1.30)	
Endpoint GA subgroup[c] n/N(%) *Eyes* *patients*	 85/1089 (7.8) 61/552 (11.1)	 0.66 (0.26–1.65) 0.69 (0.29–1.66)	
[b]Ns are stated in text as 1477 and 744. States that analyses are adjusted for age, percent of retinal area covered by drusen, level of focal hyperpigmentation, and RPE depigmentation. Also reports unadjusted risk ratios (not data extracted)			
CNV n/N(%) *Eyes* *Patients*	 222/1477 (15) 176/744 (23.7)	 1.35 (0.99–1.83) 1.32 (0.95–1.84)	
CNV subgroup, n/N(%)[c] *Eyes* *Patients*	 151/1097 (13.8) 122/553 (22.1)	 1.30 (0.82–2.04) 1.30 (0.82–2.06)	
Analyses adjusted for age, cigarette smoking status, hypertension, and level of focal hyperpigmentation. Also reports unadjusted risk ratios (not data extracted)			
Advanced AMD, n/N(%) *Eyes* *Patients*	 332/1477 (22.5) 242/744 (32.5)	 1.15 (0.87–1.52) 1.19 (0.89–1.60)	
Advanced AMD subgroup, n/N(%)[c] *Eyes* *Patients*	 231/1097 (21.1) 170/553 (30.7)	 1.06 (0.69–1.63) 1.14 (0.75–1.74)	
Analyses adjusted for risk factors for either CNV or GA. Also reports unadjusted risk ratios (not data extracted)			
[a]patient-specific analyses were the time to an event in the first affected eye, baseline ocular characteristics of the worse eye were used. Eye-specific analyses used a robust variance estimator to accommodate the correlation between 2 eyes of the same patient. [c]Patients who had no change in statin use from enrollment to the last visit (Had never used statins or used statins continuously; excluding those starting or stopping statins after enrolment into the study).			

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	X		
2. Was the study population clearly specified and defined?	X		
3. Was the participation rate of eligible persons at least 50%?	X		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	X		
5. Was a sample size justification, power description, or variance and effect estimates provided?		X	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?		X	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	X		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		X	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
10. Was the exposure(s) assessed more than once over time?		X	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	X		
12. Were the outcome assessors blinded to the exposure status of participants?		X	
13. Was loss to follow-up after baseline 20% or less?	X		
14. Were key potential confounding variables measured and adjusted statistically	X		

for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Al-Holou

Study details	**Participant details**
Al-Holou SN, Tucker WR, Agron E, Clemons TE, Cukras C, Ferris FL, 3rd, et al. The Association of Statin Use with Age-Related Macular Degeneration Progression: The Age-Related Eye Disease Study 2 Report Number 9. Ophthalmology 2015;122:2490-6. *Country:* USA *Design:* Prospective Cohort study *Number of centres:* 82 *Funding:* non-commercial (various) and commercial grants (Pfizer) *Trial ID:* not reported	*Number of Participants*: 3791 *Number of eyes:* not reported *Sample attrition/dropout*: not reported *Sample crossovers:* not applicable *Inclusion criteria:* for AREDS2 trial: aged 50-85 years, bilateral large drusen or unilateral late AMD in one eye and large drusen in fellow eye. *Exclusion criteria:* not reported

Intervention details	**Outcomes**
Intervention *1.* Statin use *Dose details:* not reported *Dose modifications:* not reported *Concurrent treatment:* AREDS2 trial participants either received placebo or lutein/zeaxanthin or docosahexaeonic acid (DHA) and eicosapentaenoic acid (EPA), or lutein/zeaxanthin and DHA plus EPA. *Duration of treatment:* not reported	*Outcomes (state if primary)* progression to late AMD (at least 2 features of neovascularisation; or any definite geographic atrophy; or history of treatment for neovascular AMD) *Length of follow-up:* median 5 years

Participant characteristics, %				
	All, n=3791 *Reviewer calculated*	**Statin use, 1659**	**No statin use, n=2132**	**P value** (statin vs no statin)
Age, years mean (SD)	72.9	73.5 (7.3)	72.3 (8.1)	<0.0001
Sex, % male	43.3	48.9	38.9	<0.0001
Ethnic origin *% White*	96.5	96.1	96.9	0.196
Classification *Bilateral large Drusen* *Unilateral late AMD*	 64.9 35.1	 61.8 38.2	 67.4 32.6	 not reported not reported
Smoking history *Never* *Former* *Current*	 43.7 49.9 6.5	 40.3 53.0 6.6	 46.2 47.4 6.4	 0.001
visual acuity	Not reported	Not reported	Not reported	
lesion size	Not reported	Not reported	Not reported	

previous treatments	Not reported	Not reported	Not reported	
Key comorbidities				
Diabetes	13.0	20.9	6.8	<0.0001
Hypertension	57.6	70.2	47.7	<0.0001
Congestive heart failure	3.0	4.2	2.1	0.0002
Coronary heart disease	9.2	16.7	3.4	<0.0001
Angina	4.6	7.8	2.1	<0.0001
Myocardial infarction	6.4	11.3	2.6	<0.0001
Stroke	4.8	7.1	3.1	<0.001
Family history	Not reported	Not reported	Not reported	
Comments				
Results				
	All, n=3791	**Hazard Ratio (HR); 95% CI (confidence interval)**		**P Value**
Progression to late AMD (any)	1650 (43.5%)	[a]1.08, (0.83, 1.41) [b]0.94 (0.72, 1.22)		p=0.56
Progression to geographic atrophy (any)	869 (22.9%)	[a]1.21 (0.85, 1.73) [b]1.06 (0.74, 1.51)		
Progression to neovascular AMD	998 (26.3%)	[a]1.24 (0.89, 1.73) [b]1.07 (0.80, 1.50)		
Progression to central geographic atrophy	479 (12.6)	[a]1.08 (0.67, 1.74) [b]0.92 (0.57, 1.48)		
Comments:				
Subgroups				
Bilateral Large Drusen at baseline	**N=2462**	**Hazard Ratio (HR); 95% CI (confidence interval)**		**P Value**
Progression to late AMD (any)		[a]1.0 (0.72, 1.41) [b]0.84 (0.60, 1.18)		
Progression to geographic atrophy (any)		[a]1.13 (0.74, 1.73) [b]0.96 (0.62, 1.48)		
Progression to neovascular AMD		[a]1.34 (0.86, 2.09) [b]1.12 (0.73, 1.74)		
Progression to central geographic atrophy		[a]1.03 (0.59, 1.80) [b]0.85 (0.48, 1.49)		
Unilateral Late AMD at baseline	**N=1329**			
Progression to late AMD (any)		[a]1.20 (0.79, 1.83) [b]1.08 (0.71, 1.65)		
Progression to geographic atrophy (any)		[a]1.42 (0.74, 2.73) [b]1.29 (0.66, 2.49)		
Progression to neovascular AMD		[a]1.11 (0.66, 1.86) [b]1.00 (0.60, 1.67)		
Progression to central geographic atrophy		[a]1.24 (0.49, 3.16) [b]1.14 (0.45, 2.87)		
[a]adjusted for propensity scores, baseline AMD status, age and not accounting for competing risk of death [b]adjusted for age and accounting for competing risk of death Also reports HRs adjusted for statin propensity score matching participants for statins use or non use. Results were similar except for 'any late AMD' in the subgroup of participants with bilateral large drusen at baseline (not extracted).				

