Appendix E: Evidence tables

E.1 Classification

RQ6: What effective classification tool should be used to classify different types of AMD?

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006
Country/ies where the study was carried out	USA
Study type	Nested case-control study
Aim of the study	To develop a fundus photographic severity scale for age-related macular degeneration (AMD)
Study dates	Published 2005
Source of funding	National Eye Institute
Sample size	3212 participants (1225 eyes were used to calculate validation outcomes)
Characteristics	Participant demographics not reported
Inclusion Criteria	Participants from the Age-Related Eye Disease Study (AREDS).
Exclusion Criteria	None reported
Tests	Photographs were scheduled at baseline, at the 2-year visit, and annually thereafter. Stereoscopic pairs of fields 1 (disc) and 2 (macula) and a single photograph of field 3 (temporal to the macula) were taken with 30° cameras and mounted in plastic sheets, which were viewed on light boxes with ×5 Donaldson stereo viewers. Graders assessed the photographs for presence, extent, and other features of the abnormalities characteristic of AMD by using a standard grid template adapted from the Early Treatment Diabetic Retinopathy Study and standard circles consisting of opaque black lines printed on transparent stock that could be placed over or under the transparency being evaluated (Figure 1). Photographs from each visit were graded independently of those from all other visits. Grid and standard circles were used in assessing size, area, and location of abnormalities. The radii of the grid circles are one-third, 1, and 2 disc diameters, respectively, and their areas are 4/9, 4, and 16 disc areas (DAs). When the diameter of the optic disc is assumed to be 1500µm, the radius of the central circle of the grid is 500µm, that of the middle (inner) circle is 1500µm, and that of the outer circle is 3000µm. The standard circles have the following diameters and areas:

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006

C-0, 63µm and 0.0017 DA;
C-1, 125µm and 0.0069 DA;
C-2, 250µm and 0.028 DA;
I-2, 354µm and 0.056 DA;
O-2, 650µm and 0.19 DA;
0.5 DA, 1061µm and 0.50 DA.

An additional circle, I-1 (diameter, 175 µm) is used to define the smallest area of depigmentation that can be classified as geographic atrophy.

Reproducibility of the scale was assessed by applying it to duplicate gradings carried out periodically throughout the course of the study as part of ongoing quality control exercises (total number of eyes, 1225).

9-step severity scale		
Step Drusen Area	Increased Pigment	Depigmentation-GA
<C-1	0	0
≥C-1, <C-2	0	0
<C-1	≥Q*	≥, <102
≥C-2, <1-2	0	0
≥1-2, <O-2	0	0
≥C-1, <102	≥Q	≥Q, <1-2
<C-2	≥0	≥1-2, <0.5DA
≥O-2, <0.5DA	0	0
≥1-2, <O-2	≥Q	≥Q, <1-2
≥C-2	≥0	≥1-2, <0.5DF
≥0.5 DA	0	0
≥O-2, <0.5DA	≥Q	≥Q, <1-2
≥1-2, <O-2	≥0	≥1-2, <0.5DA

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006

≥0.5 DA	≥Q	≥Q, <1-2
≥O-2, <0.5DA	≥0	≥1-2, <0.5DA
≥0.5 DA	≥0	≥1-2, <0.5DA
Any	≥0	≥0.5 DA
Any	≥0	Non-central GA

*Q= questionable

Geographic atrophy was defined as an area of partial or complete depigmentation of the RPE in the fundus photographs that had at least 2 of the following 3 characteristics: roughly round or oval shape, sharp margins, and visibility of underlying large choroidal vessels. Depigmentation adjacent to disciform scars was not classified as GA, even if these criteria were met.

Neovascular AMD was defined as the definite presence in the fundus photographs of 1 or more of 4 characteristics: serous sensory retinal detachment, RPE detachment, subretinal hemorrhage, or subretinal fibrous tissue; or of a report from the clinic of the application of photocoagulation for choroidal new vessels at any previous visit.

The presence of central GA was defined as questionable or definite involvement of the center of the macula by definite GA. Advanced AMD was defined as neovascular AMD or CGA.

Methods

Reproducibility

Reproducibility of the scale was assessed by applying it to duplicate gradings carried out periodically throughout the course of the study as part of ongoing quality control exercises (total number of eyes, 1225).

Development of the scale

Baseline and 5-year follow-up gradings were available for the right eyes of 3212 participants without advanced AMD in either eye at baseline (all treatment groups combined). The frequency of development of each of the 2 types of advanced AMD within 5 years in these eyes by the baseline grade for each characteristic were tabulated and cross-tabulations for pairs of characteristics were examined.

Associations between the nonadvanced AMD characteristics at baseline and development of advanced AMD at or before the 5-year follow-up visit were explored by means of tree-structured models. Models were run separately for the predictiveness of drusen characteristics alone, pigment abnormalities alone, and the 2 sets of variables together. After the scale was developed, its performance in the left eyes of these same participants was examined, and then in the eye with nonadvanced AMD of other participants who had advanced AMD in one eye at baseline (543 with neovascular AMD and 57 with CGA).

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006
Results	Interobserver Agreement Reproducibility of the scale, expanded to include CGA and neovascular AMD as additional steps, by comparing the original grading with a replicate grading: Complete agreement: 63.4% of eyes, Agreement within 1 step: 86.6%, Agreement within 2 steps in 93.6%. Unweighted κ statistic (SE): 0.58 (0.015), κ weighted to give 75% credit for 1-step disagreement: 0.73(0.013).
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently of other visits, unclear if duplicate grading was also done independently of prior grading If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability

Bibliographic reference	**The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006**
	Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes (grader the only difference) Were all patients included in the analysis? No a sample of 1225, unclear how this sample was selected Could the patient flow have introduced bias? RISK: UNCLEAR

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Bibliographic reference	**Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To describe the system for grading age-related macular degeneration from fundus photographs in the Age-Related Eye Disease Study.
Study dates	Published 2001
Source of funding	National Eye Institute, National Institutes of Health
Sample size	Sample of 1230 eyes
Characteristics	No baseline characteristics reported
Inclusion Criteria	Participants of the Age-Related Eye Disease Study
Exclusion Criteria	No exclusion criteria reported
Tests	Sterioscopic slide transparencies mounted in plastic sheets are examined in a lught box fitted with flourescent tubes with a colour rating of approximately 6200 kelvin. The grader uses a Donaldson sterioscopic viewer with 5x magnification, which, combined with the 2.43x magnification results in total magnification of 12x.

Bibliographic reference	**Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001**
	The grading process uses a standard grid template, before grading the technician centres the grid on the photograph and tapes it in place. A set of graduated circles is used to estimate maximum drusen size and total area involved by pigment abnormalities and drusen. Areas are expressed in disk areas, which for any circle is simply the square of its diameter, for example, a circle with 2 disk areas diameter, contains 4 disk areas. Age-Related Eye Diseases Study Age-related Macular Degeneration Severity Scale Levels Defined: 1- Drusen maximum size < Circle C0 (63µm diameter) and total area < circle C1 (125µm diameter) 2- Presence of one or more of the following: Drusen maximum size ≥circle C0 but < circle C1 Drusen total area ≥circle C1 Retinal pigment epithelial pigment abnormalities consistent with AMD, defined as one of more of the following in the central or inner subfields: depigmentation present, increased pigment ≥circle C1, or increased pigment present and depigmentation at least questionable 3- Presence of one or more of the following: Drusen maximum size ≥ circle C1 Drusen maximum size ≥ circle C0 and total area > circle I2 and type is soft indistinct Drusen maximum size ≥ circle C0 and total area > circle O2 and type is soft distinct Geographic atrophy within grid but none at centre of macula 4- Presence of one or more of the following: Geographic atrophy in central subfield with at least questionable involvement of centre of macula Evidence of neovascular AMD: fibrovascular/serous pigment epithelial detachment; serous (or haemorrhagic) sensory retinal detachment; subretinal pigment epithelial haemorrhage; subretinal fibrous tissue (or fibrin); photocoagulation for AMD.
Methods	During the preliminary grading for photographic quality, a grader also records an estimate of the age-related macular degeneration severity scale level for each eye. During the detailed grading, another grader performs a more extensive evaluation. Then a computorised algorithm extracts the age-related macular degeneration level from the detailed grading and compares it to the estimate from preliminary grading. If the age-related macular degeneration levels differ, a senior grader (who has not been involved in either preliminary or detailed grading) reviews the photographs and discrepant grades, determines the final result and modifies the grading accordingly. All study photographs are graded independently, that is, graders are masked to the photographs and grades from previous visits. Paired contemporaneous gradings were compared by means of cross-tabulations, and the percentages of agreement/disagreement and kappa statistics (K, a measure of inter-observer concordance on categorical scales that adjusts

Bibliographic reference	Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001
	for chance agreement) and their standard errors were calculated. For abnormalities analysed dichotomously (for example, absence/presence of advanced AMD), kappa statistics are unweighted; for abnormalities with extended scales (for example, drusen area), a weighted varient was also computed assigning a weight of 1 for perfect agreement and, 0.75 for one-step disagreements, and 0 for all other disagreements. 0-0.20 was considered slight agreement; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; and more than 0.80, almost perfect agreement.
Results	Interobserver contemporaneous reproducability AMD severity level Agreement- 82.8% Agreement within 1 step: 98.7% Kappa, unweighted (SE)- 0.77 (0.01) Kappa, weighted (SE)- 0.88 (0.01) Intraobserver temporal reproducability AMD severity level Agreement- 88.2% Agreement within 1 step: 98.3% Kappa, unweighted (SE)- 0.83 (0.04) Kappa, weighted (SE)- 0.88 (0.04)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? No- the sample was selected to include a wide range of abnormalities and age-related macular degeneration severity. Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability

Bibliographic reference	Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001
	Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was masked when assessing contemporaneous and temporal grading variability. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes (grader the only difference) Were all patients included in the analysis? No a sample of 1230 eyes chosen to represent the full range of abnormalities and age-related maculopathy severity. Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.
Country/ies where the study was carried out	USA
Study type	Retrospective cohort

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**
Aim of the study	To establish continuity with the grading procedures and outcomes from the historical data of the Age-Related Eye Disease Study (AREDS).
Study dates	Published 2013
Source of funding	Supported by National Eye Institute Grant
Sample size	1335 eyes were reviewed
Characteristics	Baseline characteristics not reported
Inclusion Criteria	Participants of the AREDS2 study
Exclusion Criteria	None reported
Tests	AREDS2 photographers and clinical site digital camera systems are certified by the reading center. Color stereoscopic fundus photographs were obtained using three photographic fields of the macula and optic nerve with 308 or 358 fundus cameras, as in AREDS. The imaging protocol specifies field position and stereoscopic technique. Seven models of digital fundus cameras were permitted for use in AREDS2. All had a minimum resolution specification of 3 megapixels. For baseline image collection, 20 of 82 clinical sites did not have approved digital fundus cameras and were allowed to use Ektachrome color slide film (Eastman Kodak Co., Rochester, NY) for photography. Subsequently, all clinical sites transitioned to digital color photography. Evaluation was performed using both the original and optimized images. Graders could use limited zoom features in the display software. An electronic Early Treatment Diabetic Retinopathy Study (ETDRS) macular grid, appropriately sized for the magnification of the digital fundus image, was overlaid to specify the location of some macular lesions by grid subfield, similar to the methodology used in AREDS with acetate overlays on color slides. Drusen area circles as employed in AREDS were also scaled to the magnification of the photograph (determined at the time of camera system certification) and overlaid on the digital image as needed. Baseline AREDS2 images were graded by two independent graders. Grading results were assessed by a software processor, and discrepancies on major questions (component questions for the AREDS2 severity scale) were adjudicated by a third, senior grader (JA). If no grading discrepancies were identified, the first grade was submitted as the grade of record. For annual follow-up images, the grading process consists of single-step grading, independent of prior visit and fellow eye images and data.

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**

Grid and standard circles were used in assessing size, area, and location of abnormalities. The radii of the grid circles are one-third, 1, and 2 optic disc diameters, respectively, and their areas are 4/9, 4, and 16 optic disc areas (DAs). When the diameter of the optic disc is assumed to be 1500µm, the radius of the central circle of the grid is 500µm, that of the middle (inner) circle is 1500µm, and that of the outer circle is 3000µm. The standard circles have the following diameters and areas:

C-0, 63µm and 0.0017 DA;
C-1, 125µm and 0.0069 DA;
C-2, 250µm and 0.028 DA;
I-2, 354µm and 0.056 DA;
O-2, 650µm and 0.19 DA;
0.5 DA, 1061µm and 0.50 DA.

9-step severity scale		
Step Drusen Area	Increased Pigment	Depigmentation-GA
<C-1	0	0
≥C-1, <C-2	0	0
<C-2	≥Q*	≥, <102
≥C-2, <1-2	0	0
≥1-2, <O-2	0	0
≥C-1, <102	≥Q	≥Q, <1-2
<C-2	≥0	≥1-2, <0.5DA
≥O-2, <0.5DA	0	0
≥1-2, <O-2	≥Q	≥Q, <1-2
≥C-2	≥0	≥1-2, <0.5DF
≥0.5 DA	0	0
≥O-2, <0.5DA	≥Q	≥Q, <1-2
≥1-2, <O-2	≥0	≥1-2, <0.5DA

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**

≥0.5 DA	≥Q	≥Q, <1-2
≥O-2, <0.5DA	≥0	≥1-2, <0.5DA
≥0.5 DA	≥0	≥1-2, <0.5DA
Any	≥0	≥0.5 DA
Any	≥0	Non-central GA

*Q= questionable

Geographic atrophy was defined as an area of partial or complete depigmentation of the RPE in the fundus photographs that had at least 2 of the following 3 characteristics: roughly round or oval shape, sharp margins, and visibility of underlying large choroidalvessels. Depigmentation adjacent to disciform scars was not classified as GA, even if these criteria were met.

Neovascular AMD was defined as the definite presence in the fundus photographs of 1 or more of 4 characteristics: serous sensory retinal detachment, RPE detachment, subretinal hemorrhage, or subretinal fibrous tissue; or of a report from the clinic of the application of photocoagulation for choroidal new vessels at any previous visit.

The presence of central GA was defined as questionable or definite involvement of the center of the macula by definite GA.
Advanced AMD was defined as neovascularAMD or CGA

Methods	Baseline AREDS2 images were graded by two independent graders. Grading results were assessed by a software processor, and discrepancies on major questions (component questions for the AREDS2 severity scale) were adjudicated by a third, senior grader (JA). If no grading discrepancies were identified, the first grade was submitted as the grade of record. For annual follow-up images, the grading process consists of single-step grading, independent of prior visit and fellow eye images and data. A temporal drift sample of 88 stratified baseline images is regraded annually by the entire grading group; the results were compared to original grades for the same sample. The temporal drift reproducibility exercises allow monitoring the shift due to grader experience, change in grading personnel, and technological advances, particularly in studies with long follow-up such as AREDS2. The contemporaneous quality control included monthly regrade of a random sample of 5% of submissions. These images were duplicated and passed through the grading process with fictitious identifiers for masked replicate grading. The

Bibliographic reference	Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.
	reproducibility of grading is assessed by calculating percentage agreement and weighted Kappa statistics for ordinal variables and correlation coefficients for continuous area measurements for the entire group. Regular training exercises are held for the entire grading group with review of difficult cases and reaffirmation of the grading protocol. Reproducibility statistics were also examined for individual graders, and targeted individual retraining was performed if the grader has reproducibility for specific questions below a set threshold. All graders were encouraged to seek out a reading center ophthalmologist for ‘‘second opinions’’ for assistance with unusual presentations or confounding ocular abnormalities. On an ongoing basis, any eyes meeting the study endpoint were reviewed by a reading center ophthalmologist to confirm the endpoint.
Results	AREDS2 Temporal Drift Regrade Year 4 Compared to BL, (intraobserver agreement) (n=88) Agreement: 92% Weighted Kappa (SE): 0.73 (0.02) Contemporaneous regrades, (interobserver agreement) (n=1335) Agreement: 96% Weighted Kappa (SE): 0.76 (0.01) Historical AREDS Temporal Drift (AREDS Report 6 and 17), (n=119) Agreement: 94% Weighted Kappa (SE): 0.73 (0.01)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Random sample of 5% of images were selected for contemporaneous regrading. Unclear selection process when choosing a stratification of images for temporal regrading. Was a case-control design avoided? Yes

Bibliographic reference	Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.
	Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently of past grades or contemporaneous grading. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes (grader the only difference, with the exception of optimized digital photographs being used in the AREDS2 study compared to film images in AREDS) Were all patients included in the analysis? No a sample of 1335, this sample was selected randomly for the contemporaneous comparisons. Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	**Klein et al., 2011. Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550.**
Country/ies where the study was carried out	USA
Study type	Prospective Cohort Study
Aim of the study	To design a risk assessment model for development of advanced age-related macular degeneration (AMD) incorporating phenotypic, demographic, environmental, and genetic risk factors.
Study dates	Published 2011 Participants in the Age-Related Eye Disease Study
Source of funding	This work was supported by the Casey Eye Institute Macular Degeneration Fund, Research to Prevent Blindness, the Bea Arveson Macular Degeneration Fund, and the Foundation Fighting Blindness.
Number of patients	2846 participants
Inclusion Criteria	• Age 55-80 years • At least one eye had to be free from vision-threatening disease other than AMD and cataract • That eye could not have had surgery, except for cataract surgery • The participants' stages of disease ranged from no evidence of AMD in either eye, to advanced AMD with vision loss in one eye but good vision (at least 20/30) in the other eye
Exclusion Criteria	None described
Diagnostic criteria	Comprehensive ocular and medical histories and examinations were performed at entrance into the study. Recorded information included age, sex, race, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), education level, cigarette smoking, diet, sunlight exposure, history of skin cancer, arthritis, systemic hypertension, other cardiovascular diseases, diabetes, and history of current and past medications and dietary supplements. For this study, the AREDS simplified severity scale was used to classify participants by their retina phenotype; This scale was designed to define risk categories for development of advanced AMD that could be readily determined by either clinical examination or fundus photography. The system uses 2 retinal abnormalities at baseline to determine a risk score: The end points of this study occurred when participants with no advanced AMD in either eye at baseline progressed to advanced AMD in either eye,and when those with advanced AMD in 1 eye at baseline developed advanced AMD in the fellow eye.

Bibliographic reference	Klein et al., 2011. Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550.
	Two forms of advanced AMD were recognized: (1) NV and (2) GA, defined as an area of well-demarcated depigmentation of the pigment epithelium, typically round or oval, and within which choroidal vessels are usually visible.
Patient characteristics	Median Age: 69 years 56% female Only white ethnicity included in the analysis
Predictors/risk factors and effect estimates	Risk factors of interest were: Very large drusen, Current smoking, Family history, AAMD in 1 eye, Age, mean (SD), y Hazard ratios were adjusted for age, cigarette smoking, family history, BMI, education, simple scale score, very large drusen (250 µm), unilateral AMD, and variants in the genes CFH, ARMS2, C3, and CFI. The C2/CFB variant. (all significant at univariable level)
Outcomes	Hazard Ratios for Progression to Advanced Age-Related Macular Degeneration
Analysis used	Cox proportional hazards analysis
Length of follow up	Follow-up averaged 9.3 years
Missing data handling/loss to follow up	Unclear: no description of missing data or how this was managed.
Results	Simple Scale Score: The Simple scale score is determined by the sum of the following risk factors in both eyes: Large drusen (>=125 um diameter) and pigment abnormality. A score of: 0) indicates no risk factors in either eye; 1) 1 risk factor in either eye; 2) total of 2 risk factors in either eye; 3) total of 3 risk factors in both eyes; 4) total of 4 risk factors in both eyes.

Bibliographic reference	Klein et al., 2011. Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550.
	Multivariate Association of Baseline Independent Variables Included in Final Model With Hazard Ratios for Progression to Advanced Age-Related Macular Degeneration at 2, 5, and 10 Years in 2602 Participants (95% Confidence Interval) 0) referent 1) 6.38 (3.48-11.69) 2) 14.12 (8.06-24.75) 3) 34.53 (19.79-60.26) 4) 50.65 (28.86-88.89)
Limitations	Treatment assignment was not considered in this analysis... Quality assessment criteria for prognostic studies as outlined in: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37 The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). PARTLY Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.
Country/ies where the study was carried out	USA, Netherlands, Australia
Study type	Retrospective cohort
Aim of the study	To describe methods to harmonize the classification of age-related macular degeneration (AMD) phenotypes across four population-based cohort studies: the Beaver Dam Eye Study (BDES), Blue Mountains Eye Study (BMES), Los Angeles Latino Eye Study (LALES), and Rotterdam Study (RS).
Study dates	Published 2014
Source of funding	The Beaver Dam Eye Study was supported by National Institutes of Health grant EY06594 (BEK Klein and R Klein) and, in part, by an unrestricted grant from Research to Prevent Blindness. The National Eye Institute provided funding for entire study including collection and analyses of data; The Blue Mountains Eye Study was supported by grants from the National Health & Medical Research Council, Canberra, Australia. The Rotterdam Study is supported by Stichting Lijf en Leven, Krimpen aan de Lek; MD Fonds, Utrecht; Rotterdamse Vereniging Blindenbelangen, Rotterdam; Stichting Oogfonds Nederland, Utrecht; Blindenpenning, Amsterdam; Blindenhulp, The Hague; Algemene Nederlandse Vereniging ter Voorkoming van Blindheid (ANVVB), Doorn; Landelijke Stichting voor Blinden en Slechtzienden, Utrecht; Swart van Essen, Rotterdam; Stichting WinckelSweep, Utrecht; Henkes Stichting, Rotterdam; Laméris Ootech BV, Nieuwegein; Medical Workshop, de Meern; Topcon Europe BV, Capelle aan de IJssel, all in the Netherlands, and Heidelberg Engineering, Dossenheim, Germany. The Los Angeles Latino Eye Study was supported by the National Institutes of Health grants, an unrestricted grant from Research to Prevent Blindness, and Pfizer, Inc.
Sample size	60 images were graded by each of the centres
Characteristics	No baseline characteristics were reported in this study.
Inclusion Criteria	Participants of the Beaver Dam Eye Study with lesions characteristic of the range of severity of AMD.
Exclusion Criteria	None reported

Bibliographic reference	**Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.**
Tests	A Three Continent AMD Consortium severity scale was developed based on harmonized cutpoints defining each early AMD lesion. This scale allowed for the common definitions of prevalence and incidence of AMD to be used. The scale has five categories of AMD severity numbered from 10 to 50, where level 10 represents no AMD and level 50 represents late AMD. Levels 20, 30, and 40 represent mild, moderate, and severe stages of early AMD, respectively. An AMD severity scale score was assigned to each eye based on lesion severity as graded by each study's grading protocol, i.e., each image had four grades, one from each study group. Definitions: Large drusen size: ≥ 125 pm in diameter Large drusen area: ≥ 650 pm in diameter Increased pigment: Any AMD related increased pigment RPE depigmentation: Any AMD related RPE depigmentation Geographic atrophy: Area of atrophy ≥350 µm in diameter and presence of at least 2 of these features: sharp edge, lack of RPE, visible choroidal vessels, and circular shape. Exudative AMD: Presence of any of the following: pigment epithelial detachment and/or retinal detachment, subretinal haemorrhage, subretinal scar, subretinal new vessels, treatment for exudative lesion. <u>Three Continent AMD Consortium age-related macular degeneration severity scale</u> 10- **No AMD:** No, questionable, small, or intermediate sized drusen (<125 µm in diameter) only, regardless of area of involvement, and no pigmentary abnormalities (defined as increased retinal pigment or RPE depigmentation present) OR No definite drusen with any pigmentary abnormality. 20- **Mild early AMD:** Small to intermediate sized drusen (<125 µm in diameter), regardless of area of involvement, with any pigmentary abnormality. OR Large drusen (≥125 µm in diameter) with drusen area <331,820 µm2 (equivalent to O-2 circle, defined as a circle with diameter of 650 µm) and no pigmentary abnormalities. 30- **Moderate early AMD:** Large drusen (≥125 µm in diameter) with drusen area <331,820 µm2 and any pigmentary abnormality OR

Bibliographic reference	Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.
	Large drusen (≥125 µm in diameter) with drusen area ≥331,820 µm2, with or without increased retinal pigment but no RPE depigmentation. 40- **Severe early AMD:** Large drusen (≥125 µm in diameter) with drusen area ≥331,820 µm2 and RPE depigmentation present, with or without increased retinal pigment. 50- **Late AMD:** Pure geographic atrophy in the absence of exudative macular degeneration OR Exudative macular degeneration with or without geographic atrophy present.
Methods	To assess lesion-specific definitional differences among the three grading centers, there were digitized a set of stereoscopic images of 60 eyes with lesions characteristic of the range of severity of AMD selected from Beaver Dam Eye Study (BDES) participants, then reprinted the images on film and sent identical copies to the 4 grading teams. The image set had a balanced distribution of lesion characteristics considered to be typical of AMD: varying drusen size, type, and area, increased retinal pigment, retinal pigment epithelium (RPE) depigmentation, geographic atrophy, RPE detachment/sensory serous retinal detachment, subretinal hemorrhage, or subretinal fibrous scars. An AMD severity scale score was assigned to each eye based on lesion severity as graded by each study's grading protocol, i.e., each image had four grades, one from each study group. To evaluate grader variability, they then compared the consortium scale score assigned based on each study's grading scheme to the score that was assigned based on each of the other studies' grading schemes. Weighted kappa statistics were calculated using the Fleiss-Cohen weighting method, which was also used by the Age-Related Eye Diseases Study for grading quality control comparisons.
Results	Using the new harmonized Three Continent AMD Consortium severity scale, the exact grading agreement of the 60 eyes between centers varied from 61.0% to 81.4% between centers, and the within-one-step agreement varied from 84.7% to 98.3% between centers. Weighted kappa scores varied from 0.66 to 0.86, indicating moderate to substantial levels of agreement among the grading centers.
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias

Bibliographic reference	Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.
	Methods of patient selection: • Was a consecutive or random sample of patients enrolled? Non-random sample of 60 images were selected for contemporaneous regrading. Images were chosen to represent the full range of AMD presentation. • Was a case-control design avoided? Yes • Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: • Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently of past grades or contemporaneous grading. • If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING

Bibliographic reference	**Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.**
	A. Risk of Bias • Was there an appropriate interval between index test(s) and reference standard? Yes • Did all patients receive a reference standard? Yes • Did patients receive the same reference standard? Yes (centre of grading the only difference) • Were all patients included in the analysis? No a sample of 60 eyes, this sample was selected non-randomly from the Beaver Dam Eye Study to represent the full range of AMD severity. Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	**Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To evaluate a clinical classification system, the Clinical Age-Related Maculopathy Staging system (CARMS) for age-related maculopathy (ARM) using a simple grading scale designed for clinical prctice and clinical research protocols
Study dates	Published 2005
Source of funding	Supported in part by Foundation Fighting Blindness
Sample size	492 eyes
Characteristics	Baseline characteristics of participants not reported
Inclusion Criteria	People recruited for the Progression of Age-Related Macular Degeneration Study

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
Exclusion Criteria	Exclusion criteria not reported
Tests	Each clinical assessment included a biomicroscopic slit-lamp examination of the macula with a 60 or 90 diopter lens. The area representing about 6000µm in diameter (approximately 4x the diameter of the disc) and centred on the fovea wasevaluated. Small drusen are <63µm; intermediate drusen ≥63µm but <125µm and large drusen ≥125µm. Retinal pigment epithelial hypopigmentation was defined as decreased pigmentation without well defined borders and visible choroidal vessels. Retinal pigment epithelial hyperpigmentation was defined as increased pigment without pigment clumping. Geographic atrophy was defined as a well-demarcated area of marked decreased retinal pigment with visualisation of the choroidal vessels involving the fovea, or non central atrophy at least 350µm in diameter (about 3x the width of the retinal vein at the disc margin). The drusenoid or confluent type of retinal pigment epithelial detachment is a well defined cluster of large confluent drusen, often with overlying increased pigment measuring ≥500µm in diameter (about one third of disc diameter) Serous retinal pigment epithelial detachment has ill defined margins with slanting edges. <u>The Clinical Age-Related Maculopathy Staging System</u> 1- No drusen or <10 small drusen without pigment abnormalities 2- Approximately ≥10 small drusen or <15 intermediate drusen or pigment abnormalities associated with ARM • a) Drusen • b) RPE changes (hyperpigmentation and hypopigmentation) • c) Both drusen and RPE changes 3- Approximately ≥15 intermediate drusen or any large drusen • a) No drusenoid RPED • b) drusenoid RPED 4- Geographic atrophy with involvement of the macular center, or noncentral geographic atrophy at least 350µm in size

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
	5- Exudative AMD, including nondrusenoid pigment epithelial detachments, serous or haemorrhagic retinal detachments, choroidal neovascular membrane with subretinal or sub RPE haemorrhages or fibrosis, or scars consistent with treatment of AMD. • a) Serous retinal pigment epithelial detachment without choroidal neovascular membrane • b) Choroidal neovascular membrane or disciform scar
Methods	Fundus photographs of 492 eyes from 246 patients were evaluated by a reader at the Wisconsin Photographic Reading Centre using their grading system. A computorized program converted these gradings to the CARMS 5 point scale. From this database, the photographic files of 50 patients were selected randomly by a co-ordinator not involved in the grading process to yeild between 5 and 15 cases in each of the 5 grades. The photographs of the 50 patients were reviewed and graded according to the CARMS system by the two observers, each of whom was masked to the clinical history and the other graders assessments. The 2 observers were both retinal specialists, one of who had extensive experience with this grading system and one of whom was a senior retinal fellow. The observations from these two observers were compared to determine the amount of interobserver agreement. One observer reviewed and graded the 50 randomly selected photographic files 2 weeks after the initial assessment, without reference to the grades previously assigned, in order to find the intraobserver agreement. Kappa statistics were calculated.
Results	Agreement between Clinical observations and Reading Centre Assessment of Steriophotographs of Eyes with Age-Related Maculopathy Using the Clinical Maculopathy Staging System (CARMS). Agreement: 75% Agreement within 1 step: 89% Kappa, unweighted (95% CI): 0.63 (0.53-0.74) Kappa, weighted (95% CI): 0.78 (0.62-0.93) Agreement between 2 observers assessments of Age-Related Maculopathy based on Steriophotographs using the CARMS. Agreement: 84% Agreement within 1 step: 90% Kappa, unweighted (95% CI): 0.79 (0.47-1.1) Kappa, weighted (95% CI): 0.86 (0.41-1.3) Intraobserver agreement

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
	Agreement: 94% Agreement within 1 step: 100% Kappa, unweighted (95% CI): 0.92 (0.58-1.3) Kappa, weighted (95% CI): 0.97 (0.49-1.4)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: • Was a consecutive or random sample of patients enrolled? A random sample of 50 images were selected for contemporaneous regrading between centres, to yield between 5-15 cases in each of the 5 CARMS grades. • Was a case-control design avoided? Yes • Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: • Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of past grades or contemporaneous grading.

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
	• If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias • Was there an appropriate interval between index test(s) and reference standard? Yes • Did all patients receive a reference standard? Yes • Did patients receive the same reference standard? Yes (grader the only difference) • Were all patients included in the analysis? No a sample of 50, this sample was selected randomly from The Progression of Age-Related Macular Degeneration Study to yield 5-15 images for each of the CARMS grades. Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
Country/ies where the study was carried out	UK

Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
Study type	Retrospective cohort
Aim of the study	To assess the value of the modified international classification system in screening high-risk patients with bilateral age-related maculopathy (ARM) from those with lower risk characteristics.
Study dates	Published 2006
Source of funding	Unclear
Sample size	164 images of 106 patients
Characteristics	Group A = bilateral ARM (drusen/drusen) group, which included 133 images. Group B = fellow eye of exudative AMD (drusen/CNV) group which involved 31 images No other baseline characteristics reported
Inclusion Criteria	• Patients with bilateral ARM (drusen in both eyes) • Fellow eye of patients with unilateral exudative AMD. • Images of poor quality
Exclusion Criteria	• no signs of ARM in both eyes • bilateral neovascular disease or advanced atrophy. • Patients with ocular comorbidity from diseases other than AMD such as diabetes.
Tests	Colour fundus images of consecutive patients referred to the Retinal Research Unit at King's College Hospital, London, between December 2002 and December 2003. All images were centred on the macula. Images were graded according to the classification below: <u>The Modified International Classification of ARM</u> 0a No signs of ARM at all 0b Hard drusen (<63 µm) only 1a Soft distinct drusen (≥63 µm) only 1b Pigmentary abnormalities only, no soft drusen (≥63 µm)

Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
	2a Soft indistinct drusen (≥125 μm) or reticular drusen only 2b Soft distinct drusen (≥63 μm) with pigmentary abnormalities 3 Soft indistinct (≥125 μm) or reticular drusen with pigmentary abnormalities 4 Atrophic or neovascular AMD
Methods	The selected images were randomised by an independent investigator and then graded by two ophthalmologists, independent of each other, using the modified International Classification of ARM. Graders were masked to the patient diagnosis. Discrepancies between the two graders were resolved by a third expert grader. The interobserver variability of the graders was assessed using the Kappa statistical method.
Results	The interobserver consistency between the two graders was high with a Kappa value of 0.82 (SE 0.34).
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: • Was a consecutive or random sample of patients enrolled? A random sample of 164 images were selected from consecutive patients patients referred to the Retinal Research Unit at King's College Hospital, London. • Was a case-control design avoided? Yes • Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants B. Concerns regarding applicability

Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
	Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: • Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. • If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias • Was there an appropriate interval between index test(s) and reference standard? Yes • Did all patients receive a reference standard? Yes • Did patients receive the same reference standard? Yes (grader the only difference) • Were all patients included in the analysis? Some were excluded due to poor photographic quality. Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To determine whether clinical tests of ocular function and macular appearence independently can help to predict which patients with unilateral neovascular age-related AMD will have a choroidal neovascular membrane develop in their fellow eye.
Study dates	Published 1997 data collected 1990 to 1995
Source of funding	Grants from National Eye Institute, the Foundation for Fighting Blindness and the Massachusetts Lions Eye Research Fund, Inc.
Number of patients	127 patients with unilateral neovascular AMD
Inclusion Criteria	• Snellen visual acuity of 20/60 or better in the fellow eye with sufficiently clear media to allow adequate visualisation of the fundus. • the presence of a choroidal neovascular membrane in the macular of the affected eye • macular drusen in both eyes • no sign of other retinal disease
Exclusion Criteria	• Bilateral dry AMD • Bilateral Neovascular AMD • Choroidal neovascularisation assoicated with high myopia
Diagnostic criteria	On the study eye, best corrected visual acuity was measured using a Snellen chart. Mucular visual field was assessed by letter recognition perimetry. Foveal glare recovery time was assessed by photostress testing. Foveal electroretinograms were recorded with a hand-held stimulator ophthalmoscope. Measurements of ocular function, biomicroscopy and direct and indirect ophthalmoscopy were performed and photographs of each macular were obtained.

Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
	Fluorescein angiography was performed if a recent one was unavailable. Or if the fundus showed recent changes that could be attributable to choroidal neovascularisation.
Patient characteristics	Age: median 74 years Gender: 57 men, 70 women Ethnicity: not described
Predictors/risk factors and effect estimates	Risk factors assessed were: age, spherical equivalent, glare recovary time, focal electroretinal implicit time, No. of large drusen (quartiles 1-4), macular appearance grade. Prognostic factors entered into the analysis were: age, body mass index, blood pressure, spherical equivalent, snellen acuity, STDRS acuity, number of visual field defects, glare recovery time, foveal electroretinogram amplitude, foveal electroretinogram implicit time, and grade of macular appearance.
Outcomes	Relative risk of developing a choroidal neovascular membrane.
Length of follow up	4.5 years follow up follow up visits every 6 months
Missing data handling/loss to follow up	93 people from the initial 127 had been lost to follow up and were censored by the end of 4.5 years.
Results	Hazards ratio for development of choroidal neovascular membrane (95% confidence intervals) Macular appearance scale (4-point scale) Grade 1: rare (<25), predominantly extrafoveal small to intermediate-size distinct soft drusen with slight granularity and minimal-to-slight pigmentary hyperplasia Grade 2: 25 or more small-to intermediate-size distinct soft drusen, rare large distinct soft drusen, and modest RPE disturbance with a few spots of hyperplasia. Grade 3: numerous large distinct soft drusen, rare large confluent drusen, and moderate atrophy and hyperplasia. Grade 4: very large (>300um) soft confluent drusen with atrophy and hyperplasia. Hazard ratio: 1.76 (1.18-2.73)

Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
Limitations	Quality assessment criteria for prognostic studies as outlined in: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37 The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). NO Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013
Country/ies where the study was carried out	USA
Study type	Prospective Cohort Study

Bibliographic reference	**Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013**
Aim of the study	The accuracy of predicting conversion from early-stage age-related macular degeneration (AMD to the advanced stages of choroidal neovascularisation (CNV) or geographic atrophy (GA) was evaluated to determine whether inclusion of clinically relevant genetic markers improved accuracy beyond prediction using phenotypic risk factors alone.
Study dates	Published 2013 Participants in the Age-Related Eye Disease Study
Source of funding	Funding was by the Sequenom Center for Molecular Medicine, San Diego. The sponsor participated in designing and conducting the study; collecting, managing, analysing and interpreting the data; and preparing and reviewing the manuscript.
Number of patients	2415 participants, 940 were disease-free subjects and 1475 were subjects with early or intermediate AMD
Inclusion Criteria	• Subjects participating in AREDS trial • White, non-hispanic • Age 55-81 years
Exclusion Criteria	None described
Diagnostic criteria	Data was derived from subjects participating in the AREDS. The AREDS trial was a multicentre, prospective, longitudinal study evaluating the clinical course of AMD and cataracts, as well as the effect of high-dose vitamin/mineral supplementation on progression of these diseases. Clinical, demographic, and environmental data for each participant were retrieved from the AREDS database of Genotype and Phenotype. The baseline disease assignment used in this study was based on the AREDS 5-step (0-4) simplified severity scale with annual visit data graded according to the AREDS 12-point severity scale. This study applied the same definition of progressors used in the AREDS trial. The term “progressors” was defined as individuals with no, early, or intermediate AMD at baseline who progressed to advanced AMD during follow up and individuals with advanced AMD in 1 eye at baseline who progressed to advanced AMD in both eyes. The definition of a control was equivalent to the designation “non-progressor,” which was used to identify subjects with early or intermediate AMD that did not progress to CNV or GA, during the follow up period. Anning the entire range of the baseline simplified severity scale were analysed with an adjustment made for the presence of advanced disease in the non-study eye.
Patient characteristics	Ethnic group: white

Bibliographic reference	**Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013**
	Age (mean (SE)): 68.57 years (0.10) Gender, n: Female- 1394, Male- 1022 Visual acuity: not reported AMD disease stage (simplified severity scale), n: 0) 940, 1) 417, 2) 397, 3) 287, 4) 368 Comorbidities affecting the eye (e.g. cataracts): not reported Current or previous treatment, n: antioxidants only- 720, antioxidants with zinc- 770, zinc only- 466, placebo- 459
Predictors/risk factors and effect estimates	Risk factors of interest were: Simplified severity scale, previous smoker, current smoker, age
Outcomes	Hazard ratios for progression to choroidal neovascularisation Hazard ratios for progression to geographic atrophy
Analysis used	Cox proportional hazards model
Length of follow up	10 year follow up
Missing data handling/loss to follow up	Unclear: no description of missing data or how this was managed. Data was taken from existing database.
Results	Simple Severity Score: The Simple Severity score is determined by the sum of the following risk factors in both eyes: Large drusen (>=125 um diameter) and pigment abnormality.

Bibliographic reference	**Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013**
	A score of: 0) indicates no risk factors in either eye; 1) 1 risk factor in either eye; 2) total of 2 risk factors in either eye; 3) total of 3 risk factors in both eyes; 4) total of 4 risk factors in both eyes. Hazard ratios for progression to choroidal neovascularisation (95% Confidence Interval) 0) referent 1) 4.76 (2.43-9.34) 2) 12.66 (6.87-23.36) 3) 26.56 (14.53-48.58) 4) 35.89 (19.75-65.21) Hazard ratios for progression to geographic atrophy (95% Confidence Interval) 0) referent 1) 6.97 (3.01-16.14) 2) 9.33 (4.13-21.05) 3) 23.29 (10.59-51.22) 4) 34.81 (16.02-75.65)
Limitations	Treatment assignment was not considered in this analysis... Quality assessment criteria for prognostic studies as outlined in: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37 The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). PARTLY

Bibliographic reference	Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013
	Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). UNSURE The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003
Country/ies where the study was carried out	Netherlands, Ireland
Study type	Retrospective cohort
Aim of the study	To compare sterio digital images with sterio 35-mm transparencies as to the quality and reliability of grading AMD in the context of the EUREYE study.
Study dates	Published 2003
Source of funding	European Commission, Macular Disease Society, the society of Prevention of Blindness, Optimex Foundation, Stichting Blindenhulp

Bibliographic reference	van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003
Sample size	91 subjects, 131 eyes
Characteristics	Participants in the EUREYE study Random sampling of people aged 65 years and older Fundus photographs were selected on the basis of their AMD status to represent the entire range of AMD severity including eyes with no AMD fundus signs. The quality of slides varied but none of them were ungradable.
Inclusion Criteria	Participants in the EUREYE study Participants aged 65 years and older
Exclusion Criteria	Lesions that were considered to be the result of generalised vascular disease such as diabetic retinopathy or chorioretinitis, high myopia, trauma, congenital disease, or photocoagulation for reasons other than AMD were excluded from AMD grading.
Tests	35-mm film and 35º sterioscopic colour fundus images were obtained for each eye. framed transparencies were mounted on plastic sheets and were examined with a portable sterio viewer that provided 5X image magnification on a tilted table viewing box with a back light. Digital images were examined on a SONY CRT monitor Two graders both having 8 years of experience in AMD grading were trained for 2 months in digital image grading. After this point graders randomly graded all 35-mm slides and digital images.
Methods	For each eye four scores were obtained by 2 different imaging techniques and 2 different graders.
Results	On all 8 stages: digital images Agreement: 59.0 Weighted kappa: 0.72 On all 8 stages: 35-mm film Agreement: 65.7% Weighted kappa: 0.78 On the 5 main stages: digital images Agreement: 64.9% Weighted kappa: 0.74 On the 5 main stages: 35-mm film

Bibliographic reference	van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003
	Agreement: 72.3% Weighted kappa: 0.79
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? No images were selected to represent the full range of AMD severity Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING

Bibliographic reference	van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003
	A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes (grader the only difference) Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.
Country/ies where the study was carried out	France
Study type	Prospective cohort
Aim of the study	To describe the types and location of choroidal neovascularisation (CNV) in exudative age-related macular degeneration (AMD), including vascularised pigment epithelial detatchments (PED), and most recently described subtypes, such as retinal choroidal anasmostosis, also termed ‘‘retinal angiomatous proliferation’’ (RAP).
Study dates	Published 2007
Source of funding	Employees of Pfizer
Sample size	207 patients with newly diagnosed exudative AMD
Characteristics	67.2% of women, Mean age 79.1±7.3

Bibliographic reference	**Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.**
	The study did not report characteristics for the following variables: Ethnic group Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts)
Inclusion Criteria	• Four private and three hospital based referral centres all over France. • Consecutive patients with newly diagnosed exudative AMD • At least one eye undergoing fluorescein angiography in the centre.
Exclusion Criteria	• Patients with myopic CNV or with CNV of origin other than AMD • Patients with idiopathic Polypoidal Choroidal Vasculopathy were not included. • Eyes having already received treatment for CNV.
Tests	Fluorescein and ICG angiography were carried out in accordance with the routine practice at each centre. Fundus camera and/or scanning laser ophthalmoscope were used according to the routine practice of the different centres. For each patient, the centre provided one red-free photograph and at least three images of fluorescein angiography: one early phase (<45s), one mid-phase (between 45 s and 3 min) and one late-phase (>5 min). In cases of suspicion of occult CNV or RAP, ICG angiography was performed in accordance with routine practice in the centres. When performed for ICG angiography, at least two images had to be provided: one early phase (<2 min) and one late-phase (>20 min).
Methods	The centre's ophthalmologist indicated (for each included eye) the size of the lesion as obtained by comparison to the disc diameter of the studied eye, the location of CNV (extrafoveal, juxtafoveal, subfoveal), and the classification of CNV types classic only, predominantly classic, minimally classic, occult without PED (with or without RAP) and vascularised PED (with or without RAP). The prescribed treatment after the visit was also recorded. The selected images and questionnaires were then reviewed by two independent experts who were blinded to the centre and the identity of the subject. All lesions were classified by both experts and the results compared after completion of the evaluation. Any disagreement was resolved by a third, independent

Bibliographic reference	**Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.**
	expert. At completion of the study, there were two diagnoses for each included subject for the size of the lesion, the location, and the classification of CNV: a local diagnosis delivered by the centre's ophthalmologist and a validated expert diagnosis.
Results	When comparing the local and centralised (final) classification, k was 0.52 for location of the lesions and 0.59 for type of the lesion, showing moderate agreement.
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Consecutive patients with newly diagnosed exudative neovascular AMD at several different centres Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants, many important characteristics were not reported. B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: MODERATE- people with polypoidal vascular choroidal neovascularisation were excluded DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. If a threshold was used, was it pre-specified? NO PRESPECIFICATION SEEMS TO HAVE BEEN USED. Each centre made the diagnosis based on their own clinical opinion with no shared criteria. Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. However the lack of a clear criteria adds to the uncertainty regarding whether discrepancies were due to interpretation or differing criteria. B. Concerns regarding applicability

Bibliographic reference	**Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.**
	Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? no (some participants also received ICG testing, there was no clear criteria who should receive this and who shouldn't, this seems to vary by centre) Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: MODERATE

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Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**
Country/ies where the study was carried out	France, Japan, Singapore
Study type	Prospective cohort
Aim of the study	To compare and analyze differences and similarities between Japanese and French patients in subtype diagnosis of exudative age-related macular degeneration (AMD) as determined by fundus photography (FP) and fluorescein angiography (FA), and a multimodal imaging involving FP, FA, indocyanine green angiography (ICGA), and optical coherence tomography (OCT).
Study dates	Published 2014
Source of funding	Author conflicts: Allergan, Bayer, Novartis, Pfizer, Roche, GlaxoSmithKline, Topcon Corporation, Nidek, Canon. This research was supported in part by the Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS).

Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**
Sample size	99 consecutive Japanese eyes and 94 consecutive French eyes with exudative AMD
Characteristics	The mean age of the 99 Japanese patients (70 men and 29 women) was 74.0 ± 8.9 years, and all patients were ethnically Japanese. The mean age of the 85 French patients (45 men and 40 women) was 73.5 ± 7.9 years, and 98% were white. The study did not report characteristics for the following variables: Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts)
Inclusion Criteria	• Consecutive patients who visited the Department of Ophthalmology, Kyoto University Hospital with a tentative diagnosis of neovascular AMD (Kyoto cases) and patients with presumed neovascular AMD at Centre d'Ophtalmologie de Paris. • Consecutive patients with presumed neovascular AMD
Exclusion Criteria	• Angiographic images of low quality (1 eye excluded)
Tests	All patients underwent comprehensive ophthalmic examinations, including the measurement of best-corrected visual acuity, intraocular pressure testing, indirect ophthalmoscopy, slitlamp biomicroscopy with a contact lens, spectral-domain OCT (Spectralis HRAþOCT; Heidelberg Engineering, Heidelberg, Germany), and FA/ICGA (HRA-2; Heidelberg Engineering). Both Kyoto and Paris cases were subgrouped into: (1) AMD with type 1 CNV; (2) AMD with type 1 + 2 CNV;

Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**
	(3) AMD with type 2 CNV only; (4) chorioretinal anastomosis. (5) PCV, either (5a) without CNV or (5b) associated with type 1 or 2 CNV. Eyes with PCV with branching vascular network without CNV were categorized to (5a) PCV without CNV. A diagnosis of PCV was made based on fundus photography, FA/ICGA, and OCT: elevated orange-red lesions, characteristic polypoidal lesions at the edge of a branching vascular network on angiography, and prominent anterior protrusion of the retinal pigment epithelium line in OCT images. A diagnosis of chorioretinal anastomosis was also made based on fundus photography, FA/ICGA, and OCT: subretinal, intraretinal, or preretinal juxtafoveal hemorrhages; dilated retinal vessels; lipid exudates; and retinal–choroidal anastomosis. For the analysis of AMD subtypes, AMD with type 1 CNV, AMD with type 2 CNV, and AMD with type 1þ2 CNV were regarded as typical exudative AMD, and PCV associated with type 1 or 2 CNV and PCV without type 1 or 2 CNV were regarded as PCV.
Methods	At Kyoto University, 2 retina specialists evaluated fundus photography and FA and made the ‘‘firststep diagnosis’’ for both Kyoto cases and Paris cases. If the specialists disagreed regarding the diagnosis, a third retina specialist (N.Y.) was consulted for the final determination. Multimodal images of fundus photography, FA, ICGA, and OCT results were used to make a ‘‘second-step diagnosis.’’ At Centre d’Ophtalmologie de Paris, 2 retina specialists evaluated fundus photography and FA for the ‘‘first-step diagnosis’’ and multimodal images of fundus photography, FA, ICGA, and OCT assessments were used to make a ‘‘second-step diagnosis.’’ In the case of disagreement, a third retina specialist determined the diagnosis. When the ‘‘second-step diagnosis’’ made by the 2 institutes agreed, the diagnosis was regarded as the ‘‘final diagnosis.’’ When the diagnosis by the 2 institutes failed to reach a consensus, retina specialists at Singapore Eye Research Institute were consulted for a diagnosis. In such cases, the diagnosis by Singapore Eye Research Institute was regarded as the ‘‘final diagnosis.’
Results	Agreement outcomes for Neovascular subtypes of AMD, compared to final diagnosis in Kyoto patients

Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**

	Kyoto investigators first step	Kyoto Investigators, second step	Paris investigators first step	Paris Investigators second step
AMD with type 1 CNV	79.4%	91.1%	82.3%	79.4%
AMD with type 1+2 CNV	66.6%	66.6%	16.6%	33.3%
AMD with type 2 CNV	40.0%	60.0%	80%	100%
Chorioretinal anastomosis	66.6%	83.3%	83.3%	83.3%
PCV with type 1 or 2 CNV	33.3%	66.6%	33.3%	66.6%
PCV without type 1 or 2 CNV	56.5%	95.6%	91.3%	95.6%
Other	88.8%	100%	66.6%	100%

For the Kyoto patients 34.3% (34/99) differed from the ‘‘final diagnosis’’ as determined by the 3 facilities together. The number of eyes for which the diagnosis involved disagreement decreased to 10 (10.1%) when considering the ‘‘second step diagnosis,’’ which was based on the additional information provided by ICGA and OCT.

First step: fundus photography and FA

Second step: fundus photography, FA, ICGA, and OCT

*Figures calculated by reviewer from Figure 1 within study, agreement with final diagnosis calculated (that agreed at the third site in Singapore)

<u>Agreement outcomes for Neovascular subtypes of AMD, compared to final diagnosis in Paris patients</u>

<table>
<tr><th>Bibliographic reference</th><th>Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.</th></tr>
<tr><td></td><td>For the Paris patients 24.5% (23/94) differed from the ‘‘final diagnosis’’ as determined by the 3 facilities together. The number of eyes with any disagreement related to diagnosis decreased to 9 (9.6%) for the ‘‘second-step diagnosis’’ based on the additional information provided by ICGA and OCT.

First step: fundus photography and FA

Second step: fundus photography, FA, ICGA, and OCT

<table>
<tr><td></td><td>Kyoto investigators first step</td><td>Kyoto Investigators, second step</td><td>Paris investigators first step</td><td>Paris Investigators second step</td></tr>
<tr><td>AMD with type 1 CNV</td><td>89.5%</td><td>97.9%</td><td>89.5%</td><td>95.8%</td></tr>
<tr><td>AMD with type 1+2 CNV</td><td>78.9%</td><td>89.5%</td><td>36.8%</td><td>68.4%</td></tr>
<tr><td>AMD with type 2 CNV</td><td>60.0%</td><td>60.0%</td><td>100%</td><td>100%</td></tr>
<tr><td>Chorioretinal anastomosis</td><td>60.0%</td><td>100.0%</td><td>80.0%</td><td>80.0%</td></tr>
<tr><td>PCV without type 1 or 2 CNV</td><td>75.0%</td><td>87.5%</td><td>33.3%</td><td>66.6%</td></tr>
<tr><td>Other</td><td>50%</td><td>75%</td><td>100%</td><td>100%</td></tr>
</table>

*Figures calculated by reviewer from Figure 2 within study, agreement with final diagnosis calculated (that agreed by the third site in Singapore)</td></tr>
<tr><td>Limitations</td><td>Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly:

QUADAS 2 QUADAS website.

DOMAIN 1: PATIENT SELECTION
A. Risk of Bias
Methods of patient selection:
Was a consecutive or random sample of patients enrolled? Consecutive patients with presumed exudative neovascular AMD at two sites</td></tr>
</table>

Bibliographic reference	Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.
	Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants, B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. If a threshold was used, was it pre-specified? NO PRESPECIFICATION SEEMS TO HAVE BEEN USED. Each centre made the diagnosis based on their own clinical opinion with no shared criteria. Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. However the lack of a clear criteria adds to the uncertainty regarding whether discrepancies were due to interpretation or differing criteria. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
Country/ies where the study was carried out	USA
Study type	Prospective cohort
Aim of the study	To determine the frequency of neovascularization subtypes as determined by fluorescein angiography (FA) alone vs FA and optical coherence tomography (OCT) grading in age-related macular degeneration (AMD).
Study dates	Published 2014
Source of funding	Macular foundation inc.
Sample size	374 treatment naïve patients with neovascular AMD in at least 1 eye
Characteristics	Mean age was 86.3 6 8.1 years; 67.7% of eyes (180/266) were from female patients and 95.5% (254/266) from white patients, followed by 2.6% (7/266) Hispanic, 1.5% (4/266) Asian, and 0.4% (1/266) African-American The study did not report characteristics for the following variables: Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts)
Inclusion Criteria	• older than 50 years • newly diagnosed treatment-naıve NV as evidenced by clinical examination and FA. • Best-corrected visual acuity was 20/20–20/800 on a Snellen chart

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
	• Eyes in the study must have had OCT imaging (time-domain or spectral-domain) performed at the time of diagnosis.
Exclusion Criteria	• Previous treatments for CNV in the study eye, including photodynamic therapy (PDT), intravitreal steroids, intravitreal pegaptanib (Macugen; Valeant, Montreal, Quebec, Canada), or thermal laser • Eyes with CNV lesions presenting with subfoveal fibrosis, central geographic atrophy (GA) at baseline, or retinal pigment epithelial tears, or composed of more than 50% hemorrhage. • Eyes with CNV secondary to other maculopathies, including degenerative myopia, angioid streaks, presumed ocular histoplasmosis syndrome, or inflammatory maculopathies.
Tests	FA images were obtained using a Topcon TRC 501x fundus camera (Topcon Imagenet, Tokyo, Japan). OCT imaging of all patients was performed with time-domain OCT (Stratus; Carl Zeiss Meditec Inc, Dublin, California, USA) or spectral-domain OCT. OCT instrumentation was necessary for additional accurate identification oflesion subtype utilizing the anatomic classification of lesion subtype. Standard methods of image acquisition were employed for all imaging modalities.
Methods	The classification of neovascular lesions was made independently by 2 experienced retina specialists who evaluated the presenting color photographs, FA, and OCT. First, all the color photographs and FA corresponding to the baseline diagnostic visit were analyzed. Neovascular lesions were subtyped according to the MPS criteria and the Digital Angiographic Reading Center (DARC) Reader's Manual as occult or classic CNV. RAP lesions were identified by criteria defined by Yannuzzi and associates and the DARC Reader's Manual. Secondly, OCT images corresponding to the same diagnostic visit were reviewed, and each case was classified according to the guidelines provided by Freund and associates. The anatomic classification, which uses OCT in combination with FA, categorizes lesions as type 1 (sub–retinal pigment epithelium [RPE]), type 2 (subretinal), type 3 (intraretinal), or mixed NV. Eyes with PCV were considered to be a form of type 1 CNV. Type 1, 2, and 3 NVs corresponded to occult, classic, and RAP angiographic lesions, respectively. Cases with multiple lesion types were identified as mixed NV and each component was also recorded. MORE DETAIL REGARDING CLASSIFICATION SYSTEM WITHIN STUDY
Results	<u>Classification system Agreement</u>

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
	Overall, there was good agreement between FA and anatomic classification with a k statistic of 0.65 (standard error 60.37, P < 0.001). In the subgroup on that used spectral domain OCT technology at baseline: Overall, again there was good agreement between FA and anatomic classification, with a k statistic of 0.67 (standard error 60.05, P < .001).
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Consecutive patients with treatment naïve exudative neovascular AMD were enrolled Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants, B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? 2 independent observers were not masked to the original diagnosis of neovascular AMD. If a threshold was used, was it pre-specified? YES. Could the conduct or interpretation of the index test have introduced bias? Unclear

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
	NA- the purpose of this study is to assess how interpretation may differ between classification systems using different tests at the same point of diagnosis. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE- we are not so much interested in the agreement between diagnostic tests but graders for a classification system. DOMAIN 3: REFERENCE STANDARD- no reference standard in this study DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No, but subgroup analysis was performed for those who received a different type of OCT analysis Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	**Friedman, S. M., & Margo, C. E. (2000). Choroidal neovascular membranes: reproducibility of angiographic interpretation. American journal of ophthalmology, 130(6), 839-841.**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To determine interobserver agreement for classifying choroidal neovascular membranes in age-related macular degeneration.
Study dates	Published 2000

<table>
<tr><th>Bibliographic reference</th><th>Friedman, S. M., & Margo, C. E. (2000). Choroidal neovascular membranes: reproducibility of angiographic interpretation. American journal of ophthalmology, 130(6), 839-841.</th></tr>
<tr><td>Source of funding</td><td>Unclear</td></tr>
<tr><td>Sample size</td><td>Six fluorescein angiograms of choroidal neovascular membranes</td></tr>
<tr><td>Characteristics</td><td>The study did not report characteristics for the following variables:
Ethnic group
Age
Gender
Visual acuity
AMD disease stage
Comorbidities affecting the eye (e.g. cataracts)
Current or previous treatment</td></tr>
<tr><td>Inclusion Criteria</td><td>• Fluorescein angiograms of choroidal neovascular membranes
• No other clear inclusion criteria</td></tr>
<tr><td>Exclusion Criteria</td><td>• Unclear</td></tr>
<tr><td>Tests</td><td>High-quality fluorescein angiograms (nonstereoscopic films) of choroidal neovascular membranes in age-related macular degeneration were reviewed by 21 ophthalmologists with fellowship training in retinal disease.</td></tr>
<tr><td>Methods</td><td>Participants were told that on clinical examination all patients had findings of exudative macular degeneration and were asked to identify the type of neovascular membrane as classic only, occult only, mixed, or unable to determine;

A total of 122 angiograms were read (96.8%); four angiograms could not be interpreted by two observers.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Case number</th><th>Membrane type % agreement</th><th>Kappa agreement</th></tr>
<tr><td>1</td><td>100</td><td>1</td></tr>
<tr><td>2</td><td>73</td><td>0.65</td></tr>
<tr><td>3</td><td>25</td><td>0.01</td></tr>
<tr><td>4</td><td>82</td><td>0.76</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Friedman, S. M., & Margo, C. E. (2000). Choroidal neovascular membranes: reproducibility of angiographic interpretation. American journal of ophthalmology, 130(6), 839-841.

5	82	0.76
6	73	0.65
Mean (standard deviation)	72.5 (23.0)	0.64 (0.30)

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Bibliographic reference	Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To assess the frequency of lesion types using fluorescein angiography (FA) in neovascular age-related macular degeneration (nAMD).
Study dates	Published 2004
Source of funding	Minnesota Lions Macular Degeneration Research and Rehabilitation Center, Research to Prevent Blindness
Sample size	200 cases of nAMD from university-based, tertiary retinal referral practice and one comprehensive, and a community-based eye clinic (100 from each center).
Characteristics	<u>Gender:</u> Female: 135 (68%) Male: 65 (32%) <u>Race:</u>

Bibliographic reference	Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.
	Caucasian: 132 (66%) N/A: 68 (24) Age (yrs), Mean: 78 ± 8 years The study did not report characteristics for the following variables: Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• Angiograms were cataloged on electronic files, these were randomly searched for either “nAMD” or “choroidal neovascularization,” • Fluorescein angiograms (n=100) from the CC were selected by reviewing the film-based files alphabetically (patient last names beginning with the letter A and selecting consecutive cases through M), until 100 cases of nAMD were identified from a total of 430 angiograms reviewed
Exclusion Criteria	• Atrophic AMD alone • Evidence of any other major retinal disorder • Quality of the FA was inadequate to interpret. • Prior PDT or transpupillary hermotherapy.
Tests	Fluorescein Angiograms cataloged on electronic files or film based fluorescein angiograms, depending upon the centre at which the investigations were collected.
Methods	Two graders reviewed the stereoscopic FAs and color fundus photographs and documented the lesion type. Determination of lesion type was based on agreement by 2 graders. When there was disagreement regarding the angiograms, they were

Bibliographic reference	Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.
	rereviewed by both graders simultaneously, and a consensus determination was made. Clinical history was not available during the angiographic evaluation. Lesion location, size, type, subtype, and PDT eligibility were documented for each angiogram. Graders were required to determine whether the nAMD lesion was predominantly classic (area of the entire lesion was 50% classic) or minimally classic (area of the classic component was 50% of the entire lesion). The senior grader subcategorized the lesion subtype of occult subfoveal nAMD. A measurement of intergrader agreement (kappa) was calculated for the graders. The definition of lesion type was based on the definitions of the Macular Photocoagulation Study Group. Occult lesions were either fibrovascular pigment epithelial detachments or late leakage of undetermined source was also defined by the Macular Photocoagulation Study Group.
Results	The kappa score between graders was 0.63.
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? A random sample was taken from one centre and a non-random alphabetical based sample was taken from the community based centre. Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear what was done for participants with PCV Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants, many important characteristics were not reported. Also in one of the centres samples were chosen with inadequate randomisation (alphabetical) B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: MODERATE- non-random selection, unclear status of PCV.

Bibliographic reference	Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.
	DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Unclear if grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Yes and cited (MPS) Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? no (some participants were graded based on FA photographs, others on electronic FA photographs) Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: MODERATE

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Bibliographic reference	Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.
Country/ies where the study was carried out	USA
Study type	Prospective cohort

Bibliographic reference	**Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.**
Aim of the study	To determine intraobserver and interobserver variation for classifying types of choroidal neovascularizations (CNV) in exudative age-related macular degeneration (ARMD).
Study dates	Published 2003
Source of funding	The State of Baden-Wurttemberg grant
Sample size	40 patients with neovascular ARMD, graded by 16 retinal specialists.
Characteristics	The study did not report characteristics for the following variables: Ethnic group Age Gender Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• Neovascular AMD
Exclusion Criteria	• No exclusion criteria reported
Tests	Digital high-quality fluorescein angiographies from 40 patients with exudative ARMD were obtained using a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph, Heidelberg, Germany). From each angiographic series four to six angiograms were selected with angiograms from early, mid, and late phase. These were printed on one page per patient, and two folders were put together with all 40 angiogram sheets in two different randomized sequences.
Methods	The angiograms of both series were presented to 16 retina specialists who are members of the European Fluorescein Angiography Club (FAN-Club) during a meeting in Lyon, France, in December 2000. After instructions on how to use the evaluation form, readers were not allowed to discuss their interpretation with each other or with the investigators present.

Bibliographic reference	**Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.**
	All 40 angiogram sheets were organised in two different randomized sequences (series A and B). Each reader had to classify membrane type into classic, occult, or mixed with classic component less or equal/greater than 50%. After completing the classification of series A, the reader was not allowed to return to the evaluation sheet or the angiogram folder when going through series B. As a measure of intraobserver variability, a coefficient for agreement between classification of angiograms in series A and in series B was calculated for each reader. For the assessment of interobserver variability, pair wise coefficients were calculated between all readers, and were given for series A and series B, respectively.
Results	Intraobserver variability (i.e., the agreement between classification of angiograms in series A and in series B by a single reader) Mean kappa: 0.64 (SD 0.11) Interobserver agreement Mean pairwise kappa coefficient was 0.40 ± 0.05 (series A) and 0.37 ± 0.05 (series B), (indicating less than moderate mean pair wise agreement)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Unclear how sample was selected Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: Unclear B. Concerns regarding applicability Is there concern that the included patients do not match the review question?

Bibliographic reference	**Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.**
	CONCERN: UNCLEAR DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: UNCLEAR (no criteria defined) DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Unclear Were all patients included in the analysis? Unclear Could the patient flow have introduced bias? RISK: UNCLEAR

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Bibliographic reference	**Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.**
Country/ies where the study was carried out	USA

Bibliographic reference	**Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.**
Study type	Retrospective cohort
Aim of the study	To evaluate new grading criteria for geographic atrophy (GA), as detected by annual stereoscopic color fundus photographs and fluorescein angiograms, and to assess whether application of the revised criteria provides earlier identification of GA than previous criteria involving only color fundus photography.
Study dates	Published 2011
Source of funding	National Eye Institute, National Institutes of Health, Department of Health and Human Services; an unrestricted grant from Research to Prevent Blindness, and a grant from the Doris Duke Charitable Foundation
Sample size	A random set of 25 photographs was independently regraded by both the original grader and senior to CAPT reading centre grader to assess intra grader agreement
Characteristics	The study did not report characteristics for the following variables: Ethnic group Age Gender Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• Geographic atrophy
Exclusion Criteria	• At baseline—if the length of time that a GA lesion had been present could not be accurately assessed • The final visit—if the presence of GA could not be confirmed on later images, which might skew the false-positive rate. • If any annual images were missing or unsuitable for grading due to inadequate photo quality.
Tests	Grading was based on features observed in the stereoscopic fundus photographs and fluorescein angiograms. According to the revised criteria, GA was defined as an area in which the RPE was absent, as evidenced by hyperfluorescence on late-stage fluorescein angiograms plus one additional feature indicative of RPE atrophy, specifically: visible choroidal vessels, sharp edges, or marked excavation on either CFP or FA. Atrophic drusen (i.e., degenerating drusen associated with

Bibliographic reference	Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.
	RPE atrophy at its margins) were not considered GA unless the drusenoid material was completely encircled by a 360° rim of atrophy. (This distinction was made to include regressing drusen located underneath a larger area of atrophy and exclude individual drusen or areas of confluent drusen that are associated with early atrophic changes.)
Methods	Photographic sets for each patient were graded sequentially. Candidate areas of GA were identified from stereoscopic color films viewed on a light box. For each atrophic area, the presence or absence of five features (visible choroidal vessels, sharp edges, circular shape, excavation, and depigmentation) was noted based on the color photographs. Similarly, film negatives of fluorescein angiograms were reviewed for candidate areas of GA, and the presence or absence of three features (sharp borders, visible choroidal vessels, and excavation) was noted for each candidate area. Final determination of whether a candidate lesion constituted GA was based on the combined features from the color fundus photographs and fluorescein angiograms. Size and shape were not used as criteria in this revised GA definition. Each area of GA was assessed independently from other areas when GA was multifocal in a given fundus image. Year 0 was assigned to the first year in which a specific GA lesion was detected in an eye, and that may or may not have been the first year in which any GA was detected in that eye. Each GA lesion was assigned an identification number, for monitoring changes over time. Monitoring involved classifying each lesion as new (not present at previous visit), previously detected, or merged (formed from two or more previously distinct atrophic areas), as well as tracking the characteristic features present on CFP and FA over time. A sample of 15 photographic sets, some of which included lesions that met the new criteria but not the previously used criteria, was reviewed by the CAPT study chair. In all instances, he confirmed the presence or absence of GA from a clinical perspective. Six months after the initial grading with the revised criteria, a random sample of 25 photographs was independently regraded by both the original grader (HSB) and a senior CAPT reading center grader (ERM), to assess inter- and intragrader agreements.
Results	<u>Interobserver variability</u> kappa: 0.536 <u>Intraobserver agreement</u> kappa: 0.845
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website.

Bibliographic reference	Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.
	DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Yes (random) Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: Unclear (status of PCV etc) B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes Grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW

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Bibliographic reference	**Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To describe the characteristics of incident choroidal neovascularisation in observed and treated eyes in the CAPT trial
Study dates	Published 2008
Source of funding	National Eye Institute, National Institutes of Health, Department of Health and Human Services;
Sample size	282 eyes of 225 patients developed choroidal neovascularisation from a total of 1052 recruited participants. A weighted sample of eyes with and without CNV or SPED was selected for regrading. All photographic images were regraded independently by 2 readers who later openly discussed their discrepancies to arrive at consensus.
Characteristics	Visual acuity (%) 20/12- 20/40- 68.7% 20/50- 20/160- 26.8% 20/200- <20/400- 4.5% The study did not report characteristics for the following variables: Ethnic group AMD disease stage Age Gender Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• >= 10 large drusen within 3000 um of the centre of the macula • Visual acuity >= to 20/40

Bibliographic reference	**Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.**
Exclusion Criteria	• Evidence of CNV, serous retinal pigment detachment, geographic atrophy >1MPS disc area in size • Geographic atrophy of any size within 500 um of the foveal centre • Any condition likely to affect visual acuity within the next 5 years
Tests	Grading was based on features observed in the stereoscopic colour fundus photographs and fluorescein angiograms. Choroidal neovascularisation was considered present when there was an expansion or persistant staining of an area of hyperflourescence as the time increased from injection of dye on fluorescein angiography. A SPED was considered present when there was a uniform, smooth elevation of the retinal pigment epithelium with sharply demarcated, fairly uniform, early hyperflourescence that persisted into the late phase of the angiogram. Classic CNV: An area of choroidal hyperfluorescence with well demarcated boundaries that could be discerned in the early phase of the angiogram and Progressive pooling of dye leakage in the overlying subsensory retinal space that usually obscures the boundaries of the CNV in the late phase Occult: An area of stippled hyperflourescence appeared within 5 minutes Persistent staining or pooling of dye by 10 minutes.
Methods	All photographic images described were graded independently by 2 trained readers in the CAPT reading centre. The readers openly discussed their discrepencies to arrive at consensus. Unresolved differences were reviewed by either the reading centre director or principle investigator. A weighted sample of eyes with and without CNV or SPED was selected for regrading. All photographic images were regraded independently by 2 readers who later openly discussed their discrepancies to arrive at consensus.
Results	<u>Interobserver variability</u> Agreement: 80-100% Weighted kappa: 0.75-100
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly:

Bibliographic reference	**Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.**
	QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Yes (random) Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: Unclear (status of PCV, no baseline characteristic reported for the grading sample) B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Unclear

Bibliographic reference	Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.
	Could the patient flow have introduced bias? RISK: Unclear

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E.2 Risk factors

E.2.1 Risk factors for development or progression of AMD

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

Bibliographic reference	Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. Macular Photocoagulation Study Group, Archives of ophthalmology (Chicago, Ill.: 1960), 115, 741-747, 1997
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To verify and quantify previously reported risk factors for the development of choroidal neovascularisation in the fellow eye of patients with 1 eye affected with CNV secondary to age-related macular degeneration.
Study dates	Published 1997 Enrolled between 1981 and 1990 for 5 years follow up
Source of funding	Support was given through National Eye Institute, National Institutes of Health and Research to Prevent Blindness
Number of patients	670 patients with unilateral CNV secondary to AMD
Inclusion Criteria	Included in the Macular Photocoagulation Study Group randomised trial of laser photocoagulation for new juxtafoveal choroidal neovascularisation (CNV), new subfoveal CNV or recurrent subfoveal CNV secondary to age related macular degeneration (AMD). Visual acuity of 20/400 or better in the study eye No restrictions on the morphological features or visual acuity of the fellow eye Only fellow eyes without CNV at enrolment were examined for characteristics of drusen and the retinal pigment epithelium.
Exclusion Criteria	Fellow eyes with missing or uninterpretable photographs at enrolment were excluded (n=21). Eyes with some missing photographs or poor quality photographs could not be graded for some features were excluded from analysis on a feature specific basis.
Diagnostic criteria	Systemic hypertension status was classified as normal (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg in the absence of antihypertensive medications, definite (systolic blood pressure >= 160 mm Hg or diastolic blood pressure >=95 mm Hg, or use of antihypertensive medication), or suspect (systolic blood pressure >=140 but <160 mm Hg or diastolic blood pressure >=95 mmHg but <95 mm Hg in the absence of antihypertensive medication. At each follow up visit stereoscopic colour photographs were taken of the macula of each eye. Fluorescein angiography was performed 3 and 12 months after enrolment and annually thereafter. If CNV in the fellow eye was suggested by signs or symptoms, the macula of the fellow eye was photographed during the fluorescein angiogram.

Bibliographic reference	Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. Macular Photocoagulation Study Group, Archives of ophthalmology (Chicago, Ill.: 1960), 115, 741-747, 1997
	All investigations were assessed independently by 2 readers. Discrepancies that could not be resolved by the two were reviewed for final resolution by an ophthalmologist.
Patient characteristics	Total (n=670) Age, y, no. 50-69: 237 70-74: 168 ≥75: 265 Gender, no. Female: 371 Male: 299 Ethnicity: not reported.
Predictors/risk factors and effect estimates	Risk factors under study included presence of 5 or more drusen, focal hyperpigmentation, definite systemic hypertension, 1 or more large drusen, medication status and blood pressure status of patients with definite hypertension were included in the analysis.
Outcomes	Risk ratios for development of choroidal neovascularisation in the fellow eye of people with choroidal neovascularisation secondary to AMD
Analysis used	Cox proportional hazard analysis
Length of follow up	Follow up visits 3 and 6 months after enrolment and at 6 months intervals thereafter until 5 years follow up.
Missing data handling/loss to follow up	Fellow eyes with missing or uninterpretable photographs at enrolment were excluded (n=21). Eyes with some missing photographs or poor quality photographs could not be graded for some features were excluded from analysis on a feature specific basis. Complete information on development of CNV within 5 years was available for 408 patients (61%). 73 patients had died or had their follow up period terminated before 3 years, 66 before 4 years and an additional 123 before 5 years. Fundus photograph reading centre gradings of the central macular zone were available for 485 patients (fellow eyes of patients assigned to observation in the clinical trial for juxtafoveal CNV were not examined)
Results	Risk of development of choroidal neovascularisation in the fellow eye of people with choroidal neovascularisation secondary to AMD. Risk ratios (95% confidence intervals):

Bibliographic reference	Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. Macular Photocoagulation Study Group, Archives of ophthalmology (Chicago, Ill.: 1960), 115, 741-747, 1997
	Presence of 5 or more drusen: 2.1 (1.3-3.5) Focal hyperpigmentation: 2.0 (1.4-2.9) Definite systemic hypertension: 1.7 (1.2-2.4) 1 or more large drusen: 1.5 (1.0-2.2) Medication status and blood pressure status of patients with definite hypertension did not influence significantly the incidence of CNV after adjustment for the other factors.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). NO Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Ajani,U.A., Christen,W.G., Manson,J.E., Glynn,R.J., Schaumberg,D., Buring,J.E., Hennekens,C.H., A prospective study of alcohol consumption and the risk of age-related macular degeneration, Annals of epidemiology, 9, 172-177, 1999**
Country/ies where the study was carried out	USA Data taken from the Physicians Health Study
Study type	Prospective prognostic study using data from a randomised controlled trial
Aim of the study	To examine the relationship between alcohol intake and development of AMD
Study dates	Published 1999
Source of funding	Supported by National Institutes of Health Grants
Number of patients	A total of 21,041 male physicians
Inclusion Criteria	Male physicians aged between 40-84 years at entry Physicians Health Study was a randomised double blind placebo controlled trial of aspirin (325 mg on alternate days) and beta-carotene (50 mg on alternate days) in the primary prevention of cardiovascular disease and cancer in 1982. • Inclusion criteria from the original trial: • Ability to give true informed consent • Knowledge of possible side effects • Accuracy and completeness of information • Ease of follow-up • Opportunity to conduct trial by mail
Exclusion Criteria	Exclusion criteria from the original trial: • Personal history of Myocardial infarction, Stroke or TIA, Cancer (except non-melanoma skin cancer), Current liver or kidney disease, Peptic ulcer or gout • Contraindication to aspirin use • Current use of aspirin or other drugs affecting platelet function • Current use of vitamin A or beta-carotene supplement
Diagnostic criteria	Any AMD was defined as a self-report confirmed by a medical record review of an initial diagnosis of AMD subsequent to randomisation AMD with vision loss was defined as above but with vision loss to 20/30 or worse attributable to AMD Exudative AMD was defined by the presence of RPE detachment, subretinal neovascular membrane, or disciform scar.
Patient characteristics	Ethnic group, mean (standard deviation): Not recorded Age, mean (standard deviation): 53.2 (9.5)

Bibliographic reference	**Ajani,U.A., Christen,W.G., Manson,J.E., Glynn,R.J., Schaumberg,D., Buring,J.E., Hennekens,C.H., A prospective study of alcohol consumption and the risk of age-related macular degeneration, Annals of epidemiology, 9, 172-177, 1999**
	Gender, mean (standard deviation): male (100%)
Predictors/risk factors and effect estimates	Crude estimates of association were derived by adjusting for effects of age The following factors were adjusted for within the model, age, randomised treatment assignment (aspirin and beta carotene), history of diabetes, history of hypertension, history of treatment for high blood pressure, obesity, physical activity, parental history of myocardial infarction before age 60, smoking status at baseline, multivitamin use at baseline, pack years of smoking. Additional models with updated alcohol data were also run to assess the time varying effect of alcohol.
Outcomes	Individuals rather than eyes were the unit of analysis. Relative risk of AMD (any kind), AMD with vision loss and exudative AMD with time varying analysis, split by 5 levels of alcohol intake: • <1 drink/week • 1 drink/week • 2-4 drinks/week • 5-6 drinks/week • ≥1 drink/day
Analysis used	Cox proportional hazard models were used to assess the independent contribution of alcohol consumption to the risk of AMD.
Length of follow up	12 years follow up
Missing data handling/loss to follow up	All recorded baseline variables appear to have been entered into the multivariable model Of 22,071 US male physicians at study entry, a total of 21,041 with complete data on alcohol use and no AMD at baseline were entered into the analysis.
Results	Adjusted relative risk for any AMD diagnosis (95% confidence intervals): • <1 drink/week- 1.0 (referent) • 1 drink/week- 0.92 (0.65-1.30) • 2-4 drinks/week- 0.70 (0.51-0.97) • 5-6 drinks/week- 1.25 (0.92-1.71) • ≥1 drink/day- 1.23 (0.96-1.57) Adjusted relative risk for exudative AMD (95% confidence intervals): • <1 drink/week- 1.0 (referent)

Bibliographic reference	Ajani,U.A., Christen,W.G., Manson,J.E., Glynn,R.J., Schaumberg,D., Buring,J.E., Hennekens,C.H., A prospective study of alcohol consumption and the risk of age-related macular degeneration, Annals of epidemiology, 9, 172-177, 1999
	• 1 drink/week- 1.12 (0.47-2.68) • 2-4 drinks/week- 0.88 (0.39-1.96) • 5-6 drinks/week- 1.20 (0.52- 2.78) • ≥1 drink/day- 1.33 (0.70-2.50)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). PARTLY Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNCLEAR Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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<table>
<tr><th>Bibliographic reference</th><th>Boekhoorn,Sharmila S., Vingerling,Johannes R., Hofman,Albert, de Jong,Paulus T.V.M., Alcohol consumption and risk of aging macula disorder in a general population: the Rotterdam Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 834-839, 2008</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>The Netherlands</td></tr>
<tr><td>Study type</td><td>Prospective, population-based cohort</td></tr>
<tr><td>Aim of the study</td><td>To investigate the possible relationship between overall alcohol consumption and risk of AMD in a general population
The Rotterdam Study included cardiovascular, locomotor, neurologic and ophthalmologic diseases in those ≥55years</td></tr>
<tr><td>Study dates</td><td>March 1990 to December 2004</td></tr>
<tr><td>Source of funding</td><td>Unrestricted grant from Topcon EuropeBV, Capelle aan de Ijssel</td></tr>
<tr><td>Number of patients</td><td>N=4229 with data on alcohol consumption (67.0% of those with gradable fundus transparencies at baseline)</td></tr>
<tr><td>Inclusion Criteria</td><td>All inhabitants ≥55years living in a suburb of Rotterdam</td></tr>
<tr><td>Exclusion Criteria</td><td>None</td></tr>
<tr><td>Diagnostic criteria</td><td>Diagnosis of AMD, 35mm-colour photographs, graded using x12.5 magnification according to the International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration (graded by 2 graders with 11years experience). Divided into early and late AMD
Grading procedures and definitions, and graders, identical at baseline and follow-up</td></tr>
<tr><td>Patient characteristics</td><td>Baseline characteristics
<table>
<tr><td></td><td>No iAMD</td><td>early iAMD</td><td>late iAMD</td></tr>
<tr><td>Age (mean, SD)</td><td>66.3 (7.2)</td><td>68.0 (7.1)</td><td>71.3 (6.4)</td></tr>
<tr><td>Female sex (no. %)</td><td>2166 (59.7)</td><td>295 (56.8)</td><td>49 (60.5)</td></tr>
<tr><td>Alcohol consumption, 0 (no.%)</td><td>704 (19.4)</td><td>90 (17.3)</td><td>15 (18.5)</td></tr>
<tr><td>Alcohol consumption, ≤10g</td><td>1638 (45.1)</td><td>235 (45.3)</td><td>37 (45.7)</td></tr>
<tr><td>Alcohol consumption, >10 to ≤20g</td><td>568 (15.7)</td><td>82 (15.8)</td><td>11 (13.6)</td></tr>
<tr><td>Alcohol consumption, >20g</td><td>719 (19.8)</td><td>112 (21.6)</td><td>18 (22.2)</td></tr>
</table></td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Alcohol consumption:
Checklist provided prior to baseline examinations; reported alcohol consumed on a weekly basis in 4 categories (beer, wine, liquor, moderately strong alcoholic beverages)
Total alcohol per participant (in grams)/day calculated</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Boekhoorn,Sharmila S., Vingerling,Johannes R., Hofman,Albert, de Jong,Paulus T.V.M., Alcohol consumption and risk of aging macula disorder in a general population: the Rotterdam Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 834-839, 2008</th></tr>
<tr><td></td><td>Daily alcohol categorised (0, ≤10g, >10g but ≤20g, >20g)
Potential confounders collected; smoking habits, BP, BMI, total cholesterol, lipids, complement factor H genotypes</td></tr>
<tr><td>Analysis used</td><td>Cox proportional hazards regression model</td></tr>
<tr><td>Length of follow up</td><td>Mean time baseline to first follow-up 2.0years
Mean time baseline to second follow-up 6.5years
Mean time baseline to third follow-up 11.1years</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>Some data on alcohol consumption unavailable for analysis due to inconsistencies in dietary interviews</td></tr>
<tr><td>Results</td><td>Results:
Risk of early or late iAMD, according to alcohol consumption
<table>
<tr><td>alcohol, g</td><td>Total no. of participants</td><td>No. of cases</td><td>HR (95%CI)*</td><td>HR (95%CI)#</td></tr>
<tr><td>early iAMD</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0</td><td>794</td><td>90</td><td>1 (ref)</td><td>1 (ref)</td></tr>
<tr><td>≤10</td><td>1873</td><td>235</td><td>1.01 (0.79 to 1.29)</td><td>1.00 (0.76 to 1.30)</td></tr>
<tr><td>>10 to ≤20</td><td>650</td><td>82</td><td>1.04 (0.76 to 1.40)</td><td>0.98 (0.70 to 1.36)</td></tr>
<tr><td>>20</td><td>831</td><td>112</td><td>1.11 (0.83 to 1.48)</td><td>1.10 (0.80 to 1.51)</td></tr>
<tr><td>late iAMD</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0</td><td>719</td><td>15</td><td>1 (ref)</td><td>1 (ref)</td></tr>
<tr><td>≤10</td><td>1675</td><td>37</td><td>0.94 (0.51 to 1.72)</td><td>1.00 (0.53 to 1.89)</td></tr>
<tr><td>>10 to ≤20</td><td>579</td><td>11</td><td>0.94 (0.43 to 2.08)</td><td>0.77 (0.33 to 1.80)</td></tr>
<tr><td>>20</td><td>737</td><td>18</td><td>1.26 (0.61 to 2.60)</td><td>1.01 (0.46 to 2.21)</td></tr>
</table>
*adjusted for age and sex
#also adjusted for smoking, BMI, BP, complement H factor genotype status, total cholesterol, HDL cholesterol</td></tr>
</table>

Bibliographic reference	**Boekhoorn,Sharmila S., Vingerling,Johannes R., Hofman,Albert, de Jong,Paulus T.V.M., Alcohol consumption and risk of aging macula disorder in a general population: the Rotterdam Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 834-839, 2008**

Risk of dry or wet late iAMD, according to alcohol consumption

alcohol, g	Total no. of participants	No. of cases	HR (95%CI)*	HR (95%CI)
Dry late iAMD				
0	708	4	1 (ref)	1 (ref)
≤10	1648	10	0.93 (0.29 to 2.99)	1.10 (0.32 to 3.80)
>10 to ≤20	573	5	1.58 (0.42 to 6.04)	1.38 (0.31 to 6.16)
>20	731	12	3.09 (0.93 to 10.27)	3.27 (0.88 to 12.19)
Wet late iAMD				
0	715	11	1 (ref)	1 (ref)
≤10	1665	27	0.95 (0.47 to 1.92)	0.96 (0.45 to 2.03)
>10 to ≤20	574	6	0.71 (0.26 to 1.96)	0.60 (0.21 to 1.72)
>20	725	6	0.59 (0.21 to 1.68)	0.40 (0.13 to 1.25)

*adjusted for age and sex
#also adjusted for smoking, BMI, BP, complement H factor genotype status, total cholesterol, HDL cholesterol

Risk of early or late iAMD, according to alcohol consumption of different types, adjusted for age and sex

	early iAMD			late iAMD		
	Total	No. of cases	HR (95%CI)	Total	No. of cases	HR (95%CI)
Beer, 0g	794	90	1 (ref)	719	15	1 (ref)
≤10	598	69	0.79 (0.53 to 1.15)	536	7	0.63 (0.20 to 1.98)
>10 to ≤20	95	8	0.66 (0.31 to 1.41)	88	1	0.82 (0.09 to 7.20)

Bibliographic reference	**Boekhoorn,Sharmila S., Vingerling,Johannes R., Hofman,Albert, de Jong,Paulus T.V.M., Alcohol consumption and risk of aging macula disorder in a general population: the Rotterdam Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 834-839, 2008**

>20	74	12	1.28 (0.66 to 2.48)	64	2	1.94 (0.35 to 10.67)
Wine, 0g	794	90	1 (ref)	719	15	1 (ref)
≤10	1738	214	0.99 (0.78 to 1.27)	1562	38	1.04 (0.57 to 1.89)
0	377	51	1.18 (0.83 to 1.67)	334	8	1.39 (0.58 to 3.32)
>20	235	35	1.32 (0.89 to 1.96)	202	2	0.60 (0.13 to 2.63)
Liquor, 0g	794	90	1 (ref)	719	15	1 (ref)
≤10	740	94	0.90 (0.66 to 1.23)	655	9	0.45 (0.18 to 1.11)
>10 to ≤20	291	34	0.81 (0.54 to 1.23)	264	7	0.92 (0.35 to 2.44)
>20	435	56	0.92 (0.64 to 1.33)	389	10	0.98 (0.40 to 2.40)

*adjusted for age 435and sex

#adjusted for smoking, BMI, BP, complement H factor genotype status, total cholesterol, HDL cholesterol

Limitations	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNCLEAR Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNCLEAR Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES

Bibliographic reference	Boekhoorn,Sharmila S., Vingerling,Johannes R., Hofman,Albert, de Jong,Paulus T.V.M., Alcohol consumption and risk of aging macula disorder in a general population: the Rotterdam Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 834-839, 2008
	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Bressler, S. B., Maguire,M.G., Bressler,N.M., Fine,S.L., Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. The Macular Photocoagulation Study Group, Archives of ophthalmology (Chicago, Ill.: 1960), 108, 1442-1447, 1990
Country/ies where the study was carried out	USA
Study type	Prospective cohort
Aim of the study	To describe the relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular AMD in the fellow eye of people diagnosed with neovascular AMD.
Study dates	Published 1990
Source of funding	Grants from the National Eye Institute and National institutes of Health.
Number of patients	127 participants were included in the analysis
Inclusion Criteria	• Diagnosis of choroidal neovascularisation associated with macular degeneration • The posterior edge of the neovascular membrane was to be between 200 and 2500 µm from the foveal center. • Fellow eye with no evidence of neovascular AMD
Exclusion Criteria	• Ungradable or missing photographs at study entry
Diagnostic criteria	The development of the neovascular or exudative form of AMD in the fellow eye was determined by prospective assessment of fundus photographs and fluorescein angiography. All study patients had colour fundus photographs and of the fellow eye submitted at study entry, at 3 months and then semi-annually for 5 years. The same intervals were used for fluorescein angiography except these were taken annually for 5 years. The neovascular form of AMD was considered present whenever hyperfluorescent leakage, a disciform scar, or a laser scar from follow up fluorescein angiogram was observed. A masked review of the follow up colour fundus photographs was performed.
Patient characteristics	No information regarding patient demographics was described
Predictors/risk factors and effect estimates	Variables under study included large drusen, confluent drusen, hyperpigmentation, cigarette smoking and hypertension. Unclear which other variables were adjusted for within the life table analysis

Bibliographic reference	**Bressler, S. B., Maguire,M.G., Bressler,N.M., Fine,S.L., Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. The Macular Photocoagulation Study Group, Archives of ophthalmology (Chicago, Ill.: 1960), 108, 1442-1447, 1990**
Outcomes	Risk of developing incident neovascular disease in the fellow eye
Analysis used	Multivariate life-table analysis
Length of follow up	Up to 5 years
Missing data handling/loss to follow up	5 years of follow up was completed for 180 of the 208 patients still alive after 5 years in the Study of the Macular Photocoagulation Study and Senile Macular Degeneration Study. No further information described regarding missing information for the 127 patients included in the analysis
Results	Multivariate analysis of the risk for incident neovascular AMD in the fellow eye, relative risk, (95% confidence intervals): • No large drusen: 1.00 (referent) • large drusen (≥50µm): 2.4 (1.1-5.1) • No focal hyperpigmentation: 1.00 (referent) • Focal hyperpigmentation: 2.5 (1.3-4.9) • No confluent drusen: 1.00 (referent) • Confluent drusen: 1.8 (0.8-3.9) Unclear which other variables were entered into the cox proportional hazards model. Definite hypertension, cigarette smoking and age were not found to influence the risk of developing neovascular AMD.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE

Bibliographic reference	**Bressler, S. B., Maguire,M.G., Bressler,N.M., Fine,S.L., Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. The Macular Photocoagulation Study Group, Archives of ophthalmology (Chicago, Ill.: 1960), 108, 1442-1447, 1990**
	Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). UNSURE The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Chew,E.Y., Sperduto,R.D., Milton,R.C., Clemons,T.E., Gensler,G.R., Bressler,S.B., Klein,R., Klein,B.E., Ferris,F.L.,III, 20090213, Risk of advanced age-related macular degeneration after cataract surgery in the Age-Related Eye Disease Study: AREDS report 25, Ophthalmology, 116, 297-303, 2009**
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To assess the risk of developing advanced age-related macular degeneration (AMD) following cataract surgery
Study dates	Published 2009 Enrolled from 1992 through 1998, follow up until 2004.
Source of funding	Supported by contracts from the National Eye Institute, National Institutes of Health, Department of Health and Human Services.
Number of patients	2880 right eyes and 2961 left eyes
Inclusion Criteria	• 55 to 80 years of age at enrolment • Best-corrected visual acuity (BCVA) of 20/32 or better in at least one eye (the study eye). • Media had to be sufficiently clear to obtain adequate quality stereoscopic fundus photographs of the macula in all study eyes.
Exclusion Criteria	• Eyes with cataract surgery or advanced AMD at baseline.