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		

5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		x	
10. Was the exposure(s) assessed more than once over time?	x		
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?	x		
13. Was loss to follow-up after baseline 20% or less?			CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Barbosa et al

Study details	**Participant details**
Barbosa DT, Mendes TS, Cintron-Colon HR, Wang SY, Bhisitkul RB, Singh K, et al. Age-related macular degeneration and protective effect of HMG Co-A reductase inhibitors (statins): results from the National Health and Nutrition Examination Survey 2005-2008. Eye 2014;28:472-80. *Country:* USA *Design:* Cross sectional study *Number of centres:* not applicable (National Program) *Funding:* non-commercial grant (NIH) *Trial ID:* not applicable	*Number of Participants*: 6797 participants eligible of which 5604 were included. 1231 were receiving statin therapy and 4873 were not. *Number of eyes:* 5604 *Sample attrition/dropout*: 1193 excluded (969 no complete ophthalmological examinations with retinal photographs, 224 unreadable photographs). *Sample crossovers:* not applicable *Inclusion criteria:* at least 40 years old, underwent both interview and examination of the National Health and Nutrition Examination Survey *Exclusion criteria:* not reported

Intervention details	**Outcomes**
Intervention *1.* Statin use (self-reported) *Dose details:* considered to be under statin therapy when reported the use of any type of statin such as lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* mean length of time on statins 57.8 months, median 48 months (IQR: 24–96).	*Outcomes (state if primary)* Diagnosis of AMD in the worse eye (made via gradable retinal photographs of the macula) sub-types as: 1) Early AMD (presence of soft drusen with grid area > 500 μ circle and pigmentary abnormality or soft drusen and pigmentary abnormality in the centre circle without signs of advanced AMD). 2) Advanced or late AMD (presence of any late lesions, e.g geographic atrophy, RPE detachments, subretinal hemorrhage, fibrous scar, or neovascularization) 3) Any AMD (both early and late AMD). *Length of follow-up:* unclear, study used 2005-2008

	data.

Participant characteristics, %			
	With AMD	**Without AMD**	**P value**
Age, years mean (SE)	68.0 (SE 0.90)	55.6 (SE 0.36)	P<0.0001
	Statin use, n=1231	**No statin use, n=4374**	**P value**
Sex, % male	54	46	P=0.002
Ethnic origin *% White*	82.1	76	p=0.0009 for all categories
Smoking history *Current* *Past* *Never*	 15.1 42.1 42.9	 22 28.2 49.9	p<0.0001
Key comorbidities *Stroke* *History cataract extraction*	 7.7 34.3	 3.3 9.9	 p<0.0001 p<0.0001
Family history			
Comments: all p-values are unadjusted.			
Results			
AMD diagnosis	9.9	5.8	p=0.0003
	Statin users with AMD, n=126, Odds ratio, OR (95% confidence interval, CI)		**P Value**
Risk of Any AMD diagnosis:	1.77 (1.32, 2.38)	Unadjusted	P<0.0001
	0.92 (0.68, 1.24)	adjusted for age	P=0.565
	0.91 (0.68, 1.22)	Adjusted for age and sex	P=0.508
	0.91 (0.68, 1.22)	Adjusted for age, sex and ethnicity	P=0.493
	0.91 (0.69, 1.20)	Adjusted for age, sex, ethnicity and social-economic status	P=0.489
	0.90 (0.68, 1.19)	Adjusted for age, sex, ethnicity, social-economic status health-related behaviours (smoking and alcohol use)	P=0.459
	0.90 (0.67, 1.20)	Adjusted for age, sex, ethnicity, social-economic status health-related behaviours, comorbidities	P=0.465
	0.91 (0.67, 1.24)	adjusted for demographic characteristics, health-related behaviours, comorbidities and self-reported general health condition	P=0.539
Comments: statin use was not independently associated with AMD			
Risk of early AMD	0.95 (0.67, 1.33)	adjusted for demographic characteristics, health-related behaviours, comorbidities and self-reported general health condition	P=0.745
Comments: early AMD was not significantly associated with the use of statins			
Risk of late AMD	0.78 (0.34, 1.80)		P=0.556
Comments: late AMD was not significantly associated with the use of statins			
Subgroups			
Study reports subgroups comparing younger (40-67 years) with older (68 years plus) as the mean age of participants was 68 years. Only data for early AMD extracted, because late AMD and any AMD include neovascular AMD cases.			
Risk of early AMD, age 40-67 years, OR (95% CI)	1.61 (0.85–3.03)		P=0.137

Risk of early AMD, age 68 + years, OR (95% CI)	0.69 (CI 0.49–0.97)		P=0.032

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?	x		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?			N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?		x	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			CD
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?			N/A
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?			NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Fair
Time frame, exposure measures self-reported, not clear if exposure was prior to outcome

*CD, cannot determine; NA, not applicable; NR, not reported

Vavvas et al

Study details	Participant details
Vavvas DG, Daniels AB, Kapsala ZG, Goldfarb JW, Ganotakis E, Loewenstein JI, et al. Regression of Some High-risk Features of Age-related Macular Degeneration (AMD) in Patients Receiving Intensive Statin Treatment. EBioMedicine 2016;5:198-203. *Country:* USA and Greece *Design:* Before and after study, one group (pilot) *Number of centres:* 2 *Funding:* non-commercial funding *Trial ID:* none	*Number of Participants*: 26 *Number of eyes:* not reported *Sample attrition/dropout*: 3 (1 cramps, 1 muscle aches, 1 hair loss) *Sample crossovers:* not applicable *Inclusion criteria:* >50 years of age, diagnosis of AMD, presence of many large (>300 μm in diameter and more than 100 μm in height) soft drusenoid pigment epithelial detachments (PED). *Exclusion criteria:* presence or history of significant geographic atrophy or choroidal neovascularization (either eye), other eye diseases that could reduce visual acuity (excluding mild cataract), history of eye surgery (other than cataract extraction), statin therapy (within the previous 2 years) at a dose equivalent to atorvastatin ≥40mg, history of liver disease, rhabdomyolysis, or allergy to statins, pregnancy or nursing, current use of medications known to interact with statins, elevated transaminases or creatine phosphokinase.

Intervention details	Outcomes
Intervention *1.* Atorvastatin *Dose details:* 80 mg, daily *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* minimum 12 months	*Outcomes (state if primary)* reduction of drusenoid pigment epithelial detachment (PED) volume >50% based on OCT imaging (primary outcome); Drusen volume *Length of follow-up:* minimum 12 months, average 1.5 years (average person years of follow-up were ~30)

Participant characteristics, %			
	Atorvastatin, n=23		**P value**
Age, years mean (SD)	68.1 (6.0)		
Sex, % male	30.4		
Ethnic origin *% White*	 100		
visual acuity, letters, mean (SD[a])	77.6 (8.3)		
Key comorbidities *Hypertension*	 43.5		
Comments [a]study reports ± which reviewer assumes is standard deviation			
Results			
	Atorvastatin, n=23		**P Value**
Significant regression of drusen	10 (43.5%)		
Near complete regression of drusen	8 (34.8%)		
Visual acuity, mean (SD[a])	77.7 (8.4)		
Comments			
	Responders, n=10	**Non-responders, n=13**	
Drusen volume, mm^3, (SD)[a] *Baseline* *Endpoint* *p-value*	 0.57 (0.47) 0.049 (0.051) p = 0.012	 0.23 (0.20) 0.35 (0.32) Not reported	
Visual acuity, mean (SD)[a] *Baseline (letters)* *End point (letters)* *Change from baseline*	 74.2 (9.9) 77.5 (10.3) 3.3	 80.2 (6) 77.9 (7.1) −2.3	 p=0.06
Comments: states on average, responders gained 3 letters, non-responders lost 2.3 letters [a]study reports ± which reviewer assumes is standard deviation			
Time to resolution of dreusenoid deposits without atrophy, months	11.7 (range 3–22).		
Comments: states no participants converted to neovascular AMD			
Adverse events			
Not explicitly reported, but 3 participants withdrew from study (and were excluded from analysis) due to adverse events (1 cramps, 1 muscle aches, 1 hair loss).			
Subgroups			
Responder vs non-responder subgroups reported for age, cholesterol levels, sex, multivitamin use, aspirin use, fish oil consumption, and anti-hypertensive agents (not data extracted)			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and	x		

clearly described?			
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	x		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	x		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?		x	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			N/A
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Fair
Not clear if all eligible participants were enrolled, withdrawals were excluded from the analysis, no statistical tests on pre-post changes for whole group

*CD, cannot determine; NA, not applicable; NR, not reported

McGwin et al

Study details	**Participant details**
McGwin G, Jr., Owsley C, Curcio CA, Crain RJ. The association between statin use and age related maculopathy. Br J Ophthalmol 2003;87:1121-5. *Country:* USA *Design:* Case-control study *Number of centres:* one *Funding:* non-commercial funding *Trial ID:* Not reported	*Number of Participants*: Total 6050 (550 age related maculopathy (ARM) cases, 5500 controls) *Number of eyes* Not reported *Sample attrition/dropout*: Not reported *Sample crossovers:* Not applicable *Inclusion criteria:* Men age ≥50 years who had at least one visit (inpatient or outpatient) at the Birmingham (Alabama) Department of Veterans Affairs Medical Center (BVAMC) between 1 January 1997 and 31 December 2001. Cases of ARM defined using the ICD-9CM codes 362.50 (macular degeneration (senile), unspecified), 362.51 (non-exudative senile macular degeneration), and 362.52 (exudative senile macular degeneration). Index date was the ARM diagnosis date. Controls were randomly selected from the study population who did not have an ARM diagnosis by the end of the observation period and must have had an encounter with the BVAMC (inpatient or outpatient) on or before the index date of the matched case. Ten controls were selected for each case and matched on age (plus or minus 1 year). *Exclusion criteria:* patients who had an ARM diagnosis before the observation period (1997–2001) of the study (prevalent cases); females excluded as a small proportion of the patient population (10.8%) that meaningful analyses impossible

Intervention details	Outcomes
Intervention *1.* Filled statin prescriptions (atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin, lovastatin) and non-statin lipid lowering agents filled before the index date for each matched set of cases and controls *Dose details:* Not applicable *Dose modifications:* Not applicable *Concurrent treatment:* Not reported *Duration of treatment:* Reported in outcomes.	*Outcomes (state if primary)* Proportion of patients with a statin prescription filled before the index date, current statin use, past statin use, duration of statin use, use of non-statin lipid lowering agents *Length of follow-up:* Not reported

Participant characteristics, %			
	Cases of ARM, n=550	**controls, n=5500**	**P value**
Age, years mean (SD)	72.9 (6.8)	73.2 (6.7)	0.8
Sex, % male	100	100	
Ethnic origin *% White*	83.5	45.6	<0.0001
Key comorbidities			
Diabetes	22.6	14.1	<0.0001
Lipid metabolism disorders	10.6	11.4	0.57
Hypertension	56.4	38.7	<0.0001
Cardiovascular disease	30.4	23.7	0.0005
Cerebrovascular disease	4.7	8.6	0.0017
Arterial disease	6.4	7.9	0.21
Comments: cases were more likely to be white, have diabetes, hypertension, cardiovascular and cerebrovascular disease; controls had higher proportions of race unknown.			
Results			
	Cases of ARM, n=550	**controls, n=5500**	**OR (95% CI)[a]**
Proportion of patients with a statin prescription filled before the index date, %	6.7	13.6	0.30 (0.21, 0.45)
Current statin use, %	4.4	8.0	0.34 (0.21, 0.53)
Past statin use, %	2.4	5.6	0.26 (0.14, 0.47)
Duration of use, %			
<12 months	2.0	4.3	0.32 (0.20, 0.52)
12-23 months	2.0	2.9	0.29 (0.12, 0.67)
> 23 months	2.7	6.3	0.29 (0.15, 0.56)
Use of non-statin lipid lowering agents	NR	NR	0.46 (0.23, 0.92)
Statin only use only	NR	NR	0.48 (0.33, 0.68)[b]
Statin and non statin use	NR	NR	0.32 (0.10, 0.99)[b]
Non statin use only	NR	NR	0.75 (0.32, 1.73)[b]
Comments [a]Adjusted for diabetes, lipid metabolism disorders, hypertension, ischaemic heart disease, cerebrovascular disease, and arterial disease. [b]unadjusted			
Adverse events			
Not reported			
Subgroups			
The association between ARM and statin use according to the presence of specified medical conditions reported (data not extracted). There were no statistically significant interactions noted between statin use and each of the medical conditions and ARM.			