Bibliographic reference	Chew,E.Y., Sperduto,R.D., Milton,R.C., Clemons,T.E., Gensler,G.R., Bressler,S.B., Klein,R., Klein,B.E., Ferris,F.L.,III, 20090213, Risk of advanced age-related macular degeneration after cataract surgery in the Age-Related Eye Disease Study: AREDS report 25, Ophthalmology, 116, 297-303, 2009
	• Patients within "category 1" were excluded from the cox proportional hazards regression analysis. [see diagnostic criteria] • Persons aged 55 to 59 years were eligible for the study only if they were in Category 3 or 4. [see diagnostic criteria]=
Diagnostic criteria	**Definitions of patient categories for cox proportional hazards regression analysis:** Category 1: a total drusen area of less than 5 small drusen (< 63 µm in diameter), and VA of 20/32 or better in both eyes. Category 2: mild age-related macular lesions (multiple small drusen, non-extensive (<20) intermediate drusen (63–124 µm in diameter), pigment abnormalities, or any combination of these) in their most advanced eye, and visual acuity of 20/32 or better in both eyes. Category 3: absence of advanced AMD in both eyes and at least 1 eye with VA of 20/32 or better with at least 1 large druse (≥125 µm in diameter), extensive (as measured by drusen area) intermediate drusen, or geographic atrophy (GA) that did not involve the centre of the macula, or any combination of these. Category 3a: both eyes met these criteria, while in Category 3b one eye had either reduced VA not due to AMD or a disqualifying ocular condition. Category 4: participants had VA of 20/32 or better and no advanced AMD (GA involving the centre of the macula or features of choroidal neovascularization) in the study eye, and the fellow eye had either lesions of advanced AMD (Category 4a) or VA less than 20/32 and AMD abnormalities sufficient to explain reduced VA (Category 4b) as determined by examination of photographs at the reading centre. Only patient categories 2, 3 and 4 were entered into the cox analysis. Persons aged 55 to 59 years were eligible for the study only if they were in Category 3 or 4. Eyes were excluded from this analysis if they were pseudophakic/aphakic or had advanced AMD at baseline. **Recording covariates:** Questionnaires were administered to obtain demographic information, history of smoking and sunlight exposure, medical history, history of specific prescription drug and non-prescription medication use, and history of vitamin and mineral use. General physical and ophthalmic examinations included height, weight, blood pressure, manifest refraction, best corrected visual acuity, intraocular pressure, slit-lamp biomicroscopy, and ophthalmoscopy. Date of cataract surgery was obtained by history at 6-month intervals. Stereoscopic film-based colour fundus photographs of the macula and lens photographs (red reflex, slit lamp and Neitz) were taken at baseline and annually beginning at the 2 year annual study visit. Photographs were graded at a reading centre, where the various lesions associated with AMD and the severity of lens opacities by type were assessed with standardized grading procedures. **Outcomes** Progression to neovascular AMD for a study eye was based on clinical centre reports of photocoagulation for choroidal neovascularization, or photographic documentation at the reading centre of at least 1 of the following: subretinal fibrosis, non-drusenoid retinal pigment epithelial detachment, serous or haemorrhagic retinal detachment, and haemorrhage under the retina or the retinal pigment epithelium.

Bibliographic reference	**Chew,E.Y., Sperduto,R.D., Milton,R.C., Clemons,T.E., Gensler,G.R., Bressler,S.B., Klein,R., Klein,B.E., Ferris,F.L.,III, 20090213, Risk of advanced age-related macular degeneration after cataract surgery in the Age-Related Eye Disease Study: AREDS report 25, Ophthalmology, 116, 297-303, 2009**
	Progression to geographic atrophy was defined by an area of atrophy >175 um in diameter within the grid to be comparable with previous studies.
Patient characteristics	Total (n=4577) Mean Age, yr (SD): 68 (5) Gender, no. (%) Female: 2555 (56) Male: 2022 (44) Race, no. (%) White: 4374 (96) Other: 203 (4)
Predictors/risk factors and effect estimates	Risk factor under study was incident cataract surgery Hazard ratios were adjusted for gender and baseline smoking status, as well as time-dependent covariates age, AMD status, and cataract surgery
Outcomes	Hazard ratio for developing neovascular AMD Hazard ratio for developing geographic atrophy
Analysis used	Cox proportional hazards regression analysis
Length of follow up	Every 6 months for up to 11 years (mean follow up 8.8 ± 2.4 years)
Missing data handling/loss to follow up	The study reports low loss to follow up: 2% during the entire clinical trial portion and 4% during the later non-intervention portion of AREDS, not including deaths) and the frequent participant contacts, information on both cataract surgery and progression to advanced AMD was captured for almost all of participants. No further information on missing data was described.
Results	**Hazard ratio for developing neovascular AMD (95% confidence intervals)** Right eye (Category 2,3,4) 1.20 (0.82–1.75) Left eye (Category 2,3,4) 1.07 (0.72–1.58)

Bibliographic reference	**Chew,E.Y., Sperduto,R.D., Milton,R.C., Clemons,T.E., Gensler,G.R., Bressler,S.B., Klein,R., Klein,B.E., Ferris,F.L.,III, 20090213, Risk of advanced age-related macular degeneration after cataract surgery in the Age-Related Eye Disease Study: AREDS report 25, Ophthalmology, 116, 297-303, 2009**
	Hazard ratio for developing geographic atrophy (95% confidence intervals) Right eye (Category 2,3,4) 0.80 (0.61–1.06) Left eye (Category 2,3,4) 0.95 (0.71–1.26)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). UNSURE Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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<table>
<tr><th>Bibliographic reference</th><th>Chiu,C.-J., Milton,R.C., Klein,R., Gensler,G., Taylor,A., Dietary carbohydrate and the progression of age-related macular degeneration: A prospective study from the Age-Related Eye Disease Study, American Journal of Clinical Nutrition, 86, 1210-1218, 2007</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>USA</td></tr>
<tr><td>Study type</td><td>Prospective cohort</td></tr>
<tr><td>Aim of the study</td><td>To prospectively evaluate the effect of baseline higher dietary glycaemic index (dGI) on the progression of AMD</td></tr>
<tr><td>Study dates</td><td>November 1992 to January 1998</td></tr>
<tr><td>Source of funding</td><td>Grants from Johnson and Johnson Focused Giving Program</td></tr>
<tr><td>Number of patients</td><td>N=3977 participants (7232 eyes, 722 participants contributed only 1 eye)
Number with large drusen or group 3 eyes =2754</td></tr>
<tr><td>Inclusion Criteria</td><td>• ≥1 eye with a visual acuity of 20/32 or better, with lens and vitreous sufficiently clear to allow good retinal photographs that would permit identification and quantification of small drusen
• ≥1 eye to be free of disease that could complicate assessment of AMD or lens opacity progression, that eye had not had previous ocular surgery</td></tr>
<tr><td>Exclusion Criteria</td><td>• Any illness or disorder that would make long-term follow-up or compliance with study protocol unlikely or difficult
• Diabetes at baseline
• Persons with missing nutritional, non-nutritional, and ophthalmologic covariates
• Persons with invalid calorie intake
• Persons lost to follow up in the AREDs study
• Eyes at the end stage (central Geographic atrophy or neovascular AMD)</td></tr>
<tr><td>Diagnostic criteria</td><td>Stereoscopic fundus photographs of the macula graded at an ophthalmic photograph reading centre
Lesions associated with AMD assessed according to the AREDS AMD Classification System
Eyes classified into 1 of 5 groups according to the size and extent of drusen, presence of geographic atrophy and neovascular changes of AMD</td></tr>
<tr><td>Patient characteristics</td><td>Baseline
<table>
<tr><td>Characteristic</td><td>High dGI</td><td>Low dGI</td></tr>
<tr><td>Age <65yrs, no. (%)</td><td>855 (24.15)</td><td>901 (24.41)</td></tr>
<tr><td>Age 65-71 yrs</td><td>1428 (40.33)</td><td>1485 (40.23)</td></tr>
<tr><td>Age ≥71yrs</td><td>1258 (35.53)</td><td>1305 (35.36)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Chiu,C.-J., Milton,R.C., Klein,R., Gensler,G., Taylor,A., Dietary carbohydrate and the progression of age-related macular degeneration: A prospective study from the Age-Related Eye Disease Study, American Journal of Clinical Nutrition, 86, 1210-1218, 2007

p2	0.97	
Race, white, no. (%)	3353 (94.69)	3596 (97.43)
Race, other	188 (5.31)	95 (2.57)
p2	<0.001	
Female, no. (%)	2048 (57.84)	2151 (58.28)
Male	1493 (42.16)	1540 (41.72)
p2	0.70	
Smoking, yes, no. (%)	1925 (54.36)	1931 (52.32)
Smoking, no	1616 (45.64)	1760 (47.68)
p2	0.08	
Alcohol, median	0.89	1.52
p2	<0.001	

Predictors/risk factors and effect estimates	Comparing high and low dietary glycaemic index in the progression of age related macular degeneration
Outcomes	Assessment of daily total carbohydrate calculated by summing the product of the frequency, serving size, and carbohydrate content per serving of individual food items derived from a nutrition database (Nutrition coordinating centre at the University of Minnesota). GI values derived from published values Dose-dependent relationship between dietary glycaemic index and the risk of developing advanced age-related AMD in people with large drusen at baseline, Relative risk (95% confidence intervals)
Analysis used	Cox regression model
Length of follow up	8 years of follow up
Missing data handling/loss to follow up	122 persons lost to follow-up and excluded. People with missing or invalid information were excluded (see exclusion criteria). No further information on missing or incomplete data provided.

Bibliographic reference	**Chiu,C.-J., Milton,R.C., Klein,R., Gensler,G., Taylor,A., Dietary carbohydrate and the progression of age-related macular degeneration: A prospective study from the Age-Related Eye Disease Study, American Journal of Clinical Nutrition, 86, 1210-1218, 2007**
Results	Dose-dependent relationship between dietary glycaemic index and the risk of developing advanced age-related AMD in people with large drusen at baseline, Relative risk (95% confidence intervals) (n=2754) Quintile 1: 1.00 (referent) Quintile 2: 1.12 (0.90- 1.40) Quintile 3: 1.14 (0.90-1.44) Quintile 4: 1.20 (1.52-0.94) Quintile 5: 1.39 (1.08-1.79) Cox regression analysis was adjusted for age, sex, race, education, alcohol intake, BMI, hypertension history, refractive error, energy adjusted dietary variables (including total carbohydrates, fat, lutein and zeaxanthin, folic acid, niacin, riboflavin, B-carotene, vitamin C, vitamin E, and zinc intake.)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY

Bibliographic reference	**Chiu,C.-J., Milton,R.C., Klein,R., Gensler,G., Taylor,A., Dietary carbohydrate and the progression of age-related macular degeneration: A prospective study from the Age-Related Eye Disease Study, American Journal of Clinical Nutrition, 86, 1210-1218, 2007**
	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Chiu,C.-J., Klein,R., Milton,R.C., Gensler,G., Taylor,A., Does eating particular diets alter the risk of age-related macular degeneration in users of the Age-Related Eye Disease Study supplements?, British Journal of Ophthalmology, 93, 1241-1246, 2009**
Country/ies where the study was carried out	USA
Study type	Prospective cohort (using data from a randomised controlled trial)
Aim of the study	To describe whether enhanced intake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and reducing dietary glycaemic index (dGI) are protective against advanced age-related macular degeneration (AMD)
Study dates	Published 2009 8 year trial period beginning November 13, 1992,
Source of funding	Financial support for this project has been provided by the US Department of Agriculture under agreements, grants from the National Institutes of Health; grants from the Johnson & Johnson Focused Giving Program and American Health Assistance Foundation, and to C-JC from the Ross Aging Initiative.
Number of patients	2924 eligible AREDS AMD trial participants Unit of analysis was the eye (5146 eyes)
Inclusion Criteria	• Participants of the AREDs AMD trial • Eyes at risk of early progression and late progression
Exclusion Criteria	• People with diabetes • Invalid Energy intake • Missing covariates • Advanced AMD at baseline • Lost to follow up
Diagnostic criteria	Data on possible risk factors for AMD were obtained from a baseline general physical and ophthalmic examination, a detailed questionnaire on basic characteristics and demographic data, and a validated food-frequency questionnaire (FFQ).

Bibliographic reference	**Chiu,C.-J., Klein,R., Milton,R.C., Gensler,G., Taylor,A., Does eating particular diets alter the risk of age-related macular degeneration in users of the Age-Related Eye Disease Study supplements?, British Journal of Ophthalmology, 93, 1241-1246, 2009**
	Stereoscopic fundus photographs of the macula were taken and graded at baseline, at the 2-year visit, and annually thereafter during the 8-year (mean: 5.4 years) of follow-up using the AREDS protocol and AMD Classification System. Eyes were classified into one of five groups, numbered serially and based on increasing severity of drusen or type of AMD: Group 1, 2 and 3 defined here as early AMD, and Groups 4 and 5 defined here as advanced AMD. Time to the first maximal AMD progression of studied eyes during the 8-year study period was considered. Progression for a study eye was defined by a more advanced AMD grade than the baseline grade. An ‘‘event’’ of AMD progression was defined as the occurrence of the first maximal AMD progression in one eye at a single visit. The dietary glycaemic index (dGI) for each subject was calculated as the weighted average of the GI values for each food item, with the amount of carbohydrate consumed from each food item as the weight.
Patient characteristics	Total number of participants(n = 2924) Age in years, mean (SD): 69.3 (4.8) Race, no. (%) White: 2829 (96.8) Others: 95 (3.3) Gender, no. (%) Female 1698 (58.1)
Predictors/risk factors and effect estimates	Risk factors of interest included: Dietary intake of beta-carotene, docosahexanoic acid, eicosapentaenoic acid, and low-glycaemic index. All analyses used eyes as the unit. The multivariate-adjusted hazard ratios (HR) (95% CIs) were calculated using the first quartile group of the nutrient intake as the referent and estimated the global effects of nutrients independent of type of AREDS intervention. The following were considered as covariates in the analyses: age, gender, education level (college or higher, and high school or less), race (white and others), body mass index (BMI, computed from weight and height; kg/m2), smoking status (past, current, and never), alcohol drinking (g/day), sunlight exposure (h/day), hypertension history, baseline AMD classification, presence of lens opacity, refractive error (hyperopic and myopic), Centrum use during the trial period, total calorie intake, and energy adjusted dietary variables including carbohydrate, protein, fat, polyunsaturated fatty acids, arachidonic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), lutein plus zeaxanthin, folic acid, niacin, riboflavin, thiamine, vitamin C, vitamin E, betacarotene and zinc. The p value for interaction evaluated if the association varied by type of AREDS intervention. The four interventions are (1) the full AREDS formulation (vitamin C, vitamin E, beta-carotene and zinc), (2) the AREDS antioxidant formulation (vitamin C, vitamin E and beta-carotene), (3) the AREDS zinc formulation and (4) placebo.

Bibliographic reference	Chiu,C.-J., Klein,R., Milton,R.C., Gensler,G., Taylor,A., Does eating particular diets alter the risk of age-related macular degeneration in users of the Age-Related Eye Disease Study supplements?, British Journal of Ophthalmology, 93, 1241-1246, 2009
Outcomes	Hazard ratios for the development of early AMD Hazard ratios for the development of late AMD
Analysis used	Cox proportional-hazards models
Length of follow up	8 year follow up
Missing data handling/loss to follow up	None described (those with missing data were excluded from analysis)
Results	Associations between dietary intakes and risk of age-related macular degeneration (AMD) Early AMD progression Beta-carotene Quartile (Q) 1: referent Q2 (1.5–2.2 mg/day): 1.02 (0.85 to 1.22) Q3 (2.2–3.2 mg/day): 0.98 (0.80 to 1.18) Q4 (>3.2 mg/day): 0.97 (0.77 to 1.21) Docosahexaenoic acid Q1: referent Q2 (26.0–41.9 mg/day): 1.13 (0.95 to 1.34) Q3 (41.9–64.0 mg/day): 0.98 (0.81 to 1.18) Q4 (>64.0 mg/day): 1.09 (0.88 to 1.35) Eicosapentaenoic acid Q1: referent Q2 (12.7–24.6 mg/day): 1.07 (0.90 to 1.28) Q3 (24.6–42.3 mg/day): 1.01 (0.84 to 1.21) Q4 (>42.3 mg/day): 1.01 (0.83 to 1.23) Low-glycaemic index >81.5: referent 78.6–81.5: 1.15 (0.96 to 1.38) 75.2–78.6: 1.05 (0.87 to 1.28) 75.2: 1.03 (0.83 to 1.29)

Bibliographic reference	Chiu,C.-J., Klein,R., Milton,R.C., Gensler,G., Taylor,A., Does eating particular diets alter the risk of age-related macular degeneration in users of the Age-Related Eye Disease Study supplements?, British Journal of Ophthalmology, 93, 1241-1246, 2009
	Late AMD progression Beta-carotene Q1: referent Q2 (1.5–2.2 mg/day): 0.97 (0.80 to 1.19) Q3 (2.2–3.2 mg/day): 1.11 (0.90 to 1.37) Q4 (>3.2 mg/day): 1.24 (0.96 to 1.59) Docosahexaenoic acid Q1: referent Q2 (26.0–41.9 mg/day): 0.97 (0.80 to 1.18) Q3 (41.9–64.0 mg/day): 1.04 (0.85 to 1.28) Q4 (>64.0 mg/day): 0.73 (0.57 to 0.94) Eicosapentaenoic acid Q1: referent Q2 (12.7–24.6 mg/day): 0.91 (0.75 to 1.11) Q3 (24.6–42.3 mg/day): 1.03 (0.85 to 1.24) Q4 (>42.3 mg/day): 0.74 (0.59 to 0.94) Low-glycaemic index >81.5: referent 78.6–81.5: 0.80 (0.67 to 0.97) 75.2–78.6: 0.77 (0.63 to 0.94) 75.2: 0.76 (0.60 to 0.96)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE

Bibliographic reference	Chiu,C.-J., Klein,R., Milton,R.C., Gensler,G., Taylor,A., Does eating particular diets alter the risk of age-related macular degeneration in users of the Age-Related Eye Disease Study supplements?, British Journal of Ophthalmology, 93, 1241-1246, 2009
	Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). YES Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Christen,W.G., Glynn,R.J., Ajani,U.A., Schaumberg,D.A., Chew,E.Y., Buring,J.E., Manson,J.E., Hennekens,C.H., Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians, Archives of ophthalmology (Chicago, Ill.: 1960), 119, 1143-1149, 2001
Country/ies where the study was carried out	USA
Study type	Double masked, Randomised controlled trial
Aim of the study	To examine the development of age-related maculopathy (ARM) in a large-scale trial of low-dose aspirin treatment.
Study dates	Published 2001
Source of funding	Supported by research grants from the National Institutes of Health
Number of patients	22 071 US male physicians 10,617 in the aspirin group and 10,599 in the placebo group
Inclusion Criteria	• Male physicians • Ages 40 to 84

Bibliographic reference	Christen,W.G., Glynn,R.J., Ajani,U.A., Schaumberg,D.A., Chew,E.Y., Buring,J.E., Manson,J.E., Hennekens,C.H., Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians, Archives of ophthalmology (Chicago, Ill.: 1960), 119, 1143-1149, 2001
	• No history of stroke, myocardial infarction, cancer, or renal disease • No contraindications to aspirin or beta-carotene. • No current usage of aspirin or Vitamin A tables greater than once per week • Followed up for at least 7 years • Did not report Age-related macular degeneration at baseline
Exclusion Criteria	• Physicians who died during the first 7 years of follow-up and therefore did not respond to the 84-month questionnaire were excluded
Diagnostic criteria	Information concerning the occurrence of ARM during the first 7 years of the trial was requested on the 84-month questionnaire. Physicians were asked, "Have you ever had macular degeneration diagnosed in your right (left) eye?" If yes, they were requested to provide the month and year of the diagnosis. Subsequent annual questionnaires requested information on diagnoses during the preceding year. Signed permission to examine medical and hospital records pertaining to the diagnosis was also requested on the questionnaire and in separate follow-up mailings when necessary. Ophthalmologists and optometrists were contacted by mail and asked to complete an ARM questionnaire supplying information about the date of initial diagnosis of ARM, the best-corrected visual acuity at the time of diagnosis, and the date when visual acuity reached 20/30 or worse (if different from the date of initial diagnosis). Information was also requested about the pathological findings observed (drusen, retinal pigment epithelium [RPE] hypopigmentation/hyperpigmentation, geographic atrophy, RPE detachment, subretinal neovascular membrane, or disciform scar) when visual acuity was first noted to be 20/30 or worse and the date when exudative disease was first noted (defined by the presence of RPE detachment, subretinal neovascular membrane, or disciform scar). In addition, they asked whether there were other ocular abnormalities that would explain or contribute to visual loss and, if so, whether the ARM, by itself, was significant enough to cause best-corrected visual acuity to be reduced to 20/30 or worse.
Patient characteristics	Mean age, y (*Aspirin group, **placebo group) Total: *52.8 **52.8 40−49 *42.2 **42.3 50-59 *34.2 **34.1 60-69 *18.0 **17.9 70-84 *5.6 **5.7 Gender: Male

Bibliographic reference	**Christen,W.G., Glynn,R.J., Ajani,U.A., Schaumberg,D.A., Chew,E.Y., Buring,J.E., Manson,J.E., Hennekens,C.H., Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians, Archives of ophthalmology (Chicago, Ill.: 1960), 119, 1143-1149, 2001**
	Ethnicity: Not reported
Predictors/risk factors and effect estimates	The risk factor of interest was treatment with low-dose aspirin. (325mg of aspirin on alternate days) Models were adjusted for age, and beta carotene treatment assignment.
Outcomes	Risk ratios for the development of any AMD or advanced AMD in those treated with low dose aspirin.
Analysis used	Cox proportional hazards regression
Length of follow up	At least 7 years follow up Aspirin treatment period lasted average of 60.2 months follow up (trial terminated early.
Missing data handling/loss to follow up	No further information provided on missing data
Results	Relative risk of aspirin group vs placebo group for the outcome of development of any incident AMD RR = 0.77 (0.54−1.11)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY

Bibliographic reference	Christen,W.G., Glynn,R.J., Ajani,U.A., Schaumberg,D.A., Chew,E.Y., Buring,J.E., Manson,J.E., Hennekens,C.H., Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians, Archives of ophthalmology (Chicago, Ill.: 1960), 119, 1143-1149, 2001
	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Christen,W.G., Glynn,R.J., Chew,E.Y., Buring,J.E., Low-dose aspirin and medical record-confirmed age-related macular degeneration in a randomized trial of women, Ophthalmology, 116, 2386-2392, 2009
Country/ies where the study was carried out	USA
Study type	Randomised controlled trial
Aim of the study	To test whether alternate day low-dose aspirin affects incidence of age-related macular degeneration (AMD) in a large-scale randomized trial of women.
Study dates	2009
Source of funding	Supported by research grants from the National Institutes of Health, Bethesda. Md. Pills and packaging were provided by Bayer Healthcare and the Natural Source Vitamin E Association
Number of patients	39,876 female health professionals 19,716 in the aspirin group and 19,705 in the placebo group
Inclusion Criteria	• Healthy women • No previous history of cardiovascular disease or cancer • No contraindications to aspirin or vitamin E • A total of 39,421 women were without a diagnosis of AMD at baseline and are included in these analyses
Exclusion Criteria	None described
Diagnostic criteria	Information on new diagnoses of AMD was requested on annual questionnaires. Participants were asked “In the past year, have you had any of the following?” with response options including “macular degeneration right eye” and “macular degeneration left eye”. If yes, participants were requested to provide the month and year of the diagnosis. Ophthalmologists and optometrists were contacted by mail and requested to complete an AMD questionnaire supplying information about the date of initial diagnosis, the best-corrected visual acuity at the time of diagnosis, and the date when best-corrected visual acuity reached 20/30 or worse (if different from the date of initial diagnosis). Information was also requested about signs of AMD observed. They were also asked whether there were other ocular abnormalities that would

Bibliographic reference	Christen,W.G., Glynn,R.J., Chew,E.Y., Buring,J.E., Low-dose aspirin and medical record-confirmed age-related macular degeneration in a randomized trial of women, Ophthalmology, 116, 2386-2392, 2009
	explain or contribute to vision loss and if so, whether the AMD, by itself, was significant enough to cause the best-corrected visual acuity to be reduced to 20/30 or worse. Medical records were reviewed without knowledge of treatment assignment. The primary endpoint was visually-significant AMD defined as a self-report confirmed by medical record evidence of an initial diagnosis after randomization but before March 31, 2004, with best corrected vision loss to 20/30 or worse attributable to AMD (not outcomes of interest). Two secondary endpoints were: advanced AMD, comprised of those cases of exudative neovascular AMD (defined by presence of RPE detachment, subretinal neovascular membrane, or disciform scar) plus cases of geographic atrophy; and AMD with or without vision loss, comprised of all incident cases confirmed by medical records.
Patient characteristics	Mean age, y (*Aspirin group, **placebo group) Total: *54.5 **54.5 45−54 *60.7 **60.6 55−64 *29.4 **29.4 65+ *9.9 **9.9 Gender: Female Ethnicity: Not reported
Predictors/risk factors and effect estimates	The risk factor of interest was treatment with low-dose aspirin. (100mg of aspirin on alternate days) Models were adjusted for age, vitamin E and beta carotene treatment assignment.
Outcomes	Risk ratios for the development of any AMD or advanced AMD in those treated with low dose asiprin.
Analysis used	Cox proportional hazards regression
Length of follow up	10 years of treatment and follow up
Missing data handling/loss to follow up	Of 19,934 allocated aspirin, 19,716 were included in the analysis. Of 19,942 allocated placebo, 19,705 were included in the analysis.
Results	Relative risk of aspirin group vs placebo group for the outcome of development of advanced AMD RR = 0.90 (0.53−1.52) Relative risk of aspirin group vs placebo group for the outcome of development of AMD (with or without vision loss) RR = 1.03 (0.88−1.21)
Limitations	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNCLEAR

Bibliographic reference	Christen,W.G., Glynn,R.J., Chew,E.Y., Buring,J.E., Low-dose aspirin and medical record-confirmed age-related macular degeneration in a randomized trial of women, Ophthalmology, 116, 2386-2392, 2009
	Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNCLEAR Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group, 20080911, Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial, Ophthalmology, 115, 1474-1479, 2008.
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To determine risk factors for choroidal neovascularisation and of geographic atrophy in eyes with large drusen
Study dates	Published 2008 Enrolled May 1999 through March 2001, 5 years follow up with 6 month and annual visits
Source of funding	Supported by the National Eye Institute, National Institutes of Health grants.
Number of patients	1052 participants in a randomised controlled trial of laser treatment for the prevention of vision loss from advanced age-related macular degeneration
Inclusion Criteria	• The presence of 10 or more drusen at least 125um in diameter within 2 disc diameters of the fovea Standardised visual acuity measurement of 20/40 or better in each eye

Bibliographic reference	Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group, 20080911, Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial, Ophthalmology, 115, 1474-1479, 2008.
	50 years of age and older Free of conditions likely to preclude 5 years of follow up
Exclusion Criteria	• Evidence of choroidal neovascularisation, serous pigment epithelial detachment, geographic atrophy within 500um of the foveal centre or more than 1 Macular Photocoagulation Study (MPS) disc area. Other ocular conditions that were likely to compromise visual acuity or contraindicate application of laser treatment. CNV, serous epithelial detachment, geographic atrophy at baseline (from the analysis)
Diagnostic criteria	At baseline participants provided a brief medical history. Participants provided information on demographic characteristics, history of diabetes mellitus, history of smoking, current use of aspirin, current use of antihypertensive medication. Blood pressure was measured while patient was sitting. Hypertension was classified according to the BP measured at initial visit and the reported use of antihypertensive medications. Definite hypertension was defined as systolic BP of 95 mmHg or more or current use of antihypertensive medications. Suspect hypertension was defined as either systolic BP of 140 mmHg or more but less than 160 mmHg or diastolic BP of 90 mmHg or more but less than 95 mmHg in participants not taking antihypertensive medications. At initial visit, 6 months and annually thereafter, certified photographers adhering to a standardised protocol obtained stereoscopic funds photographs on film. All photographic images were graded according to the Wisconsin Age-related Maculopathy Grading System and the International Classification and Grading system for Age-related maculopathy and age related macular degeneration. Photographs were graded by 2 readers who later agreed any discrepancies openly to drive at consensus. Fluorescein angiograms were used to identify choroidal neovascularisation defined as expansion or persistent staining of an area of hyper fluorescence as the time from injection increased Geographic atrophy was considered present when the colour photograph showed an area of atrophy of the RPE with a diameter of at least 250um with 2 of the following features: visible choroidal vessels, sharp edges and a more or less circular shape. Endpoint GA was defined as the development of a total of more than 1 MPS disc area of a new, additional atrophy when all areas of GA were within 3000um of the foveal centre were combined.
Patient characteristics	Mean age: 71 years Gender: unclear Ethnicity: 99% white
Predictors/risk factors and effect estimates	Risk factors under analysis included: age, cigarette smoking, hypertension, focal hyper pigmentation, precent of area covered by duress, focal hyper pigmentation, RPE depigmentation. Other risk factors that did not reach significance at univariate level were not entered into the final cox proportional hazards model. Treatment was included as a covariate in this model.

Bibliographic reference	**Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group, 20080911, Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial, Ophthalmology, 115, 1474-1479, 2008.**
Outcomes	Risk factors for choroidal neovascularisation from multivariate analysis, relative risk (95% confidence intervals) Risk factors for geographic atrophy from multivariate analysis, relative risk (95% confidence intervals)
Analysis used	Cox proportional hazards analysis
Length of follow up	5 years follow up with 6 month and annual visits
Missing data handling/loss to follow up	Through 5 years of follow up, 5891 (97.2%) of visits were completed of the 6061 6 month an annual visits scheduled for surviving CAPT participants in this trial.
Results	**Risk factors for choroidal neovascularisation from multivariate analysis, relative risk (95% confidence intervals)** Age 50-59 years: 1.00 60-69 years: 2.06 (1.06-3.97) 70-79 years: 2.61 (1.39-4.92) >79: 2.81 (1.33-5.94) Cigarette smoking Never: 1.00 Quit: 1.01 (0.76-1.35) Current: 1.98 (1.16-3.39) Hypertension Normal: 1.00 Suspect: 0.69 (0.45-1.07) Definite: 1.23 (0.90-1.68) Focal hyperpigmentation None/questionable: 1.00 <250 um: 1.28 (0.94-1.75) >=250 um: 1.84 (1.22-2.76) **Risk factors for geographic atrophy from multivariate analysis, relative risk (95% confidence intervals)** Age 50-59 years: 1.00 60-69 years: 6.09 (1.72-21.5) 70-79 years: 4.12 (1.18-14.4)

Bibliographic reference	Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group, 20080911, Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial, Ophthalmology, 115, 1474-1479, 2008.
	>79: 6.39 (1.64-24.9) Hypertension Normal: 1.00 Suspect: 1.01 (0.76-1.35) Definite: 1.98 (1.16-3.39) % of area covered by drusen: <10%: 1.00 10-24%: 2.39 (1.44-3.97) >=25%: 5.10 (2.57-10.1) Focal hyperpigmentation None/questionable: 1.00 <250 um: 2.82 (1.30-6.12) >=250 um: 10.4 (4.51-24.0) Retinal pigment epithelium depigmentation: No: 1.00 Yes: 2.64 (1.26-5.53)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES

Bibliographic reference	**Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group, 20080911, Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial, Ophthalmology, 115, 1474-1479, 2008.**
	Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Finger,Robert P., Wu,Zhichao, Luu,Chi D., Kearney,Frances, Ayton,Lauren N., Lucci,Lucia M., Hubbard,William C., Hageman,Jill L., Hageman,Gregory S., Guymer,Robyn H., Reticular pseudodrusen: a risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization, Ophthalmology, 121, 1252-1256, 2014**
Country/ies where the study was carried out	USA and Australia
Study type	Retrospective cohort study
Aim of the study	To determine whether reticular pseudodrusen (RPD) confer an increased risk of progression to late-stage age-related macular degeneration (AMD) in fellow eyes of those recently diagnosed with unilateral choroidal neovascularization (CNV).
Study dates	Published 2014 Participants recruited from 2010 to 2012
Source of funding	This work was in part supported by the German Research Council, the Perpetual Foundation, Novartis Australia, Bayer Australia, and by the National Health and Medical Research Council (NHMRC) project grants and Centre for Clinical Research Excellence grant, a Macular Degeneration Foundation Australia Research Grant (RHG & GSH), the BrightFocus Foundation, a National Institutes of Health grant, the American Macular Degeneration Foundation, Inc., the Helen K. and Arthur E. Johnson Foundation, the Willard L. Eccles Charitable Foundation, Sylvia E. Prahl-Brodbeck, Sharon E. Steele-McGee and an unrestricted grant to the University of Utah John A. Moran Eye Center and Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness, Inc. CERA receives Operational Infrastructure Support from the Victorian Government.
Number of patients	200 consecutive participants with CNV secondary to AMD in one eye and no signs of late stage AMD in the fellow eye.

Bibliographic reference	**Finger,Robert P., Wu,Zhichao, Luu,Chi D., Kearney,Frances, Ayton,Lauren N., Lucci,Lucia M., Hubbard,William C., Hageman,Jill L., Hageman,Gregory S., Guymer,Robyn H., Reticular pseudodrusen: a risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization, Ophthalmology, 121, 1252-1256, 2014**
Inclusion Criteria	• Participants were recruited from the medical retina clinic at the Royal Victorian Eye and Ear Hospital at the University of Melbourne, Australia, and the John A. Moran Eye Center at the University of Utah, USA from 2010 until 2012. • All consecutive subjects who presented with a newly diagnosed CNV secondary to AMD were recruited. • Data was retrospectively reviewed to address the question of the fellow eye by including only those participants with non late-stage AMD in their fellow eye and follow-up for at least one year, unless they developed late-stage AMD in the fellow eye in less than one year, in which case they were not excluded from analyses.
Exclusion Criteria	• Exclusion criteria, for all participants, based upon the assessment of all images, included the presence of late-stage AMD (including any geographic atrophy (GA) and CNV) or other retinal pathology such as diabetic retinopathy or significant epiretinal membrane in the fellow study eye, and any corneal or media opacity that obscured the macula and prevented the assessment of disease state. • Participants had to have all required imaging, i.e. SD-OCT, NIR and colour fundus photography.
Diagnostic criteria	All participants underwent imaging with colour fundus photography, NIR and a 20°×20° volume scan with at least 19 B-scans on SD-OCT. Fluorescein angiography (FA) was performed at baseline presentation, and indocyanine green angiography (ICGA) and fundus autofluorescence (FAF) were performed as clinically indicated. End-stage disease was classified as either GA or CNV depending on whichever late stage was developed first. CNV was defined based on clinical examination and confirmed by SD-OCT and FA. GA was defined based on clinical examination and colour photography with lesions larger than 175 µm and within two disc diameters of the fovea and confirmed on SD-OCT and NIR. The presence of RPD was defined as groups of hypo-reflective lesions against a background of mild hyper-reflectance on NIR with corresponding hyper-reflective signal above the retinal pigment epithelium (RPE) on SD-OCT.
Patient characteristics	Participants (n=200) Age (years): 76.77 ±7.10 Gender Male: 79(39.5%) Female: 121(60.5%) Ethnicity: not reported
Predictors/risk factors and effect estimates	Risk factors of interest include: Retinal pseudodrusen, pigmentary changes, drusen ≥125 µm Hazard ratios were adjusted for the above factors and age and gender.

Bibliographic reference	**Finger,Robert P., Wu,Zhichao, Luu,Chi D., Kearney,Frances, Ayton,Lauren N., Lucci,Lucia M., Hubbard,William C., Hageman,Jill L., Hageman,Gregory S., Guymer,Robyn H., Reticular pseudodrusen: a risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization, Ophthalmology, 121, 1252-1256, 2014**
Outcomes	Hazard ratios for late-stage AMD Hazard rates for choroidal neovascularisation Hazard rates for geographic atrophy
Analysis used	Cox regression analysis
Length of follow up	All participants were followed up for an average of two years (±1.3 years standard deviation, median 2 years, range 7.4 years).
Missing data handling/loss to follow up	Participants had to have all required imaging to be included (no loss to follow up or missing data described)
Results	Results for hazard rates of late-stage AMD, controlling for age and gender **Choroidal neovascularisation (CNV)** Reticular pseudodrusen: 1.19 (0.72-1.94) Drusen ≥125µm: 1.96 (1.14-3.36) Pigmentary Changes: 2.49 (1.51-4.10) **Geographic atrophy (GA)** Reticular pseudodrusen: 4.93 (1.06-22.93) Drusen ≥125µm: 11.73 (1.47-93.81) Pigmentary Changes: 5.75 (2.09-15.84) **CNV or GA** Reticular pseudodrusen: 1.20 (0.76-1.89) Drusen ≥125µm: 2.08 (1.25-3.49) Pigmentary Changes: 2.55 (1.64-3.96)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE

Bibliographic reference	Finger,Robert P., Wu,Zhichao, Luu,Chi D., Kearney,Frances, Ayton,Lauren N., Lucci,Lucia M., Hubbard,William C., Hageman,Jill L., Hageman,Gregory S., Guymer,Robyn H., Reticular pseudodrusen: a risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization, Ophthalmology, 121, 1252-1256, 2014
	Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). UNSURE The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Grunwald,Juan E., Daniel,Ebenezer, Huang,Jiayan, Ying,Gui Shuang, Maguire,Maureen G., Toth,Cynthia A., Jaffe,Glenn J., Fine,Stuart L., Blodi,Barbara, Klein,Michael L., Martin,Alison A., Hagstrom,Stephanie A., Martin,Daniel F., CATT Research Group, Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials, Ophthalmology, 121, 150-161, 2014
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To describe risk factors for geographic atrophy (GA) in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).
Study dates	July 2010 and September 2011
Source of funding	Supported by cooperative agreements from the National Eye Institute, National Institutes of Health, Department of Health and Human Services.
Number of patients	1024 patients were analysed
Inclusion Criteria	• Age ≥50 years

Bibliographic reference	Grunwald,Juan E., Daniel,Ebenezer, Huang,Jiayan, Ying,Gui Shuang, Maguire,Maureen G., Toth,Cynthia A., Jaffe,Glenn J., Fine,Stuart L., Blodi,Barbara, Klein,Michael L., Martin,Alison A., Hagstrom,Stephanie A., Martin,Daniel F., CATT Research Group, Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials, Ophthalmology, 121, 150-161, 2014
	• Active, untreated CNV secondary to AMD • VA between 20/25 and 20/320 in the study eye
Exclusion Criteria	• Eyes with any GA at baseline • Missing or ungradable fundus photography
Diagnostic criteria	At enrolment, patients provided a medical history and had bilateral colour fundus photography (CFP), fluorescein angiography (FA), and time-domain optical coherence tomography (OCT). Follow-up examinations were scheduled every 28 days for 2 years. Graders at the Photograph Reading Centre were required to indicate whether there were signs of GA at the initial visit in the study eye as well as the fellow eye. Two trained and certified graders at the CATT Fundus Photograph Reading Centre reviewed images acquired at the initial and follow-up visits. Discrepancies between the 2 graders were adjudicated. The diagnosis of GA required the presence within the macular vascular arcades of ≥1 patches ≥250 μ in longest linear dimension of partial or complete depigmentation in the CFP that had ≥1 of these additional characteristics: sharply demarcated borders seen in CFP and/or FA, visibility of underlying choroidal vessels, excavated or punched out appearance on stereoscopy of CFP or FA, or uniform hyperfluorescence bounded by sharp borders on late-phase angiography. OCT scans were not used for the determination of the presence of GA.
Patient characteristics	Total (n=1024) Age (yrs), No. 50–69: 128 70–79: 354 80–89: 476 ≥90: 66 Sex, No. Female 634 Male 390 Ethnicity (not reported)
Predictors/risk factors and effect estimates	Risk factors of interest for which hazard ratios were provided included: Baseline VA in study eye, retinal angiomatous proliferation lesion, geographic atrophy in fellow eye

Bibliographic reference	**Grunwald,Juan E., Daniel,Ebenezer, Huang,Jiayan, Ying,Gui Shuang, Maguire,Maureen G., Toth,Cynthia A., Jaffe,Glenn J., Fine,Stuart L., Blodi,Barbara, Klein,Michael L., Martin,Alison A., Hagstrom,Stephanie A., Martin,Daniel F., CATT Research Group, Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials, Ophthalmology, 121, 150-161, 2014**
	Covariates and risk factors at the univariate level included: age, baseline VA of the study eye, baseline VA of fellow eye, location of lesion, lesion type, blocked fluorescence, RAP lesion, CNV in fellow eye, GA in fellow eye, retinal thickness in the foveal centre, subretinal thickness in the foveal centre, subretinal tissue complex thickness in the foveal centre, intraretinal fluid, subretinal fluid, vitreomacular attachment, drug, and regimen, atrophic or fibrotic scar, gender, cigarette smoking, hypertension, diabetes, dietary supplement use, hypercholesterolemia
Outcomes	Multivariate Analysis and hazard ratios for factors Associated with Incidence of Geographic Atrophy (GA) at 2 Years
Analysis used	Cox proportional hazard models
Length of follow up	2 years
Missing data handling/loss to follow up	Those with missing data were excluded (for instance missing information on presence of geographic atrophy). No imputations were made
Results	Multivariate Analysis for Factors Associated with Incidence of Geographic Atrophy (GA) at 2 Years Baseline VA in study eye 20/25–40: 1.00 (referent) 20/50–80: 1.66 (1.14–2.44) 20/100–160: 1.70 (1.10–2.62) 20/200–320: 2.65 (1.43–4.93) Retinal angiomatous proliferation lesion No: 1.00 (referent) Yes: 1.69 (1.16–2.47) GA in fellow eye None/questionable: 1.00 (referent) Present: 2.07 (1.40–3.08) Initial model includes age, baseline VA of the study eye, baseline VA of fellow eye, location of lesion, lesion type, blocked fluorescence, RAP lesion, CNV in fellow eye, GA in fellow eye, retinal thickness in the foveal centre, subretinal thickness in the foveal centre, subretinal tissue complex thickness in the foveal centre, intraretinal fluid, subretinal fluid, vitreomacular attachment, drug, and regimen. The final multivariate model only included the significant variables listed in this table. Risk factors found non-significant at univariate level included: atrophic or fibrotic scar, gender, cigarette smoking, hypertension, diabetes, dietary supplement use, hypercholesterolemia

Bibliographic reference	**Grunwald,Juan E., Daniel,Ebenezer, Huang,Jiayan, Ying,Gui Shuang, Maguire,Maureen G., Toth,Cynthia A., Jaffe,Glenn J., Fine,Stuart L., Blodi,Barbara, Klein,Michael L., Martin,Alison A., Hagstrom,Stephanie A., Martin,Daniel F., CATT Research Group, Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials, Ophthalmology, 121, 150-161, 2014**
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Hahn,Paul, Acquah,Kofi, Cousins,Scott W., Lee,Paul P., Sloan,Frank A., Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among medicare beneficiaries, Retina (Philadelphia, Pa.)Retina, 33, 911-919, 2013**
Country/ies where the study was carried out	USA
Study type	Longitudinal retrospective cohort analysis

Bibliographic reference	**Hahn,Paul, Acquah,Kofi, Cousins,Scott W., Lee,Paul P., Sloan,Frank A., Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among medicare beneficiaries, Retina (Philadelphia, Pa.)Retina, 33, 911-919, 2013**
Aim of the study	To compare the longitudinal incidence over 10 years of dry and wet age-related macular degeneration (AMD) in a U.S. sample of Medicare beneficiaries with: no diabetes mellitus (no DM); diabetes mellitus without retinopathy (DM); non-proliferative diabetic retinopathy (NPDR); and proliferative diabetic retinopathy (PDR).
Study dates	Published 2013 Patients enrolled between 1995-2005
Source of funding	Publication of this article was supported in part by a grant from the National Institute on Aging. Paul Hahn received support from the Ronald G. Michels Foundation and the Heed Ophthalmic Foundation. Paul P. Lee has served as a consultant for Allergan, Pfizer, and Genentech, and he has received financial support from Alcon, the National Institute of Health, and the Washington University Award
Number of patients	Diabetes mellitus (n=6621) Non-proliferative diabetic retinopathy (n=1307) Proliferative diabetic retinopathy (n=327) Compared to an equivalent number of controls without diabetes
Inclusion Criteria	• A sample of individuals first diagnosed with DM, NPDR, or PDR in 1995. • Individuals with a new diagnosis of PDR required exclusion of any previous PDR code in the prior 4 years. • Individuals with a new diagnosis of NPDR required exclusion of any previous NPDR or PDR diagnosis in the prior 4 years. • Individuals with a new diagnosis of DM required exclusion of any previous DM, NPDR, or PDR diagnosis in the prior 4 years.
Exclusion Criteria	• Individuals age 95+ in 1995 and persons who entered a Medicare risk plan (HMO) or • Lived outside of the U.S for 12 months or more during the look-back period. • Any individual initially diagnosed with AMD prior to a diabetes mellitus or diabetic retinopathy diagnosis in 1995. • Any individual who had not seen an eye care provider at least once during the look-back and at least once during both the first and the last five years of the follow-up period.
Diagnostic criteria	Under a Duke University Institutional Review Board-approved protocol, Medicare 5% inpatient, outpatient, and Part B claims files were used to identify a nationally representative sample of Medicare beneficiaries aged 65 or older who were diagnosed with DM, NPDR, and PDR or dry AMD and wet AMD from 1991–2005. Diagnosis was based on ICD-9-CM codes for the appropriate disease state (Table 1). Individuals with no DM were identified by exclusion of all diabetes mellitus codes; individuals with no AMD were identified by exclusion of all AMD codes.