Case-control Studies

Criteria	Yes	No	Other

			(CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated and appropriate?	x		
2. Was the study population clearly specified and defined?	x		
3. Did the authors include a sample size justification?		x	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	x		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	x		
6. Were the cases clearly defined and differentiated from controls?	x		
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA
8. Was there use of concurrent controls?	x		
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?		x	
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	x		
11. Were the assessors of exposure/risk blinded to the case or control status of participants?		x	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?		X (not age)	

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Vanderbeek et al

Study details	**Participant details**
VanderBeek BL, Zacks DN, Talwar N, Nan B, Stein JD. Role of statins in the development and progression of age-related macular degeneration. Retina 2013;33:414-22. *Country:* US *Design:* case-control *Number of centres:* one *Funding:* non-commercial funding *Trial ID:* Not reported	*Number of Participants*: 486,124 before exclusions due to diagnosis during initial 2 yr period or missing lab values. Total for non-exudative AMD analysis: 107,007, Total for neovascular AMD analysis: 113,111; total for AMD progression analysis: 10753 *Number of eyes* Not reported *Sample attrition/dropout*: Not applicable *Sample crossovers:* Not reported *Inclusion criteria:* aged 60 years or older who were in the national insurance claims database ≥ 2 consecutive years and had ≥1 visits to an eye care provider during their time in the medical plan. Cases determined by ICD-9-CM codes, nonexudative AMD (362.50, 362.51, or 362.57) or exudative AMD (362.52) *Exclusion criteria:* in the medical plan for <2 years; not in the medical plan continuously from their beginning to their ending date of enrolment. To ensure events were incident cases of AMD, individuals diagnosed with exudative or nonexudative AMD in the first 2 years they were enrolled in the plan were excluded; and for analysis on those already diagnosed with nonexudative AMD to assess the association of statin use on the hazard of experiencing disease progression, those who were diagnosed with exudative AMD during this initial 2-year period were also excluded. Also excluded those without serum lipid levels

	recorded.
Intervention details	**Outcomes**
Intervention *1.* Prescription of statins and other lipid-lowering medications (identified by National Drug Codes) *Dose details:* Not reported *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 751 (SD 634) days (nonexudative AMD analysis); 804 (SD 641) days (exudative AMD analysis); 797 (SD 649) days (progression from nonexudative to exudative AMD analysis)	*Outcomes (state if primary)* adjusted hazard ratios (HRs) of developing nonexudative AMD, exudative AMD, and conversion from nonexudative to exudative AMD *Length of follow-up:* duration in plan 4.2 (SD 1.4) years

Participant characteristics, %			
Age, years mean (SD)	65.6		
Sex, % male	45.6		
Ethnic origin *% White*	69.0		
Results			
Development of Nonexudative AMD	N=107,007		
Developed non-exudative AMD during medical plan	4647/107,007 (4.3%)		
Statin use	56,630/107,007 (52.9%)		
Statin use in those developing non-exudative AMD	2460/4647 (52.9%)		
Hazard of Developing Nonexudative AMD Model, HR (95% CI)			
Statin use:			
0-6 months	REF		
7-12 months	0.93 (0.81-1.07), p=0.324		
13-18 months	0.99 (0.86-1.14), p=0.886		
19-24 months	0.97 (0.87-1.07), p=0.515		
Development of Exudative AMD	N=113,111		
Developed exudative AMD during medical plan	792/113,111 (7.0%)		
Statin use	59,531/113,111 (52.6%)		
Statin use in those developing exudative AMD	455/792 (57.5%)		
Hazard of Developing Exudative AMD Model, HR (95% CI)			
Statin use:			
0-6 months	REF		
7-12 months	0.99 (0.69-1.41), p=0.952		
13-18 months	1.57 (1.16-2.13), p=0.003		
19-24 months	1.48 (1.17-1.88), p=0.001		
Progression From Nonexudative AMD to Exudative AMD	N=10,753		
Progressed from nonexudative to exudative AMD during the study period	404/10,753 (3.8%)		

Statin use	5,341/5341 (49.7%)		
Statin use in those progressing to exudative AMD	222/404 (55%)		
Progression From Nonexudative to Exudative AMD Model, HR (95% CI)			
Statin use:			
0-6 months	REF		
7-12 months	1.04 (0.62-1.75), p=0.870		
13-18 months	1.27 (0.78-2.06), p=0.337		
19-24 months	1.63 (1.16-2.29), p=0.005		
Comments Analysis controlled for age, sex, race, region of the country, education level, net worth, coagulopathies, skin cancer, iron deficiency anemia, blood loss anemia, renal disease, diabetes, hypertension, cerebrovascular accidents, myocardial infarction, congestive heart failure, peripheral vascular disease, obesity, hypotension, use of other lipid-lowering medications, cataract, pseudophakia or aphakia, open-angle glaucoma, and diabetic eye disease.			
Individuals with the highest lipid levels (HDL, LDL, or TG) had increased hazards for developing or progressing from nonexudative to exudative AMD compared with people with similar lipid profiles who used statins for >12 months (P<0.05 for all groups); data reported not extracted.			
Adverse events			
Comments Not reported			

Case-control Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated and appropriate?	x		
2. Was the study population clearly specified and defined?	x		
3. Did the authors include a sample size justification?		x	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	x		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			CD
6. Were the cases clearly defined and differentiated from controls?	x		
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA
8. Was there use of concurrent controls?	x		
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?		x	
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			CD
11. Were the assessors of exposure/risk blinded to the case or control status of participants?		x	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	x		

Quality Rating Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Kaiserman et al

Study details	Participant details
Kaiserman N, Vinker S, Kaiserman I. Statins do not decrease the risk for wet age-related macular degeneration. Curr Eye Res	*Number of Participants*: Study 1: 139,894 eligible; 283 had AMD meeting inclusion criteria (of 305 with AMD); 29417 had used statins. Study 2: 334 AMD cases and 1670 controls

2009;34:304-10. *Country:* Israel *Design:* Case control study (includes a second case control study with matched controls). *Number of centres:* 1 *Funding:* not reported *Trial ID:* not reported	*Number of eyes:* not reported *Sample attrition/dropout*: N/A *Sample crossovers:* N/A *Inclusion criteria:* aged >50 years; did not terminate membership to the health maintenance organisation before 31st May 2005. Having photodynamic therapy was a proxy for a diagnosis of neaovascular AMD. At least two-years of statin use prior to photodynamic therapy (for the with statin group). *Control (second study only)* 5 participants matched for each of 334 AMD cases, matched by age, gender, hyperlipidemia, congestive heart failure, diabetes, and ischemic heart disease), place of birth (Ashkenazi or Sephardic origin), and socioeconomic status. Also states 'randomly selected'. *Exclusion criteria:* not reported

Intervention details	**Outcomes**
Intervention (same for both studies) *1.* Any statin, e.g atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. *Dose details:* standardised dose and potency by converting to World Health Organisation standard defined daily dose (DDD) per day (details reported but not extracted). The total DDDs taken by each patient were recorded. *Dose modifications:* no details. *Concurrent treatment:* no details. *Duration of treatment:* only prescriptions filled before the first photodynamic therapy were included.	*Outcomes (state if primary)* Association between prior statin use and diagnosis of AMD. *Length of follow-up:* not reported as such, study looked at those diagnosed between a 53 month period (January 2001 to May 2005)

Participant characteristics, %			
Study 1	**All members taking statins, n=29,417[a]**	**All members not taking statins, n=110,477[a]**	**P value**
Age, years mean (SD)	68.67 (9.26)	63.51 (11.16)	
Sex, % male	44.7	46.3	
Key comorbidities, % *Ischaemic heart disease* *Hypertension* *Congestive Heart Failure* *Hyperlipidemia* *Diabetes*	 43.2 62.0 10.9 91.8 33.8	 10.7 30.5 3.3 25.6 12.9	
Family history			
[a]only baselines reported were for the total groups, extracted to give an indication of the sample, p-values not extracted as not relevant to the review			
Study 2	**AMD n=334**	**Matched controls, n=1670**	**P value**
Age, years mean (SD)	77.80 (8.35)	77.16 (8.52)	0.21
Sex, % male	47.31	47.31	0.95

Key comorbidities, %			
Ischaemic heart disease	37.43	37.37	0.97
Hyperlipidemia	56.29	56.23	0.97
Congestive Heart Failure	10.78	11.02	0.97
Chronic Renal Failure	5.99	6.65	0.75
Diabetes	22.16	21.86	0.96
Hypertension	63.47	63.71	0.98
Results			
Study 1	**Statins, n=107**	**No Statins, n=176**	**P Value**
Proportion with AMD (had PDT)	0.27% (95% CI: 0.20, 0.34)	0.16% (95% CI: 0.14, 0.18)	p=0.002
Unadjusted Relative risk: 1.66, 95% CI: 1.29, 2.19 After adjusting for age, gender, socioeconomic status, place of residence, hypertension, hyperlipidemia, place of birth, IHD, diabetes, and CHF the association was no longer statistically significant, p=0.07. When standardised DDDs were used there was no association identified.			
Study 2	**AMD n=334**	**Matched controls, n=1670**	**P value**
Proportions using statins, Any[b]	126 (37.7%)	628 (37.6%)	0.97
Odds ratio: 1 (95% CI 0.8, 1.3) [b]Also reports by statin type, not extracted			
Outcome 3			
Comments			
Adverse events	Not reported		
Comments			

Case-control Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated and appropriate?	x		
2. Was the study population clearly specified and defined?	x		
3. Did the authors include a sample size justification?			N/A
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	x		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			CD
6. Were the cases clearly defined and differentiated from controls?	x		
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			N/A[a]
8. Was there use of concurrent controls?	x		
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	x		
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	x		
11. Were the assessors of exposure/risk blinded to the case or control status of participants?		x	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?		x[b]	

[a] For study 2 – 5 matched controls were randomly selected

[b]reported that not significant when adjusted but no results for adjusted analysis were reported to check

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Fong et al

Study details	**Participant details**
Fong DS, Contreras R. Recent statin use and 1-year incidence of exudative age-related macular degeneration. Am J Ophthalmol 2010;149:955-8.e1. *Country:* USA *Design:* Case control study *Number of centres:* up to 11 *Funding:* none *Trial ID:* not reported	*Number of Participants*: 79369 (cases 719; controls 78,650) of 86,635 who underwent an eye examination. *Number of eyes* not reported *Sample attrition/dropout*: not applicable *Sample crossovers:* not applicable *Inclusion criteria:* all patients with a diagnosis of exudative AMD in the 2007 who did not have exudative AMD in 2006, at least 60 years old, enrolled in Kaiser Permanente Southern California for at least 5 years in 2007. Cases were identified using outpatient diagnosis data. Controls had undergone an eye examination during the same year without the diagnosis of AMD. *Exclusion criteria:* not reported

Intervention details	**Outcomes**
Intervention *1.* Statins (atorvastin, ezetimibesimvastatin, lovastatin, pravastatin, and simvastatin) Also undertook analyses with all lipid-lowering agents, cholestyramine, colestipol, ezetimibe, fenofibrate, and gemfibrozil. 2. no statin use *Dose details:* Drug use defined as use before case determination. Recent use, defined as filled prescription in the year before the year of diagnosis, recent longer-term use defined as a filled prescription in each of 3 years before diagnosis. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* not reported	*Outcomes (state if primary)* Association between statin use and new exudative AMD. *Length of follow-up:* not reported

Participant characteristics, %			
	Wet AMD, n=719	**Controls, n=78,650**	**P value**
Age, years mean (SD)	78.6	72.7	P=0.0001
Sex, % male	45.5	42.7	P=0.13
Ethnic origin *% White*	 70.1	 48.8	 P=0.0001
Key comorbidities, % *Myocardial infarction* *Stroke*	 8.3 17.4	 6.4 13.7	 P=0.03 P=0.006
Results			
Statin use in 2006	**Statin use, n=43026**	**No Statin use, n=36343**	**P Value**
Wet AMD, % *No Wet AMD, %*	51.5 54.2	48.5 45.8	OR 0.89 (95% CI, 0.77, 1.03). P=0.14

Comments: study shows no association with wet AMD and statin use. After adjustment for age, gender, and history of myocardial infarction and of stroke, statin use still was not associated with exudative AMD (data not extracted).			
Recent longer-term use of Statins (3 years to 2007)	**Statin use, n=32743**	**No Statin use, n=46626**	**P Value**
Wet AMD, % *No Wet AMD, %*	38.5 41.3	61.5 58.7	OR 0.89 (95% CI 0.77, 1.04), p=0.14
Comments: study shows no association with wet AMD and statin use.			
Lipid-lowering agent use in 2006	**Statin use, n=5016**	**No Statin use, n=74353**	**P Value**
Wet AMD, % *No Wet AMD, %*	5.3 6.3	94.7 93.7	OR 0.83 (95% CI 0.59, 1.14), p=0.64
Comments: study shows no association with wet AMD and other lipid lowering agents.			