Bibliographic reference	**Hahn,Paul, Acquah,Kofi, Cousins,Scott W., Lee,Paul P., Sloan,Frank A., Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among medicare beneficiaries, Retina (Philadelphia, Pa.)Retina, 33, 911-919, 2013**
	To ensure these were incident cases of diabetes mellitus or diabetic retinopathy and to identify other comorbidities, authors employed a 4-year look-back period, which necessitated all individuals to be age 69+ in 1995 in order to have a full look-back. Individuals with a new diagnosis of PDR required exclusion of any previous PDR code in the look-back; individuals with a new diagnosis of NPDR required exclusion of any previous NPDR or PDR diagnosis in the look-back; individuals with a new diagnosis of DM required exclusion of any previous DM, NPDR, or PDR diagnosis in the look-back period.
Patient characteristics	Individuals with DM, NPDR, and PDR were matched at baseline to an equivalent number of 'no DM' controls by age, gender, race, history of hypertension, atherosclerosis, stroke, coronary heart disease, hyperlipidaemia, and Charlson index. All variables were matched between diabetic/diabetic retinopathy subtypes and controls except for the Charlson index, which could not be matched to a standard difference <10% for individuals with NPDR or PDR.
Predictors/risk factors and effect estimates	Risk factors under study included: Diabetes, diabetic proliferative retinopathy and diabetic non-proliferative retinopathy
Outcomes	Hazard Ratio (95% CI) for Development of Dry AMD Hazard Ratio (95% CI) for Development of Wet AMD
Analysis used	Cox proportional hazard modelling
Length of follow up	10 year follow up
Missing data handling/loss to follow up	The Medicare database represents information collected for billing purposes and not for the analysis of clinical investigations. Relevant conditions may sometimes have been incorrectly coded. The database includes clinically ambiguous codes, including 362.81 (retinal haemorrhage: preretinal, retinal (deep) (superficial), subretinal), which may arise secondary to either non-proliferative or proliferative/neovascular aetiologies or 362.57 (drusen), which is often used to code for peripheral drusen not diagnostic for macular degeneration. While they did not include these ambiguous codes in our final analysis, a parallel analysis was performed with inclusion of these codes (data not shown), resulting in similar results with significantly increased risk of wet AMD (but not dry AMD) in patients with NPDR and PDR only.
Results	**Hazard Ratio (95% CI) for Development of Dry AMD** Diabetes mellitus 1.03 (0.97 1.09) Non-proliferative diabetic retinopathy 1.24 (1.08 1.43) Proliferative diabetic retinopathy 1.10 (0.83 1.47) **Hazard Ratio (95% CI) for Development of Wet AMD** Diabetes mellitus 1.11 (0.97 1.27)

Bibliographic reference	Hahn,Paul, Acquah,Kofi, Cousins,Scott W., Lee,Paul P., Sloan,Frank A., Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among medicare beneficiaries, Retina (Philadelphia, Pa.)Retina, 33, 911-919, 2013
	Non-proliferative diabetic retinopathy 1.68 (1.23 2.31) Proliferative diabetic retinopathy 2.15 (1.07 4.33) Controlled for other variables in the Cox proportional analysis including systemic comorbidities and the Charlson index
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). YES Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). NO Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Howard,Kerri P., Klein,Barbara E.K., Lee,Kristine E., Klein,Ronald, Measures of body shape and adiposity as related to incidence of age-related eye diseases: observations from the Beaver Dam Eye Study, Investigative ophthalmology & visual science, 55, 2592-2598, 2014**
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To examine the effect of obesity on the incidence of age-related eye disease.
Study dates	Published 2014 1988-1990 through 2008-2010
Source of funding	Supported by National Institutes of Health Grant. The National Eye Institute provided funding for entire study, including collection and analyses of data. Additional support was provided by an unrestricted grant from Research to Prevent Blindness.
Number of patients	2641 participants (870 female non-smokers, 640 female smokers, 368 male non-smokers, and 763 male smokers contributing 1824, 1334, 803, and 1606 person-visits, respectively)
Inclusion Criteria	A private census of the population of Beaver Dam, Wisconsin All residents aged 43- 84 years To contribute to analysis in a given 5-year interval, a person must have had complete data on the risk factors of interest (BMI, WHR, WC, or WHtR) and the outcome (incident nuclear, cataract, cortical cataract, or PSC, cataract surgery, or early or late AMD) and all covariates included in the maximally adjusted model (age, sedentary lifestyle, diabetes, hypertension).
Exclusion Criteria	None described
Diagnostic criteria	Photographs of the retina were taken to determine presence and severity of lesions associated with AMD and the Wisconsin Age-related Maculopathy Grading System was used to assess the fundus photographs. Early AMD was defined by the presence of soft indistinct drusen or any type of drusen associated with pigmentary abnormality (i.e., retinal pigment epithelium depigmentation or increased retinal pigment). Late AMD was defined by the presence of neovascular macular degeneration or pure geographic atrophy (GA).
Patient characteristics	Original sample Age at baseline (n=4755) 43- 54: 1500 55-64: 1295 65-74: 1242 75-86: 718 Gender (n):

Bibliographic reference	**Howard,Kerri P., Klein,Barbara E.K., Lee,Kristine E., Klein,Ronald, Measures of body shape and adiposity as related to incidence of age-related eye diseases: observations from the Beaver Dam Eye Study, Investigative ophthalmology & visual science, 55, 2592-2598, 2014**
	Women: 2642 Men: 2113 Ethnicity: 99% white
Predictors/risk factors and effect estimates	Risk factors of interest under study included: Gender, smoking, BMI Outcomes were adjusted for: age (age and age squared for cataract outcomes), sedentary lifestyle, hypertension, diabetes, posterior subscapular cataract.
Outcomes	Hazard ratios for the risk of developing early AMD stratified by gender (and smoking status) Hazard ratios for the risk of developing late AMD stratified by gender (and smoking status)
Analysis used	Discrete-time hazard model with complementary log-log link function and time varying predictors
Length of follow up	15 years
Missing data handling/loss to follow up	Generally, persons who were excluded from analysis were older and had more comorbid conditions compared with those included. For those included, female smokers tended to be younger than non-smokers. There were no significant differences between female non-smokers and smokers with respect to systolic or diastolic blood pressure, education level, BMI, WC, WHR, WHtR, heavy drinking, cardiovascular disease, hypertension, diabetes, having a sedentary lifestyle, or using vitamins. In males, non-smokers tended to be older and have more years of education and smaller WC as compared with male smokers. Male smokers were more likely to have ever been a heavy drinker, have cardiovascular disease, or diabetes and were less likely to have a sedentary lifestyle. No description of how missing data or loss to follow up was dealt, with as participants were not included in the analysis unless they had complete information.
Results	**Hazard ratios for the risk of developing early AMD stratified by gender (and smoking status)** Female, non-smoker: BMI (per 2.5 kg/m²): 1.10 (1.02, 1.19) Male, non-smoker: BMI (per 2.5 kg/m²): 0.90 (0.75, 1.07) **Hazard ratios for the risk of developing late AMD stratified by gender (and smoking status)** Female, non-smoker

Bibliographic reference	Howard,Kerri P., Klein,Barbara E.K., Lee,Kristine E., Klein,Ronald, Measures of body shape and adiposity as related to incidence of age-related eye diseases: observations from the Beaver Dam Eye Study, Investigative ophthalmology & visual science, 55, 2592-2598, 2014
	BMI (per 2.5 kg/m²): 1.31 (1.15, 1.50) Male, non-smoker BMI (per 2.5 kg/m²): 0.86 (0.61, 1.20) **Hazard ratios for the risk of developing early AMD stratified by gender (and smoking status)** Female smoker BMI (per 2.5 kg/m²): 1.07 (0.98, 1.17) Male smoker BMI (per 2.5 kg/m²): 1.00 (0.90, 1.10) **Hazard ratios for the risk of developing late AMD stratified by gender (and smoking status)** Female smoker BMI (per 2.5 kg/m²): 0.99 (0.81, 1.21) Male smoker BMI (per 2.5 kg/m²): cannot estimate Hazard ratios adjusted for: age (age and age squared for cataract outcomes), sedentary lifestyle, hypertension, diabetes, posterior subscapular cataract.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). NO Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNCLEAR

Bibliographic reference	Howard,Kerri P., Klein,Barbara E.K., Lee,Kristine E., Klein,Ronald, Measures of body shape and adiposity as related to incidence of age-related eye diseases: observations from the Beaver Dam Eye Study, Investigative ophthalmology & visual science, 55, 2592-2598, 2014
	Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Klein,Barbara E.K., Howard,Kerri P., Gangnon,Ronald E., Dreyer,Jennifer O., Lee,Kristine E., Klein,Ronald, Long-term use of aspirin and age-related macular degeneration, JAMA, 308, 2469-2478, 2012
Country/ies where the study was carried out	USA
Study type	Longitudinal prospective cohort study
Aim of the study	To examine the association of regular aspirin use with incidence of AMD.
Study dates	Published 2012 1988–1990 through 2008–2010
Source of funding	This research is supported by National Institutes of Health grant EY06594. The National Eye Institute provided funding for entire study, including collection and analyses of data.
Number of patients	4926 person participated in the baseline examination
Inclusion Criteria	• To be eligible for incidence of a specified type of AMD (early, late, neovascular, pure GA) and inclusion in the analysis, a participant must • Be free of the given AMD outcome at the baseline examination and have complete AMD data from consecutive follow-up examinations, until incidence or censoring occurred.

Bibliographic reference	Klein,Barbara E.K., Howard,Kerri P., Gangnon,Ronald E., Dreyer,Jennifer O., Lee,Kristine E., Klein,Ronald, Long-term use of aspirin and age-related macular degeneration, JAMA, 308, 2469-2478, 2012
	• A participant must have had complete data for self-reported aspirin use, age, sex, education, history of arthritis, and history of CVD.
Exclusion Criteria	• Participants with missing aspirin data were excluded
Diagnostic criteria	Participants were asked if they regularly used aspirin at least twice per week for more than 3 months. This self-report of regular aspirin use was the main exposure measure of interest in our primary analysis because it was asked at every examination. Additional information concerning frequency of aspirin use (<1 every other day, 1 every other day, 1/day, 2/day, 3–7/day or ≥8/day) and dosage were obtained at the third, fourth, and fifth examinations. Participants were asked to bring all currently used medications to the examinations. All medications, including NSAIDs and anticoagulants (e.g. warfarin), were recorded. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or history of blood pressure medication use. Blood samples were obtained and analysed for glycosylated haemoglobin A1c and inflammatory factors, e.g. leukocyte count and C-reactive protein (CRP). CRP was measured only at the baseline examination, and leukocyte count was measured at the baseline and second examinations. Diabetes was defined as self-report confirmed by use of insulin or diet to control diabetes, self-report with glycosylated haemoglobin A1c level above 6.5%, or no self-report with glycosylated haemoglobin A1c above 7%. Photographs of the retina were taken after pupillary dilation and graded in masked fashion by experienced graders using the Wisconsin Age-Related Maculopathy Grading System to assess the presence and severity of lesions associated with AMD.
Patient characteristics	Persons aged 43–86 years were included 99% was white 56% was female
Predictors/risk factors and effect estimates	Risk factors under study included aspirin use at the examination 5 years prior to incidence as well as aspirin use reported at the previous examination, 10 years prior to observed incidence. Variables potentially associated with risk of AMD were first analysed individually in age- and sex-adjusted models. These variables included body mass index, annual income, education, diabetes, systolic and diastolic blood pressure, hypertension, history of cancer, smoking (never, past, current), ever drinking, ever heavy drinking, history of arthritis, and history of CVD. All significant factors in the age- and sex-adjusted models were then included in a maximally adjusted model.
Outcomes	Hazard ratios for the development of early AMD, any late AMD, neovascular AMD or geographic atrophy.
Analysis used	Discrete-time hazard model using the complementary log-log link function with time-varying predictors
Length of follow up	20 year follow up. The mean duration of follow-up time was 14.8 years, with a median duration of 15.9 years

Bibliographic reference	Klein,Barbara E.K., Howard,Kerri P., Gangnon,Ronald E., Dreyer,Jennifer O., Lee,Kristine E., Klein,Ronald, Long-term use of aspirin and age-related macular degeneration, JAMA, 308, 2469-2478, 2012
Missing data handling/loss to follow up	For incident early AMD, 2547 persons of the 4926 seen at baseline were excluded from analysis (1008 had prevalent early or late AMD at baseline, 84 persons were missing a covariate, 448 were missing AMD data at baseline, and 1007 did not have data at the first follow-up examination). For incidence of late AMD, 1794 persons of the 4926 seen at baseline were excluded from analysis (74 persons had prevalent late AMD at baseline, 104 were missing a covariate, 407 had missing AMD data at baseline, and 1209 had missing data at the first follow-up examination). Participants included in these analyses tended to be younger and have fewer comorbidities at baseline than those excluded.
Results	Relationships of Incidence of Age-related Macular Degeneration Outcomes with Self-Reported Regular Aspirin Use 5 Years Prior Over 20 Years in the Beaver Dam Eye Study. Hazard ratios (95% confidence intervals). Early AMD* No regular aspirin use: Referent Regular aspirin use: 0.86 (0.71, 1.05) Any Late AMD No regular aspirin use: Referent Regular aspirin use: 1.21 (0.84, 1.74) Neovascular AMD No regular aspirin use: Referent Regular aspirin use: 1.07 (0.68, 1.67) Pure GA No regular aspirin use: Referent Regular aspirin use: 1.65 (0.91, 2.99) Hazard ratios were adjusted for age, arthritis history, and education level
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD;

Bibliographic reference	Klein,Barbara E.K., Howard,Kerri P., Gangnon,Ronald E., Dreyer,Jennifer O., Lee,Kristine E., Klein,Ronald, Long-term use of aspirin and age-related macular degeneration, JAMA, 308, 2469-2478, 2012
	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). YES Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). YES Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Klein,Michael L., Francis,Peter J., Ferris,Frederick L., Hamon,Sara C., Clemons,Traci E., Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550, 2011
Country/ies where the study was carried out	USA
Study type	Prospective Cohort Study
Aim of the study	To design a risk assessment model for development of advanced age-related macular degeneration (AMD) incorporating phenotypic, demographic, environmental, and genetic risk factors.
Study dates	Published 2011 Participants in the Age-Related Eye Disease Study
Source of funding	This work was supported by the Casey Eye Institute Macular Degeneration Fund, Research to Prevent Blindness, the Bea Arveson Macular Degeneration Fund, and the Foundation Fighting Blindness.
Number of patients	2846 participants

Bibliographic reference	Klein,Michael L., Francis,Peter J., Ferris,Frederick L., Hamon,Sara C., Clemons,Traci E., Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550, 2011
Inclusion Criteria	• Age 55-80 years • At least one eye had to be free from vision-threatening disease other than AMD and cataract • That eye could not have had surgery, except for cataract surgery • The participants' stages of disease ranged from no evidence of AMD in either eye, to advanced AMD with vision loss in one eye but good vision (at least 20/30) in the other eye
Exclusion Criteria	None described
Diagnostic criteria	Comprehensive ocular and medical histories and examinations were performed at entrance into the study. Recorded information included age, sex, race, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), education level, cigarette smoking, diet, sunlight exposure, history of skin cancer, arthritis, systemic hypertension, other cardiovascular diseases, diabetes, and history of current and past medications and dietary supplements. For this study, the AREDS simplified severity scale was used to classify participants by their retina phenotype; This scale was designed to define risk categories for development of advanced AMD that could be readily determined by either clinical examination or fundus photography. The system uses 2 retinal abnormalities at baseline to determine a risk score: The end points of this study occurred when participants with no advanced AMD in either eye at baseline progressed to advanced AMD in either eye or when those with advanced AMD in 1 eye at baseline developed advanced AMD in the fellow eye. Two forms of advanced AMD were recognized: (1) NV and (2) GA, defined as an area of well-demarcated depigmentation of the pigment epithelium, typically round or oval, and within which choroidal vessels are usually visible.
Patient characteristics	Median Age: 69 years 56% female Only white ethnicity included in the analysis
Predictors/risk factors and effect estimates	Risk factors of interest were: Very large drusen, Current smoking, Family history, AAMD in 1 eye, Age, mean (SD), y Hazard ratios were adjusted for age, cigarette smoking, family history, BMI, education, simple scale score, very large drusen (250 µm), unilateral AMD, and variants in the genes CFH, ARMS2, C3, and CFI. The C2/CFB variant. (all significant at univariate level)
Outcomes	Hazard Ratios for Progression to Advanced Age-Related Macular Degeneration
Analysis used	Cox proportional hazards analysis
Length of follow up	Follow-up averaged 9.3 years

Bibliographic reference	Klein,Michael L., Francis,Peter J., Ferris,Frederick L., Hamon,Sara C., Clemons,Traci E., Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550, 2011
Missing data handling/loss to follow up	Unclear: no description of missing data or how this was managed.
Results	Multivariate Association of Baseline Independent Variables Included in Final Model With Hazard Ratios for Progression to Advanced Age-Related Macular Degeneration at 2, 5, and 10 Years in 2602 Participants Very large drusen No: 1 (referent) Yes: 1.79 (1.50-2.14) Current smoking No: 1 (referent) Yes: 1.78 (1.37-2.31) Family history No: 1 (referent) Yes: 1.40 (1.16-1.70) AAMD in 1 eye No: 1 (referent) Yes 1.21 (1.02-1.45) Age, mean (SD), y: 1.03 (1.01-1.05) Education and BMI were not significant at the multivariate level.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in Studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). PARTLY Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE

Bibliographic reference	Klein,Michael L., Francis,Peter J., Ferris,Frederick L., Hamon,Sara C., Clemons,Traci E., Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550, 2011
	Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Klein,R., Klein,B.E., Knudtson,M.D., Meuer,S.M., Swift,M., Gangnon,R.E., 20070220, Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, Ophthalmology, 114, 253-262, 2007
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To describe the 15-year cumulative incidence of signs of early and late age-related macular degeneration (AMD)
Study dates	1988-1990 to 1993-1995 follow up and/or 2003-2005 follow up.
Source of funding	Supported by National Institutes of Health, National Eye institute, and, in part, Research to Prevent Blindness.
Number of patients	Included 3917 persons
Inclusion Criteria	A private census of the population of Beaver Dam, Wisconsin All residents aged 43- 84 years
Exclusion Criteria	None reported
Diagnostic criteria	Similar procedures were performed at baseline and follow up examinations. Stereoscopic 30° colour fundus photographs were taken, focused on the disc and macula and a non-stereoscopic colour fundus photograph temporal to but including the fovea of each eye. A circular grid was placed on one photographic slide of the stereoscopic pair, which divided the macular area into nine subfields, consisting of a central circle (a single subfield), inner ring (comprised of the four inner subfields), and outer ring

Bibliographic reference	Klein,R., Klein,B.E., Knudtson,M.D., Meuer,S.M., Swift,M., Gangnon,R.E., 20070220, Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, Ophthalmology, 114, 253-262, 2007
	(comprised of four outer subfields). Circles of defined size printed on clear acetate were used to estimate size of drusen and areas involved by drusen, increased retinal pigment and retinal pigment epithelial (RPE) depigmentation. Two gradings were performed for each eye at examination. First, a preliminary masked grading was done by one of two senior graders. Next, detailed gradings were performed by one of three other experienced graders. Each eye was graded independently of the fellow eye. The assessment consisted of a subfield-by-subfield, lesionby-lesion, evaluation of each photograph set using the Wisconsin Age-Related Maculopathy Grading System. Increasing order of severity of drusen were defined as follows: hard distinct, soft distinct, and soft indistinct. The incidence of a specific lesion, e.g., reticular drusen, geographic atrophy (GA), or exudative AMD, was defined by its presence at follow-up when it was not present at baseline. The incidence of late AMD was defined by the appearance of either exudative macular degeneration or pure GA at follow-up when neither lesion was present at baseline. Incidence of early AMD was defined by either the presence of either soft indistinct drusen or RPE depigmentation, or increased retinal pigment together with any type of drusen at follow-up when none of these lesions was present at baseline. Incidence of late AMD was defined by the appearance of either exudative macular degeneration or pure geographic atrophy at follow up when neither lesion was present at baseline.
Patient characteristics	Age at baseline 43- 54: 58% 55-64: 26% 65-74: 26% 75-86: 16% Gender (n): Women: 2642 Men: 2113 Ethnicity: 99% white
Predictors/risk factors and effect estimates	Risk factors of interest under study included: Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years); Drusen > 125µm vs <63µm in diameter; Soft distinct drusen vs hard distinct drusen; Soft indistinct vs soft distinct drusen or hard distinct drusen; Drusen area >16877 µm² vs ≤2596 µm²; Pigmentary abnormalities present vs absent; Increased pigment present vs absent; RPE depigmentation present vs absent. Odds ratios were adjusted by age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years).
Outcomes	Risk of developing early AMD, odds ratios (95% confidence intervals) Risk of developing late AMD, odds ratios (95% confidence intervals)

Bibliographic reference	Klein,R., Klein,B.E., Knudtson,M.D., Meuer,S.M., Swift,M., Gangnon,R.E., 20070220, Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, Ophthalmology, 114, 253-262, 2007
	Risk of developing geographic atrophy, odds ratios (95% confidence intervals) Risk of developing exudative AMD, odds ratios (95% confidence intervals):
Analysis used	Cox proportional hazards model
Length of follow up	15 year follow up
Missing data handling/loss to follow up	In general, persons who did not participate in the 15-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to have fewer years of education completed and higher systolic blood pressure than persons who participated.
Results	Fifteen-year cumulative incidence of Age-related macular degeneration (AMD) **Risk of developing early AMD, odds ratios (95% confidence intervals)** Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 2.3 (2.1-2.6) Drusen > 125µm vs <63µm in diameter: 5.5 (3.5-8.7) Soft distinct drusen vs hard distinct drusen: 3.0 (2.2-4.1) Drusen area >16877 µm² vs ≤2596 µm²: 5.2 (3.7-7.5) **Risk of developing late AMD, odds ratios (95% confidence intervals)** Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 3.5 (2.8- 4.4) Drusen > 125µm vs <63µm in diameter: 29.6 (14.4-60.7) Soft distinct drusen vs hard distinct drusen: 3.6 (1.5-8.6) Soft indistinct vs soft distinct drusen or hard distinct drusen: 17.5 (10.3-29.8) Drusen area >16877 µm² vs ≤2596 µm²: 32.3 (7.8-133) Pigmentary abnormalities present vs absent: 10.8 (6.5-18.0) Increased pigment present vs absent: 9.8 (5.9-16.3) RPE depigmentation present vs absent: 10.5 (5.9-18.5) **Risk of developing exudative AMD, odds ratios (95% confidence intervals)** Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 2.9 (2.2-3.8) Drusen > 125µm vs <63µm in diameter: 60.4 (17.7-206) Soft distinct drusen vs hard distinct drusen: 7.4 (2.4-22.6) Soft indistinct vs soft distinct drusen or hard distinct drusen: 18.3 (8.9-37.4)

Bibliographic reference	Klein,R., Klein,B.E., Knudtson,M.D., Meuer,S.M., Swift,M., Gangnon,R.E., 20070220, Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, Ophthalmology, 114, 253-262, 2007
	Drusen area >16877 µm² vs ≤2596 µm²: 40.4 (5.5-297) Pigmentary abnormalities present vs absent: 7.2 (3.6-14.1) Increased pigment present vs absent: 5.8 (2.9-11.7) RPE depigmentation present vs absent: 7.8 (3.6-16.6) **Risk of developing geographic atrophy, odds ratios (95% confidence intervals)** Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 4.2 (2.9-6.1) Drusen > 125µm vs <63µm in diameter: 14.5 (5.9-35.7) Soft distinct drusen vs hard distinct drusen: 1.2 (0.3-5.7) Soft indistinct vs soft distinct drusen or hard distinct drusen: 14.6 (6.8-31.1) Drusen area >16877 µm² vs ≤2596 µm²: 24.0 (3.2-179) Pigmentary abnormalities present vs absent: 15.2 (7.3-31.6) Increased pigment present vs absent: 15.8 (7.6-32.8) RPE depigmentation present vs absent: 11.1 (5.0-24.4)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES

Bibliographic reference	Klein,R., Klein,B.E., Knudtson,M.D., Meuer,S.M., Swift,M., Gangnon,R.E., 20070220, Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, Ophthalmology, 114, 253-262, 2007
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Klein,R., Meuer,S.M., Knudtson,M.D., Iyengar,S.K., Klein,B.E., 20080320, The epidemiology of retinal reticular drusen, American journal of ophthalmology, 145, 317-326, 2008
Country/ies where the study was carried out	Beaver Dam, USA
Study type	Prospective cohort study
Aim of the study	To document the long term incidence of reticular drusen, its risk factors and association with a high risk of incident late AMD.
Study dates	From fall 1987 to April 30, 2005
Source of funding	The National Eye Institute provided funding for entire study including collection and analyses and of data
Number of patients	4,926 persons 3,684 participated in 5 year follow up 2,764 participated in 10 year follow up 2,119 participated in 15 year follow up examinations
Inclusion Criteria	A private census of the population of Beaver Dam, Wisconsin All residents aged 43- 84 years
Exclusion Criteria	None reported
Diagnostic criteria	In brief, a circular grid was placed on one photographic slide of the stereoscopic pair, which divided the macular area into nine subfields, consisting of a central circle (a single subfield), inner ring (comprised of the four inner subfields), and outer ring (comprised of four outer subfields). Reticular and other types of drusen were graded in each subfield, outside the grid in DRS field 2, and nasal to the disc in Field 1. Two gradings were performed for each eye at each examination. First, a preliminary masked grading was done by one of two senior graders. Next, detailed gradings were performed by one of three other experienced graders. Each eye was graded independently of the fellow eye. The assessment consisted of a subfield-by-subfield, lesionby-lesion, evaluation of each photograph set using the Wisconsin Age-Related Maculopathy Grading System.

Bibliographic reference	Klein,R., Meuer,S.M., Knudtson,M.D., Iyengar,S.K., Klein,B.E., 20080320, The epidemiology of retinal reticular drusen, American journal of ophthalmology, 145, 317-326, 2008
	Increasing order of severity of drusen were defined as follows: hard distinct, soft distinct, and soft indistinct. The incidence of a specific lesion, e.g., reticular drusen, geographic atrophy (GA), or exudative AMD, was defined by its presence at follow-up when it was not present at baseline. The incidence of late AMD was defined by the appearance of either exudative macular degeneration or pure GA at follow-up when neither lesion was present at baseline.
Patient characteristics	Age at baseline (n=4755) 43- 54: 1500 55-64: 1295 65-74: 1242 75-86: 718 Gender (n): Women: 2642 Men: 2113 Ethnicity: 99% white
Predictors/risk factors and effect estimates	Controlling for gender (male/female), education (<high school, high school, some college, higher than college), income (<10K, 10-19K, 20-29K, 30-44K, 45 plus), smoking history (never/past/current), history of current wine drank (none, 1 per week, 2 plus per week), History of current liquor drank (none, 1 per week, 2-3 per week, 4 plus per week), history of sunlight at work (<25%, 25%, >25%), History of UV protection (none, little moderate, high) Diabetes, History of average distance walk/day (none, 1-4 blocks, 5-12 blocks, 13 plus blocks), History of sedentary lifestyle, history of antidepressant use.
Outcomes	Multivariable model of relationships of characteristics to incident reticular drusen, and relationship of reticular drusen at baseline to the 15-year cumulative incidence of late AMD, Geographic atrophy and exudative AMD
Analysis used	Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from discrete logistic hazard regression models for incidence.
Length of follow up	15 years
Missing data handling/loss to follow up	In general, persons who did not participate in the 15-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to have fewer years of education completed and higher systolic blood pressure than persons who participated.
Results	Multivariable model of relationships of characteristics to incident reticular drusen in the Beaver Dam Eye study **Odds Ratio 95% (confidence interval)**

Bibliographic reference	Klein,R., Meuer,S.M., Knudtson,M.D., Iyengar,S.K., Klein,B.E., 20080320, The epidemiology of retinal reticular drusen, American journal of ophthalmology, 145, 317-326, 2008
	Age 75-86 vs 43-54 years 47.3 (15.5, 144.3) 65-74 vs 43-54 years 22.9 (8.1, 65.3) 55-64 vs 43-54 years 5.8 (1.9, 17.3) Female sex 2.8 (1.6, 4.9) Increasing education 0.6 (0.4, 0.8) Smoking Current vs never smoker 1.9 (1.03, 3.6) Past vs never smoker 1.4 (0.9, 2.3) Increased wine drinking 0.6 (0.3, 1.1) Diabetes history 0.1 (0.02, 0.8) While controlling for age, history of pack-years smoked, current beer and heavy alcohol consumption, cumulative UV-exposure, hypertension status, weight, body mass, serum total and HDL cholesterol, cardiovascular disease history, iris colour, refractive error, cataract surgery, retinal pigmentary abnormalities were not related to the 15-year cumulative incidence of reticular drusen (data not shown). **Most Severe Drusen Type at Baseline OR (95% Confidence interval)** Risk of late AMD Reticular drusen vs Soft distinct drusen: 28.29 (9.48, 84.44) [reticular drusen higher risk] Reticular drusen vs Soft indistinct drusen: 6.34 (2.28, 17.63) Risk of incident Geographic Atrophy Reticular drusen vs Soft distinct drusen: 41.78 (9.43,185.14) [reticular drusen higher risk] Reticular drusen vs Soft indistinct drusen: 6.23 (1.70, 22.73) Exudative AMD Reticular drusen vs Soft distinct drusen: 9.89 (2.16, 45.23) [reticular drusen higher risk] Reticular drusen vs Soft indistinct drusen: 2.82 (0.66, 12.01)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD;

Bibliographic reference	Klein,R., Meuer,S.M., Knudtson,M.D., Iyengar,S.K., Klein,B.E., 20080320, The epidemiology of retinal reticular drusen, American journal of ophthalmology, 145, 317-326, 2008
	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis) YES

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Bibliographic reference	Klein,Ronald, Knudtson,Michael D., Cruickshanks,Karen J., Klein,Barbara E.K., Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration: the Beaver Dam Eye Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 115-121, 2008
Country/ies where the study was carried out	Beaver Dam, USA
Study type	Longitudinal Cohort Study
Aim of the study	To describe the association between baseline smoking status, age at initiation, duration, intensity, pack-years, age at quitting, and time from the baseline examination since quitting and the 15-year cumulative incidence and progression of AMD.
Study dates	From fall 1987 to April 30, 2005
Source of funding	National Eye institute, National Institute of aging, Research to Prevent Blindness.
Number of patients	4,926 persons

Bibliographic reference	**Klein,Ronald, Knudtson,Michael D., Cruickshanks,Karen J., Klein,Barbara E.K., Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration: the Beaver Dam Eye Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 115-121, 2008**
	3,684 participated in 5 year follow up 2,764 participated in 10 year follow up 2,119 participated in 15 year follow up examinations
Inclusion Criteria	A private census of the population of Beaver Dam, Wisconsin All residents aged 43- 84 year
Exclusion Criteria	Not specified
Diagnostic criteria	Informed consent was obtained from each participant at the beginning of the examination. Pertinent parts of the examinations included taking stereoscopic 30° colour fundus photographs cantered on the macula. The Wisconsin Age-Related Maculopathy Grading System was used to assess the presence and severity of lesions associated with AMD. The incidence of early AMD was defined by the presence of soft, indistinct drusen or any type of drusen associated with RPE depigmentation or increased retinal pigment at follow-up when none of these lesions were seen at baseline. The incidence of exudative macular degeneration and pure geographic atrophy was defined by their presence at follow-up when neither was present at baseline. For each eye, a 6-level severity scale for AMD was defined as follows: Level 10. No drusen or hard drusen; or small soft drusen (125 µm in diameter) only, regardless of area of involvement, and no pigmentary abnormalities (increased retinal pigment or RPE depigmentation). Level 20. Hard drusen; or small soft drusen (125 µm in diameter), regardless of area of involvement, with increased retinal pigment but no RPE depigmentation; or soft drusen (125 µm in diameter) with a drusen area smaller than 196 350 µm2 (equivalent to a circle with a diameter of 500µm) and no pigmentary abnormalities. Level 30. Soft drusen (125 µm in diameter) with a drusen area smaller than 196 350 µm2 and RPE depigmentation; or soft drusen (125 µm in diameter) with an area 196 350 µm2 or larger with or without increased retinal pigment but no RPE depigmentation. Level 40. Soft drusen (125 µm in diameter) with a drusen area involvement 196 350 µm2 or larger and RPE depigmentation with or without increased retinal pigment. Level 50. Geographic atrophy in absence of exudative macular degeneration. Level 60. Exudative macular degeneration with or without geographic atrophy. Level 10 is equivalent to not having AMD; levels 20, 30, and 40 involve lesions that define early AMD of increasing severity (by type, size, area of drusen, and pigmentary abnormalities); while levels 50 and 60 involve lesions that define late AMD.
Patient characteristics	Age at baseline (n=4755)

Bibliographic reference	**Klein,Ronald, Knudtson,Michael D., Cruickshanks,Karen J., Klein,Barbara E.K., Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration: the Beaver Dam Eye Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 115-121, 2008**
	43- 54: 1500 55-64: 1295 65-74: 1242 75-86: 718 Gender, no.: Women: 2642 Men: 2113 Ethnicity: 99% white
Predictors/risk factors and effect estimates	Smoking variables under study: baseline smoking status, age at initiation, duration, intensity, pack-years, age at quitting, and time from the baseline examination since quitting. Controlling for age (categorically), sex (when appropriate) and baseline AMD severity level.
Outcomes	15 year cumulative incidence of Early AMD 15 year cumulative incidence of exudative AMD 15 year cumulative incidence of geographic atrophy
Analysis used	Multivariate odds ratios and 95% confidence intervals were calculated from discrete logistic hazard models.
Length of follow up	15 years
Missing data handling/loss to follow up	The analytical approach described above, allowed those who were right-censored (not seen after the 5- or 10-year examination owing to death or nonparticipation) to contribute information to the estimates. In general, persons who did not participate in the 15-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to have fewer years of education completed and higher systolic blood pressure than persons who participated.
Results	**15 year cumulative incidence of Early AMD** Adjusted odds ratios (95% confidence intervals) Past vs never smokers: 1.16 (0.91-1.48) Current vs never smokers:1.47 (1.08-1.99) Intensity, packs/d

Bibliographic reference	Klein,Ronald, Knudtson,Michael D., Cruickshanks,Karen J., Klein,Barbara E.K., Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration: the Beaver Dam Eye Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 115-121, 2008
	Ever smoked: 0.93 (0.75-1.15) Current smokers: 1.06 (0.65-1.73) Duration, per 10 y Ever smoked: 1.02 (0.92-1.13) Current smokers: 0.98 (0.74-1.30) Pack-years, per 20 y Ever smoked: 1.02 (0.91-1.14) Current smokers: 1.08 (0.87-1.34) Age at initiation, per 10 y Ever smoked: 1.13 (0.97-1.31) Current smokers: 1.16 (0.88-1.52) Time since quitting, per 10 y Past smokers: 0.97 (0.83-1.13) Age at quitting, per 10 y Past smokers: 1.06 (0.91-1.23) **15 year cumulative incidence of Exudative AMD** Adjusted odds ratios (95% confidence intervals): Past vs never smokers: 1.12 (0.62-2.01) Current vs never smokers: 0.69 (0.27-1.76) Intensity, packs/d Ever smoked: 0.94 (0.58-1.54) Current smokers: 1.12 (0.16-7.84) Duration, per 10 y

Bibliographic reference	Klein,Ronald, Knudtson,Michael D., Cruickshanks,Karen J., Klein,Barbara E.K., Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration: the Beaver Dam Eye Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 115-121, 2008
	Ever smoked: 1.16 (0.90-1.50) Current smokers: 0.76 (0.34-1.70) Pack-years, per 20 y Ever smoked 1.04 (0.83-1.31) Current smokers: 0.89 (0.37-2.14) Age at initiation, per 10 y Ever smoked: 1.03 (0.72-1.48) Current smokers: 1.42 (0.66-3.07) Time since quitting, per 10 y Past smokers: 0.78 (0.55-1.11) Age at quitting, per 10 y Past smokers: 1.38 (0.96-1.99) **15 year cumulative incidence of geographic atrophy** Adjusted odds ratios (95% confidence intervals): Past vs never smokers: 0.88 (0.41-1.88) Current vs never smokers: 0.18 (0.02-1.40) Intensity, packs/d: Ever smoked: 1.19 (0.58-2.44) Duration, per 10 y Ever smoked: 1.13 (0.78-1.64) Pack-years, per 20 y

Bibliographic reference	**Klein,Ronald, Knudtson,Michael D., Cruickshanks,Karen J., Klein,Barbara E.K., Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration: the Beaver Dam Eye Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 115-121, 2008**
	Ever smoked:1.03 (0.73-1.46) Age at initiation, per 10 y Ever smoked: 0.73 (0.40-1.33) Time since quitting, per 10 y Past smokers: 0.84 (0.51-1.39) Age at quitting, per 10 y Past smokers: 1.23 (0.74-2.03) The above controlled for age, sex and baseline AMD severity level
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES

Bibliographic reference	**Klein,Ronald, Knudtson,Michael D., Cruickshanks,Karen J., Klein,Barbara E.K., Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration: the Beaver Dam Eye Study, Archives of ophthalmology (Chicago, Ill.: 1960), 126, 115-121, 2008**
	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis) YES

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Bibliographic reference	**Klein,Ronald, Cruickshanks,Karen J., Myers,Chelsea E., Sivakumaran,Theru A., Iyengar,Sudha K., Meuer,Stacy M., Schubert,Carla R., Gangnon,Ronald E., Klein,Barbara E.K., The relationship of atherosclerosis to the 10-year cumulative incidence of age-related macular degeneration: the Beaver Dam studies, Ophthalmology, 120, 1012-1019, 2013**
Country/ies where the study was carried out	Beaver Dam, USA
Study type	Longitudinal Cohort study
Aim of the study	To describe the relationships of intima-media layer thickness, plaque in the carotid artery, angina, myocardial infarction and stroke to the 10 year cumulative incidence of early and late age-related macular degeneration and progression of AMD.
Study dates	From 1998 to 2010
Source of funding	This study was supported by National Institutes of Health grants, and Research to Prevent Blindness, New York, NY. The National Eye Institute and National Institute on Aging provided funding for entire study including collection and analyses of data; RPB provided additional support for data analyses.
Number of patients	1700 persons who participated in both the Epidemiology of Hearing Loss Study and the Beaver Dam Eye Study.
Inclusion Criteria	• Persons aged 53–96 years participating in both the Epidemiology of Hearing Loss Study (EHLS) and the Beaver Dam Eye Study (BDES).
Exclusion Criteria	• Exudative AMD at baseline examination • People who did not participate in follow up • No fundus photograph that were gradable for AMD at the 1998-2000 or any follow-up exam • No carotid artery ultrasonography at the baseline examination
Diagnostic criteria	Stereoscopic 30° colour fundus photographs centred on the macula (Diabetic Retinopathy Study standard field 2) were taken of each eye. Two gradings were performed for the pair of photographs of each macula at each examination using the Wisconsin Age-Related Maculopathy Grading System. Graders were masked as to any information related to the participant and to the fellow eye. High resolution B-mode carotid artery ultrasound images were obtained using a modification of the Atherosclerosis Risk In Communities (ARIC) study ultrasound scanning protocol. The severity of AMD was determined using the modified 5-step BDES AMD Severity Scale:

Bibliographic reference	Klein,Ronald, Cruickshanks,Karen J., Myers,Chelsea E., Sivakumaran,Theru A., Iyengar,Sudha K., Meuer,Stacy M., Schubert,Carla R., Gangnon,Ronald E., Klein,Barbara E.K., The relationship of atherosclerosis to the 10-year cumulative incidence of age-related macular degeneration: the Beaver Dam studies, Ophthalmology, 120, 1012-1019, 2013
	10 (No AMD): Hard drusen or small soft drusen (<125 µm in diameter only) regardless of area of involvement and no pigmentary abnormalities (defined as increased retinal pigment or retinal pigment epithelial [RPE] depigmentation present); or no definite drusen with any pigmentary abnormality. 20 (Minimally severe early AMD): Hard drusen or small soft drusen (<125 µm in diameter), regardless of area of involvement, with any pigmentary abnormality; or soft drusen (≥ 125 µm in diameter) with drusen area <331,820 µm2 and no pigmentary abnormalities. 30 (Moderately severe early AMD): Soft drusen (≥ 125 µm in diameter) with drusen area <331,820 µm2 (equivalent to O2) and with any pigmentary abnormality; or soft drusen (≥ 125 µm in diameter) with drusen area ≥331,820 µm2 (equivalent to O2) with or without increased retinal pigment but no RPE depigmentation. 40 (Severe early AMD): Soft drusen (≥125 µm in diameter) with drusen area ≥331,820 µm2 (equivalent to O2) and RPE depigmentation present, with or without increased retinal pigment. 50 (Late AMD): Pure geographic atrophy (GA) in the absence of exudative macular degeneration; or exudative macular degeneration with or without GA present.
Patient characteristics	Age, years, mean (SD): 71.9 (10.7) Sex, male, 42.7%
Predictors/risk factors and effect estimates	Risk factors studied: Mean IMT, Maximum IMT, Plaque sites, History of MI present, History of stroke present, History of CVD present, History of angina present Adjusted for: Age (years), Sex (male), Mean arterial blood pressure, Hypertension present, Current smoker, Serum total cholesterol, Serum HDL, cholesterol, History of statin use, History of MI present, History of stroke present, History of CVD present, History of angina present, History of multivitamin use, Diabetes present, Body mass index, Sedentary lifestyle, Serum C-reactive protein, White blood cell count, CFH genotype, C/T, C/C, ARMS2, genotype, G/T, T/T.
Outcomes	Adjusted odds ratios for the incidence of AMD or the progression to Late AMD, Geographic atrophy or exudative AMD.
Analysis used	Discrete logistic hazard regression was used to estimate odds ratios (ORs)
Length of follow up	10 years
Missing data handling/loss to follow up	Of 2609 people 909 were excluded: Persons included in the analyses were more likely to be younger (mean age 66.8 vs. 71.8 years) than those excluded. While adjusting for age, persons excluded were more likely to lead a sedentary lifestyle, more likely to have a history of stroke or CVD, and have higher serum C-reactive protein levels and white blood cell counts.

Bibliographic reference	**Klein,Ronald, Cruickshanks,Karen J., Myers,Chelsea E., Sivakumaran,Theru A., Iyengar,Sudha K., Meuer,Stacy M., Schubert,Carla R., Gangnon,Ronald E., Klein,Barbara E.K., The relationship of atherosclerosis to the 10-year cumulative incidence of age-related macular degeneration: the Beaver Dam studies, Ophthalmology, 120, 1012-1019, 2013**
	There were no statistically significant differences between persons included and persons excluded by sex, mean arterial blood pressure, body mass index, history of smoking, history of taking multivitamins, and distributions of Complement Factor H and Age-Related Maculopathy Susceptibility 2 single nucleotide polymorphisms.
Results	Adjusted odds ratios for risk of early AMD 1060 (n at risk) 161 (n of events) History of MI present 1.13 (0.60, 2.14) History of stroke present 1.25 (0.46, 3.38) History of CVD present 0.79 (0.46, 1.37) History of angina present 0.90 (0.48, 1.71) Adjusted odds ratios for risk of late AMD 1400 (n at risk) 54 (n of events) History of MI present 1.04 (0.36, 3.02) History of CVD present 1.33 (0.59, 3.01) History of angina present 0.89 (0.32, 2.50) Adjusted odds ratios for risk of Geographic Atrophy History of MI present 0.61 (0.07, 5.34) History of CVD present 1.31 (0.32, 5.27) History of angina present 1.53 (0.30, 7.85) Adjusted odds ratios Exudative AMD History of MI present 1.56 (0.48, 5.08) History of CVD present 1.66 (0.65, 4.26) History of angina present 0.92 (0.27, 3.13) Adjusted for all factors as well as BMI, smoking status, history of multivitamin use, serum high-density lipoprotein cholesterol and C-reactive protein levels, hypertension status, diabetes status, history of statin use, white blood cell count, and CFH and ARMS2 genotypes.

Bibliographic reference	**Klein,Ronald, Cruickshanks,Karen J., Myers,Chelsea E., Sivakumaran,Theru A., Iyengar,Sudha K., Meuer,Stacy M., Schubert,Carla R., Gangnon,Ronald E., Klein,Barbara E.K., The relationship of atherosclerosis to the 10-year cumulative incidence of age-related macular degeneration: the Beaver Dam studies, Ophthalmology, 120, 1012-1019, 2013**
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). YES Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis) YES

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Bibliographic reference	**Knudtson,M.D., Klein,R., Klein,B.E., 20061211, Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, British Journal of Ophthalmology, 90, 1461-1463, 2006**
Country/ies where the study was carried out	Beaver Dam, USA
Study type	Longitudinal Cohort Study
Aim of the study	To explore the relationship between physical activity and the long term incidence of AMD

Bibliographic reference	Knudtson,M.D., Klein,R., Klein,B.E., 20061211, Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, British Journal of Ophthalmology, 90, 1461-1463, 2006
Study dates	1988-2003
Source of funding	This study was supported by the National Institutes of Health grant and partly by the Research to Prevent Blindness
Number of patients	4,926 persons 3,684 participated in 5 year follow up 2,764 participated in 10 year follow up 2,119 participated in 15 year follow up examinations
Inclusion Criteria	A private census of the population of Beaver Dam, Wisconsin All residents aged 43- 84 years
Exclusion Criteria	None stated
Diagnostic criteria	Fundus photographs of the retina were obtained at each examination and graded in a blinded fashion using the Wisconsin Age-Related Maculopathy Grading System to determine the AMD status. Early AMD was defined as presence of soft indistinct drusen or pigmentary abnormalities in the presence of drusen. Geographic atrophy (pure form) and exudative AMD were defined according to the standard definitions. Participants were asked three questions on physical activity: ‘‘On average, how many flights of stairs do you climb each day?’’; ‘‘On average, how many city blocks do you walk each day?’’; ‘‘At least once a week, do you engage in a regular activity long enough to work up a sweat?’’ and if so, ‘‘How many times per week do you do this?’’ For the purpose of analyses, stair climbing was categorised as none, 1–3 flights, 4–6 flights, .6 flights/day; walking was categorised as none, 1–4 blocks, 5–12 blocks, .12 blocks/day; active lifestyle was defined as engaging in regular activity with or without sweating >3 times/week; and sedentary lifestyle was defined as regular activity 3 times/week.
Patient characteristics	Age at baseline (n=4755) 43- 54: 1500 55-64: 1295 65-74: 1242 75-86: 718 Gender (n): Women: 2642 Men: 2113 Ethnicity: 99% white

Bibliographic reference	Knudtson,M.D., Klein,R., Klein,B.E., 20061211, Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, British Journal of Ophthalmology, 90, 1461-1463, 2006
Predictors/risk factors and effect estimates	Risk factors under study were Active/sedentary lifestyle, stair climbing, walking Multivariate odds ratios (ORs) adjusted for age, sex, history of arthritis, systolic blood pressure, smoking, education and body mass index
Outcomes	Adjusted odds ratios for developing early AMD Adjusted odds ratios for developing geographic atrophy Adjusted odds ratios for developing exudative AMD
Analysis used	Discrete logistic hazard regression.
Length of follow up	15 years
Missing data handling/loss to follow up	In general, persons who did not participate in the 15-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to have fewer years of education completed and higher systolic blood pressure than persons who participated. All those who contributed some follow-up information at the baseline examination were included in the analysis (n=3874).
Results	Odds of early AMD (adjusted odds ratios) Exercise status Sedentary: reference Active: 0.9 (0.7 to 1.1) Odds of Geographic atrophy (adjusted odds ratios) Exercise status Sedentary: reference Active: 1.1 (0.5 to 2.3) Odds of exudative AMD Exercise status Sedentary: reference Active: 0.3 (0.1 to 0.7) Above adjusted for age, sex, arthritis, systolic blood pressure, body mass index, smoking and education.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD;

Bibliographic reference	Knudtson,M.D., Klein,R., Klein,B.E., 20061211, Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study, British Journal of Ophthalmology, 90, 1461-1463, 2006
	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). NO (disputable cut points, definitions) Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis) YES

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Bibliographic reference	Lechanteur,Yara T.E., van de Ven,Johannes P.H., Smailhodzic,Dzenita, Boon,Camiel J.F., Klevering,B.Jeroen, Fauser,Sascha, Groenewoud,Joannes M.M., van der Wilt,Gert-Jan, den Hollander,Anneke I., Hoyng,Carel B., Genetic, behavioral, and sociodemographic risk factors for second eye progression in age-related macular degeneration, Investigative ophthalmology & visual science, 53, 5846-5852, 2012
Country/ies where the study was carried out	Netherlands
Study type	Retrospective cohort study
Aim of the study	To investigate the correlation of genetic, sociodemographic, and behavioural risk factors with second eye progression to end-stage AMD.
Study dates	All 108 subjects were selected by means of chart review from the European Genetic Database (EUGENDA) and were entered into the database between January 1997 and December 2006. EUGENDA is a multicentre database of AMD

Bibliographic reference	**Lechanteur,Yara T.E., van de Ven,Johannes P.H., Smailhodzic,Dzenita, Boon,Camiel J.F., Klevering,B.Jeroen, Fauser,Sascha, Groenewoud,Joannes M.M., van der Wilt,Gert-Jan, den Hollander,Anneke I., Hoyng,Carel B., Genetic, behavioral, and sociodemographic risk factors for second eye progression in age-related macular degeneration, Investigative ophthalmology & visual science, 53, 5846-5852, 2012**
	patients and control subjects founded by the Radboud University Nijmegen Medical Centre and the University of Cologne Medical Centre.
Source of funding	Supported by MD fonds, Oogfonds, and Algemene Nederlandse Vereniging ter Voorkoming van Blindheid.
Number of patients	191 patients were selected according to inclusion criteria 83 patients were excluded 108 patients remained
Inclusion Criteria	• End-stage AMD in one or both eyes
Exclusion Criteria	• No end-stage AMD in both eyes; • Unknown or unclear time of end-stage AMD in one or both eyes; • Other retinal diseases that interfered with the diagnosis of end-stage AMD, such as central serous chorioretinopathy; • Laser treatment or radiotherapy for a retinal disease or treatment for AMD in a stage that could not be determined as end-stage (e.g., laser therapy for extensive drusen).
Diagnostic criteria	Colour fundus photographs and fluorescein angiography images were taken with a digital fundus camera. End-stage AMD was defined as either choroidal neovascularization within the central 6 mm ETDRS grid or geographic atrophy of an area of at least 175 µm including the fovea. Development of advanced AMD in the first eye was taken as starting-point (T[0]) and had to be known with an accuracy range of 1 month; an accuracy range of 6 months was accepted if the second eye did not develop end-stage AMD within 4 years. Progression time until the development of end-stage AMD in the fellow eye was calculated in months after T(0).
Patient characteristics	Mean age was 74.3 years (range 54.3–93.4; standard deviation ±7.2) in our studied cohort. There were 37 males (34.3%) and 71 females (65.7%). The type of end-stage AMD in the first eye was CNV in 82.4% and GA in 3.7% of cases.
Predictors/risk factors and effect estimates	Sex, Age, BMI, cigarette smoking (pack years), education level and various genetic SNPs were the risk factors of interest. hazard ratios were corrected for sex, age, BMI and pack years (statistically significant at univariate level)
Outcomes	Association between socioeconomic risk factors and progression towards end-stage AMD in the Fellow eye of patients with unilateral advanced AMD.
Analysis used	Variables were entered in a Cox regression model for survival analysis and were first analysed in a univariate model. Statistically significant variables ($P < 0.05$) were analysed in a multivariate model.
Length of follow up	4 years

Bibliographic reference	**Lechanteur,Yara T.E., van de Ven,Johannes P.H., Smailhodzic,Dzenita, Boon,Camiel J.F., Klevering,B.Jeroen, Fauser,Sascha, Groenewoud,Joannes M.M., van der Wilt,Gert-Jan, den Hollander,Anneke I., Hoyng,Carel B., Genetic, behavioral, and sociodemographic risk factors for second eye progression in age-related macular degeneration, Investigative ophthalmology & visual science, 53, 5846-5852, 2012**
Missing data handling/loss to follow up	Of 191 eligible participants, 83 were subsequently excluded for the following reasons: Passed away (n=22) Could not be contacted (n=42) Discrepancy between patients story and chart information (n=5) Unwilling to participate (n=4) No information received (n=10)
Results	Hazard ratios for progression towards end-stage AMD in the Fellow eye of patients with unilateral advanced AMD. (95% confidence intervals) Sex Male: 1.0 (reference) Female: 2.6 (1.4–5.0) Age, years <65: 1.0 (reference) 65 to 70: 1.2 (0.5–2.7) 70 to 75: 1.5 (0.7–3.1) 75 to 80: 2.6 (1.3–5.3) ≥80: 5.0 (2.0–12.5) BMI Normal weight (18–25): 1.0 (reference) Overweight (25–30):1.3 (0.8–2.1) Obese (≥30): 2.2 (1.1–4.1) Pack years 0 to 1: 1.0 (reference) 1 to 40: 2.4 (1.3–4.5) ≥40: 4.4 (1.4–14.3)

Bibliographic reference	Lechanteur,Yara T.E., van de Ven,Johannes P.H., Smailhodzic,Dzenita, Boon,Camiel J.F., Klevering,B.Jeroen, Fauser,Sascha, Groenewoud,Joannes M.M., van der Wilt,Gert-Jan, den Hollander,Anneke I., Hoyng,Carel B., Genetic, behavioral, and sociodemographic risk factors for second eye progression in age-related macular degeneration, Investigative ophthalmology & visual science, 53, 5846-5852, 2012
	Education ≤ High school: 1.0 (reference) > High school: 0.6 (0.4–1.1) Hazard ratios corrected for sex, age, BMI, and Pack years.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis) YES

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Bibliographic reference	Reynolds,Robyn, Rosner,Bernard, Seddon,Johanna M., Dietary omega-3 fatty acids, other fat intake, genetic susceptibility, and progression to incident geographic atrophy, Ophthalmology, 120, 1020-1028, 2013
Country/ies where the study was carried out	USA
Study type	Prospective longitudinal cohort study
Aim of the study	To investigate associations between dietary omega-3 fatty acids and other fat intake, genes related to age-related macular degeneration (AMD) and progression to geographic atrophy (GA)
Study dates	Published 2012 AREDs trial: 1992 start with follow up until 2005
Source of funding	Supported by in part by Grants from the National Institutes of Health; Massachusetts Lions Eye Research Fund, Inc.; Unrestricted grant from Research to Prevent Blindness, Inc; the American Macular Degeneration Foundation; and the Macular Degeneration Research Fund of the Ophthalmic Epidemiology and Genetics Service.
Number of patients	2128 individuals (4165 eyes)
Inclusion Criteria	• Age 55-80 years • At least one eye had to be free from vision-threatening disease other than AMD and cataract • That eye could not have had surgery, except for cataract surgery • The participants' stages of disease ranged from no evidence of AMD in either eye, to advanced AMD with vision loss in one eye but good vision (at least 20/30) in the other eye. • Eyes had media that were sufficiently clear to obtain adequate-quality stereoscopic fundus photographs of the macula.
Exclusion Criteria	• Eyes with the end point (4 or 5) at baseline were excluded from the analysis. • Individuals with intake < 600 were excluded from the analysis and, men and women with total caloric intake ≥4200 or ≥3200, respectively, were excluded from the analyses.
Diagnostic criteria	Eyes were assigned a grade of no AMD, early, intermediate, or two different forms of advanced or late stage AMD based on the 5 Stage Clinical Age-Related Maculopathy Grading System (CARMS), in order to combine central and non-central GA into one grade, and to separate NV as a separate grade, regardless of visual acuity. Grades were defined as follows based on fundus and examination data: Neovascular disease, or grade 5, if there were any definitive signs of neovascular AMD such as haemorrhagic retinal detachment, haemorrhage under the retina or retinal pigment epithelium, or subretinal fibrosis; Geographic atrophy, or grade 4 if there was geographic atrophy either in the centre grid or anywhere within the grid and had no record of haemorrhage; Large drusen (≥125µm) were assigned to grade 3; Intermediate drusen (63–124µm) were assigned to grade 2, as long as there were no signs of advanced AMD; No drusen or only a few small drusen (<63µm) were assigned to grade 1.

Bibliographic reference	Reynolds,Robyn, Rosner,Bernard, Seddon,Johanna M., Dietary omega-3 fatty acids, other fat intake, genetic susceptibility, and progression to incident geographic atrophy, Ophthalmology, 120, 1020-1028, 2013
	Progression was defined as either eye progressing from a grade 1, 2, or 3 to grade 4 (GA), at any point in time. Eyes with the end point (4 or 5) at baseline were excluded from the analysis. Follow-up ended when an eye progressed to GA. Eyes that had no record of GA were censored when they reached grade 5
Patient characteristics	AREDs cohort (n= 2914) Age, y, n <65: 565 65-74: 1899 ≥75: 450 Sex Female: 1648 Male: 1266 Ethnicity- not described Baseline characteristics of the sample used for this study were not described.
Predictors/risk factors and effect estimates	Risk factors under study: Demographic (age and sex), behavioural (BMI, smoking, antioxidant status), and dietary information at baseline was obtained from dbGAP. Antioxidant treatment was defined as “yes” for subjects in the antioxidants alone or the antioxidants plus zinc groups, and “no” for subjects in the placebo or the zinc groups. Antioxidant treatment groups were randomly assigned in the AREDS clinical trial. Diet data were obtained from food frequency questionnaires (FFQs), including measurements of total fat, saturated fat, total polyunsaturated fatty acids, monounsaturated fat, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), combined long chain polyunsaturated fatty acids DHA and EPA, linolenic, and linoleic acid (an omega-6 fatty acid). Models were adjusted for the following factors: baseline AMD status, genetic, environmental, demographic, and dietary fat intake.
Outcomes	Hazard ratios (HR) and 95% confidence intervals (CI) for progression to geographic atrophy in individual eyes
Analysis used	Cox proportional hazards model
Length of follow up	Up to 12 years of follow up

Bibliographic reference	Reynolds,Robyn, Rosner,Bernard, Seddon,Johanna M., Dietary omega-3 fatty acids, other fat intake, genetic susceptibility, and progression to incident geographic atrophy, Ophthalmology, 120, 1020-1028, 2013
Missing data handling/loss to follow up	Unclear (none described)
Results	Multivariate Associations Between Dietary Fats and Progression to Geographic Atrophy, hazard ratios, (95% confidence intervals) Total Fat (g) Quintile 1: 1.0 Quintile 2: 1.14 (0.82 – 1.59) Quintile 3: 0.99 (0.70 – 1.39) Quintile 4: 1.54 (1.13 – 2.11) Quintile 5: 1.18 (0.85 – 1.64) Saturated Fat (g) Quintile 1: 1.0 Quintile 2: 1.09(0.78 – 1.51) Quintile 3: 1.42 (1.03 – 1.95) Quintile 4: 1.18 (0.85 – 1.64) Quintile 5: 1.19 (0.87 – 1.64) Monounsaturated Fat (g) Quintile 1: 1.0 Quintile 2: 1.37 (0.98 – 1.91) Quintile 3: 1.22 (0.86 – 1.71) Quintile 4: 1.38 (0.99 – 1.94) Quintile 5: 1.47 (1.05 – 2.05) Total Polyunsaturated Fatty Acids (g) Quintile 1: 1.0 Quintile 2: 0.95 (0.68 – 1.33) Quintile 3: 1.10 (0.80 – 1.52) Quintile 4: 1.34 (0.97 –1.85) Quintile 5: 1.13 (0.82 – 1.55) Omega-3 Fatty Acids

Bibliographic reference	Reynolds,Robyn, Rosner,Bernard, Seddon,Johanna M., Dietary omega-3 fatty acids, other fat intake, genetic susceptibility, and progression to incident geographic atrophy, Ophthalmology, 120, 1020-1028, 2013
	Eicosapentaenoic Acid (EPA)(g) Quintile 1: 1.0 Quintile 2: 0.92 (0.65 – 1.30) Quintile 3: 1.16 (0.86 – 1.58) Quintile 4: 1.00 (0.71 – 1.39) Quintile 5: 0.84 (0.59 – 1.18) Docosahexaenoic Acid (DHA)(g) Quintile 1: 1.0 Quintile 2: 0.99 (0.73 – 1.36) Quintile 3: 1.14 (0.84 – 1.53) Quintile 4: 0.93 (0.68 – 1.27) Quintile 5: 0.72 (0.52 – 1.01) DHA + EPA (g) Quintile 1: 1.0 Quintile 2: 0.98 (0.70 – 1.38) Quintile 3: 1.20 (0.88 – 1.64) Quintile 4: 0.91 (0.64 – 1.29) Quintile 5: 0.79 (0.55 – 1.12) Linolenic Acid (g) Quintile 1: 1.0 Quintile 2: 0.90 (0.64 – 1.23) Quintile 3: 1.02 (0.74 – 1.42) Quintile 4: 1.06 (0.77 – 1.47) Quintile 5: 1.08(0.80 – 1.46) Omega-6 Fatty Acids Linoleic Acid (g) Quintile 1: 1.0 Quintile 2: 0.98 (0.70 – 1.37) Quintile 3: 1.04 (0.75 – 1.44) Quintile 4: 1.36 (0.99 – 1.87) Quintile 5: 1.11 (0.81 – 1.53)

Bibliographic reference	Reynolds,Robyn, Rosner,Bernard, Seddon,Johanna M., Dietary omega-3 fatty acids, other fat intake, genetic susceptibility, and progression to incident geographic atrophy, Ophthalmology, 120, 1020-1028, 2013
	Arachidonic Acid (g) Quintile 1: 1.0 Quintile 2: 0.92 (0.67 – 1.26) Quintile 3: 0.85 (0.62 – 1.17) Quintile 4: 0.91 (0.66 – 1.25) Quintile 5: 0.84 (0.62 – 1.14) Hazard ratios adjusted for: baseline grade, demographic and environmental characteristics: age, gender, education, smoking, antioxidants and body mass index
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). UNSURE Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To determine whether clinical tests of ocular function and macular appearance independently can help to predict which patients with unilateral neovascular age-related AMD will have a choroidal neovascular membrane develop in their fellow eye.
Study dates	Published 1997 Data collected 1990 to 1995
Source of funding	Grants from National Eye Institute, the Foundation for Fighting Blindness and the Massachusetts Lions Eye Research Fund, Inc.
Number of patients	127 patients with unilateral neovascular AMD
Inclusion Criteria	• Snellen visual acuity of 20/60 or better in the fellow eye with sufficiently clear media to allow adequate visualisation of the fundus. • The presence of a choroidal neovascular membrane in the macular of the affected eye • Macular drusen in both eyes • No sign of other retinal disease
Exclusion Criteria	• Bilateral dry AMD • Bilateral Neovascular AMD • Choroidal neovascularisation associated with high myopia
Diagnostic criteria	On the study eye, best corrected visual acuity was measured using a Snellen chart. Mucular visual field was assessed by letter recognition perimetry Foveal glare recovery time was assessed by photostress testing Foveal electroretinograms were recorded with a hand-held stimulator ophthalmoscope. Measurements of ocular function, biomicroscopy and direct and indirect ophthalmoscopy were performed and photographs of each macular were obtained. Fluorescein angiography was performed if a recent one was unavailable. Or if the fundus showed recent changes that could be attributable to choroidal neovascularisation.
Patient characteristics	Age: median 74 years Gender: 57 men, 70 women Ethnicity: not described

Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
Predictors/risk factors and effect estimates	Risk factors assessed were: age, spherical equivalent, glare recovery time, focal electroretinal implicit time, No. of large drusen (quartiles 1-4), macular appearance grade. Prognostic factors entered into the analysis were: age, body mass index, blood pressure, spherical equivalent, Snellen acuity, STDRS acuity, number of visual field defects, glare recovery time, foveal electroretinogram amplitude, foveal electroretinogram implicit time, and grade of macular appearance.
Outcomes	Relative risk of developing a choroidal neovascular membrane.
Length of follow up	4.5 years follow up Follow up visits every 6 months
Missing data handling/loss to follow up	93 people from the initial 127 had been lost to follow up and were censored by the end of 4.5 years.
Results	Relative risk of choroidal neovascular membrane Age, y, continuous (95% confidence intervals) RR: 1.08 (1.02-1.14) No. of large drusen, quartile (95% confidence interval) Quartile 1: reference Quartile 2: 2.09 (0.66-7.84) Quartile 3: 0.83 (0.20-3.52) Quartile 4: 3.25 (1.11-11.75)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). NO Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES

Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
	Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Seddon,Johanna M., Cote,Jennifer, Rosner,Bernard, Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 1728-1737, 2003
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To advise patients with a high risk for advanced forms of AMD about preventive measures through our evaluation of the relationship between dietary alterations and the progression of early or intermediate AMD to the advanced stages of the disease associated with visual loss.
Study dates	Between July 1989 and May 1998,
Source of funding	This study was supported by grants from the Foundation Fighting Blindness Inc, Owings Mills, Md; the Massachusetts Lions Eye Research Fund Inc, Northboro; Research to Prevent Blindness Inc, New York, NY; the Epidemiology Unit Research Fund, Massachusetts Eye and Ear Infirmary, Boston; and a Lew R. Wasserman Merit Award from Research to Prevent Blindness.
Number of patients	397 people were eligible for enrolment 366 (92%) enrolled n=261
Inclusion Criteria	• Patients with AMD, seen for examination at the Massachusetts Eye and Ear Infirmary, Boston. • Other inclusion criteria included willingness to participate in a long-term study that involved annual dilated eye examinations and fundus photography.

Bibliographic reference	**Seddon,Johanna M., Cote,Jennifer, Rosner,Bernard, Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 1728-1737, 2003**
Exclusion Criteria	• Unable to speak English • Decreased hearing or cognitive function such that they would not be able to understand a health status and dietary interview.
Diagnostic criteria	Stereoscopic colour fundus photographs of the macula were obtained. They used a 5-grade classification scale of AMD, modified from the Age-Related Eye Disease Study grading system. Macular characteristics were graded within a 3000-µm radius centred on the foveal centre. Eyes with extensive small drusen (15 small drusen; 63 µm), non-extensive intermediate drusen (20 drusen; 63 µm but 125 µm), or pigment abnormalities associated with AMD were assigned a grade of. Eyes with extensive intermediate or large (125-µm) drusen were assigned a grade of 3. Eyes with geographic atrophy received a grade of 4. If there was evidence of retinal pigment epithelial detachment or choroidal neovascular membrane, a grade of 5 was assigned. Eyes received a grade of 1 if none of these signs was present. Advanced AMD is defined as grades 4 and 5. To evaluate intergrader reliability, fundus photographs of participants with at least 3 years of follow-up (n=222) were sent to the Wisconsin Fundus Photographic Reading Center, Madison, for detailed age-related maculopathic grading.
Patient characteristics	Subjects were aged 60 years and older, were primarily white (99.9%), and had at least 1 eye with a best corrected visual acuity of 20/200 or better and non-exudative AMD.
Predictors/risk factors and effect estimates	Risk factors under study include: intake of nuts, fish, meat, saturated and unsaturated fat and processed baked goods. Multivariable analysis was adjusted for: age-sex group adjusted for age-sex group (men aged 60-69 years, men aged 70-79 years, men aged ≥80 years, women aged 60-69 years, women aged 70-79 years, women aged ≥80 years), log energy (continuous), log carotenoid intake (continuous), initial AMD grade (categorical), and education (at least less than high school).
Outcomes	Relative Risks for Progression to Advanced Age-Related Macular Degeneration by Quartiles of Fat Intake Relative Risks for Progression to Advanced Age-Related Macular Degeneration by Energy-Adjusted Quartiles of Various Types of Saturated and Unsaturated Fat Relative Risks for Progression to Advanced Age-Related Macular Degeneration by Frequency of Fish Intake Relative Risks for Progression to Advanced Age-Related Macular Degeneration According to Intake of Select Food Groups: high fat dairy; meat, processed baked goods. Relative Risks for Progression to Advanced Age-Related Macular Degeneration According to Intake of Nuts
Analysis used	The principal method of analysis was the Cox proportional hazards model.
Length of follow up	Average follow up time was 4.6 years
Missing data handling/loss to follow up	Of the 366 participants enrolled 36 were not considered for analyses because of: Inability to complete the initial study examination (n=5),

Bibliographic reference	Seddon,Johanna M., Cote,Jennifer, Rosner,Bernard, Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 1728-1737, 2003
	Lack of follow-up data (n=17), Lack of 1 or more primary independent variables (n=14) Nineteen individuals (7%) were lost to follow-up because of unwillingness to return for additional follow-up examinations. These individuals did not differ significantly from the remaining participants (n=242) with regard to age or education; however, significantly more women were lost to follow-up (10%) compared with men (3%).
Results	Relative Risks for Progression to Advanced Age-Related Macular Degeneration by Quartiles of Fat Intake: (95% confidence intervals) Total fat 1st quartile: 1.0 2nd quartile: 1.27 (0.63-2.53) 3rd quartile: 2.29 (1.08-4.88) 4th quartile: 2.90 (1.15-7.32) Animal fat 1st quartile: 1.0 2nd quartile: 0.81 (0.41-1.57) 3rd quartile: 1.14 (0.55-2.37) 4th quartile: 2.29 (0.91-5.72) Vegetable fat 1st quartile: 1.0 2nd quartile: 1.64 (0.86-3.13) 3rd quartile: 2.27 (1.12-4.59) 4th quartile: 3.82 (1.58-9.28) Saturated fat 1st quartile: 1.0 2nd quartile: 0.97 (0.49-1.93)

Bibliographic reference	Seddon,Johanna M., Cote,Jennifer, Rosner,Bernard, Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 1728-1737, 2003
	3rd quartile: 1.46 (0.66-3.20) 4th quartile: 2.09 (0.83-5.28) Monounsaturated fat 1st quartile: 1.0 2nd quartile: 1.27 (0.65-2.45) 3rd quartile: 2.13 (1.03-4.43) 4th quartile: 2.21 (0.90-5.47) Polyunsaturated fat 1st quartile: 1.0 2nd quartile: 1.57 (0.82-3.02) 3rd quartile: 1.90 (0.94-3.84) 4th quartile: 2.28 (1.04-4.99) Transunsaturated fat 1st quartile: 1.0 2nd quartile: 1.67 (0.83-3.36) 2nd quartile: 3.22 (1.63-6.36) 3rd quartile: 2.39 (1.10-5.17) Relative Risks for Progression to Advanced Age-Related Macular Degeneration by Frequency of Fish Intake (95% confidence intervals) Number of servings of fish a week <1: 1.0 1: 1.30 (0.78-2.16) ≥2: 0.88 (0.49-1.60) Relative Risks for Progression to Advanced Age-Related Macular Degeneration by type of food group (95% confidence intervals)

Bibliographic reference	**Seddon,Johanna M., Cote,Jennifer, Rosner,Bernard, Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 1728-1737, 2003**
	High-fat dairy 1st quartile: 1.0 2nd quartile: 2.08 (1.09-3.97) 3rd quartile: 1.80 (0.96-3.38) 4th quartile: 1.91 (0.98-3.73) Meat 1st quartile: 1.0 2nd quartile: 1.75 (0.91-3.34) 3rd quartile: 1.62 (0.81-3.24) 4th quartile: 2.09 (0.98-4.47) Processed baked goods 1st quartile: 1.0 2nd quartile: 1.21 (0.69-2.26) 3rd quartile: 2.02 (1.06-3.85) 4th quartile: 2.42 (1.21-4.84) Relative Risks for Progression to Advanced Age-Related Macular Degeneration by number of servings of nuts per week (95% confidence intervals) <1: 1.0 1: 0.69 (0.40-1.17) ≥2: 0.60 (0.32-1.02) Above risk ratios adjusted for Adjusted for age-sex group (men aged 60-69 years, men aged 70-79 years, men aged 80 years, women aged 60-69 years, women aged 70-79 years, women aged 80 years), education (high school vs high school), smoking (current, past, or never), body mass index (25, 25-29.9, or 30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical), total intake of energy-adjusted log zinc, vitamin C, and vitamin E.
Limitations	Quality assessment criteria for prognostic studies as outlined in:

Bibliographic reference	**Seddon,Johanna M., Cote,Jennifer, Rosner,Bernard, Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 1728-1737, 2003**
	Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNCLEAR Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003**
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To advise patients with a high risk for advanced forms of AMD about preventive measures through our evaluation of the relationship between different variables and the progression of early or intermediate AMD to the advanced stages of the disease associated with visual loss.

Bibliographic reference	**Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003**
Study dates	Between July 1989 and May 1998
Source of funding	This study was supported by grants from the Foundation Fighting Blindness Inc, Owings Mills, Md; the Massachusetts Lions Eye Research Fund Inc, Northboro; Research to Prevent Blindness Inc, New York, NY; the Epidemiology Unit Research Fund, Massachusetts Eye and Ear Infirmary, Boston; and a Lew R. Wasserman Merit Award from Research to Prevent Blindness.
Number of patients	397 people were eligible for enrolment 366 (92%) enrolled n=261
Inclusion Criteria	• Patients with AMD, seen for examination at the Massachusetts Eye and Ear Infirmary, Boston. • Other inclusion criteria included willingness to participate in a long-term study that involved annual dilated eye examinations and fundus photography.
Exclusion Criteria	• Unable to speak English • Decreased hearing or cognitive function such that they would not be able to understand a health status and dietary interview.
Diagnostic criteria	Stereoscopic colour fundus photographs of the macula were obtained. They used a 5-grade classification scale of AMD, which we modified from the Age-Related Eye Disease Study grading system. Macular characteristics were graded within a 3000-µm radius centred on the foveal centre. Eyes with extensive small drusen (15 small drusen; 63 µm), non-extensive intermediate drusen (20 drusen; 63 µm but 125 µm), or pigment abnormalities associated with AMD were assigned a grade of. Eyes with extensive intermediate or large (125-µm) drusen were assigned a grade of 3. Eyes with geographic atrophy received a grade of 4. If there was evidence of retinal pigment epithelial detachment or choroidal neovascular membrane, a grade of 5 was assigned. Eyes received a grade of 1 if none of these signs was present. Advanced AMD is defined as grades 4 and 5. To evaluate intergrader reliability, fundus photographs of participants with at least 3 years of follow-up (n=222) were sent to a reading centre for detailed age-related maculopathic grading.
Patient characteristics	Subjects were aged 60 years and older, were primarily white (99.9%), and had at least 1 eye with a best corrected visual acuity of 20/200 or better and non-exudative AMD.
Predictors/risk factors and effect estimates	Risk factors under study include: BMI, Physical activity, smoking, Cardiovascular disease Multivariable analysis was adjusted for: age-sex group (men aged 60-69 years, men aged 70-79 years, men aged 80 years, women aged 60-69 years, women aged 70-79 years, women aged 80 years), education (high school vs high school), smoking (current, past, or never), body mass index (25, 25-29.9, or 30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol

Bibliographic reference	Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003
	intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical), total intake of energy-adjusted log zinc, vitamin C, and vitamin E.
Outcomes	Relative Risks for Progression of AMD using measures of BMI, Physical activity, smoking, Cardiovascular disease
Analysis used	Cox proportional hazards model
Length of follow up	Average follow up time was 4.6 years
Missing data handling/loss to follow up	Of the 366 participants enrolled 36 were not considered for analyses because of: Inability to complete the initial study examination (n=5), Lack of follow-up data (n=17), Lack of 1 or more primary independent variables (n=14) Nineteen individuals (7%) were lost to follow-up because of unwillingness to return for additional follow-up examinations. These individuals did not differ significantly from the remaining participants (n=242) with regard to age or education; however, significantly more women were lost to follow-up (10%) compared with men (3%).
Results	Relative risk for progression of AMD from multivariate models including measures of obesity and other risk factors (95% Confidence Intervals) BMI <25: 1.0 (reference) 25-29: 2.32 (1.32-4.07) ≥30: 2.35 (1.27-4.34) Physical activity (vigorous activity 3 times a week): 0.75 (0.57-1.01) Smoking Never: 1.0 (reference) Past: 1.32 (0.82- 2.12) Current: 1.99 (0.90- 4.43) Cardiovascular disease: No: 1.0 (reference)

Bibliographic reference	Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003
	Yes: 1.21 (0.73-2.02) Adjusted for age-sex group (men aged 60-69 years, men aged 70-79 years, men aged 80 years, women aged 60-69 years, women aged 70-79 years, women aged 80 years), education (high school vs high school), smoking (current, past, or never), body mass index (25, 25-29.9, or 30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical), total intake of energy-adjusted log zinc, vitamin C, and vitamin E.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNCLEAR Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003**
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To advise patients with a high risk for advanced forms of AMD about preventive measures through our evaluation of the relationship between different variables and the progression of early or intermediate AMD to the advanced stages of the disease associated with visual loss.
Study dates	Between July 1989 and May 1998
Source of funding	This study was supported by grants from the Foundation Fighting Blindness Inc, Owings Mills, Md; the Massachusetts Lions Eye Research Fund Inc, Northboro; Research to Prevent Blindness Inc, New York, NY; the Epidemiology Unit Research Fund, Massachusetts Eye and Ear Infirmary, Boston; and a Lew R. Wasserman Merit Award from Research to Prevent Blindness.
Number of patients	397 people were eligible for enrolment 366 (92%) enrolled n=261
Inclusion Criteria	• Patients with AMD, seen for examination at the Massachusetts Eye and Ear Infirmary, Boston. • Other inclusion criteria included willingness to participate in a long-term study that involved annual dilated eye examinations and fundus photography.
Exclusion Criteria	• Unable to speak English • Decreased hearing or cognitive function such that they would not be able to understand a health status and dietary interview.
Diagnostic criteria	Stereoscopic colour fundus photographs of the macula were obtained. They used a 5-grade classification scale of AMD, which we modified from the Age-Related Eye Disease Study grading system. Macular characteristics were graded within a 3000-µm radius centred on the foveal centre. Eyes with extensive small drusen (15 small drusen; 63 µm), non-extensive intermediate drusen (20 drusen; 63 µm but 125 µm), or pigment abnormalities associated with AMD were assigned a grade of. Eyes with extensive intermediate or large (125-µm) drusen were assigned a grade of 3. Eyes with geographic atrophy received a grade of 4. If there was evidence of retinal pigment epithelial detachment or choroidal neovascular membrane, a grade of 5 was assigned. Eyes received a grade of 1 if none of these signs was present. Advanced AMD is defined as grades 4 and 5. To evaluate intergrader reliability, fundus photographs of participants with at least 3 years of follow-up (n=222) were sent to a reading centre for detailed age-related maculopathic grading.

Bibliographic reference	Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003
Patient characteristics	Subjects were aged 60 years and older, were primarily white (99.9%), and had at least 1 eye with a best corrected visual acuity of 20/200 or better and non-exudative AMD.
Predictors/risk factors and effect estimates	Risk factors under study include: BMI, Physical activity, smoking, Cardiovascular disease Multivariable analysis was adjusted for: age-sex group (men aged 60-69 years, men aged 70-79 years, men aged 80 years, women aged 60-69 years, women aged 70-79 years, women aged 80 years), education (high school vs high school), smoking (current, past, or never), body mass index (25, 25-29.9, or 30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical), total intake of energy-adjusted log zinc, vitamin C, and vitamin E.
Outcomes	Relative Risks for Progression of AMD using measures of BMI, Physical activity, smoking, Cardiovascular disease
Analysis used	Cox proportional hazards model
Length of follow up	Average follow up time was 4.6 years
Missing data handling/loss to follow up	Of the 366 participants enrolled 36 were not considered for analyses because of: Inability to complete the initial study examination (n=5), Lack of follow-up data (n=17), Lack of 1 or more primary independent variables (n=14) Nineteen individuals (7%) were lost to follow-up because of unwillingness to return for additional follow-up examinations. These individuals did not differ significantly from the remaining participants (n=242) with regard to age or education; however, significantly more women were lost to follow-up (10%) compared with men (3%).
Results	Relative risk for progression of AMD from multivariate models including measures of obesity and other risk factors (95% Confidence Intervals) BMI <25: 1.0 (reference) 25-29: 2.32 (1.32-4.07) ≥30: 2.35 (1.27-4.34) Physical activity (vigorous activity 3 times a week): 0.75 (0.57-1.01)

Bibliographic reference	**Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003**
	Smoking Never: 1.0 (reference) Past: 1.32 (0.82- 2.12) Current: 1.99 (0.90- 4.43) Cardiovascular disease: No: 1.0 (reference) Yes: 1.21 (0.73-2.02) Adjusted for age-sex group (men aged 60-69 years, men aged 70-79 years, men aged 80 years, women aged 60-69 years, women aged 70-79 years, women aged 80 years), education (high school vs high school), smoking (current, past, or never), body mass index (25, 25-29.9, or 30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical), total intake of energy-adjusted log zinc, vitamin C, and vitamin E.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNCLEAR Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES

Bibliographic reference	Seddon,Johanna M., Cote,Jennifer, Davis,Nancy, Rosner,Bernard, Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio, Archives of ophthalmology (Chicago, Ill.: 1960), 121, 785-792, 2003
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Daly,Mark J., Rosner,Bernard, Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors, Ophthalmology, 118, 2203-2211, 2011
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To expand predictive models for progression to advanced stages of age-related macular degeneration (AMD) based on demographic, environmental, genetic, and ocular factors, using longer follow-up, time varying analyses, calculation of absolute risks, adjustment for competing risks, and detailed baseline AMD and drusen status.
Study dates	Published 2011
Source of funding	Supported by grants from the National Institutes of Health; the Massachusetts Lions Eye Research Fund Inc; unrestricted grants from Research to Prevent Blindness Inc., New York, NY; the American Macular Degeneration Foundation; Virginia B Smith Fund; and the Age-Related Macular Degeneration Research Fund.
Number of patients	2937 individuals in the Age Related Eye Disease Study
Inclusion Criteria	• Age 55-80 years • At least one eye had to be free from vision-threatening disease other than AMD and cataract • That eye could not have had surgery, except for cataract surgery • The participants' stages of disease ranged from no evidence of AMD in either eye, to advanced AMD with vision loss in one eye but good vision (at least 20/30) in the other eye
Exclusion Criteria	• Non-Caucasian participants
Diagnostic criteria	Based on ocular examination and photographic grading of fundus photographs, participants were defined at baseline as AREDS category 1 in both eyes (essentially free of age-related macular abnormalities), category 2 in the worse eye (mild changes including multiple small drusen, non-extensive intermediate drusen, and/or pigment abnormalities), category 3 in the worse eye (≥1 large drusen of ≥125 micron in diameter, extensive intermediate drusen, and/or non-central GA),

Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Daly,Mark J., Rosner,Bernard, Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors, Ophthalmology, 118, 2203-2211, 2011
	category 4 in 1 eye (advanced AMD, either neovascular or central GA, or visual loss owing to AMD regardless of phenotype), or category 4 in both eyes. Because group 3 patients in the original AREDS classification included non-central GA and group 4 included both advanced forms of AMD as well as visual loss regardless of phenotype, we reclassified these groups independent of visual acuity level into grades 4 and 5, with grade 4 including both non-central and central GA, and grade 5 including NV, using the Clinical Age-Related Maculopathy Grading System. Maximum drusen size within the grid (a 3000-micron [μm] radius centred on the fovea) at baseline was used to assess drusen phenotypes for eyes without advanced AMD. Drusen size was based on standard circles with diameters corresponding to 63, 125, and 250 μm. Drusen size was divided into the following categories: <63, 63 to 124, 125 to 249, and ≥250 μm. Progression was defined as either eye progressing from a grade 1, 2, or 3 to either a 4 or a 5 at any follow-up visit to the end of the study within each individual. Time to progression was recorded for the first eye to progress if both eyes were at risk, and for the fellow eye if 1 eye was at risk. Individuals were considered progressors if there was no advanced AMD in either eye at baseline and they developed AMD in ≥1 eye during follow-up (group A), or they had advanced AMD in 1 eye at baseline and progressed to AMD in the fellow eye during follow-up (group B). For subjects in group A, drusen size was controlled for in each eye at baseline and time to progression was evaluated in each eye. The earlier of the 2 progression times was used if both eyes progressed at different times. For subjects in group B, we controlled for AMD category in the affected eye at baseline (i.e., GA or NV), drusen size in the unaffected eye at baseline, and evaluated the time to progression in the fellow eye. Demographic and risk factor data, including education, smoking history, and BMI, were obtained at the baseline visit from questionnaires and height and weight measurements. Antioxidant status was defined as taking antioxidants (antioxidants alone or antioxidants and zinc) or no antioxidants (placebo or zinc alone) in the clinical trial. The clinical trial treatment groups included placebo, antioxidants alone, zinc, and antioxidants plus zinc.
Patient characteristics	Ethnicity: 100% Caucasian
Predictors/risk factors and effect estimates	Variables understudy included: age, gender, education, smoking, body mass index, antioxidants, advanced AMD in 1 eye at baseline, largest drusen size in non-advanced fellow eye, size of drusen in eyes with no advanced AMD at baseline. Models were adjusted for age, sex education, treatment assignment, smoking, BMI, genotypes, drusen phenotypes, and AMD status.

Bibliographic reference	**Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Daly,Mark J., Rosner,Bernard, Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors, Ophthalmology, 118, 2203-2211, 2011**
Outcomes	Multivariate Association Between Demographic, Environmental, Genetic and Macular Characteristics and Progression to Advanced Age-Related Macular Degeneration Hazard Ratio (95% CI)
Analysis used	Cox proportional hazards model
Length of follow up	12 years of follow up. The average follow-up time was 9.2 years (range, 0.5–13) for individuals without advanced AMD in either eye at baseline (n = 2519), and was 6.7 years (range, 0.5–12) for subjects who had 1 eye with advanced AMD at baseline (n = 418)
Missing data handling/loss to follow up	Overall, there were 341 people who were not followed for 5 years and did not progress within 5 years (12%), and 423 people who were not followed for 10 years and did not progress within 10 years (14%). Persons lost to follow-up over 10 years were slightly older (mean age of 69.9 vs 68.5 years), and tended to have better macular status at baseline than subjects who were followed for ≥10 years. There were no differences according to gender or smoking status.
Results	Multivariate Association Between Demographic, Environmental, Genetic and Macular Characteristics and Progression to Advanced Age-Related Macular Degeneration Hazard Ratio (95% CI) **Demographic variables** Age (y) <65: 1.0 65–74: 1.4 (1.1–1.7) ≥75: 1.8 (1.5–2.3) Gender Female: 1.0 Male: 1.0 (0.9–1.2) Education ≤High school: 1.0 >High school: 0.9 (0.8–1.0) **Environmental variables**

Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Daly,Mark J., Rosner,Bernard, Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors, Ophthalmology, 118, 2203-2211, 2011
	Smoking Never: 1.0 Past: 1.1 (1.0–1.3) Current: 1.8 (1.4–2.3) Body mass index (kg/m2) <25: 1.0 25–29: 1.1 (0.9–1.3) ≥30: 1.3 (1.1–1.6) Antioxidants No: 1.0 Yes: 0.9 (0.8–1.0) **Ocular variables** Advanced AMD in 1 eye at baseline Neither eye: 1.0 1 eye with geographic atrophy: 7.3 (2.9–18.4) 1 eye with neovascular disease: 5.1 (2.1–12.2) Largest drusen size (microns) in non-advanced fellow eye <63: 1.0 63–124: 4.1 (1.9–9.2) 125–249: 7.3 (3.4–15.8) ≥250: 11.7 (5.4–25.3) No advanced AMD at baseline: size of drusen (microns) OU <63, <63: 1.0 63–124, <63: 3.5 (1.9–6.3) 63–124, 63–124: 7.6 (4.2–13.5) 125–249,<63: 7.8 (4.1–14.7) 125–249, 63–124: 15.1 (8.8–25.7)

Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Daly,Mark J., Rosner,Bernard, Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors, Ophthalmology, 118, 2203-2211, 2011
	125–249, 125–249: 26.0 (15.4–43.7) ≥ 250, <124: 28.0 (15.2–51.6) ≥ 250, 125–249: 43.9 (26.1–73.9) ≥ 250, ≥250: 53.7 (32.2–89.4)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). PARTLY Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Rosner,Bernard, Validation of a prediction algorithm for progression to advanced macular degeneration subtypes, JAMA ophthalmology, 131, 448-455, 2013
Country/ies where the study was carried out	USA

Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Rosner,Bernard, Validation of a prediction algorithm for progression to advanced macular degeneration subtypes, JAMA ophthalmology, 131, 448-455, 2013
Study type	2 prospective cohorts
Aim of the study	To develop and validate a predictive model for progression to advanced stages of AMD in 2 independent cohorts.
Study dates	Published 2013 Study cohort based upon people in the Age-Related Eye Disease Study and an independent validation cohort
Source of funding	This work was supported by grants from the National Institutes of Health, the Massachusetts Lions Eye Research Fund Inc, unrestricted grants from Research to Prevent Blindness Inc, the Macula Vision Research Foundation, and the Age-Related Macular Degeneration Research Fund, Ophthalmic Epidemiology and Genetics Service, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts.
Number of patients	AREDs cohort n= 2914 Validation cohort n= 980
Inclusion Criteria	For AREDs study: • Age 55-80 years • At least one eye had to be free from vision-threatening disease other than AMD and cataract • That eye could not have had surgery, except for cataract surgery • The participants' stages of disease ranged from no evidence of AMD in either eye, to advanced AMD with vision loss in one eye but good vision (at least 20/30) in the other eye • For independent validation cohort: unclear • This consisted of white patients (excluding first-degree relatives) who were enrolled in ongoing studies to identify genetic and environmental factors for onset and progression of macular degeneration. Subjects were derived from clinic populations and referrals
Exclusion Criteria	None defined
Diagnostic criteria	Participants were classified using the Clinical Age-Related Maculopathy Staging System, based on ocular examination and grading of fundus photographs at baseline, into 5 stages: normal or stage 1 in both eyes (essentially free of age-related macular abnormalities or having only a few small drusen), early AMD or stage 2 in the worse eye (mild changes including multiple small drusen, non-extensive intermediate drusen, and/or pigment abnormalities), intermediate AMD or stage 3 in the worse eye (drusen with a diameter125 m, extensive intermediate drusen), stage 4 in one eye (advanced dry AMD with central or non-central GA), and stage 5 with advanced NV AMD in one eye at baseline.

Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Rosner,Bernard, Validation of a prediction algorithm for progression to advanced macular degeneration subtypes, JAMA ophthalmology, 131, 448-455, 2013
	Because category 3 in the original Age-Related Eye Disease Study classification included non-central GA and category 4 included both advanced forms of AMD as well as vision loss regardless of phenotype, we reclassified these groups independent of visual acuity level into Clinical Age-Related Maculopathy Staging System grades 4 (GA) and 5 (NV) as described herein. Progression was defined as either eye progressing from stage 1, 2, or 3 to either stage 4 or stage 5 at any follow-up visit to the end of the study within each individual.
Patient characteristics	**AREDS cohort** (n= 2914) Age, y, n <65: 565 65-74: 1899 ≥75: 450 Sex Female: 1648 Male: 1266 Ethnicity - not described **Validation cohort** (n= 980) Age, y, n <65: 120 65-74: 383 ≥75: 450: 476 Sex Female: 546 Male: 434

Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Rosner,Bernard, Validation of a prediction algorithm for progression to advanced macular degeneration subtypes, JAMA ophthalmology, 131, 448-455, 2013
	Ethnicity - white patients (excluding first degree relatives)
Predictors/risk factors and effect estimates	Risk factors under study were: Age (<65/65-74/≥75), Sex (Female/Male), Education (≤High school/High school), Smoking (Never/Past/Current), BMI, Genotype.
Outcomes	Hazard ratios for the development of incident advanced age-related macular degeneration:
Analysis used	Cox proportional hazards model
Length of follow up	AREDs: 0.5-13 years (mean 8.8 years) Independent Cohort: 0.10 to 17.9 years (mean, 6.2 years)
Missing data handling/loss to follow up	Unclear/not described
Results	Hazard ratios for the development of incident advanced age-related macular degeneration (95% confidence intervals) *AREDs sample **Validation cohort Age, y <65: 1 [Reference] 65-74: *1.4 (1.1-1.7) **1.5 (1.0-2.3) ≥75: *2.0 (1.6-2.5) **2.6 (1.7-4.1) Sex Female: 1 [Reference] Male: *1.0 (0.8-1.1) **1.0 (0.8-1.2) Education ≤High school: 1 [Reference] >High school: *0.9 (0.8-1.0) **0.8 (0.6-1.0) Smoking Never: 1 [Reference] Past: *1.2 (1.1-1.4) **1.0 (0.8-1.4) Current: *1.6 (1.3-2.1) **2.2 (1.4-3.3)

Bibliographic reference	Seddon,Johanna M., Reynolds,Robyn, Yu,Yi, Rosner,Bernard, Validation of a prediction algorithm for progression to advanced macular degeneration subtypes, JAMA ophthalmology, 131, 448-455, 2013
	BMI <25: 1 [Reference] 25-29: *1.1 (0.9-1.3) **1.2 (0.9-1.5) ≥30: *1.3 (1.1-1.6) **1.1 (0.8-1.5) Grade in each eye for individuals without advanced AMD at baseline 1/1, 1/2, or 2/2: *0.09 (0.07-0.1) **0.3 (0.1-0.4) 1/3, 2/3, or 3/3 1 [Reference] 1/4, 2/4, or 3/4 *2.2 (1.6-2.9) **1.4 (0.9-2.1) 1/5, 2/5, or 3/5 *1.2 (1.0-1.4) **1.0 (0.8-1.3)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Seddon,Johanna M., Silver,Rachel E., Kwong,Manlik, Rosner,Bernard, Risk Prediction for Progression of Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates, Investigative ophthalmology & visual science, 56, 2192-2202, 2015**
Country/ies where the study was carried out	USA
Study type	Prospective Cohort
Aim of the study	To develop and validate a predictive model for progression to advanced stages of AMD in 2 independent cohorts.
Study dates	Published 2015 Based on data from AREDs study
Source of funding	Supported by Grants from the National Institutes of Health; the Massachusetts Lions Eye Research Fund, Inc.; unrestricted grants from Research to Prevent Blindness, Inc; Foundation Fighting Blindness; the American Macular Degeneration Foundation; and the Age-Related Macular Degeneration Research Fund.
Number of patients	n=2951
Inclusion Criteria	For AREDs study: • Age 55-80 years • At least one eye had to be free from vision-threatening disease other than AMD and cataract • That eye could not have had surgery, except for cataract surgery • The participants' stages of disease ranged from no evidence of AMD in either eye, to advanced AMD with vision loss in one eye but good vision (at least 20/30) in the other eye
Exclusion Criteria	Not described
Diagnostic criteria	Progression was defined as transition from no AMD, early AMD, or intermediate AMD (Clinical Age-Related Maculopathy Staging System [CARMS] grade of 1, 2, or 3) to advanced AMD (CARMS grade 4 or 5) in either eye during a follow-up visit. Progressors were classified using the following two criteria: (1) No advanced AMD was present in either eye at baseline and at least one eye became advanced during follow-up, or (2) advanced AMD was present in one eye at baseline and the fellow eye became advanced during follow-up.
Patient characteristics	AREDs cohort (n= 2914) Age, y, n 54-65: 567 65-74: 1924 ≥75: 460

Bibliographic reference	**Seddon,Johanna M., Silver,Rachel E., Kwong,Manlik, Rosner,Bernard, Risk Prediction for Progression of Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates, Investigative ophthalmology & visual science, 56, 2192-2202, 2015**
	Sex Female: 1661 Male: 1290 Ethnicity - Caucasian
Predictors/risk factors and effect estimates	Demographic, environmental, and ocular variables understudy in the analyses were age (55–64, 65–74, ‡75), sex, education (high school, >high school), body mass index (BMI) (<25, 25–29, ‡30), smoking status (never, past, current), presence or absence of unilateral advanced AMD at baseline (either central or noncentral geographic atrophy [GA] in one eye [CARMS grade 4] or neovascular disease [NV] in one eye [CARMS grade 5]), and drusen size in eyes without advanced AMD. Drusen size was reported in micrometres for each non-advanced eye as follows: <63, 63 to 124, 125 to 249, and ≥250.
Outcomes	Multivariate Associations Between Baseline Demographic, Environmental, and Macular Variables and Progression to Incident Advanced Age-Related Macular Degeneration (hazard ratios)
Analysis used	Cox proportional hazards Models used individual subjects as the unit of analysis.
Length of follow up	Follow-up time ranged from 6 months to 13 years (mean 8.8 years).
Missing data handling/loss to follow up	For missing demographic or environmental variables, NHANES 2009 data was used to estimate the proportion of subjects with specific levels of education, smoking, and BMI as a function of age–sex groups. Unclear how much information was missing, or loss to follow up.
Results	Multivariate Associations Between Baseline Demographic, Environmental, and Macular Variables and Progression to Incident Advanced Age-Related Macular Degeneration Age, y ≥75: Referent 65–74: 0.8 (0.6–0.9) 55–64: 0.6 (0.5–0.7) Sex Female: Referent Male: 1.1 (0.9–1.2)

Bibliographic reference	Seddon,Johanna M., Silver,Rachel E., Kwong,Manlik, Rosner,Bernard, Risk Prediction for Progression of Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates, Investigative ophthalmology & visual science, 56, 2192-2202, 2015
	Education High school: Referent >High school: 0.9 (0.8–1.0) Smoking Never: Referent Past: 1.1 (1.0–1.3) Current: 1.8 (1.4–2.3) BMI <25: Referent 25–29: 1.1 (0.9–1.3) ≥30: 1.2 (1.0–1.5) Advanced AMD Neither eye: Referent Grade 4: 8.3 (3.2–19.9) Grade 5: 5.8 (2.3–13.2) Advanced AMD in one eye: largest drusen size in non-advanced eye, μm None to <63: Referent 63–124: 3.9 (1.7–8.6) 125–249: 8.4 (3.9–18.3) ≥250: 13.8 (6.4–29.5) No advanced AMD: largest drusen size in each eye, μm None to <63, none to <63: Referent 63–124, none to <63: 3.0 (1.7–5.3) 63–124, 63–124: 7.9 (4.5–13.8) 125–249, none to <63: 7.2 (3.9–13.3) 125–249, 63–124: 15.2 (9.1–25.2) 125–249, 125–249: 29.0 (17.7–47.5) ‡250, ≤124: 31.0 (17.2–55.9)

Bibliographic reference	Seddon,Johanna M., Silver,Rachel E., Kwong,Manlik, Rosner,Bernard, Risk Prediction for Progression of Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates, Investigative ophthalmology & visual science, 56, 2192-2202, 2015
	‡250, 125–249: 50.3 (30.8–82.2) ‡250, ≥250: 72.0 (44.7–116.2) Hazard ratios are adjusted for all variables in table and the four AREDS treatment groups.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). UNSURE Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). UNSURE Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**Submacular Surgery Trials Research Group, Solomon,S.D., Jefferys,J.L., Hawkins,B.S., Bressler,N.M., Bressler,S.B., 20091202, Risk factors for second eye progression to advanced age-related macular degeneration: SST report No. 21 Submacular Surgery Trials Research Group, Retina (Philadelphia, Pa.)Retina, 29, 1080-1090, 2009**
Country/ies where the study was carried out	USA
Study type	Prospective cohort
Aim of the study	To identify characteristics predictive of progression to advanced age-related macular degeneration (AMD) in second (fellow) eyes of participants in the Submacular Surgery Trials (SST) who had unilateral neovascular AMD at study entry.
Study dates	Published 2009
Source of funding	Sponsored by the National Eye Institute, National Institutes of Health, U.S. Department of Health and Human Sciences.
Number of patients	370 fellow eyes of participants in the submacular surgery trials who had a unilateral neovascular AMD at study entry.
Inclusion Criteria	• From the two submacular surgery trials • Confirmed to be at risk of choroidal neovascularisation or foveal geographical atrophy in the second eye (advanced AMD)
Exclusion Criteria	• Choroidal neovascularisation or foveal geographical atrophy in the second eye (advanced AMD) at baseline
Diagnostic criteria	Baseline stereoscopic film-based colour photographs of the fellow eye of participants with a second eye at risk of progression to choroidal neovascularisation or focal geographic atrophy were re-evaluated by two trained and experienced Wilmer Reading Centre graders who were masked as to the presenting clinical features and subsequent course. Each grader provided an independent assessment utilizing a system that was largely adapted from the AREDS criteria for classifying features of AMD. Key examination tools of the AREDS system were a set of standard and example photographs, a standard transparent grid overlay, and graduated measurement circles.
Patient characteristics	Total (n=370) Age, years <75: 37% 75-79: 31% ≥80: 33% Gender Women: 49% Male: 51%

Bibliographic reference	**Submacular Surgery Trials Research Group, Solomon,S.D., Jefferys,J.L., Hawkins,B.S., Bressler,N.M., Bressler,S.B., 20091202, Risk factors for second eye progression to advanced age-related macular degeneration: SST report No. 21 Submacular Surgery Trials Research Group, Retina (Philadelphia, Pa.)Retina, 29, 1080-1090, 2009**
Predictors/risk factors and effect estimates	Risk factors under study included: non-foveal geographic atrophy, nongeographic atrophy, focal hyperpigmentation, maximum drusen size and maximum drusen area. Other covariates adjusted for were: gender, age, smoking, hypertension history, predominant lesion component in the first eye, visual acuity of the eye at risk.
Outcomes	Multivariate analysis of risk of advanced AMD of ocular factors in the study eye, Hazard ratios (95% confidence intervals) Multivariate analysis of risk of advanced AMD, of ocular factors in the fellow eye, Hazard ratios (95% confidence intervals)
Analysis used	Cox proportional hazards model
Length of follow up	Up to 4 years
Missing data handling/loss to follow up	Loss to follow up/missing data not described
Results	Multivariate analysis of risk of advanced AMD of ocular factors in the study eye, Hazard ratios (95% confidence intervals) Drusen <250 µm in diameter: 1.00 (referent) Drusen ≥250 µm in diameter: 1.73 (1.12-2.66) No focal hyperpigmentation: 1.00 Mild/moderate focal hyperpigmentation: 1.43 (0.86-2.40) Severe focal hyperpigmentation: 2.26 (1.30-3.94) No geographic atrophy: 1.00 (referent) Geographic atrophy that spares the foveal centre: 1.82 (1.08-3.08) Multivariate analysis of risk of advanced AMD, of ocular factors in the fellow eye, Hazard ratios (95% confidence intervals) Drusen <250 µm in diameter in the fellow eye: 1.00 (referent) Drusen ≥250 µm in diameter in the fellow eye: 2.32 (1.49-3.61) Nongeographic atrophy (retinal pigment epithelium depigmentation) not present in the fellow eye: 1.00 (referent) Nongeographic atrophy (retinal pigment epithelium depigmentation) present in the fellow eye: 1.79 (1.14-2.82)

Bibliographic reference	Submacular Surgery Trials Research Group, Solomon,S.D., Jefferys,J.L., Hawkins,B.S., Bressler,N.M., Bressler,S.B., 20091202, Risk factors for second eye progression to advanced age-related macular degeneration: SST report No. 21 Submacular Surgery Trials Research Group, Retina (Philadelphia, Pa.)Retina, 29, 1080-1090, 2009
	Cox proportional hazard model was adjusted for gender, age, smoking, hypertension history, predominant lesion component in the first eye, visual acuity of the eye at risk. Non-significant factors included: maximum drusen area
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	van,Leeuwen R., Boekhoorn,S., Vingerling,J.R., Witteman,J.C., Klaver,C.C., Hofman,A., de Jong,P.T., 20051230, Dietary intake of antioxidants and risk of age-related macular degeneration, JAMA, 294, 3101-3107, 2005
Country/ies where the study was carried out	Netherlands, Rotterdam study

Bibliographic reference	van,Leeuwen R., Boekhoorn,S., Vingerling,J.R., Witteman,J.C., Klaver,C.C., Hofman,A., de Jong,P.T., 20051230, Dietary intake of antioxidants and risk of age-related macular degeneration, JAMA, 294, 3101-3107, 2005
Study type	Prospective cohort study
Aim of the study	To investigate whether regular dietary intake of antioxidants is associated with a lower risk of incident AMD.
Study dates	Published 2005 Data collected 1990- 1993
Source of funding	This study was supported by unrestricted grants from the following organizations: Netherlands Organization for Scientific Research, the Hague; Optimix, Amsterdam; Physico Therapeutic Institute, Rotterdam; Blindenpenning, Amsterdam; Sint Laurens Institute, Rotterdam; Bevordering van Volkskracht, Rotterdam; Blindenhulp, the Hague; Rotterdamse Blindenbelangen Association, Rotterdam; Oogheelkundige Ondersteuning, the Hague; kfHein, Utrecht; Ooglijders, Rotterdam; Prins Bernhard Cultuurfonds, Amsterdam; Van Leeuwen Van Lignac, Rotterdam; Verhagen, Rotterdam; General Netherlands Society for the Prevention of Blindness, Doorn; Landelijke Stichting voor Blinden en Slechtzienden, Utrecht; and Elise Mathilde, Maarn. An unrestricted grant was obtained from Topcon Europe BV, Capelle aan de IJssel.
Number of patients	5836 persons at risk of AMD 4765 had reliable dietary data and 4170 participated in the follow up
Inclusion Criteria	• Population-based cohort of all inhabitants aged 55 years or older in a middleclass suburb of Rotterdam. • No AMD in either eye at baseline; i.e. with no drusen or pigment irregularities, hard drusen only, or soft drusen without pigment irregularities.
Exclusion Criteria	• Participants with decreased cognitive function (defined as a score 80 on the Cambridge Examination of Mental Disorders in the Elderly) • Nursing home residents because their food was prepared by nursing home staff and would not reflect past dietary habits. • Logical inconsistencies in dietary interviews, missing the baseline dietitian visit when the food frequency questionnaire was administered, or various other logistical reasons
Diagnostic criteria	The eye examination included 35° fundus photography. Two experienced graders, masked to dietary intake, graded the follow-up transparencies and afterward compared these with the baseline ones. The grading procedures, definitions, and graders were identical at baseline and follow-up. Early-stage AMD was defined as the presence of either large (63 µm), soft, distinct drusen with pigment irregularities or indistinct (125 µm) or reticular drusen with or without pigment irregularities. Late-stage AMD, mostly leading to blindness, was defined as geographic atrophy (both central and noncentral), choroidal neovascularization, or a combination of both. At baseline, participants completed a checklist at home that queried foods and drinks they had consumed at least twice a month during the preceding year as well as dietary habits, use of supplements, and prescribed diets. Next, during their visit

Bibliographic reference	van,Leeuwen R., Boekhoorn,S., Vingerling,J.R., Witteman,J.C., Klaver,C.C., Hofman,A., de Jong,P.T., 20051230, Dietary intake of antioxidants and risk of age-related macular degeneration, JAMA, 294, 3101-3107, 2005
	to the research centre, they underwent a standardized interview with a dietitian based on the checklist, using a 170-item semi-quantitative food frequency questionnaire
Patient characteristics	Baseline Characteristics: *Incident Age-Related Macular Degeneration at follow up (n = 560), **No Age-Related Macular Degeneration at Follow-up (n = 3610) Age, y, mean (SD) *68.2 (7.1) **66.4 (7.2) Women, No. (%) *321 (57.3) **2151 (59.6) Ethnicity: not described
Predictors/risk factors and effect estimates	Risk factors under study: Total energy intake and nutrient intake per day with the computerized Dutch Food Composition Table: carotenoids alpha and beta carotene, beta cryptoxanthin, lutein/zeaxanthin, lycopene, vitamins A (retinol equivalents), C, and E, and iron and zinc as cofactors for antioxidant enzymes. People who reported taking supplements containing carotenoids, vitamins A, C, or E, iron, or zinc, as well as multivitamins or multiminerals, were classified as supplement users. Confounders included in analysis: Smoking status (current, former, or never, and number of pack-years), Serum total cholesterol level, Blood pressure, ankle-arm index, carotid intimamedia thickness and atherosclerotic plaques, subclinical atherosclerosis composite.
Outcomes	Risk of Age-Related Macular Degeneration per Standard Deviation (SD) Increase in Dietary Intake of Antioxidant Nutrients. Risk of Age-Related Macular Degeneration by Category of Combined Intake of 4 Predefined Antioxidant Nutrients (Vitamins C and E, Beta Carotene, and Zinc).
Analysis used	Cox proportional hazards regression analysis
Length of follow up	Mean follow-up of 8.0 years (range, 0.3-13.9 years).
Missing data handling/loss to follow up	Analysis: Dietary intake was not assessed in 227 participants with decreased cognitive function (defined as a score 80 on the Cambridge Examination of Mental Disorders in the Elderly) because their dietary history was deemed unreliable. Also excluded were 179 nursing home residents because their food was prepared by nursing home staff and would not reflect past dietary habits. Reliable dietary data were missing in 665 participants because of logical inconsistencies in dietary interviews, missing the baseline dietitian visit when the food frequency questionnaire was administered, or various other logistical reasons.

Bibliographic reference	van,Leeuwen R., Boekhoorn,S., Vingerling,J.R., Witteman,J.C., Klaver,C.C., Hofman,A., de Jong,P.T., 20051230, Dietary intake of antioxidants and risk of age-related macular degeneration, JAMA, 294, 3101-3107, 2005
	Baseline characteristics were similar in the 2 groups, although eligible respondents without dietary data were, on average, somewhat older compared with those with data and included fewer women. Follow up: Of the baseline cohort, 156 participants died, 419 refused any follow-up examination, and 20 were lost to follow-up before the first follow-up examination. Nonparticipants tended to be older; included more women, nursing home residents, and smokers; and more often had systemic hypertension. They did not differ from participants in their dietary intake of antioxidants;
Results	Risk of Age-Related Macular Degeneration per Standard Deviation (SD) Increase in Dietary Intake of Antioxidant Nutrients. Hazard ratios (95% confidence intervals) Carotenoids Alpha carotene 0.99 (0.94-1.06) Beta carotene: 1.00 (0.94-1.06) Beta cryptoxanthin: 1.01 (0.92-1.10) Lutein/zeaxanthin: 1.01 (0.93-1.09) Lycopene: 1.01 (0.97-1.04) Vitamins Vitamin A (retinol equivalents): 0.95 (0.86-1.05) Vitamin C: 1.02 (0.94-1.10) Vitamin E: 0.92 (0.84-1.00) Trace elements Iron: 0.95 (0.86-1.04) Zinc: 0.91 (0.83-0.98) Hazard ratios were adjusted for age, sex, body-mass index, smoking status, pack-years of smoking, systolic blood pressure, atherosclerosis composite score, serum total cholesterol, and alcohol intake. Risk of Age-Related Macular Degeneration by Category of Combined Intake of 4 Predefined Antioxidant Nutrients (Vitamins C and E, Beta Carotene, and Zinc). Low: 1.20 (0.92-1.56) Medium: 1.00 (referent)

Bibliographic reference	van,Leeuwen R., Boekhoorn,S., Vingerling,J.R., Witteman,J.C., Klaver,C.C., Hofman,A., de Jong,P.T., 20051230, Dietary intake of antioxidants and risk of age-related macular degeneration, JAMA, 294, 3101-3107, 2005
	High: 0.65 (0.46-0.92) Categories were defined by using the median energy-adjusted daily intake per nutrient as a cutoff value and classifying above-median intake of all nutrients as high intake and below-median intake of all nutrients as low intake. Cutoff values were 114 mg for vitamin C, 13 mg for vitamin E, 3.6 mg for beta carotene, and 9.6 mg for zinc. Hazard ratios were adjusted for age, sex, body mass index, smoking status, pack-years of smoking, systolic blood pressure, atherosclerosis composite score, serum total cholesterol, and alcohol intake.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). NO Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	**VanderBeek,Brian L., Zacks,David N., Talwar,Nidhi, Nan,Bin, Musch,David C., Stein,Joshua D., Racial differences in age-related macular degeneration rates in the United States: a longitudinal analysis of a managed care network, American journal of ophthalmology, 152, 273-282, 2011**
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To investigate the association between race and the development of AMD in the USA population
Study dates	From January 1, 2001 through December 31, 2007
Source of funding	Grant support from National Eye Institute K23 Mentored Clinician Scientist Award (JDS; EY019511), Blue Cross Blue Shield of Michigan Foundation (JDS), an unrestricted grant from Research to Prevent Blindness, Research to Prevent Blindness Lew R. Wasserman Merit Award (DCM), Research to Prevent Blindness Sybil B. Harrington Special Scholar Award for Macular Degeneration (DNZ).
Number of patients	2,259,061 individuals in the medical plan who met the inclusion criteria, 1,772,962 individuals (79%) were able to be classified according to race. There were 1,535,008 whites (87%), 78,315 blacks (4%), 99,518 Latinos (6%), and 44,103 Asian Americans (3%).
Inclusion Criteria	• This study only included patients insured through one specific managed care network
Exclusion Criteria	• Non-continuous enrolment in a medical plan • Enrolment in a medical plan up to one year • Individuals with duplicate or erroneous data • Enrolees without one or more CPT codes indicating a visit to an ophthalmologist or optometrist • Having received a prior diagnosis of AMD
Diagnostic criteria	All individuals age 40 or older who were in the i3 InVision Data Mart database for more than one consecutive year and had one or more visits to an eye care provider during their time in the medical plan were identified. The race of each beneficiary was identified by the managed care company using information provided from two sources: public records (driver's license data) and from E-Tech (Ethnic Technologies, LLC., South Hackensack, NJ), a tool that uses information from the name of the beneficiary and the census block he or she lives in to assign race. Races were categorized as non-Hispanic white (referred to as white), black, Latino, and Asian American. All other races were categorized as "Other". ICD-9CM codes were used to determine whether each beneficiary had one or more diagnoses of AMD during their time in the medical plan. Incidence and prevalence rates were determined for non-exudative AMD and exudative AMD.
Patient characteristics	Age: The median age at entry into the plan was 52 years (range 40–87 years) Gender: overall gender break down of sample not provided

Bibliographic reference	VanderBeek,Brian L., Zacks,David N., Talwar,Nidhi, Nan,Bin, Musch,David C., Stein,Joshua D., Racial differences in age-related macular degeneration rates in the United States: a longitudinal analysis of a managed care network, American journal of ophthalmology, 152, 273-282, 2011
	Ethnicity: There were 1,535,008 whites (87%), 78,315 blacks (4%), 99,518 Latinos (6%), and 44,103 Asian Americans (3%).
Predictors/risk factors and effect estimates	Risk factors of interest included: Ethnicity: Black, Latino, Asian American, White Analysis was adjusted for: age, sex, household net worth, education level, geographic region of residence within the US, systemic hypertension, skin cancer, anaemia, heart disease, myocardial infarction, stroke, peripheral vascular disease, renal disease, systemic hypotension, obesity, diabetes mellitus, hyperlipidaemia, coagulopathies, open-angle glaucoma, cataract, pseudophakia / aphakia, and diabetic retinopathy.
Outcomes	Multivariable adjusted hazard of developing non-exudative or exudative AMD stratified by race and age (compared to white populations at similar ages)
Analysis used	Cox regression analysis
Length of follow up	Average enrolment time within the plan was 3.75 ± 1.81 years. Persons were followed one year after enrolment until they either were diagnosed with the condition (non-exudative or exudative AMD) or were censored (either when they left the medical plan or the last day for which we had data, December 31, 2007)
Missing data handling/loss to follow up	No information regarding missing data was provided. Participants with erroneous data were excluded.
Results	Multivariable adjusted hazard of developing non-exudative or exudative AMD stratified by race and age (compared to white populations at similar ages) (95% confidence intervals): Whites at similar age= referent Blacks at age 60: Non-exudative AMD: 0.75 (0.71-0.79) Exudative AMD: 0.70 (0.59-0.83) Blacks at age 80 Non-exudative AMD: 0.56 (0.52-0.60) Exudative AMD: 0.45 (0.37-0.54)

Bibliographic reference	**VanderBeek,Brian L., Zacks,David N., Talwar,Nidhi, Nan,Bin, Musch,David C., Stein,Joshua D., Racial differences in age-related macular degeneration rates in the United States: a longitudinal analysis of a managed care network, American journal of ophthalmology, 152, 273-282, 2011**
	Latinos at age 60 Non-exudative AMD: 0.99 (0.94-1.04) Exudative AMD: 1.28 (1.13-1.45) Latinos at age 80 Non-exudative AMD: 0.82 (0.76-0.88) Exudative AMD: 0.89 (0.76-1.05) Asian Americans at age 60 Non-exudative AMD: 1.28 (1.20-1.36) Exudative AMD: 1.08 (0.89-1.31) Asian Americans at age 80 Non-exudative AMD: 0.92 (0.83-1.02) Exudative AMD: 0.54 (0.40-0.73)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). NO Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO

Bibliographic reference	VanderBeek,Brian L., Zacks,David N., Talwar,Nidhi, Nan,Bin, Musch,David C., Stein,Joshua D., Racial differences in age-related macular degeneration rates in the United States: a longitudinal analysis of a managed care network, American journal of ophthalmology, 152, 273-282, 2011
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Williams,P.T., 20090116, Prospective study of incident age-related macular degeneration in relation to vigorous physical activity during a 7-year follow-up, Investigative ophthalmology & visual science, 50, 101-106, 2009
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To test whether the risk of age-related macular degeneration (AMD) decreases with vigorous physical activity.
Study dates	Published 2009 Recruiting between 1991 and 1993
Source of funding	Unclear
Number of patients	Male (n=29,532) and female (n=12,176)
Inclusion Criteria	National Runners Health Study: Cohort of runners, 18 years old and older, was recruited between 1991 and 1993 by distributing a two-page questionnaire nationally to runners identified through subscription lists to running magazines and among participants of foot race events.
Exclusion Criteria	• Subjects reporting being diagnosed in the same year as their baseline survey or before were excluded from the analyses. • Subjects who were diabetic at baseline were excluded from all analyses.
Diagnostic criteria	Participants reported whether they had received a clinical diagnosis of macular degeneration since their baseline questionnaire and provided the year of diagnosis. The questionnaire solicited information on demographics, running history, weight history, smoking habits, prior history of heart attacks and cancer, and medications for blood pressure, thyroid, cholesterol, and diabetes. Running distances were reported in usual miles run per week at baseline.

Bibliographic reference	Williams,P.T., 20090116, Prospective study of incident age-related macular degeneration in relation to vigorous physical activity during a 7-year follow-up, Investigative ophthalmology & visual science, 50, 101-106, 2009
	BMI was calculated as self-reported weight in kilograms divided by the square of self-reported height in meters. Self-reported waist circumferences were elicited by the question, “Please provide, to the best of your ability, your body circumference in inches.” without further instruction. Intakes of meat, fish, and fruit were based on the questions: “During an average week, how many servings of beef, lamb, or pork do you eat,” “...servings of fish do you eat,” and “...pieces of fruit do you eat?” Alcohol intake was estimated from the corresponding questions for 4-oz. (112 mL) glasses of wine, 12-oz. (336 mL) bottles of beer, and mixed drinks and liqueurs. Alcohol was computed as 10.8 g per 4-oz glass of wine, 13.2 g per 12 oz. bottle of beer, and 15.1 g per mixed drink. For this report, baseline cardiorespiratory fitness was defined as speed in meters per second of the participant’s best time in a 10-km race during the previous 5 years (reported as finishing time in minutes).
Patient characteristics	Incident AMD: *Present (n=152), **Absent Present Absent (41,556) Female (%): *27.63 **29.20 Age (y), mean and standard deviation: *54.22 ± 0.92 **43.09 ± 0.05*
Predictors/risk factors and effect estimates	The dose–response relationships of incident AMD to baseline running distance, cardiorespiratory fitness, body weight, and circumferences was under study. Models were adjusted for: Reported weekly intakes of alcohol, meat, fish, and fruit, age, and BMI when analysing physical activity.
Outcomes	Relative Risk for AMD with Physical Activity (km/day) Relative Risk for AMD with Cardiorespiratory Fitness (m/s)
Analysis used	Cox proportional hazards analyses
Length of follow up	7 year follow up
Missing data handling/loss to follow up	Approximately 15% returned baseline questionnaires among the total original eligible number contacted (the exact number is not known because of uncertainty of the number actually distributed and the proportion of subjects who receive duplicate questionnaires). Eighty percent of the original cohort, who provided baseline questionnaires provided follow-up surveys to us 7 years later or were known dead.
Results	Relative Risk for AMD, Physical Activity (km/day) (95% confidence intervals) 0.90 (0.83-0.97) Relative Risk for AMD, Cardiorespiratory Fitness (m/s) (95% confidence intervals) 0.92 (0.60-1.39)* *34,035 men and women provided 10-km performance times (to calculate cardiorespiratory fitness).

Bibliographic reference	Williams,P.T., 20090116, Prospective study of incident age-related macular degeneration in relation to vigorous physical activity during a 7-year follow-up, Investigative ophthalmology & visual science, 50, 101-106, 2009
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). NO Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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Bibliographic reference	Wilson,H.L., Schwartz,D.M., Bhatt,H.R., McCulloch,C.E., Duncan,J.L., 20040427, Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among patients with age-related macular degeneration, American journal of ophthalmology, 137, 615-624, 2004
Country/ies where the study was carried out	USA
Study type	Retrospective cohort study of people with AMD
Aim of the study	To find the association between statin or aspirin therapy and the development of choroidal neovascularisation
Study dates	January 1 1990 to March 1 2003

Bibliographic reference	Wilson,H.L., Schwartz,D.M., Bhatt,H.R., McCulloch,C.E., Duncan,J.L., 20040427, Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among patients with age-related macular degeneration, American journal of ophthalmology, 137, 615-624, 2004
Source of funding	Career development award from Research to Prevent Blindness and grants from the National Eye Institute and That Man May See, Inc. and The Foundation for Fighting Blindness
Number of patients	326 patients with AMD, 104 with CNV, 204 with dry AMD and 18 with Geographic atrophy.
Inclusion Criteria	• 60 years or older • Diagnosed with AMD • Followed in the SFVA eye and medical practice during the study period
Exclusion Criteria	• Ocular diseases other than AMD that are associated with CNV, • Younger than 60 years old • Not enrolled in the medical practice clinic or with incomplete medication data in the medical records, • Treated with statins for less than 6 months.
Diagnostic criteria	All eye photography files were reviewed by a retina specialist (D.M.S. or J.L.D.) masked to the subject's medical record and classified as having either non-neovascular AMD or angiographically evident choroidal neovascularization (CNV), according to standard definitions of non-neovascular and neovascular AMD based on fundus photographic and angiographic characteristics. Fundus photographs of subjects with non-neovascular (dry) AMD showed at least five soft indistinct drusen with or without retinal pigment epithelial abnormalities within the macula in each eye. In addition to these findings, subjects with dry AMD and geographic atrophy (GA) also showed a discrete area of retinal depigmentation, at least 175 m in diameter, with a sharp border and visible choroidal vessels with no evidence of CNV.9 Subjects with dry AMD were required to have a dilated funduscopic examination including biomicroscopy in the medical record confirming the absence of CNV. Fundus photographs of subjects with CNV showed drusen and/or retinal pigment epithelial changes in at least one eye, in addition to CNV evidenced by subretinal macular haemorrhage, lipid deposits in the macula, fibrotic macular scarring, or retinal pigment epithelial detachment on fundus photographs. All CNV subjects had angiographic evidence of CNV or a clinic note documenting a disciform scar with prior photos demonstrating drusen.
Patient characteristics	Baseline characteristics: Median Age (range): CNV- 75 (61-93) Early AMD- 77 (60-97) Geographic atrophy- 78 (61-91)

Bibliographic reference	**Wilson,H.L., Schwartz,D.M., Bhatt,H.R., McCulloch,C.E., Duncan,J.L., 20040427, Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among patients with age-related macular degeneration, American journal of ophthalmology, 137, 615-624, 2004**
	Ethnicity White (percentage) CNV- 84 Early AMD- 75 Geographic atrophy- 94 Men (%) CNV- 95 Early AMD- 95 Geographic atrophy- 94 All of the above entered into multivariable analysis
Predictors/risk factors and effect estimates	Variables associated with disease status (P.05) were tested in a multi-predictor model, along with possible confounding variables that might be associated with statin use, aspirin use, or CNV, including hypertension; antihypertensive medication use; coronary artery disease; family history of coronary artery disease; prior myocardial infarction; prior stroke; prior Hollenhorst plaques; diabetes; and baseline serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and triglycerides to test for the independent effects of the variables.
Outcomes	Significant variables associated with the risk of developing CNV in a person with AMD Reported as hazard ratios
Analysis used	Because observation times were unequal, a parametric, interval censored data regression was performed on age of onset of CNV using Proc LIFEREG in SAS for Windows version 9 (SAS Institute, Inc., Cary, North Carolina, USA) assuming a Weibull distribution. A sensitivity analysis was performed and a probability plot generated to check the Weibull parametric assumption. Predictors were eliminated sequentially on the basis of statistically insignificant tests based on Wald 2 statistics.
Length of follow up	Retrospective data collected over 13 years
Missing data handling/loss to follow up	Because observation times were unequal, parametric, interval censored data regression was performed. Retrospective therefore no loss to follow up.
Results	Hazard ratios (95% Confidence interval): Current smoker: 1.77 (1.06-2.97) Aspirin user: 0.63 (0.40- 0.98)

Bibliographic reference	**Wilson,H.L., Schwartz,D.M., Bhatt,H.R., McCulloch,C.E., Duncan,J.L., 20040427, Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among patients with age-related macular degeneration, American journal of ophthalmology, 137, 615-624, 2004**
	Non-significant factors of interest on the univariate level: Ethnicity, Gender, Age, Hypertension, history of MI, Diabetes, history of CVA (cerebrovascular accident) or TIA (transient ischaemic attack), Coronary artery disease.
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD; The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). YES Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). YES Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). PARTLY Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis) YES

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Bibliographic reference	**Stein,Joshua D., VanderBeek,Brian L., Talwar,Nidhi, Nan,Bin, Musch,David C., Zacks,David N., Rates of nonexudative and exudative age-related macular degeneration among Asian American ethnic groups, Investigative ophthalmology & visual science, 52, 6842-6848, 2011**
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To determine whether the risk for non-exudative and exudative age-related macular degeneration (AMD) varies for Americans of different Asian ethnicities.
Study dates	From January 1, 2001 through December 31, 2007
Source of funding	Grant support from National Eye Institute K23 Mentored Clinician Scientist Award (JDS; EY019511), Blue Cross Blue Shield of Michigan Foundation (JDS), an unrestricted grant from Research to Prevent Blindness, Research to Prevent Blindness Lew R. Wasserman Merit Award (DCM), Research to Prevent Blindness Sybil B. Harrington Special Scholar Award for Macular Degeneration (DNZ).
Number of patients	44,103 Asian Americans
Inclusion Criteria	• This study only included patients insured through one specific US managed care network • All persons aged 40 and older who had >=1 visit to an eye care provider and were in the database for >=1 consecutive year
Exclusion Criteria	• Non-continuous enrolment in a medical plan • Enrolment in a medical plan up to one year • Individuals with duplicate or erroneous data • Enrolees without one or more CPT codes indicating a visit to an ophthalmologist or optometrist • Having received a prior diagnosis of AMD
Diagnostic criteria	ICD-9CM codes were used to determine whether each beneficiary had 1 diagnosis of non-exudative AMD (ICD-9CM codes 362.50, 362.51, and 362.57) or exudative AMD (362.52) during their time in the medical plan. Incidence and prevalence rates were determined for both AMD types. Each enrolee could have more than one form of AMD during their time in the plan. Two sources were used by the managed care company to identify race and ethnicity: public records (driver's license data) and E-Tech (Ethnic Technologies, South Hackensack, NJ), a tool that uses information from the beneficiary name and the census block to assign race and ethnicity. Previous comparisons between information collected by patient self-report and assignment of race using E-Tech demonstrated that E-Tech has a positive predictive value of 71%, and information from the company indicates this software actually has a 96% accuracy at correctly classifying patients based on race and ethnicity. Patients of Asian American descent were identified, and each was classified by ethnicity: Chinese, Filipino, Indian, Japanese, Korean, Pakistani, and Vietnamese. There were inadequate numbers of Bangladeshis, Burmese, Laotians,

Bibliographic reference	**Stein,Joshua D., VanderBeek,Brian L., Talwar,Nidhi, Nan,Bin, Musch,David C., Zacks,David N., Rates of nonexudative and exudative age-related macular degeneration among Asian American ethnic groups, Investigative ophthalmology & visual science, 52, 6842-6848, 2011**
	Thais, Indonesians, Malaysians, Hawaiians, Samoans, and Sri Lankans to study these groups separately. Those of these ethnicities were classified as “other.”
Patient characteristics	Age: The median age at entry into the plan was 52 years (range 40–87 years), for white Americans, the median age was 52 years; for Asian Americans it was 50 years. Gender: overall gender break down of sample not provided Ethnicity: Overall sample, n= 225,9061 Non-Asian Whites 1,535,008 Vietnamese 5,420 228 Japanese 4,771 Chinese 15,918 Filipino 2,514 Korean 3,948 Indian 8,312 Pakistani 1,000 Other Asian 2,220
Predictors/risk factors and effect estimates	Risk factors of interest included: Ethnicity: Vietnamese, Japanese, Chinese, Filipino, Korean, Indian, Pakistani Analysis was adjusted for: Multivariable analyses were adjusted for age, sex, region of residence within the United States, education level, household net worth, diabetes mellitus, hypertension, hyperlipidaemia, obesity, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, renal insufficiency, coagulopathy, blood-loss anaemia, deficiency anaemias, systemic, hypotension, skin cancer, cataract, pseudophakia or aphakia, diabetic retinopathy, and open-angle glaucoma.
Outcomes	Multivariable adjusted hazard of developing non-exudative or exudative AMD stratified by race and cge (compared to white populations at similar ages)
Analysis used	Cox regression analysis
Length of follow up	Not all participants were in the plan for the full 7 years.

Bibliographic reference	**Stein,Joshua D., VanderBeek,Brian L., Talwar,Nidhi, Nan,Bin, Musch,David C., Zacks,David N., Rates of nonexudative and exudative age-related macular degeneration among Asian American ethnic groups, Investigative ophthalmology & visual science, 52, 6842-6848, 2011**
	Incidence rates of non-exudative and exudative AMD were calculated by dividing the number of newly diagnosed beneficiaries with each AMD type by their time, in person-years, in the plan at risk.
Missing data handling/loss to follow up	No information regarding missing data was provided. Participants with erroneous data were excluded.
Results	Hazard ratios for the risk of non-exudative AMD (95% confidence intervals) Reference group - white Americans Vietnamese: 1.15 (0.96–1.38) Japanese: 0.71 (0.59–0.85) Chinese: 1.63 (1.50–1.77) Filipino: 0.96 (0.76–1.22) Korean: 1.11 (0.92–1.34) Indian: 0.99 (0.85–1.16) Pakistani: 1.97 (1.40–2.77) Hazard ratios for the risk of exudative AMD (95% confidence intervals) Reference group - white Americans Vietnamese: 0.70 (0.37–1.35) Japanese: 0.64 (0.40–1.04) Chinese: 0.95 (0.71–1.27) Filipino: 1.18 (0.67–2.09) Korean: 0.97 (0.56–1.66) Indian: 1.08 (0.71–1.62) Pakistani: 0.45 (0.06–3.21)
Limitations	Quality assessment criteria for prognostic studies as outlined in: Assessing bias in studies of prognostic factors Jill A. Hayden, DC, PhD; Danielle A. van der Windt, PhD;

Bibliographic reference	**Stein,Joshua D., VanderBeek,Brian L., Talwar,Nidhi, Nan,Bin, Musch,David C., Zacks,David N., Rates of nonexudative and exudative age-related macular degeneration among Asian American ethnic groups, Investigative ophthalmology & visual science, 52, 6842-6848, 2011**
	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). NO Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). PARTLY The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

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E.22 Strategies to slow the progression of age-related macular degeneration (AMD)

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

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

Statin for age-related macular degeneration

Bibliographic reference	Guymer RH, Baird PN, Varsamidis M, Busija L, Dimitrov PN, Aung KZ, et al. Proof of concept, randomized, placebo-controlled study of the effect of simvastatin on the course of age-related macular degeneration. PloS One 2013;8 (12):e83759.
Methods	**Study design:** randomized controlled trial **Number randomized:** 114 total; 57 simvastatin; 57 placebo **Exclusions after randomization:** none **Number analysed: at 36 months:** 114 total; 57 simvastatin; 57 placebo **Unit of analysis:** individuals **Losses to follow up:** 34 participants total; 20 simvastatin; 14 placebo **How was missing data handled?:** last-observation-carried-forward method used for 34 participants; 11 participants with baseline data only and 23 participants who missed the 3-year follow-up visit **Power calculation:** 58 participants in each arm for power of 80% at alpha 0.05 to detect a 50% reduction in progression of disease
Participants	**Country:** Australia **Mean age:** 74.6 years overall; 74.8 years for simvastatin group; 74.4 years for placebo group **Gender:** 77/114 (68%) women 37/114 (32%) men total39/57 (68%) women 18/57 (32%) men in the simvastatin group 38/57 (67%) women 19/57 (33%) men in the placebo group **Inclusion criteria:** 1) males and females aged 50 years and older; 2) able to assess the macula in at least one eye; 3) visual acuity = 20/60 in study eye; 4) high risk drusen in both eyes: one or more large soft drusen, > 10 intermediate

	drusen, or late AMD in one eye and any drusen or pigment change in study eye; 5) normal cholesterol levels; and 6) not currently on cholesterol-lowering medications **Exclusion criteria:** 1) bilateral end-stage AMD; 2) medical or ophthalmic conditions which could potentially affect visual function, such as cataract, diabetes, glaucoma; 3) use of medications that may affect visual function, such as plaquenil, chloroquine, major tranquillizers; 4) currently on cholesterol-lowering medication; 5) use of statins is contraindicated; 6) alanine aminotransferase (ALT) two times the upper limit of normal; and 7) previous severe adverse or allergic reactions to statins **Equivalence of baseline characteristics:** no; more participants in simvastatin group had unilateral advanced AMD as compared with placebo; less smokers in placebo group than simvastatin group
Interventions	**Intervention 1:** two tablets of simvastatin (40 mg daily) for three years **Intervention 2:** placebo with an identical appearance for three years **Length of follow-up:** Planned: three years Actual: three years
Outcomes	**Primary outcome, as defined in study reports:** "Primary outcome was progression of non-advanced AMD to either advanced AMD or higher severity scores of non-advanced AMD", evaluated every 6 months. "Advanced AMD was defined as presence of either CNV or geographic atrophy (GA). CNV was confirmed on angiography and GA was defined as an area of hypopigmentation 175 mm with a choroidal vessel in its base on colour photography." **Secondary outcomes, as defined in study reports**: (1) change in visual function over time; (2) genotype as an effect modifier of the association between statins and progression of AMD **Adverse events reported**: yes **Intervals at which outcomes assessed:** 1, 6, 12, 18, 24, 30, and 36 months
Notes	**Funding sources**: Ian Potter Foundation, John Reid Charitable Trust and Royal Victorian Eye and Ear Hospital; National Health and Medical Research Council (NHMRC) supported the study through a Centre for Clinical Research Excellence award to CERA (#529923), a Practitioner Fellowship (#529905) and a Senior Research Fellowship (#1028444); Wagstaff Fellowship; Victorian Government

	Disclosures of interest: co-author Paul Baird is a PLOS ONE Editorial Board member **Study period:** 3 years; 2003 to 2006 **Reported subgroup analyses:** yes Trial investigators provided information on loss to follow-up by intervention at three-year follow-up (email communication) Trial reported at ARVO (abstract); trial registration number: ACTRN12605000320651 (registered at WHO International Clinical Trials Registry Platform)

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Risk of bias	Bias Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by a biostatistician using permuted blocks of randomly varying size.
Allocation concealment (selection bias)	Low risk	The hospital pharmacist packed the medication into identical containers according to the randomization code. The sequentially numbered containers were allocated to the participants by the study coordinator in order of enrolment." "The allocation list was stored at a remote site."
Masking (performance bias and detection bias)	Low risk	"The study staff, the participants, and data analysts were masked to treatment allocation until the analysis was finalised."
Incomplete outcome data (attrition bias) All outcomes	High risk	Data missing for 34/114 (30%) participants at 3 years follow-up: 20/57 (35%) in the simvastatin group and 14/57 (25%) in the placebo group. Reasons for missing the 3-year visit were: personal, poor health, unable to contact, adverse reaction to study medication, reached late AMD, sick at 3-year follow-up, deceased, or developed macular hole. The study investigators imputed missing data using the last-observation-carried-forward method.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported in the 2013 results paper matched the protocol published in 2008.