Case-control Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated and appropriate?	x		
2. Was the study population clearly specified and defined?	x		
3. Did the authors include a sample size justification?			N/A
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	x		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			CD
6. Were the cases clearly defined and differentiated from controls?	x		
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			n/a
8. Was there use of concurrent controls?	x		
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	x		
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			CD
11. Were the assessors of exposure/risk blinded to the case or control status of participants?		x	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	x		

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Etminan et al

Study details	Participant details
Etminan M, Brophy JM, Maberley D. Use of statins and angiotensin converting enzyme inhibitors (ACE-Is) and the risk of age-related macular degeneration: nested case-control study. Current Drug Safety 2008;3:24-6. *Country:* Canada *Design:* nested Case-control	*Number of Participants*: Total 14,335 (Wet AMD cases 2867, control 11,468) *Number of eyes* Not reported *Sample attrition/dropout*: Not applicable *Sample crossovers:* Not applicable *Inclusion criteria:* People who had undergone revascularization

Number of centres: Not applicable *Funding:* Not reported *Trial ID:* Not reported	interventions. Data obtained from administrative health insurance and vital statistics databases Cohort members were elderly people (≥65 years) who had received a revascularization procedure (percutaneous coronary angioplasty and or bypass grafting) during April, 1995, to December 2002. Cases were identified as those who had an ICD-9 code for the wet form of AMD. For each case, four controls were chosen randomly from the cohort and matched by age. A current user was defined as a person who was using a statin / ACE-Is prescription within 90 days of the index date (the date of diagnosis of AMD). *Exclusion criteria:* < 65 years of age at the time of their revascularization procedure, non-Quebec residents or died in the hospital during their initial revascularization

Intervention details	**Outcomes**
Intervention *1.* Statin and ACE-I use *Dose details:* Not applicable *Dose modifications:* Not applicable *Concurrent treatment:* Not applicable *Duration of treatment:* Not applicable	*Outcomes (state if primary)* Association between statin and angiotensin-converting enzyme inhibitors (ACE-Is) and risk of AMD. *Length of follow-up:* Not reported

Participant characteristics, %			
	Cases, n=2867	**Controls, n=11,468**	**P value**
Age, years mean (SD)	70.2 (8.5)	70.2 (8.4)	
Sex, % male	55.4	58.6	
Key comorbidities, % *Myocardial infarction* *Stroke* *Ischemic heart disease*	 5.9 1.5 28.0	 4.7 1.0 23.4	
Mean (SD) number of prescriptions used prior to index	70.9 (75.7)	61.0 (87.7)	
Mean (SD) number of diabetic medications prior to index.	4.0 (10.4)	2.8 (9.5)	
Family history			
Comments States number of prescription drugs is an indirect measure of comorbidity.			
Results			
	Cases, n=2867	**Controls, n=11,468**	**Adjusted RR (95% CI)**
Current users: ACE-Is, n	534	1767	1.19 (1.07-1.33)
Current users: Statins, n	642	2042	1.30 (1.17-1.44)
Use in past year: ACE-Is, n	1102	3637	1.26 (1.15-1.38)
Use in past year: statins, n	1268	4268	1.31 (1.20-1.43)
Comments: The regression model adjusted for potential confounders including gender, age, comorbidity (computed as the number of prescription drugs used prior to the index), prior history of diabetic medications, myocardial infarction, stroke, ischemic heart disease and congestive heart disease.			
Comments			

Case-control Studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated and	x		

appropriate?			
2. Was the study population clearly specified and defined?	x		
3. Did the authors include a sample size justification?		x	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	x		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	x		
6. Were the cases clearly defined and differentiated from controls?	x		
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			CD
8. Was there use of concurrent controls?	x		
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	x		
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	x		
11. Were the assessors of exposure/risk blinded to the case or control status of participants?		x	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	x		

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Tandospirone

Jaffe et al

Study details	**Participant details**
Jaffe GJ, Schmitz-Valckenberg S, Boyer D, Heier J, Wolf-Schnurrbusch U, Staurenghi G, et al. Randomized Trial to Evaluate Tandospirone in Geographic Atrophy Secondary to Age-Related Macular Degeneration: The GATE Study. American Journal of Ophthalmology 2015;160:1226-34 *Country:* USA, Germany, Italy, Switzerland, Ireland, France, Australia, Israel, Austria, Belgium, United Kingdom, Japan, Portugal and Canada *Design:* RCT *Number of centres:* 48 *Funding:* commercial funding *Trial ID:* NCT00890097	*Number of Participants*: total 772 randomised: tandospirone 1.0% 252; tandospirone 1.75% 259; placebo vehicle solution 261 *Number of eyes* total 768 treated tandospirone 1.0% 250; tandospirone 1.75% 258; vehicle solution 260. Both eyes were treated but only one was designated as the study eye, either the one with the best BCVA or the dominant eye if BCVA was the same. *Sample attrition/dropout*: total 231; tandospirone 1.0% 68 (adverse events 21; unrelated to adverse events 15; withdrew consent 9; lost to follow-up 5; other 18) – figures shows 2 not treated but numbers do not add up; tandospirone 1.75% 86 (adverse events 32; unrelated to adverse events 12; withdrew consent 6; lost to follow-up 5; noncompliance 4; other 27) – figures shows 1 not treated but numbers do not add up; vehicle solution 77 (not treated 1; adverse events 28; unrelated to adverse events 17; withdrew consent 9; lost to follow-up 5; noncompliance 4; other 14). *Sample crossovers:* none *Inclusion criteria:* ≥55 years, GA secondary to AMD, no evidence of CNV, well-demarcated area of atrophy (if multifocal, ≥1 focal lesion ≥1.25 mm^2), and a total lesion size of ≤20 mm^2, hyperautofluorescence adjacent to the area of atrophy, BCVA of ≥35 letters (20/200 Snellen), clear ocular media and adequate pupillary dilation.