Other bias	Unclear risk	"Analysis was done 'by person' and used the data from the eye showing greatest progression. If one eye of a person worsened and the other eye showed improvement, the person was classified as having progressed", but AMD progression by eye also was reported; at baseline, "the number of participants with unilateral advanced AMD was twice as large in the simvastatin group compared to the placebo group (x2 = 9.2, P = 0.002). Smoking also was less prevalent in the placebo group; the difference was marginally significant (x2 = 3.5, P = 0.06)."

70 **Omega 3 fatty acids for preventing or slowing the progression of age-relate macular degeneration**

Bibliographic reference	**Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)**
Study details	**Country/ies:** Switzerland
	Study type: open label RCT
	Aim of the study: To investigate the effects of lutein/zeaxanthin supplementation as well as supplementation with lutein/zeaxanthin in a fixed combination with polyunsaturated fatty acid (PUFA).
	Study dates: study recruitment between July 2007 and June2008
	Sources of funding: supported by Novartis, the Swiss National Science Foundation and Velux Foundation Zurich
Participants	**Sample size:** Lutein (n=40); Lutein +Omega (n=39)
	Inclusion Criteria: people were age over 50 years with early or intermediate AMD. Only one eye of each patient was included in the study. If both eyes were eligible for the study, the eye with more advanced AMD changes was included.
	Exclusion Criteria: People were with other eye disease in the study eye and opacities of optical media precluding fundus photography.

<table>
<tr><td>Bibliographic reference</td><td>Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><th></th><th>Lutein (n=40)</th><th>Lutein + Omega (n=39)</th><th>P values</th></tr>
<tr><td>Mean age, year (range)</td><td>75.2 (54, 88)</td><td>72.5 (54, 88)</td><td>>0.05</td></tr>
<tr><td>% of female (n)</td><td>55 (22)</td><td>61 (26)</td><td></td></tr>
<tr><td>Mean BM (range)</td><td>25 (16, 36)</td><td>25 (18,32)</td><td>>0.005</td></tr>
<tr><td>No. of early AMD</td><td>22</td><td>18</td><td></td></tr>
<tr><td>No. of intermediate AMD</td><td>18</td><td>21</td><td></td></tr>
<tr><td>Mean visual acuity, ETDRs letter (SD)</td><td>79.7 (7.4)</td><td>78.6 (10.5)</td><td>>0.05</td></tr>
<tr><td>Lutein serum, µg/ml (SD)</td><td>0.147 (0.076)</td><td>0.163 (0.117)</td><td>>0.05</td></tr>
<tr><td>Zeaxanthin serum, µg/ml (SD)</td><td>0.025 (0.011)</td><td>0.025 (0.012)</td><td>>0.05</td></tr>
</table></td></tr>
<tr><td>Methods</td><td>Study visits and procedures:

All patients received supplementation for a period of 6 months and were followed for a total of 12 months. Examinations were scheduled at baseline, month 1, and months 3,6,7,8,9, and 12. At each visit a comprehensive ocular examination with best-corrected visual acuity using ETDRs charts. At each visit the empty blisters from the study medication were collected and a pill count was performed to ensure compliance with the study medication.</td></tr>
<tr><td></td><td>Intervention: Lutein and other vitamins (VitaluxPlus)</td></tr>
<tr><td></td><td>Comparator: Lutein, omega-3, and other vitamins (VitaluxOmega)</td></tr>
<tr><td></td><td>Outcomes: primary outcome: the effect of supplementation on contract sensitivity (CS) and macular pigment optical density (MPOD) after 6 months; secondary outcome: the change of CS, MPOD, BCVA and serum concentrations of lutein and zeaxanthin over the time period of 12 months.</td></tr>
</table>

Bibliographic reference	**Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)**
	Analyses: Analysis of variance; paired t-test
	Length of follow up: 12 months

Results

	Lutein (n=40)	**Lutein + Omega (n=39)**	**Effect (95%CI)**
Macular pigment optical density			
baseline (SD)	0.54 (0.19)	0.56 (0.21)	-0.02 (-0.11 to 0.07)
6 months	0.66 (0.18)	0.60 (0.22)	0.06 (-0.03 to 0.15)
Contrast sensitivity			
baseline	1.29 (0.25)	1.23 (0.27)	0.06 (-0.05 to 0.17)
6 months	1.69 (0.22)	1.30 (0.25)	0.39 (0.29 to 0.49)
Best-corrected visual acuity			
Baseline	80 (7)	79 (11)	1.00 (-3.08 to 5.08)
6 months	79 (7)	80 (11)	-1.00 (-5.08 to 3.08)

Bibliographic reference	**Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)**
	12 months 81 (5) 80 (10) 1.00 (-2.50 to 4.50)
	Missing data handling/loss to follow up: none reported
Comments	**Was allocation adequately concealed?** Open label
	Was knowledge of the allocated intervention adequately prevented during the study? No description was found in the article
	Was the allocation sequence adequately generated? No description was found in the article
	Was the study apparently free of other problems that could put it at a high risk of bias? No
	Were incomplete outcome data adequately addressed? No description was found in the article
	Are reports of the study free of suggestion of selective outcome reporting? Primary and secondary outcomes reported

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Bibliographic reference	**AREDS2** **Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309(19):2005-15.**
Methods	Parallel group RCT, 2 x 2 factorial design Both eyes included in the trial, both eyes received same treatment, adjustment made for within person correlation
Participants	**Country**: USA

	Setting: community **Number of participants**: 2080, 55% women **Average age**: 74 years **Age range**: 50 to 85 years **Inclusion criteria**: • bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye • consent to follow-up of at least 5 years • took at least 75% of the run-in supplements and agreed to stop the use of other supplements containing lutein, zeaxanthin, DHA, EPA, vitamin C, vitamin E, beta-carotene, zinc, or copper **Exclusion criteria**: • other ocular diseases such as high myopia, glaucoma, clinically significant diabetic retinopathy (10 or more microaneurysms or retinal haemorrhages), and other diseases that might confound the assessment of the ocular outcome measurements • eyes that had undergone intraocular (apart from cataract) surgeries • systemic diseases, including oxalate kidney stones, Wilson disease, haemochromatosis, lung cancer, or other diseases associated with poor 5-year survival Approximately 90% of participants were taking an additional multivitamin supplement
Interventions	• Omega 3 fatty acids (n = 1068 people, 1753 eyes) • Placebo (n = 1012 people, 1695 eyes) Omega 3 fatty acids were DHA (350 mg per day) and EPA (650 mg per day). Composition of placebo not specified All participants were asked to take the original AREDS formulation (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg, zinc oxide 80 mg, cupric oxide 2 mg). Those who agreed to take AREDS and consented to a second randomisation were assigned as follows • Original AREDS formula: omega 3 fatty acids group n = 147 (13.8%); placebo group n = 168 (16.6%) • No beta-carotene: omega 3 fatty acids group n = 231 (21.6%); placebo group n = 201 (19.9%) • Low-dose zinc (25 mg): omega 3 fatty acids group n = 179 (16.8%); placebo group n = 184 (18.2%) • No beta-carotene and low-dose zinc: omega 3 fatty acids group n = 201 (18.8%); placebo group n = 190 (18.8%) The participants who did not agree to a secondary randomisation largely took the AREDS

	formula: omega 3 fatty acids group n = 305 (28.6%); placebo group n = 265 (26.2%) Participants who were current smokers or former smokers who had stopped smoking within the year before enrolment were randomly assigned to 1 of the 2 arms without beta-carotene Duration: 5 years
Outcomes	**Primary outcome**: • Development of advanced AMD, defined as central geographic atrophy or retinal features of choroidal neovascularization detected on central grading of the stereoscopic fundus photographs or a history of treatment for advanced AMD after study enrolment **Secondary outcomes**: • Progression to moderate vision loss (3 lines) from baseline or treatment for choroidal neovascularisation • Serious adverse events • Mortality **Follow-up**: annually
Dates participants recruited	10/2006 to 09/2008
Declaration of interest	Yes - reported in paper. Including patent for AREDS formula
Sources of funding	This study was supported by the intramural program funds and contracts from the National Eye Institute (NEI), National Institutes of Health (NIH), Department of Health and Human Services, Bethesda, Maryland (contract HHS-N-260-2005-00007-C; ADB contract N01-EY-5-0007). Funds were contributed by the following NIH institutes: Office of Dietary Supplements; National Center for Complementary and Alternative Medicine; National Institute on Aging; National Heart, Lung, and Blood Institute; and National Institute of Neurological Disorders and Stroke. The study medications and raw materials were provided by Alcon, Bausch & Lomb, DSM, and Pfizer
Notes	In the primary randomisation 84% of participants took 75% of the study medications http://clinicaltrials.gov/show/NCT00345176

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Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	"A random block design was implemented using the AREDS2 Advantage Electronic Data Capture system by the AREDS2 Coordinating Centre (The EMMES Corporation, Rockville, MD) and stratified by clinical centre and AMD status (large drusen both eyes or large drusen in 1 eye and advanced AMD in the fellow eye) to ensure approximate balance across centres over time." Page 2285 of protocol paper
Allocation concealment (selection bias)	Low risk	Placebo-controlled study "Participants and study personnel were masked to treatment assignment in both randomizations. Page E2 of main study report
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Participants and study personnel were masked to treatment assignment in both randomizations. Page E2 of main study report
Blinding of participants and personnel (performance bias) Progression of AMD	Low risk	"Participants and study personnel were masked to treatment assignment in both randomizations." Page E2 of main study report
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Placebo-controlled study "Participants and study personnel were masked to treatment assignment in both randomizations." Page E2 of main study report
Blinding of outcome assessment (detection bias) Progression of AMD	Low risk	Placebo-controlled study "Participants and study personnel were masked to treatment assignment in both randomizations." Page E2 of main study report CNV was determined by masked readers from stereoscopic fundus photographs

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was high and balanced across groups DHA/EPA: 1062/1068 (99.4%) Placebo: 1007/1012 (99.5%)
Selective reporting (reporting bias)	Low risk	Not detected

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Bibliographic reference	**NAT2** **Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. Ophthalmology 2013;120(8):1619-31.**
Methods	Parallel-group RCT One eye only included, study eye was selected on the basis of early AMD with neovascular AMD (CNV) in the fellow eye
Participants	**Country**: France **Setting**: community **Number of participants**: 300, 65% women **Average age**: 74 years **Age range**: 55 to 85 years **Inclusion criteria**: • bilateral large drusen or large drusen in 1 eye and CNV in the fellow eye (grading performed using a validated classification grid http://www.ncbi.nlm.nih.gov/pubmed/16988630) • visual acuity better than 0.4 logarithm of minimum angle of resolution units in the study eye • patients likely to attend follow-up visits during the study period and consent to follow-up of at least 5 years

	Exclusion criteria: • CNV in both eyes or no CNV in either eye • wide central subfoveal atrophy of the study eye • progressive ocular diseases (severe glaucoma or other severe retinopathy) • major corneal or lens opacities precluding retinal evaluation • serious systemic disease (cancer, stroke, etc.) preventing long-term participation • known allergy to the substances used in the study (fish oil, fluorescein, indocyanine green) • anticoagulant therapy (prohibited medication) or bleeding tendency • current or recent treatment (< 6 months) with nutritional supplements (oral supplement containing long-chain omega 3 fatty acids or alpha tocopherol acetate) • any concomitant nutritional supplement • participation in a clinical trial within the previous 30 days • history of drug use or excessive use of medication • patients likely to be lost to follow-up or unlikely to comply with the study protocol • monocular patients for reasons other than AMD • patients not covered by the French National Health system or wards of the court
Interventions	Omega 3 fatty acid (n = 150 people) Placebo (n = 150 people) Omega 3 fatty acids were 3 fish oil capsules, each capsule contained: DHA (280 mg), EPA (90 mg) and vitamin E (2 mg) (Reti-Nat, provided by Bausch & Lomb, Montpellier, France) Placebo contained 602 mg of olive oil Duration: 3 years
Outcomes	**Primary outcome**: • time to occurrence of CNV in the study eye **Secondary outcome**: • percentage of patients in whom CNV developed • changes in visual acuity from baseline (logMAR) • visual acuity decrease of 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart • drusen burden and progression, based on automatic detection of their number, size, and area on fundus photography • changes in red blood cell membrane (RBCM) EPA plus DHA levels

	• lens opacity • blood lipids including fasting plasma lipoprotein profile • signs of intolerance related to fish oil consumption • occurrence of systemic adverse events **Follow-up**: annually
Dates participants recruited	12/2003 to 10/2005
Declaration of interest	Eric H Souied: Consultant and lecturer—Laboratoire Bausch & Lomb Chauvin Pascale Benlian: Financial support and lecturer—Laboratoire Bausch & Lomb Chauvin Cécile Delcourt: Consultant and financial support—Laboratoire Bausch & Lomb Chauvin; Consultant and financial support—Laboratoires Théa; Consultant—Novartis
Sources of funding	Sponsored by Laboratoire Bausch & Lomb Chauvin, Montpellier
Notes	http://www.controlled-trials.com/ISRCTN98246501

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	QL-Ranclin software (Qualilab, Olivet, France) was used to generate the randomization list before enrolment. Souied et al 2013 p3
Allocation concealment (selection bias)	Low risk	The patients and the study personnel both were blinded to the treatment assignment. Souied et al 2013 p3
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personnel), however it is likely that they remained masked as to the allocation

Blinding of participants and personnel (performance bias) Progression of AMD	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personal), however it is likely that they remained masked as to the allocation
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personal), however it is likely that they remained masked as to the allocation
Blinding of outcome assessment (detection bias) Progression of AMD	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personal), however it is likely that they remained masked as to the allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used a per protocol analysis. Main reason for protocol deviation was premature withdrawal which occurred at a similar rate in DHA and placebo groups. Other protocol deviations included 'non-compliance with study medication or use of non-permitted medication'; 263 of the original 300 patients randomised were included in the analysis
Selective reporting (reporting bias)	Low risk	All pre-specified primary outcomes reported. All secondary outcomes (with the exception of mERG listed in trial protocol) were reported

76 **Laser treatment of drusen to prevent progression to advanced age-related macular degeneration**

Bibliographic reference	**CAPT (Complications of Age-Related Macular Degeneration)** Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: the complications of age-related macular degeneration prevention trial. Ophthalmology 2006;113(11):1974–86.
Methods	**Method of allocation**: treatment assignments were generated using a randomly permuted block method, stratified by clinical centre and using a randomly chosen block size. A member of the CAPT Co-ordinating

	Centre reviewed an eligibility checklist with the local ophthalmologist and clinic co-ordinator during a teleconference before disclosing which of the 2 eyes was assigned to laser treatment **Masking**: masked VA examiners. Unclear if participants and care providers were masked. Not reported if anatomic outcomes assessors were masked (i.e. Photograph Reading Centre), but masking was unlikely to be achieved since photocoagulation generates visible scars **Exclusions after randomisation**: none reported **Losses to follow-up**: during 5 years of follow-up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants. This percentage was relatively stable over time **Unusual study design**: bilateral or paired study, i.e. 1 eye randomised to treatment or control and the fellow eye to the other study arm
Participants	**Country**: US **Number randomised**: 1052 participants **Enrolment period**: May 1999 to March 2001 **Age**: mean 71 years **Sex**: 637 women (60.6%) **Inclusion criteria**: at least 10 drusen of size = 125 µm within 3000 µm of FAZ centre; BCVA: 20/40 or more; aged = 50 years **Exclusion criteria**: CNV or serous retinal PED in either eyes; geographic atrophy within 500 µm of FAZ centre; any ocular disease that might affect VA
Interventions	**Treatment**: 60 burns in a grid pattern using a 100-µm spot size, 0.1-second duration and power to achieve a barely visible lesion. The burns were applied within an annulus between 1500 and 2500 µm from the FAZ centre **Control**: observation
Outcomes	Primary: loss of >= 15 letters Secondary: change in VA; change in contrast sensitivity; change in critical print size; incidence of late AMD (CNV, serous PED, geographic atrophy)

Notes	Since 2001, the participants were informed of the AREDS results and were left free to consume antioxidants Supported by the National Eye Institute, Bethesda, Maryland (grant no: EY012211, EY012261, EY012279) COI declaration: the Manuscript Writing Team had no COI with regard to the material presented in the article

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly permuted block method used, stratified by clinical centre and using a randomly chosen block size
Allocation concealment (selection bias)	Low risk	Eligibility assessed before randomisation and central allocation by telephone
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Low risk	Masked VA examiners, unclear if care providers were masked. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Appendix 8. Throughout 5 years of follow-up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants. This percentage was relatively stable over time. In the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

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Bibliographic reference	**CNVPT** Choroidal neovascularization in the Choroidal Neovascularization Prevention Trial. The Choroidal Neovascularization Prevention Trial Research Group. Ophthalmology 1998;105(8):1364–72.
Methods	**BILATERAL**: method of allocation: right eye randomly assigned to either laser treatment or observation. Left eye assigned to alternate treatment **UNILATERAL**: random allocation to laser treatment or observation Stratified by clinical centre and study (bilateral/unilateral) and blocked using a randomly selected block size. Issued over telephone from central location **Masking**: participant: no; provider: unclear; outcome: no for fundus features; yes for VA **Exclusions after randomisation**: not reported **Losses to follow-up**: among participants alive at 12 months, 57/57 were examined in the laser group and 58/61 in the observation group. At 2 years, 46/57 (80.7%) treated eyes compared to 47/58 (81%) control eyes were still followed. However, causes of loss to follow-up other than death were not reported
Participants	**Country**: US in 15 clinical centres **Enrolment period**: October 1994 to December 1996 **BILATERAL**: number randomised: 156 participants (312 eyes). Age: mean 71 years. Sex: 61% women **UNILATERAL**: number randomised: 120 participants. Age: mean 73 years. Sex: 63% women in treatment group; 59% women in control group **Inclusion criteria**: aged = 50 years with colour stereo photographs and a fluorescein angiogram of both eyes taken within 14 days of enrolment, free of any condition that would preclude 2 years' follow-up. No exudative AMD. Study eye: > 10 large drusen (> 63 µm) within 3000 µm of the FAZ with VA of 20/40 or better and no evidence of current or past CNV **BILATERAL**: no exudative AMD in both eyes **UNILATERAL**: no evidence of current or past CNV. Exudative AM in fellow (non-study) eye

	Exclusion criteria: evidence of serous PED = 1 MPS disc area, geographic atrophy within 500 µm of the centre of the FAZ, myopia (= 8 dioptres spherical equivalent), previous laser treatment to the retina, severe non-proliferative or proliferative diabetic retinopathy or diabetic macular oedema, progressive ocular disease
Interventions	**Treatment**: low-intensity laser treatment. 3 different laser treatment protocols: 1. Laser 20: 20 laser burns, 100 µm in diameter, in a pattern of 3 rows placed between the 12 and 6 o'clock positions beyond the temporal perimeter of the FAZ. The desired intensity of the burns was a grey-white lesion. Direct application of laser burns to drusen to be avoided. Whenever the area of drusen had not been reduced by = 50% at 6 months of enrolment, a second treatment was applied nasal to the fovea in a mirror image of the first treatment. During the last 6 months of enrolment, a second laser treatment protocol was adopted that specified 24 laser burns, 100 µm in diameter in a circular pattern of 2 rows surrounding the macular drusen **Control**: observation of fellow eyes
Outcomes	VA (EDTRS); contrast threshold (Pelli Robson); reading ability (MN Read charts) Development of CNV, development of geographic atrophy, disappearance of drusen (stereoscopic colour photographs of the macular and disc of each eye and fluorescein angiogram)
Notes	Enrolment in these pilot studies was suspended after recommendation by the Data and Safety Monitoring Committee (DSMC) because there was a higher incidence of CNV within 12 months of study enrolment in laser-treated eyes than in observed eyes, predominantly in the Fellow Eye Study Furthermore, data from the bilateral study arm were reported at 12 months but not thereafter Supported by an unrestricted gift from Research to Prevent Blindness, New York, NY, to the University of Pennsylvania; gifts to the Macular Degeneration Research Fund, Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA; grants from the Macula Foundation, New York, NY; Research Foundation of the University of Pennsylvania, Philadelphia, PA; and Mackall Trust, New York, NY; and grant R21 EY11275 from the National Eye Institute, National Institutes of Health, Bethesda, MD COI declaration: none of the authors have a proprietary interest in this study

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by clinical centre and study (bilateral/unilateral) and blocked using a randomly selected block size

Allocation concealment (selection bias)	Low risk	Issued over the telephone from central location
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	High risk	Participant and outcome assessors were not masked, unclear if care providers were masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8, Figure 3. UNILATERAL: 81% followed at 2 years in both study arms; loss to follow-up was balanced but causes of loss were not reported
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	High risk	Enrolment in these pilot studies was suspended under recommendation by the Data and Safety Monitoring Committee (DSMC) because there was a higher incidence of CNV within 12 months of study enrolment in laser-treated eyes than in observed eyes, predominantly in the Fellow Eye Study

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Bibliographic reference	**DLS** Owens SL, Bunce C, Brannon AJ, Wormald R, Bird AC, Drusen Laser Study Group. Prophylactic laser treatment appears to promote choroidal neovascularisation in high risk ARM: results of an interim analysis. Eye 2003;17(5): 623–7. Owens SL, Bunce C, Brannon AJ, Xing W, Chisholm IH, Gross M, et al. Prophylactic laser treatment hastens choroidal neovascularization in unilateral age-related maculopathy: final results of the drusen laser study. American Journal of Ophthalmology 2006;141(2):276–81.

Methods	**Method of allocation**: randomisation was conducted with a computerised weighted coin method in the Research and Development office. The randomisation assignment was provided by telephone, and the clinic co-ordinator printed the randomisation assignment on the participant's baseline form. The clinical investigator was then informed of the randomisation allocation. All study eyes of eligible participants in the UNILATERAL group were randomised. The study eye was randomised to laser treatment or no laser treatment. All right eyes of eligible participants in the BILATERAL group were randomised to laser treatment or no laser treatment; the fellow eye received the alternate treatment **Masking**: participant: unclear; provider: unclear; outcome assessor: masked VA examiner **Exclusions after randomisation**: none reported **Losses to follow-up**: UNILATERAL: at 3 years, VA was obtained in 73/92 (80.7%) laser-treated eyes vs. 66/85 (77.6%) control eyes. Development of CNV was recorded in 91/92 treated eyes and 85/85 control eyes. BILATERAL: VA obtained in 72/105 participants at 3 years, and CNV development assessed in 103/105 eyes at 3 years **Unusual study design**: some participants had both eyes randomised (BILATERAL group) and within-person correlation was taken into account
Participants	**Country**: UK **BILATERAL**: number randomised: 105 participants (210 eyes). Age: 70.1 years (range: 52 to 100). Sex: 31 men/74 women **UNILATERAL**: number randomised: 177 participants. Age: 72 years (range: 54 to 87). Sex: 80 men/97 women **Inclusion criteria**: drusen with/without focal RPE hyperpigmentation in the study eye and CNV in the fellow eye; BCVA at least 6/12 (20/40); aged at least 50 years **Exclusion criteria**: geographic atrophy in either eye; any other eye disease able to influence VA; allergy to fluorescein
Interventions	**Treatment**: argon green/yellow dye laser with 200-µm spot size, 0.2 second duration and the lowest energy to produce a very faint burn; overall 12 burns: 4 burns placed 750 µm from FAZ centre (12, 3, 6, 9 o'clock), and 8 burns 1500 µm from FAZ centre (12, 1.30, 3, 4.30, 6, 7.30, 9. 10.30, 12 o'clock); drusen treated directly if they were coincident with protocol treatment allocation **Control**: observation

Outcomes	Proportion of participants who developed CNV; VA
Notes	Protocol of treatment revised after 23 months: 12 burns (0.2 seconds to 200-µm spot size) placed in circular pattern at 1000 µm from FAZ centre Supported in part by Deutsche Forschungsgemeinschaft (DFG GR 1007/3-1 and Ho 1926/1-2) and the Deutsche Akademischer Austauschdienst ARC IX-95/32 (MG) COI declaration: not reported

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated method
Allocation concealment (selection bias)	Low risk	The clinical investigator was informed of the randomisation allocation by the co-ordinator by telephone after eligibility was assessed
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Low risk	Masked VA examiners. Participants cannot be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8. Losses to follow-up were balanced but causes were not reported; no risk of bias given the paired study design for the BILATERAL study arm
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes

Other bias	High risk	The trial was stopped early after an interim analysis suggested that laser treatment induced CNV in treated eyes of participants in the unilateral group

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Bibliographic reference	**Figueroa 1994** Figueroa MS, Regueras A, Bertrand J. Laser photocoagulation to treat macular soft drusen in age-related macular degeneration. Retina 1994;14(5):391-6.
Methods	**Method of allocation**: not reported. 1 eye of participants with bilateral drusen was assigned to treatment and the fellow eye to control **Masking**: not reported if participants and providers, but participants could not be masked since there was no sham procedure. VA examiners were masked **Exclusions after randomisation**: none reported **Losses to follow-up**: since they reported on results at last examination (mean follow-up 3 years), assessing the impact of loss to follow-up was difficult **Unusual study design**: paired or bilateral study; authors also reported on a parallel case series of people with CNV in 1 eye who were all treated in the fellow eye
Participants	**Country**: Spain **Number randomised**: 30 participants (60 eyes) **Age**: 69 years (range: 62 to 74) **Inclusion criteria**: AMD with large confluent soft drusen involving the fovea **Exclusion criteria**: not specified
Interventions	**Treatment**: green argon laser; 0.1 mW, 0.1 seconds, 100-µm spot; laser spot on drusen in the temporal fovea, or grid pattern if drusen > 300 µm **Control**: observation **Duration**: mean 3 years (range: 1.5 to 5)

Outcomes	Occurrence of CNV, reduction of drusen, VA
Notes	Drusen resolution possible also for drusen located far from the laser application Supported in part by National Institutes of Health grant NEI EY12769 and 5 P30 EY 01583, the Vivian Simkins Lasko Research Fund, the Nina C. Mackall Trust, and an unrestricted grant from Research to Prevent Blindness, New York, NY COI declaration: not reported

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Low risk	Masked visual examiner
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8 . Data at mean follow-up were reported. Since 12/30 participants were followed for < 3 years, it was difficult to assess the impact of this type of reporting. However, in the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Unclear risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes

Other bias	Unclear risk	Unclear

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Bibliographic reference	**Frennesson 1995** Frennesson IC, Nilsson SE. Effects of argon (green) laser treatment of soft drusen in early age-related maculopathy: a 6 month prospective study. British Journal of Ophthalmology 1995;79(10):905-9.
Methods	**Method of allocation**: not reported; in 5 participants with both eyes eligible the eye with better VA was randomised **Masking**: participant: unclear; provider: unclear; outcome: unclear **Exclusions after randomisation**: none reported **Losses to follow-up**: 2/19 participants in the treated group vs. 0/19 in the control group lost to follow-up at 3 years Unusual study design
Participants	**Country**: Sweden **Number randomised**: 38 participants **Age**: 71.6 years (SD 6.5) treated participants; 68.5 years (SD 6.2) control participants **Inclusion criteria**: soft drusen; VA at least 0.8 **Exclusion criteria**: CNV, PED, pigmentary clumping, macular atrophy, haemorrhage, any other eye disorder that could affect VA
Interventions	**Treatment**: argon green laser with 200-µm spot size, 0.05 seconds' duration, power to produce a barely visible lesion. Treatment with a temporal horse shoe-shaped area extending to the vascular arcades, with direct treatment of the drusen **Control**: observation **Duration**: 3-8 years
Outcomes	Anatomic: mean drusen area, development of CNV. Functional: Snellen VA; colour vision (Farnsworth panel D-15); central visual field (Humphrey 10-2)
Notes	The study was supported by grants from the Swedish Medical Research Council (Project No 12X-734), from the Research Committee of the County of Östergötland and from Synfrämjandet's Research Foundation COI declaration: not reported

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Unclear risk	Not reported. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8. 2/19 (11%) participants in the treated group vs. 0/19 in the control group lost to follow-up at 3 years; causes of loss to follow-up not reported
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

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Bibliographic reference	**Frennesson 2009** Frennesson CI, Bek T, Jaakkola A, Nilsson SE. Prophylactic Laser Treatment Study Group. Prophylactic laser treatment of soft drusen maculopathy: a prospective, randomized Nordic study. Acta Ophthalmologica 2009;87(7):720-4.
Methods	**Method of allocation**: randomisation generated as a permuted block design; the randomisation was delivered from Linkoping University Hospital. Enrolling doctors were not masked to treatment allocation (personal communication) **Masking**: participant: yes; provider: no; outcome: no (personal communication)

	Outcome: incidence of CNV, VA **Follow up**: mean 3.7 years (range 1-7.5 years) **Exclusions after randomisation**: none reported **Losses to follow-up**: two-thirds of participants were followed up to 4 years, with losses balanced across groups **Unusual study design**: nothing reported
Participants	**Country**: Sweden, Denmark, Finland **Number randomised**: 135 participants **Age**: mean 70.4 years **Inclusion criteria**: people with soft drusen with or without mild pigmentary changes; VA = 0.8 (20/25) in the study eye, aged = 50 years **Exclusion criteria**: including pigmentary clumping, PED, CNV, haemorrhage or macular atrophy, and any other ophthalmological disease in the study eye that might possibly influence the outcome
Interventions	**Treatment**: laser treatment (subthreshold or barely visible laser spots). About 100 mild argon green laser spots with a size of 200 µm and a duration of 0.05 seconds **Unspecified control**, possibly observation only
Outcomes	VA, occurrence of CNV
Notes	The study was supported by grants from the Health Research Council in the South-East Region of Sweden, Crown Princess Margareta's Foundation for the Visually Handicapped and Synframjandet's Research Foundation COI information: not reported

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, permuted block design

Allocation concealment (selection bias)	High risk	Randomisation was delivered from Linkoping University Hospital. Enrolling doctors were not masked to treatment allocation
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Participants masked and doctors unmasked, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	High risk	Care providers were unmasked. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Mean follow-up time was about 3.5 years and two-thirds of participants were followed up to 4 years, with losses balanced across groups. Study authors reported causes of missingness were death or illness in 5 of 6 cases at 2 years
Selective reporting (reporting bias)	Low risk	Main relevant outcome measure were reported
Other bias	Unclear risk	Unclear

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Bibliographic reference	**Laser to Drusen Study 1995** Bressler SB, Vitale S, Hawkins BS, Alexander J, Orr PR, Schachat AP, et al. Laser to Drusen Trial: an assessment of short term safety within randomized, prospective, controlled clinical trial. Investigative Ophthalmology and Visual Science 1995;36:ARVO E-abstract 1028.
Methods	**Method of allocation**: computer-generated randomisation list with randomly selected block sizes. **Allocation groups**: observation vs. laser (1 : 1), laser further divided (1 : 1) in temporal vs. nasal and temporal treatment **Masking**: participant: unclear; provider: unclear; outcome: unclear **Exclusions after randomisation**: none reported **Losses to follow-up**: 7/47 (15%) of treatment group and 10/52 (19%) of control group seen at 2 years
Participants	**Country**: US

	Number randomised: 99 participants **Age**: mean 74 years (SD 6.6), range 55 to 84 years **Sex**: 69.7% women **Inclusion criteria:** large drusen (> 63 µm in diameter) and focal hyperpigmentation, and no neovascular AMD in 1 eye only (study eye) evidence of neovascular AMD (CNV, disciform scar, laser scar for CNV) in 1 eye only (fellow eye) VA 20/40 or better in study eye (other information says 20/50 or better) no significant co-existing ocular disorder in study eye aged = 50 years **Exclusion criteria:** history of laser surgery or vitreous surgery in study eye low probability of completing 2-year follow-up schedule (poor health, live far from clinical centre, unwilling to return) geographic atrophy within 3000 µm of foveal centre other conditions associated with CNV, including pathological myopia (spherical equivalent exceeding -8.00 dioptres or clinical evidence of lacquer cracks), angioid streaks, histo spots, pattern dystrophies of RPE, etc. in study eye severe non-proliferative or worse diabetic retinopathy or diabetic macular oedema in study eye other progressive ocular disease that could impair VA such as glaucoma in the study eye lensectomy or intraocular lens implantation within 3 months
Interventions	Laser wavelength: dye yellow laser (577 nm) or infrared diode (very early - was discontinued). Number of burns: various, 2 scatter patterns described below; spot size: 50 µm; duration: 0.1 seconds; intensity: very light grey burn (just visible); no treatment within 500 µm of foveal centre and beyond 3000 µm from foveal centre; scatter burns approximately 2-3 burn widths apart, trying to avoid placing burns directly over focal clumps of hyperpigmentation. Do not have to place directly on drusen, but in placing scatter, small placement changes (< 50 µm) should be done to centre spot on drusen

	Pattern 1: (temporal = 180 degree) - not placed in nasal portion of macula (vertical line intersects foveal centre) Pattern 2: (temporal and nasal = 360 degree) - burns placed in scatter both nasal and temporal portion of macula (exclusive of central macula within 500 µm of foveal centre and not beyond 3000 µm of foveal centre)
Outcomes	Development of CNV; VA; information on other outcomes not available
Notes	Randomisation changed - originally 1 : 1 (laser vs. observation), then laser group randomised 1 : 1 (infrared diode vs. yellow dye) - each colour laser was randomised 1:1 (temporal vs. temporal and nasal) The red diode laser arm was stopped early (probably December 1995) Pilot study nature - so some clinical centres did not do all tests (reading, contrast) - not all clinical photographs graded Funding source unknown

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated. Randomly selected block size (Marta M Gilson, personal communication)
Allocation concealment (selection bias)	Low risk	Serially numbered sealed opaque envelopes. Co-ordinator had to fill out checklist - document eligibility - then open sequentially numbered envelope, record date opened, time opened, participant number, name code and sign the form (2 copies - keep 1, and fax other to co-ordinating centre within 24 hours of opening). Faxed forms were later mailed to co-ordinating centre (Marta M Gilson personal communication)
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Participants: unclear; care providers: ophthalmologists (applying laser) were not masked; care providers - co-ordinators: unclear; outcome assessors: Photograph Reading Centre graders were to be masked, but it was possible that some of the laser scars may have unmasked the graders (Marta M Gilson, personal communication)
Blinding (performance bias and detection bias)	Unclear risk	VA examiners: unclear

Measurement of vision		
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Figure 3. 7/47 (15%) of treatment group and 10/52 (19%) of control group lost at 2 years. No information on reasons for loss to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes selected by review author
Other bias	Unclear risk	Unclear

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Bibliographic reference	**Little 1995** Little HL, Showman J. A pilot randomized, controlled study on the effect of laser photocoagulation of confluent soft macular drusen. American Academy of Ophthalmology 1995:120.
Methods	**Method of allocation**: after participants eligibility was ascertained and participant consent was obtained, 1 eye was randomised to photocoagulation treatment; the right eye was assigned to treatment if participant's birth date was an odd month, the left if it was an even month **Masking**: participant: unclear; provider: unclear; outcome assessor: unclear **Exclusions after randomisation**: none reported **Losses to follow-up**: a minimum 1-year follow-up was obtained (mean 3.2 years) **Unusual study design**: paired study
Participants	**Country**: US **Number randomised**: 27 participants (54 eyes) **Age**: mean 69.7 years **Sex**: 9 men/18 women **Inclusion criteria**: symmetrical drusen; minimum drusen size 100 µm; at least 20 drusen or 10 drusen + 2 drusen at least 500 µm in diameter; drusen within 500 µm from foveola; VA at least 20/60

	Exclusion criteria: PED; atrophy; subretinal fluid, haemorrhage, exudate; any other eye disorder which could affect VA
Interventions	**Treatment**: 577- to 620-nm wavelength laser with 100-200 µm spot size, 0.05-0.1 seconds' duration, 100-200 power. Direct treatment of the drusen **Control**: observation **Duration:** 1- to 6-year follow-up
Outcomes	Snellen VA; colour vision (Farnsworth panel D-15 colour-test); central visual field with Humphrey 10-2
Notes	No COI for any author

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	After participants eligibility was ascertained and participant consent was obtained, 1 eye was randomised to photocoagulation treatment; the right eye was assigned to treatment if person's birth date was an odd month, the left if it was an even month
Allocation concealment (selection bias)	High risk	See above, the enrolling researcher could have foreseen which eye would have been treated. Nonetheless, this can be irrelevant since both eyes of each participant were included, i.e. there was no risk of confounding
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	High risk	Not reported. Participants could not be masked since no sham procedure was mentioned

Incomplete outcome data (attrition bias) All outcomes	Low risk	Unclear: only last visit data reported, thus being impossible to reconstruct the pattern of missing data; 4/27 participants were followed for = 1 year but < 2 years. However, in the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

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Bibliographic reference	**Olk 1999** Olk RJ, Friberg TR, Stickney KL, Akduman L, Wong KL, Chen MC, et al. Therapeutic benefits of infrared (810-nm) diode laser macular grid photocoagulation in prophylactic treatment of nonexudative age-related macular degeneration: two-year results of a randomized pilot study. Ophthalmology 1999;106 (11):2082-90.
Methods	**Method of allocation**: not reported; BILATERAL: 1 eye was assigned to treatment and 1 eye to observation. UNILATERAL: 1 eye eligible that eye was assigned to either treatment or observation. BILATERAL/UNILATERAL: eyes assigned to treatment were further randomised to either 'visible' or 'subthreshold' treatment **Masking**: participant: unclear; provider: unclear; outcome: unclear **Exclusions after randomisation**: 25/152 participants (35 eyes) were enrolled initially in the pilot study but subsequently determined to be ineligible for various reasons, mainly violation of inclusion criteria **Losses to follow-up**: at 24 months, 33 eyes had missed visits: 9 eyes (4 observation, 2 visible, 3 subthreshold) were in deceased participants, 14 eyes were in the observation group, and 10 eyes were in the treatment group (5 eyes, visible; 5 eyes, subthreshold) **Unusual study design**: some eyes
Participants	**Country**: US **Number randomised**: BILATERAL: 77 participants (154 eyes) with both eyes eligible. UNILATERAL: 75 participants (75 eyes) with 1 eye eligible (unilateral study arm), that eye was assigned to either treatment or observation

	Enrolment period: July 1994 to June 1996 **Sex**: 152 participants enrolled; 57 men, 95 women **Age**: mean 74.5 years, range 54-88 years **Inclusion criteria**: aged > 50 years; diagnosis of AMD with = 5 large (= 63 µm), soft drusen within 2250 µm of the centre of the FAZ in both eyes (bilateral study arm) or in 1 eye (unilateral study arm) if the fellow eye had evidence of exudative AMD; and VA of = 20/63 on the ETDRS chart in all eligible eyes **Exclusion criteria**: exudative macular degeneration in either eye for bilateral participants and in both eyes for unilateral participants; other ocular diseases
Interventions	Eyes were treated with a slit-lamp integrated diode photocoagulator using 810-nm wavelength (IRIS Medical OcuLight SLx; IRIDEX Corp., Mt. View, CA). 48 diode laser lesions of 125 mm were applied in 4 concentric circles outside the FAZ in a scatter or grid pattern between 750 and 2250 mm from the centre of the fovea. Test spot laser lesions were applied to the retina nasal to the optic nerve using 200-millisecond duration, and the power was increased to produce a mild grey lesion (visible burn). For eyes assigned to visible treatment, this intensity was then applied in a grid pattern as described above. For eyes assigned to subthreshold treatment, the energy needed for the visible test burn was kept constant, but the duration was halved to 100 milliseconds and treatment then carried out. Only 1 laser treatment was applied to each eye throughout the duration of the study
Outcomes	Anatomic: reduction of drusen, development of CNV. Functional: VA
Notes	Within-person correlation of outcomes in the bilateral arm not analysed and reported Supported in part by grants from IRIS Medical, Mountain View, CA (producer of the laser used in the study), and The University of Pittsburgh Eye and Ear Foundation, Pittsburgh, PA COI declaration: not reported

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	High risk	Not reported. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8 and Figure 3. Losses to follow-up: at 24 months, 33 eyes had missed visits: 9 eyes (4 observation, 2 visible, 3 subthreshold) were in deceased participants, 14 eyes were in the observation group, and 10 eyes were in the treatment group (5 eyes, visible; 5 eyes, subthreshold). Causes of loss to follow-up other than death were not reported. In the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed. Thus, only losses in unilateral arm was considered
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

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Bibliographic reference	**PTAMD bilateral 2009** Friberg TR, Brennen PM, Freeman WR, Musch DC, PTAMD Study Group. Prophylactic treatment of age-related macular degeneration report number 2: 810-nanometer laser to eyes with drusen: bilaterally eligible patients. Ophthalmic Surgery, Lasers and Imaging 2009;40 (6):530-8.
Methods	**Method of allocation**: study eyes were assigned randomly to either treatment or observation by a computer-generated, centre-specific, variable block size randomisation at a 1: 1 ratio. These random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent

	Masking: participant: unclear; provider: unclear; outcome: unclear **Participant**: 1278 eyes of 639 participants **Outcome**: development of CNV and change in best-corrected VA **Exclusions after randomisation**: none reported **Losses to follow-up**: 374/639 (54.3%) participants followed to 2 years **Unusual study design**: paired study
Participants	**Country**: US **Number randomised**: 1278 eyes of 639 participants **Enrolment period**: April 1996 to March 2000 **Mean age**: 73.0 years (SD 2.5) **Inclusion criteria:** aged = 50 years. Eligible eye must have had BCVA of = 20/63 on the ETDRS chart in both eyes; AMD with = 5 drusen that were = 63 µm in diameter and were located within 2250 µm of the centre of the fovea; unilateral participants must have had 1 eye ineligible due to vision loss that was attributed to advanced AMD **Exclusion criteria**: other ocular disease causing visual loss
Interventions	Eyes randomised to treatment received a single-session treatment of a grid of 48 diode laser lesions of 125 µm in diameter. Laser treatment was applied in an annular grid that extended from 0.5 (750 µm) to 2.0 (3000 µm) disc diameters from the centre of the FAZ. A slit lamp-based diode laser photocoagulation system (IRIS Medical, Mountain View, CA) emitting energy at 810 nm was used to deliver the laser treatment. Laser lesions were placed in a subthreshold manner by first delivering test spot(s) of 200-millisecond duration placed outside of the macula at a low power (e.g. 200 mW) and then incrementally increasing the power in small (50 mW) increments until a faint grey (threshold) lesion could be detected visually through the treatment lens. While the power setting was left unchanged, the pulse duration was reduced to a 100-millisecond interval to achieve an invisible subthreshold lesion. Laser lesions were then scattered within the annular grid as defined above, beginning by placing 12 spots in a given quadrant and then proceeding to adjacent quadrants to complete the treatment pattern. The drusen were not targeted specifically or preferentially. If a visible lesion was produced while the annular grid treatment was performed, the power setting was reduced to achieve subthreshold lesions with the remainder