	Exclusion criteria: other ocular disease that may confound assessment of GA lesions, or may affect central visual acuity, a history of cataract surgery (past 3 months) or serious ocular trauma or intraocular surgery (past 6 months), current or previous use of serotonin receptor agonists, selective serotonin reuptake inhibitors, selective serotonin/epinephrine reuptake inhibitors, monoamine oxidase inhibitors, and triptans (past 30 days)

Intervention details	**Outcomes**
Intervention *1.* Tandospirone 1.0% *2.* Tandospirone 1.75% *3.* Vehicle solution (placebo) *Dose details:* 1 drop into each eye twice daily (interval of approximately 12 hours between drops). Both eyes were treated but only one was designated as the study eye. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 24 months	*Outcomes (state if primary)* mean annualized lesion enlargement (primary outcome) BCVA (ETDRS) Near activity scores, Distance activity, Vision-specific dependency subscales of the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25), not analysed. *Length of follow-up:* 30 months (study terminated after 600 had completed the month 24 visit)

Participant characteristics, %				
	tandospirone 1.0% n=252	**tandospirone 1.75% n=259**	**vehicle solution n=261**	**P value**
Age, years mean (SD)	77.9 (8.0)	78.3 (7.7)	78.8 (7.1)	
Sex, % male	48	37	44	
Ethnic origin *% White*	96	98	96	
lesion size, mm^2, mean (SD)	7.4 (4.6)	7.5 (4.4)	7.6 (4.5)	
Results				
	tandospirone 1.0% n=250	**tandospirone 1.75% n=258**	**vehicle solution n=260**	**P Value**
Annualised lesion growth rate, mean (95% CI)	1.725 (1.595, 1.855)	1.758 (1.626, 1.890)	1.707 (1.585, 1.830)	See below
tandospirone 1.0% vs vehicle solution mean difference 0.017 (95% CI -0.161, 0.196); tandospirone 1.75 vs. vehicle solution mean difference 0.051 (95% CI -0.129, 0.231)				
Change in lesion size, mean at month 30 (estimated from figure), mm^2	3.8	4.1	4.1	
BCVA change (ETDRS) estimated from figure	-0.8	-0.6	-0.7	ns
% with ≥10-letter decrease at 30 months	38	35	NR	
Comments				
Any ocular adverse events in study eye, %	66	67	60	
Serious ocular adverse events in study eye, %	0	1	2	
Comments: Categories of adverse events reported not extracted				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Used a randomization schedule generated by a statistical group

Allocation concealment (selection bias)	Unclear	No details
Blinding participants and personnel (performance bias), Objective outcomes	Low	States patients, investigators, and the manufacturer personnel were masked with regard to treatment assignments, but details of how masking was maintained not reported
Blinding participants and personnel (performance bias), Subjective outcomes	Low	States patients, investigators, and the manufacturer personnel were masked with regard to treatment assignments, but details of how masking was maintained not reported
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not described
Blinding outcome assessors (detection bias), Subjective outcomes	Unclear	Not described
Incomplete outcome data (attrition bias), Objective outcomes	Low	High drop out but numbers similar across groups, reasons provided, and analysis included most participants
Incomplete outcome data (attrition bias), Subjective outcomes	Low	High drop out but numbers similar across groups, reasons provided, and analysis included most participants
Selective reporting (reporting bias)	High	Visual function questionnaire data were not analysed because the study stopped early because of lack of efficacy
Other biases	Unclear	Study stopped for futility

Trimetazidine

Cohen et al

Study details	**Participant details**
Cohen SY, Bourgeois H, Corbe C, Chaine G, Espinasse-Berrod MA, Garcia-Sanchez J, et al. Randomized clinical trial France DMLA2: effect of trimetazidine on exudative and nonexudative age-relatedmacular degeneration. Retina 2012;32:834-43. *Country:* France, Belgium and Spain *Design:* RCT *Number of centres:* 324 *Funding:* Laboratoires Servier *Trial ID:* ISRCTN99532788	*Number of Participants*: 1,192; TMZ 35mg 594; Placebo 598 Full analysis set: 1,086; TMZ 546; Placebo 540 *Number of eyes:* same as above *Sample attrition/dropout*: 299 withdrew; TMZ 135; Placebo 164 *Sample crossovers:* none *Inclusion criteria:* AMD with unilateral CNV for 12 months (preferably). Study eye was the unaffected eye: had at least 5 isolated soft drusen (diameter >63 µm) (Subgroup 1, N = 473), other types of drusen (hard, calcified, or serogranular) or RPE lesions (Subgroup 2 N = 545) or isolated RPE lesions excluding atrophy larger than 1/3 DD (Subgroup 3 N = 68). White, aged 55-83 years, ocular media clear enough for good-quality fundus photographs. Central review of eligibility based on fluorescein angiograms for maximum of 3 months. *Exclusion criteria:* (for study eye): CNV, chorioretinal atrophy in the central and/or the intermediate field (>1/3 DD), RPE detachment, pseudovitelliform dystrophy, myopia (>6 diopters for corrected distance vision), diabetic retinopathy, proven glaucomatous neuropathy, toxic or inflammatory neuropathy, or any other macular pathology, allergy to fluorescein, dense cataract or corneal/vitreous opacity, insufficient pupil dilatation for angiography, current treatment with TMZ that could not be discontinued (a 15-day washout period required), long-term treatment with a drug with retinal toxicity

	potential, or laser coagulation therapy of the study eye.
Intervention details	**Outcomes**
Intervention *1.* Trimetazidine (TMZ) one tablet twice a day *2.* Placebo, matched, one tablet twice a day *Dose details:* TMZ 35 mg modified release *Dose modifications:* not reported *Concurrent treatment:* vitamins or antioxidants for at least 1 year: 36 TMZ and 36 placebo *Duration of treatment:* mean (SD) 37.6 (16.3) months.	*Outcomes (state if primary)* Time to occurrence of CNV (defined as the time from treatment initiation to the first angiogram showing a CNV), (primary outcome). Incidence of atrophy larger than 1/3 DD (disk diameters), number and area of drusen, number and area of retinal pigment epithelium (RPE) lesions, characteristics of CNV assessed by retinal fluorescein angiography, adverse events (clinical acceptability). *Length of follow-up:* Minimum of 3 years, prolonged up to 5 years for those enrolled during the first 2 years. Follow-up assessments every 6 months.

Abbreviations: AMD: Age-related Macular Degeneration; CNV: choroidal neovascularization; RPE: retinal pigment epithelium; TMZ: Trimetazidine

Participant characteristics, %			
	TMZ, n=546	**Placebo, n=540**	**P value**
Age, years mean (SD)	Combined groups only: 73.5 (5.6)		
Sex, % male	Combined groups only: 38		
Ethnic origin *% White*	100		
Classification			
Smoking history Former Current	Combined groups only 25 11		
Distance visual acuity *≥ 0.5 (20/40) Snellen equivalent*	91.5	93	
lesion size			
Hypopigmentation *Hyperpigmentation*	Combined groups only 42 53		
Duration of diagnosis in nonstudy eye, mean (SD)	Combined groups only 22.9 (29.2)		
previous treatments			
Key comorbidities Arterial hypertension Angina pectoris Diabetes mellitus Myocardial infarction Stroke	Combined groups only 51 11 8 5 4		
Family history	Combined groups only 12		
BMI (kg/m^2), mean (SD)	Combined groups only 25.9 (4.1)		
Comments: states TMZ and placebo had similar baseline profiles			
Results			
	TMZ, n=546	**Placebo, n=540**	**P Value**
***CNV incidence**, N(%)*	181 (33%)	177 (33%)	NR
CNV Incidence per 100 patient-years	10.86	11.13	HR = 0.97; (95% CI: 0.79–1.19); p=0.78
CNV 5-year cumulative incidence, mean (SD) %	45.35 (3.27)	48.50 (3.59)	NR
Comments			

Atrophy >1/3 Disk Diameters in the central +/or intermediate field, N(%)	78 (15)	93 (17.5%)	NS
Atrophy >1/3 DD incidence per 100 patient-years	5.11	6.45	HR = 0.76; 95% CI, 0.56–1.02; p = 0.07
Atrophy >1/3 DD 5-year cumulative incidence, mean (SD) %	30.78 (4.14)	37.94 (4.66)	NR
Comments			
Adverse events, % *Any* *Eye disorders* *Vascular disorders* *Cardiac disorders* *Gastrointestinal disorders*	 75 24.6 17 10.3 14.2	 79 23.2 20.5 13.1 16.8	
Comments: note unclear what the numbers are for the safety analysis set.			
Reports outcomes of CNV and Atrophy incidence by subgroups age, gender and type of lesions at inclusion. Atrophy >13/ DD, incidence per 100 patient years: differences within some prespecified subgroups showed superiority of TMZ in men (2.85 vs. 5.45 HR = 0.50; 95% confidence interval, 0.28–0.89; p = 0.02), in patients aged ≤75 years (3.73 vs. 5.99 HR = 0.57; 95% confidence interval, 0.38–0.88; p = 0.01), or in patients presenting with isolated pigmentary changes (2.77 vs. 14.03 HR = 0.19; 95% confidence interval, 0.05–0.69; p = 0.005). No significant differences for other subgroups.			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	computer generated random allocation schedule with minimization on 3 criteria: age, gender, and subgroup (1, 2, or 3) of AMD lesions in the study eye
Allocation concealment (selection bias)	Low	randomization centre used
Blinding participants and personnel (performance bias), Objective outcomes	Low	Participants and investigators blind to treatment group assignment.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	low	States all investigators blind
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	High	Analysis of the primary outcome was based on participants who took at least 1 treatment and had at least 1 follow-up angiogram read and validated by the Reading Committee, no intention to treat analysis was undertaken. Analysis of clinical acceptability was based on a safety set (participants who had at least 1 treatment). Some imbalance in rates of withdrawals between groups (TMZ 23%, placebo 27%). Reasons for withdrawals provided

Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	High	Trial register suggests secondary outcomes of effects on serous drusen and pigment epithelium lesions were outcomes, these were not reported in the trial publication, although they were listed in the introduction.
Other biases	Low	none

Visaline

Kaiser et al

Study details	**Participant details**
Kaiser HJ, Flammer J, Stumpfig D, Hendrickson P. Visaline in the treatment of age-related macular degeneration: a pilot study. Ophthalmologica 1995;209:302-5. *Country:* Switzerland *Design:* RCT (pilot) *Number of centres:* one *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: total 20; visaline 9; placebo 11 *Number of eyes* total 20; visaline 9; placebo 11 *Sample attrition/dropout*: none *Sample crossovers:* none *Inclusion criteria:* over 50 years, non-serous AMD (early AMD), corrected visual acuity between 20/100 – 20/25; distance correction <4.0 dpt spherical equivalent. If bilateral, the better eye was selected. *Exclusion criteria:* serous AMD, diabetes mellitus, endocrine problems, cardiac dysrhythmia, status following cardiac infarction, uncontrolled hypertension, other ocular diseases

Intervention details	**Outcomes**
Intervention *1.* Visaline *2.* Placebo *Dose details:* visaline contains buphenine HCI 1.5mg, beta-carotine 10mg, tocopherol acetate 10mg and ascorbic acid 50mg. Two tablets twice daily, 5 days per week. *Dose modifications:* none reported *Concurrent treatment:* unable to take vitamin A containing substances, beta-blockers, sympathomimetics, sympatholytics, diuretics, vasoactive substances, chloroquine or tuberculostatics for 1 month prior to or during the study duration. *Duration of treatment:* 6 months	*Outcomes (state if primary)* Far and near visual acuity Visual field defects (not extracted) Intraocular pressure (not extracted) Lens opacity (not extracted) Contrast sensitivity Visual function (subjective measure) *Length of follow-up:* 6 months

Participant characteristics, %			
	Visaline, n=9	**Placebo, n=11**	**P value**
Age, years mean (SD)	72 (6.2)	74 (7.6)	
Sex, % male	55.6	9.1	
Classification, % Regional atrophy of the pigment epithelium.	100	100	
Mean far visual acuity	0.60 (0.15)	0.55 (0.15)	

Mean near visual acuity	0.57 (0.19)	0.45 (0.13)	
Comments: 2 participants in the placebo and 1 in the visaline group had hard, non-confluent drusen.			
Results			
	Visaline, n=9	**Placebo, n=11**	**P Value**
Far visual acuity at 6 months, mean (SD)	0.67 (0.2)	0.6 (0.22)	NS
Near visual acuity at 6 months, mean (SD)	0.62 (0.14)	0.55 (0.23)	NS
Comments: states not significantly, no p-value reported			
Contrast sensitivity			
Comments: states in both groups contrast sensitivity at all test frequencies were worse and there were no differences between groups			
Visual function, % *Improved* *Unchanged* *Worsened*	 44.4 44.4 0	 27.3 36.4 27.3	
Comments: appears to be some missing data			
Adverse events	0	0	
Comments			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	No description
Allocation concealment (selection bias)	Unclear	No description
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	States double blind but no description
Blinding participants and personnel (performance bias), Subjective outcomes	Unclear	States double blind but no description
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	States double blind but no description
Blinding outcome assessors (detection bias), Subjective outcomes	Unclear	States double blind but no description
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	No discussion, some results appear to show missing data.
Incomplete outcome data (attrition bias), Subjective outcomes	Unclear	No discussion, some results appear to show missing data.
Selective reporting (reporting bias)	Unclear	Not enough information to assess
Other biases	Low	No other apparent biases