Outcomes	Anatomic: drusen reduction, development of CNV. Functional: VA
Notes	Supported by IRIDEX Corporation, Mountain View, CA (the producer of the laser used in the study); the Eye and Ear Foundation of Pittsburgh, Pittsburgh, PA; Research to Prevent Blindness, Inc., New York, NY and unrestricted funds from several participating centres COI declaration: the authors had no financial or proprietary interest in the materials presented

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, centre-specific, variable block size randomisation at a 1 : 1 ratio
Allocation concealment (selection bias)	Low risk	These random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Unclear risk	Not reported, masking of care providers and photograph graders might be achieved since subthreshold photocoagulation should not generate visible scars. Participants cannot be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Large proportion of participants lost to follow-up, but this was unlikely to bias effect estimates since this was a paired study. In the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

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Bibliographic reference	PTAMD unilateral 2002 Friberg TR, Musch DC, Lim JI, Morse L, Freeman W, Sinclair S, et al. Prophylactic treatment of age-related macular degeneration. Report number 1: 810-nanometer laser to eyes with drusen. Unilaterally eligible patients. Ophthalmology 2006;113(4):612-22.
Methods	**Method of allocation**: study eyes were assigned randomly to either treatment or observation by a computer-generated, centre-specific, variable block size randomisation at a 1 : 1 ratio. These random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent **Masking**: participant: unclear; provider: unclear; outcome: unclear **Exclusions after randomisation**: not reported **Losses to follow-up**: at 1 year, 184/244 (75%) participants followed (5 deaths), 92 treated eyes and 99 control eyes followed. At 3 years, 124/244 (51%) participants followed (20 deaths), 64 treated eyes and 55 control eyes followed **Unusual study design**: another arm of the study included participants with both eyes eligible, but this report deals with unilateral participants only
Participants	**Country:** US **Number randomised**: 244 participants **Age**: mean 75.4 years for treated participants, 75.1 years for observed participants **Gender** (% women): 59.3 treated participants, 61.5 observed participants **Inclusion criteria**: aged = 50 years. Eligible eye must have had BCVA of = 20/63 on the ETDRS chart; AMD with = 5 drusen that were 63 µm in diameter and were located within 2250 µm of the centre of the fovea; unilateral participants must have had 1 eye ineligible due to vision loss that was attributed to advanced AMD Exclusion criteria: other ocular disease causing visual loss

Interventions	Eyes randomised to treatment received a single-session treatment of a grid of 48 diode laser lesions of 125 µm in diameter. Laser treatment was applied in an annular grid that extended from 0.5 (750 µm) to 2.0 (3000 µm) disc diameters from the centre of the FAZ. A slit lamp-based diode laser photocoagulation system (IRIS Medical, Mountain View, CA) emitting energy at 810 nm was used to deliver the laser treatment. Laser lesions were placed in a subthreshold manner by first delivering test spot(s) of 200-millisecond duration placed outside of the macula at a low power (e.g. 200 mW) and then incrementally increasing the power in small (50 mW) increments until a faint grey (threshold) lesion could be detected visually through the treatment lens. While the power setting was left unchanged, the pulse duration was reduced to a 100-millisecond interval to achieve an invisible subthreshold lesion. Laser lesions were then scattered within the annular grid as defined above, beginning by placing 12 spots in a given quadrant and then proceeding to adjacent quadrants to complete the treatment pattern. The drusen were not targeted specifically or preferentially. If a visible lesion was produced while the annular grid treatment was performed, the power setting was reduced to achieve subthreshold lesions with the remainder
Outcomes	Anatomic: drusen reduction, development of CNV. Functional: VA
Notes	Supported by IRIDEX Corporation, Mountain View, CA (the producer of the laser used in the study); the Eye and Ear Foundation of Pittsburgh, Pittsburgh, PA; Research to Prevent Blindness, Inc., New York, NY and unrestricted funds from several participating centres COI declaration: the authors had no financial or proprietary interest in the materials presented

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, centre-specific, variable block size randomisation
Allocation concealment (selection bias)	Low risk	Random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias)	Unclear risk	Not reported, masking of care providers and photograph graders might be achieved since subthreshold photocoagulation should not generate visible

Measurement of vision		scars. Participants could not be masked since no sham procedure was mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	See Results, Appendix 8, Figure 3. Survival analysis used. Losses to follow-up: at 1 year, 184/244 (75%) participants followed (5 deaths), 92 treated eyes and 99 control eyes followed. At 3 years, 124/244 (51%) participants followed (20 deaths), 64 treated eyes and 55 control eyes followed. Causes of loss other than death were not reported
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 or more lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

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99 **Antioxidant vitamins and mineral supplements for slowing the progression of age-related macular degeneration**

100 **Multivitamin supplements**

Bibliographic reference	**AMDSG 1996** Richer S. Multicenter ophthalmic and nutritional age-related macular degeneration study-part 2: antioxidant intervention and conclusions. Journal of the American Optometry Association 1996;67(1):30-49.
Methods	Parallel group RCT **Method of allocation**: sponsor prepared coded tablets **Masking**: participant - not clear; provider - yes; outcome - yes **Losses to follow-up**: 4 died (2 treatment, 2 control); 1 adverse effect withdrawn (treatment); 7 lost to follow-up (1 treatment, 6 control)
Participants	**Country**: USA **Number of people randomised**: 71 (NR eyes) **Number (%) of people followed-up**: 59 (83%) (NR eyes) **Average age (range):** 72 years (NR)

	Percentage women: 7% **Ethnic group**: NR **Baseline visual acuity**: NR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria**: people with a monocular one line drop in Snellen visual acuity not attributable to cataract, amblyopia, systemic or ophthalmic disease AMD clinically observable drusen, RPE disruption and loss of macular reflex **Exclusion criteria:** greater than 1 year use of vitamin sex-prisoners of war chronic alcoholics with tobacco/nutritional amblyopia gastrointestinal absorption disorders
Interventions	**Intervention**: Ocuguard (Twin Lab Inc, Ronkonkoma, NY) broad-spectrum antioxidant: beta-carotene 20,000 IU, vitamin E 200 IU, vitamin C 750 mg, citrus bioflavonoid complex 125 mg, quercitin (bioflavonoid) 50 mg, bilberry extract (bioflavonoid) 5 mg, rutin (bioflavonoid) 50 mg, zinc picolinate 12.5 mg, selenium 50 µg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B2 25 mg, chromium 100 µg (daily)NR people randomised (NR eyes)39 (NR%) people followed-up (NR eyes) **Comparator**: placebo, starch NR people randomised (NR eyes)32 (NR%) people followed-up (NR eyes) Duration: 18 months
	Similarity between intervention and comparator: Treatment and placebo may not have been identical
Outcomes	**Primary:** not specified **Secondary**: not specified Outcomes reported in the paper: Snellen acuity with best refraction converted to logMAR units for analysisnear vision M units with dual sided Bailey-Lovie chart contrast sensitivity retinal grading score (adapted from Chesapeake Bay Study)subjective perception of vision; adverse gastrointestinal reactions **Follow-up:**

	Eyes: Reported right and left eyes separately
Notes	**Source of funding**: Twin Laboratories Inc, Ronkokoma NY; Stereo Optical Inc, Chicago, IL; Eye Communications Inc, Upland, CA; Illinois College of Optometry, Chicago, IL; Pacific University College of Optometry, Forest Grove, OR; Ezell Foundation, American Academy of Optometry, Rockville, MD Declaration of interest: NR Date study conducted: NR Trial registration number: NR

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote "Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules."
Allocation concealment (selection bias)	Unclear risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote "Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules."

Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote "Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"Quote "Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"Quote "Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules."

Incomplete outcome data (attrition bias)	Unclear risk	17 patients withdrew from the study over 18 months. 4 patients died. 1 patient experienced an idiosyncratic reaction and was dropped. Attrition data were as follows: "71 patients at baseline, 67 patients at 6 m, 59 patients at 12 m, 59 patients at 18 m." Similar numbers of drop outs from groups 1 and 2 but the numbers were not clearly described.
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information given - no access to study protocol and trial was not registered.

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Bibliographic reference	**AREDS 2001** Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report No. 8. Archives of Ophthalmology 2001;119(10):1417-36.
Methods	Parallel group RCT 2 x 2 factorial design. 67% participants took additional supplements to RDA levels (Centrum). In 1996 current smokers offered option of discontinuing supplementation; 2% of participants and 18% of smokers did so. A further 2.3% reassigned to no beta-carotene group. Intention-to-treat analysis maintained. **Method of allocation**: coded bottles **Masking**: participant - yes; provider - yes; outcome – yes **Losses to follow-up**: 2.4% balanced across study groups
Participants	**Country**: USA **Number of people randomised**: 3640 (NR eyes) **Number (%) of people followed-up**: 2.4% lost to follow up **Average age (range):** 69 years (55 to 80) **Percentage women**: 56% **Ethnic group**: 96% white **Baseline visual acuity**: NR

	Comorbidities affecting the eye: NR **Percentage current smokers**: 8% Inclusion criteria: • 20/32 or better in at least 1 eye • ocular media clear and therefore able to obtain adequate stereoscopic fundus photographs • at least 1 eye free from eye disease that could complicate assessment of AMD Exclusion criteria: • illness or disorders that would make long-term follow-up or compliance with study protocol unlikely or difficult
Interventions	**Intervention:** • antioxidants vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg (daily) • zinc 80mg as zinc oxide, copper 2mg as cupric oxide (daily) 2737 people randomised (NR eyes) (945 antioxidants only, 904 zinc only, 888 antioxidants plus zinc) 2.4% lost to follow-up but numbers by group not reported. Quote "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups." **Comparator**: • placebo 903 people randomised (NR eyes) 2.4% lost to follow-up but numbers by group not reported. Quote "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups." **Duration:** average follow-up 6.3 years **Similarity between intervention and comparator**: Quote "Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste.
Outcomes	**Primary:** • progression to advanced AMD (assessed using stereoscopic fundus colour photograph) • 15 letter or more decrease in visual acuity score (EDTRS logMAR chart) **Secondary:**

	• safety outcomes included: reported adverse events; serum levels of haemoglobin; hospitalisations and mortality. **Follow-up**: annual follow-up for at least 5 years **Eyes**: outcome was Quote "in at least one eye" i.e. reported by person
Notes	Source of funding: Quote "Supported by contracts from the National Eye Institute, National Institutes of Health, with additional support from Bausch and Lomb Pharmaceuticals." Declaration of interest: Quote "The AREDS investigators have no commercial or proprietary interest in the supplements used in this study." Date study conducted: 1992 to 2001 Trial registration number: NR

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Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Simple randomization, stratified by clinical center and AMD category, was used to assign treatment. Participants in Categories 2, 3, and 4 were assigned with probability one quarter to each treatment group" Quote "Multiple unique bottle codes were randomly assigned to each of the 4 treatments for Categories 2, 3, and 4, and also to each of the 2 treatments for participants in Category 1. A bottle code corresponding to the assigned treatment was randomly selected for each participant".
Allocation concealment (selection bias)	Low risk	Quote "Multiple unique bottle codes were randomly assigned to each of the 4 treatments for Categories 2, 3, and 4, and also to each of the 2 treatments for participants in Category 1. A bottle code corresponding to the assigned treatment was randomly selected for each participant".

Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "The 4 treatment interventions were double-masked..." Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste. The coordinating center was custodian of the treatment code Quote "Four participants (0.1%) were reported to have been unmasked during the trial"
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "The 4 treatment interventions were double-masked..." Quote "Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste. The coordinating center was custodian of the treatment code" Quote "Four participants (0.1%) were reported to have been unmasked during the trial"
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "Visual acuity was assessed by certified examiners using the ETDRS logMAR chart and a standardized refraction and visual acuity protocol (AREDS Manual of Operations; The EMMES Corporation, Rockville, Md)"
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "Stereoscopic fundus photographs of the macula were taken at baseline and annually beginning 2 years after randomization and graded centrally using standardized grading procedures."
Incomplete outcome data (attrition bias)	Low risk	Quote "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups." Quote "Only 2.4% of AREDS participants were lost to follow-up (missed at least their last 2 consecutive visits). Losses to follow-up were balanced across treatment groups" Quote "Of almost 50000 possible follow-up visits, 10% were missed. The frequency of missed visits and mean follow-up time (6.3 years) did not differ by treatment group. Most participants (90%) had at least 5 years of follow-up."
Selective reporting (report bias)	Low risk	Quote "At the start of the study, 2 primary outcomes were defined for study eyes in the AMD trial: (1) progression to advanced AMD and (2) at least a 15-letter decrease in visual acuity score."

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Bibliographic reference	**Bartlett 2007** Bartlett HE, Eperjesi F. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. European Journal of Clinical Nutrition 2007;61(9):1121-7
Methods	**Parallel group RCT** **Method of allocation**: sponsor prepared coded tablets **Masking**: participant - yes; provider - yes; outcome - yes **Losses to follow-up**: 5 (2 treatment, 3 control)
Participants	**Country**: UK **Number of people randomised**: 30 (30 eyes) **Number (%) of people followed-up**: 25 (83%) (25 eyes) **Average age (range):** 69 years (55 to 82) **Percentage women**: 53% **Ethnic group**: 100% white **Baseline visual acuity**: average visual acuity in intervention group was 0.20 logMAR and in control group as 0.08 logMAR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria**: • provide written informed consent • be available to attend one of the research centres • present with no ocular pathology in at least 1 eye, or no ocular pathology other than soft or hard drusen, and areas of increased or decreased pigment associated with drusen. Fundus examination was used to determine the presence of AMD. **Exclusion criteria:** • type I and II diabetes • prescribed antiplatelet or anticoagulant medication • concurrent use of nutritional supplements • advanced AMD in 1 or both eyes

Interventions	**Intervention:** • lutein esters 6 mg, retinol 750 mg, vitamin C 250 mg, vitamin E 34 mg, zinc 10 mg, copper 0.5 mg (daily) 17 people randomised (17 eyes) 15 (88%) people followed-up (15 eyes) **Comparator:** • placebo tablets containing cellulose (daily) 13 people randomised (13 eyes) 10 (77%) people followed-up (10 eyes) **Duration**: 9 months **Similarity between intervention and comparator**: Quote "The study formulation and placebo tablets were produced by Quest Vitamins Ltd, and were identical in external and internal appearance, and taste."
Outcomes	**Primary**: NR **Secondary**: NR Outcome measures specified on trial registration entry • Distance and near Visual Acuity (VA) measured using Bailey-Lovie logMAR charts • Contrast sensitivity (CS) measured using a Pelli-Robson chart • Colour vision measured using the PV-16 quantitative colour vision test • Macular Mapping (MM) test • Eger Macular Stressometer (EMS) used to assess glare recovery • Fundus photographs of the macular will be assessed using colour and edge analysis software Trial publication provided data on contrast sensitivity at 9 months follow-up. Protocol listed more outcomes (see below under selective reporting) and specified 9 and 18 months follow-up. Follow-up: 9 months (reported) and 18 months (not reported) Eyes: Trial eye selected (initial visit only). If both eyes were eligible for inclusion, the right eye was used
Notes	Sample size calculations reported in trial report: "A group size of nine was calculated to be sufficient to provide 80% power at the 5% significance level for CS based on an effect size of 0.3 log units, and mean and standard deviation

	(s.d.) values taken from a sample of 50 ARM and atrophic AMD patients of the University optometry clinic (1.3970.22 log CS)." Sample size calculations reported in protocol paper "From initial data collection we have calculated the treatment group sizes required in order to have 80% power at the 5% significance level for VA, CS, MM test, and the EMS. These values suggest that a total of 63 normal, and 96 age-related macular disease participants are required." Source of funding: Quote "The project was sponsored by the UK College of Optometrists. Intervention and placebo tablets were provided by Quest Vitamins Ltd UK." Declaration of interest: NR Date study conducted: March 2003 and December 2004 Trial registration number: ISRCTN78467674 (registered retrospectively)

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random number generator function in Microsoft Excel is being used to allocate participants to μ and λ groups. Odd numbers allocate to the μ group Bartlett 2003 (protocol report) page 3 Only one investigator (HB) was involved in the randomization process, which employed the random number generator in Microsoft Excel for Windows XP. Odd and even numbers were used to identify group. Bartlett 2007, page 1122
Allocation concealment (selection bias)	Low risk	Enrolment was carried out by HB, who, along with FE, was masked to group assignment. Bartlett 2007, page 1121 Only one investigator (HB) was involved in the randomization process, which employed the random number generator in Microsoft Excel for Windows XP. Odd and even numbers were used to identify group. Bartlett 2007, page 1122 Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation. Bartlett 2003 (protocol report) page 3

Blinding of participants and personnel (performance bias) Visual acuity	Low risk	The study formulation and placebo tablets have been produced by Quest Vitamins Ltd, Aston Science Park, Birmingham, B7 4AP, and are identical in external and internal appearance, and taste. The manufacturer has allocated distinguishing symbols, μ and λ. The tablets are packaged in identical, sealed, white containers; the only difference being the symbol on the label. Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation. Bartlett 2003 (protocol report) page 3
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Not reported
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	The study formulation and placebo tablets have been produced by Quest Vitamins Ltd, Aston Science Park, Birmingham, B7 4AP, and are identical in external and internal appearance, and taste. The manufacturer has allocated distinguishing symbols, μ and λ. The tablets are packaged in identical, sealed, white containers; the only difference being the symbol on the label. Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation. Bartlett 2003 (protocol report) page 3 End of trial assessment using questionnaires indicated masking success. Out of those participants taking the placebo tablet, 10% correctly guessed which tablet they were taking, and 10% incorrectly guessed. Out of those taking nutritional supplement, 13% guessed correctly which tablet they were taking, and 7% incorrectly guessed. The remaining participants did not know which group they were randomized to.
Blinding of outcome assessment (detection bias) Progression AMD	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Statistical analysis was carried out on a per protocol basis.

Selective reporting (reporting bias)	High risk	Protocol report: following outcomes listed: visual acuity, contrast sensitivity, colour vision, macular mapping test, glare recovery, fundus photographs analysed by colour and edge analysis software. Trial report only contrast sensitivity (CS) reported: Quote "Outcome measure CS was measured using a Pelli-Robson chart (Clement Clarke International, Edinburgh Way, Harlow, Essex, CM20 2TT, UK) and scored per letter."

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Bibliographic reference	**Berrow 2013** Berrow EJ, Bartlett HE, Eperjesi F, Gibson JM. The effects of a lutein-based supplement on objective and subjective measures of retinal and visual function in eyes with age-related maculopathy -- a randomised controlled trial. British Journal of Nutrition 2013;109(11):2008-14.
Methods	**Parallel group RCT** **Method of allocation**: unclear **Masking:** participant - no; provider - no; outcome - yes **Loss to follow-up**: unclear, either no loss to follow-up or 2/16 (12.5%) loss to follow-up
Participants	**Country**: UK **Number of people randomised**: 14 (14 eyes) **Number (%) of people followed-up**: 14 (100%) (14 eyes) **Average age (range):** 68 years (56 to 83) **Percentage women**: NR **Ethnic group**: Caucasian **Baseline visual acuity**: NR **Comorbidities affecting the eye**: NR

	Percentage current smokers: NR but average 7 pack-years in antioxidant group and 13.5 pack-years in the placebo group **Inclusion criteria:** • best-corrected distance VA of 0·2 LogMAR or better (for good mfERG central fixation) • clear optical media, as determined by a clear view of the fundus • no signs of other retinal or optic nerve disease other than ARM (as determined by fundal photography and questionnaire) in the study eye • good general health (as determined by health questionnaire) • no prescribed medication that could affect the retina (as determined by health questionnaire) **Exclusion criteria:** • moderate-to-dense lens opacities • intraocular lens • corneal opacities • glaucoma or ocular hypertension • previous history of intraocular inflammation • previous history of retinal detachment • retinal disease (other than ARM) • previous retinal laser • diabetes • systemic hypertension • history of ocular trauma • neurological disease • age-related macular degeneration (AMD) in the study eye • drugs causing retinal toxicity • previous ocular surgery • epilepsy
Interventions	**Intervention:** • Ocuvite Duo (Bausch and Lomb) vitamin C 150mg, cupric oxide 400µg, vitamin E 15mg, zinc oxide 20mg, lutein 12mg, zeaxanthin 0.6mg, EPA 240mg, DHA 840mg 8 people randomised (8 eyes) 8 (100%) people followed-up (8 eyes) **Comparator:** • no treatment 6 people randomised (6 eyes) 6 (100%) people followed-up (6 eyes)

	Duration: 40 weeks **Similarity between intervention and comparator**: different because no placebo group
Outcomes	from clinical trial registry entry Primary: • multifocal electroretinogram amplitudes and latencies, assessed every 20 weeks for a period of 80 weeks Secondary: • macular pigment optical density, assessed every 20 weeks for a period of 80 weeks No numeric data on outcomes reported. Quote "All participants undertook VA and CS assessment at all three visits. There were no significant changes between the treated and non-treated groups over 40 weeks for these measures." Follow-up: 40 weeks and 60 weeks Eyes: Quote "Only one eye from each participant was studied.[...] The eye with the best-corrected distance VA was determined at the participant's first visit and this eye was assessed for subsequent visits. If one eye had ARM, this eye was used. If both eyes had ARM, the eye with the best-corrected distance VA was used to ensure good mfERG fixation."
Notes	**Source of funding**: Quote "The authors would like to thank Bausch and Lomb, Kingston-Upon-Thames, Surrey, UK for funding the research position and supplying the Ocuvite Duo nutritional supplement." Declaration of interest: Quote "The authors declare no competing financial interests" Date study conducted: January 2009 to December 2011 Trial registration number: ISRCTN17842302 (retrospectively registered)

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A total of fourteen participants with ARM were randomly allocated, using Microsoft Excel random number generator, to either receive a lutein-based oral supplement (treated group) or no supplement (non-treated group) at visit one."

Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Not clearly reported.
Blinding of participants and personnel (performance bias)Visual acuity	High risk	Judgement Comment: No placebo - control group did not receive any intervention.
Blinding of participants and personnel (performance bias)Progression AMD	High risk	Judgement Comment: No placebo - control group did not receive any intervention.
Blinding of outcome assessment (detection bias)Visual acuity	Unclear risk	Judgement Comment: No placebo - control group did not receive any intervention but study was described as "single masked" so outcome assessors were not aware of group assignment up to 40 weeks when unmasking occurred. However, measurement of visual acuity may be influenced by participants knowledge of intervention.
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Judgement Comment: No placebo - control group did not receive any intervention but study was described as "single masked" so outcome assessors were not aware of group assignment up to 40 weeks when unmasking occurred.
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "A total of fourteen participants with ARM were randomly allocated, using Microsoft Excel random number generator, to either receive a lutein-based oral supplement (treated group) or no supplement (non-treated group) at visit one. These were from an original cohort of sixteen participants, two of which withdrew without giving reason. Only one eye from each" Judgement Comment: Unclear to which group the 2 participants who withdrew had been randomly allocated.
Selective reporting (reporting bias)	High risk	Judgement Comment: Trial was registered retrospectively so not possible to check this. Follow-up at 80 weeks was not reported.

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Bibliographic reference	**CARMA 2013**

	Beatty S, Chakravarthy U, Nolan JM, Muldrew KA, Woodside JV , Denny F, et al. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. Ophthalmology 2013;120(3):600-6.
Methods	**Parallel group RCT** **Method of allocation**: labelled containers **Masking**: participant - yes; provider - yes; outcome - yes **Loss to follow-up**: high attrition after 12 months - 9% follow-up at 3 years
Participants	**Country**: Ireland **Number of people randomised**: 433 (614 eyes) **Number (%) of people followed-up**: at 12 months 493 eyes (80%) ; at 24 months 260 eyes (42%) and at 36 months 58 eyes (9%) **Average age (range):** 74 years (NR) **Percentage women**: 57% **Ethnic group**: NR **Baseline visual acuity**: average 80 letters on logMAR chart **Comorbidities affecting the eye**: NR **Percentage current smokers**: 14% **Inclusion criteria:** • 50 years and older • any severity of early AMD in one eye and late AMD (neovascular AMD or central GA) in the fellow eye. The study eye was the eye free of late-stage AMD. • features of early AMD in at least 1 eye when both eyes were free of late-stage AMD. The minimum severity level was 20 soft distinct or indistinct drusen in the central macular field; if there were fewer than 20 drusen, focal hyperpigmentation was required to be present. Both eyes could be study eyes. • visual acuity of 0.3 logMAR units or better (70 letters or better on the ETDRS chart equivalent to Snellen 20/40) in the eye selected to be study eye

	Exclusion criteria: not explicitly stated
Interventions	**Intervention:** • Ocuvite (Bausch and Lomb, Berlin, Germany) lutein 12mg, zeaxanthin 0.6mg, vitamin E 15mg, vitamin C 150mg, zinc oxide 20 mg, copper 0.4mg (daily dose) one tablet twice daily 216 people randomised (304 eyes) NR (NR%) people followed-up (243 eyes) at 12 months **Comparator:** • Placebo (cellulose microcrystalline, lactose and magnesium stearate) (twice daily) 217 people randomised (310 eyes) NR (NR%) people followed-up (250 eyes) at 12 months **Duration**: Total study duration 3 years but high attrition after 12 months **Similarity between intervention and comparator:** Quote "The placebo consisted of cellulose, lactose, and magnesium stearate and was manufactured to be indistinguishable from the active preparation in size, colour, smell, and taste."
Outcomes	**Primary:** • distance visual acuity Secondary: • retinal visual acuity • morphological progression of AMD (grading of stereoscopic colour fundus photographs) • macular pigment levels and serum levels of antioxidants Follow-up: every 6 months for 3 years but high attrition after 12 months Eyes: mixture of one or two eyes per person (see above for details). Analysed by eye but eyes were not considered independent.
Notes	Source of funding: Quote "Supported by a grant from Bausch and Lomb, Dr. Mann Pharma, Berlin, Germany. The data set was managed and analysed by the independent statistician (MRS) and his team. The senior corresponding author (UC) had full access to the data outputs. The funders had no access to the data, were not involved in the data analysis, and had no role in the construction of the manuscript, except in the approval of the final draft."

	Declaration of interest: Quote "The author(s) have no proprietary or commercial interest in any materials discussed in this article." Date study conducted: June 2004 to April 2008 Trial registration number: ISRCTN94557601 (retrospectively registered)

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Each participant enrolled in the CARMA Study is allocated a unique number, which determines treatment allocation according to the computerized randomization database." " Quote "A block randomization design was used with stratification by center and by group status, and separate block randomized lists were provided to each site."
Allocation concealment (selection bias)	Low risk	Quote "Each participant enrolled in the CARMA Study is allocated a unique number, which determines treatment allocation according to the computerized randomization database." This unique number exists on the identification label of each study preparation box. The masked study-preparation boxes are kept in the hospital pharmacy, and released in a sequential manner by the pharmacist on randomization of each participant, beginning with the first in the numerical series assigned to each clinical center. The participants are advised to take 1 tablet twice daily with a meal. The CARMA Study is strictly a double-masked clinical trial in that neither the CARMA participants nor the study staff, including the study investigator, are aware of the nature of study preparation allocated to the participants. To ensure masking, the study-preparation boxes are labeled with pre-assigned numbers at the site of manufacturing, and then shipped to both clinical centers for distribution. A single pharmacist involved with manufacturing of the study preparation holds the key to randomization of the CARMA supplements."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote "The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all respects from each other." and "Participants and study staff were masked to treatment assignments"
Blinding of participants and personnel (performance bias)	Low risk	Quote "The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all

Progression AMD		respects from each other." and "Participants and study staff were masked to treatment assignments"
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote "The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all respects from each other." and "Participants and study staff were masked to treatment assignments"
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Judgement Comment: Fundus images graded by masked graders and all study personnel masked to intervention allocation
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: High attrition and people with CNV and geographic atrophy excluded from analyses of visual acuity.
Selective reporting (reporting bias)	Low risk	Judgement Comment: Negative primary outcome eventually published (in Ophthalmology) as letter separately from the publication of the positive results in the secondary analysis which appeared as a full paper in the same journal

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Bibliographic reference	**CARMIS 2011** Piermarocchi S, Saviano S, Parisi V, Tedeschi M, Panozzo G, Scarpa G, et al. Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study. European Journal of Ophthalmology 2011;22(2):216-25.
Methods	**Parallel group RCT** **Method of allocation**: random list, unclear how delivered **Masking**: participant - no; provider - no; outcome – unclear **Losses to follow-up**: 18% in supplement group, 38% in no supplement group
Participants	**Country**: Italy **Number of people randomised**: 145 (145 eyes) **Number (%) of people followed-up**: 84 (58%) (84 eyes)

	Average age (range): 73 years (NR) **Percentage women**: 59% **Ethnic group**: NR **Baseline visual acuity**: average 82 letters (ETDRS chart) **Comorbidities affecting the eye**: 30% of intervention group had had cataract surgery but none of the control group **Percentage current smokers**: 17% **Inclusion criteria:** • age 55 to 80 • diagnosis of nonexudative (dry) age-related macular degeneration (AMD) in at least one eye having extensive (as measured by drusen area) intermediate (>= 63 mm, <125 mm) drusen; and at least one large (>=125 mm) drusen or geographic atrophy not involving the center of the macula • best-corrected visual acuity in the trial eye >=20/32 (0.2 logarithm of the minimum angle of resolution [logMAR]), 74 letters of Early Treatment Diabetic Retinopathy Study [ETDRS] chart) • able to understand and comply with the requirements of the trial • no condition limiting view of the fundus (e.g., vitreous hemorrhage, cataracts, epiretinal membrane) • available for a minimum trial duration of approximately 6 months • agree to take only the nutritional supplement that is provided during this study Exclusion criteria: • ocular disease that causes irreversible reduction of visual acuity (amblyopia, uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant macular edema) • lens opacity and score 4+ (Lens Opacity Classification System II) • insufficient pupil dilation • previous laser treatment of the posterior pole for any other reason • macular changes not attributable to AMD • carotenoids intolerance • major chronic disease • life expectation lower than 6 months • withdrawal of informed consent • enrolment in another clinical study with experimental product within the last 4 weeks or during the current study
Interventions	**Intervention:**

	• vitamin C 180 mg, vitamin E 30 mg, zinc 22.5 mg, copper 1 mg, lutein 10 mg, zeaxanthin 1 mg and astaxanthin 4 mg (AZYR SIFI, Catania, Italy) (daily) 103 people randomised (103 eyes) 84 (82%) people followed-up (84 eyes) **Comparator:** • no dietary supplementation 42 people randomised (42 eyes) 26 (62%) people followed-up (26 eyes) Duration: 24 months Similarity between intervention and comparator: different, no placebo group
Outcomes	reported in methods section of paper Primary: • change in BCVA (the number of letters read on the logMAR chart) Secondary: • changes in macular function by CS using a Pelli-Robson chart (Clement Clarke International, Harlow Essex, UK) scored per lines • changes in visual function via the Italian-validated version of the 25-item NEI VFQ-25 reported in results section • multi-focal electroretinograms (ERG) at 6 and 12 months Follow-up: 6, 12 and 24 months Eyes: One eye per person. Quote "When patients fulfilled the inclusion criteria (Tab. I), the eye with the best VA was selected. When both eyes had the same VA, the right eye was chosen for final analysis."
Notes	Source of funding: NR Declaration of interest: Quote "The authors report no proprietary interest or financial support". Date study conducted: December 2003 to September 2006 Trial registration number: NR

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "A permuted blocks allocation scheme was used to perform this random allocation"
Allocation concealment (selection bias)	Unclear risk	Quote "A 24-month prospective open-label randomized study... " Quote "The study coordinator allocated study numbers sequentially, as participants were enrolled. Participants were then randomly allocated to the treatment or no treatment group. A permuted blocks allocation scheme was used to perform this random allocation. The allocation list was stored at a remote site." Quote "Study drug was administered by an unmasked physician who had no other role in the study." No mention was made of allocation ratios but 103 people recruited to treatment group and 42 to no treatment group
Blinding of participants and personnel (performance bias)Visual acuity	High risk	Quote "A 24-month prospective open-label randomized study... "
Blinding of participants and personnel (performance bias)Progression AMD	High risk	Quote "A 24-month prospective open-label randomized study... "
Blinding of outcome assessment (detection bias)Visual acuity	High risk	Quote "A 24-month prospective open-label randomized study... " Quote "In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator." However, as patients were not masked this could have affected the measurement of visual acuity
Blinding of outcome assessment (detection bias)Progression AMD	Unclear risk	Quote "A 24-month prospective open-label randomized study... " Quote "In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator."
Incomplete outcome data (attrition bias)	High risk	Quote "Nineteen people in the group T-AMD, and 16 subjects from the group NT-AMD, were excluded from final data analysis." This exclusion was uneven between 2 groups: 19/103 (18.4%) and 16/42 (38.1%) and also inconsistent with the data in table III, page 6. In table III 14 people withdrew from the carotenoids group and 3 from the control group; 20 people discontinued the intervention in the carotenoids group and 17 in the control group.

Selective reporting (reporting bias)	Unclear risk	Unclear. Fundus examination but progression of AMD was not reported.

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113 **Lutein**

Bibliographic reference	**AREDS2 2013** Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, Clemons TE, Sangiovanni JP, Danis RP, Ferris FL 3rd, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. JAMA Ophthalmology 2014;132(2):142-9.
Methods	**Parallel group RCT** **Method of allocation**: coded tablets **Masking**: participant - yes; provider - yes; outcome - yes Loss to follow-up: Quote "Of the 4203 randomized participants, 141 (3%) were lost to follow-up and 368 (9%) died during the course of the study. Distributions were similar across the 4 treatment groups." Quote "Participants lost to follow-up or who died during the course of the study were censored at the time of last contact." See follow-up data below - 99% of participants were included in the analysis.
Participants	**Country**: USA **Number of people randomised**: 4203 (6916 eyes) **Number (%) of people followed-up**: 4176 (99%) using LOCF (6891 eyes) **Average age (range)**: 74 years (68 to 79) **Percentage women**: 56% **Ethnic group**: 97% white **Baseline visual acuity**: average 78 letters on EDTRS chart **Comorbidities affecting the eye**: 25% bilateral pseudophakic, 13% with diabetes

	Percentage current smokers: 7% **Inclusion criteria**: • high risk of progression to advanced AMD with either bilateral large drusen or non-foveal geographic atrophy (no advanced AMD) or large drusen or non-foveal geographic atrophy in one eye and advanced AMD in the fellow eye (AREDS Simple Scale Score of 2, 3 or 4) • age 50 to 85 years • took at least 75% of study medication during the run-in phase • able and willing to consent to both the qualification and the randomisation/follow-up phases of the study • likely, willing and able to undergo yearly examinations for at least five years • agreed to stop current use of supplements containing lutein, zeaxanthin, omega-3 LCPUFAs (specifically DHA+EPA), vitamin C, vitamin E, beta-carotene, zinc or copper, other than those supplied by AREDS2 • fundus photographs of adequate quality as assessed with a standardized protocol by the Reading Center (University of Wisconsin Fundus Photograph Reading Center) • randomized within three months following the qualification visit **Exclusion criteria:** • the presence of ocular disease in either eye that may have confounded evaluation of the retina • previous retinal or other ocular surgical procedures (other than cataract extraction) that may have complicated assessment of the progression of AMD • a chronic requirement for any systemic or ocular medication administered for other diseases and known to be toxic to the retina or optic nerve • previous daily supplementation with 2mg or more of lutein and/or 500 mg or more of omega-3 LCPUFAs for a period of 1 year or more prior to the date of randomization (A participant was eligible for the study if he/she agreed to stop taking these supplements during the study run-in period) • intraocular pressure of 26 mm Hg or higher or some reason to believe that the participant might have glaucoma • cataract surgery within 3 months or capsulotomy within 6 weeks prior to the qualification visit history of lung cancer • any systemic disease with a poor five year survival prognosis • hemochromatosis • Wilson’s disease • recent diagnosis of oxalate kidney stones • any condition that would make adherence or follow-up difficult or unlikely • current participation in other studies that might affect adherence to the AREDS2 follow-up schedule • use of systemic anti-angiogenic therapy for treatment of choroidal neovascularization or cancer

Interventions	**Intervention**: • lutein 10mg and zeaxanthin 2mg (1 tablet/day) 2123 people randomised (3468 eyes) 2107 (99%) people followed-up (3451 eyes) **Comparator**: • placebo (1 tablet/day) 2080 people randomised (3448 eyes) 2069 (99%) people followed-up (3440 eyes) Almost all participants in both intervention and comparator groups took AREDS supplement and multivitamin with the study medication. **Duration**: 5 years (median) **Similarity between intervention and comparator**: The placebo was composed from free flowing corn starch-coated matrix of bead lets formed into a tablet of identical shape, size, and coating/internal colour (using the same quantity of colouring agents) as that containing lutein+zeaxanthin. **Other study arm**: There was another study arm looking at docosahexaenoic acid (DHA) 350mg and eicosapentaenoic acid (EPA) 650mg (2 soft-gel capsules/day) not included in this review
Outcomes	**Primary**: • progression to advanced AMD in people at moderate to high risk for progression **Secondary**: • progression to moderate vision loss • adverse events • progression of lens opacity or incidence of cataract surgery • effect of study supplements on cognitive function • effect of DHA/EPA on cardiovascular morbidity and mortality **Follow-up**: annual follow-up for 5 years

	Eyes: Quote "The unit of analysis for ophthalmic outcomes was by eye. The primary efficacy outcome, time to progression to advanced AMD, was assessed using a Cox proportional hazards model incorporating the method of Wei et al for obtaining robust variance estimates that allows for dependence among multiple event times (1 or 2 study eyes)."
Notes	Source of funding: Quote "This study is supported by the intramural program funds and contracts from the National Eye Institute/National Institutes of Health (NEI/NIH), Department of Health and Human Services, Bethesda, MD. Contract No. HHS-N-260-2005-00007-C. ADB Contract No. N01-EY-5-0007. Funds were generously contributed to these contracts by the following NIH institutes: Office of Dietary Supplements (ODS), National Center for Complementary and Alternative Medicine (NCCAM), National Institute on Aging (NIA), National Heart, Lung and Blood Institute (NHLBI), and National Institute of Neurological Disorders and Stroke (NINDS)" Declaration of interest: Quote "A complete list of all AREDS2 investigator financial disclosures, which were collected for regulatory purposes, pursuant to US FDA regulations in 21 CFR Part 54, can be found at www.areds2.org. The member(s) of the writing committee have made the following disclosure(s): Frederick L. Ferris III; Bausch & Lomb (P) and the remainder had no conflicts of interest." Date study conducted: September 2006 to October 2012 (from clinical trials.gov entry) Trial registration number: NCT00345176

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A random block design was implemented using the AREDS2 Advantage Electronic Data Capture system (Advantage EDC SM) by the AREDS2 Coordinating Centre (The EMMES Corporation, Rockville, Maryland) and stratified by clinical centre and AMD status (large drusen both eyes or large drusen in one eye and advanced AMD in the fellow eye) to assure approximate balance across centres over time."
Allocation concealment (selection bias)	Low risk	Judgement Comment: Central co-ordinating centre organised the random allocation and placebo controlled study
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Judgement Comment: Placebo controlled trial. Personnel measuring visual acuity unaware of allocation.

		Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Judgement Comment: Placebo controlled trial. Fundus images graded by masked graders. Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Judgement Comment: Placebo controlled trial. Personnel measuring visual acuity unaware of allocation. Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Judgement Comment: Placebo controlled trial. Fundus images graded by masked graders. Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."
Incomplete outcome data (attrition bias)	Low risk	Quote "Of the 4203 randomized participants, 141 (3%) were lost to follow-up and 368 (9%) died during the course of the study. Distributions were similar across the 4 treatment groups."
Selective reporting (reporting bias)	Low risk	Judgement Comment: AMD outcomes pre-specified on clinical trials registry and in published protocol paper were reported

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Bibliographic reference	**CLEAR 2013** Murray IJ, Makridaki M, van der Veen RL, Carden D, Parry NR, Berendschot TT. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. Investigative Ophthalmology and Visual Science 2013;54(3):1781-8.
Methods	**Parallel group RCT** **Method of allocation**: coded tablets prepared by manufacturer **Masking**: participant - yes; provider - yes; outcome - yes

	Loss to follow-up: 13%
Participants	**Country**: The Netherlands and the UK **Number of people randomised**: 84 (84 eyes) **Number (%) of people followed-up**: 73 (87%) (73 eyes) **Average age (range)**: 71 years (NR) **Percentage women**: 61% (56% in intervention group 67% in control group) **Ethnic group**: NR **Baseline visual acuity**: average 0.1 logMAR intervention group and 0.05 logMAR in control group respectively **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria:** • 50 to 80 years • AMD grade 0 to 4 in one eye (Rotterdam grading) • best corrected visual acuity (BCVA) of LogMAR 0.5 or better • minimal cataract. **Exclusion criteria:** • any ophthalmic disorder, such as diabetic retinopathy; optic atrophy; pigmentary abnormalities considered by the investigating ophthalmologist to be less typical of AMD than of some other condition (e.g., myopia); • history of glaucoma • any dietary supplements containing lutein, zeaxanthin or meso-zeaxanthin within 3 months of the start of the study. • unable to understand the study procedures or unable to give informed consent
Interventions	**Intervention:** • lutein 10mg (daily) 42 people randomised (42 eyes) 36 (86%) people followed-up (36 eyes) **Comparator:**

	• placebo soya bean oil (daily) 42 people randomised (42 eyes) 37 (88%) people followed-up (37 eyes) **Duration**: 12 months **Similarity between intervention and comparator**: Quote "The [..] capsules and their packaging were completely indistinguishable"
Outcomes	**Primary:** • not described in paper but main aim was to investigate effects on MPOD and VA **Secondary:** • not described in paper Quote "Other measurements conducted as part of the study were scanning laser ophthalmoscope (SLO)–based MPOD, retinal reflectometry–based MPOD, dark adaptometry, optical coherence tomography (OCT), and ocular scatter. These data will be described in separate reports." from clinical trials registry entry (but note retrospectively registered) Primary Outcome Measures: Macular Pigment Optical Density [Time Frame: Baseline, 4 months, 8 months, 12 months] [Designated as safety issue: No]Secondary Outcome Measures: Visual Acuity [Time Frame: Baseline, 4 months, 8 months, 12 months] [Designated as safety issue: No] **Follow-up:** 3, 8 and 12 months **Eyes**: one eye per person unclear how selected Quote "According to the inclusion criteria, a ‘‘test eye’’ was allocated to each patient and data from only this eye were analysed".
Notes	Source of funding: Quote "Supported partly by BASF, the UK Medical Research Council, the Manchester Biomedical Research Centre, and the Greater Manchester Comprehensive Local Research Network." Declaration of interest: All authors reported no declaration of interest Date study conducted August 2007 to August 2009 (from clinical trials registry entry) Trial registration number: NCT01042860 (registered retrospectively)

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization code was generated by the sample manufacturer. Treatment numbers were allocated in ascending order using the next available consecutive number and capsules distributed accordingly." Judgement Comment: Unclear how code was generated but we have assumed it was unpredictable.
Allocation concealment (selection bias)	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups."
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups"
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups"
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups"
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups"
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Follow-up high and similar between lutein (86%) and placebo groups (88%).
Selective reporting (reporting bias)	Low risk	Judgement Comment: Outcomes in trials registry entry were reported.

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Bibliographic reference	**Huang 2015**

	Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lu XR, et al. Changes following supplementation with lutein and zeaxanthin in retinal function in eyes with early age-related macular degeneration: a randomised, double-blind, placebo-controlled trial. British Journal of Ophthalmology 2015;99(3):371-5.
Methods	**Parallel group RCT** **Method of allocation**: unclear **Masking**: participant - yes; provider - yes; outcome - yes **Loss to follow-up**: unclearly reported
Participants	**Country**: China **Number of people randomised**: 112 (NR eyes) **Number (%) of people followed-up**: 108 (96%) (NR eyes) **Average age (range):** 69 years (NR) **Percentage women**: 57% **Ethnic group**: NR **Baseline visual acuity**: average 0.32 logMAR **Comorbidities affecting the eye**: 23% had early cataract **Percentage current smokers:** 7% **Inclusion criteria:** • clinical diagnosis of early AMD (defined as the presence of soft drusen, presence of retinal pigmentary abnormalities with no signs of late AMD, or both) according to the Age-Related Eye Disease Study System • clear ocular media • agreement to adhere to the study regimen
	Exclusion criteria: • ocular disorders • unstable systemic or chronic illness • consumed dietary supplements containing antioxidants or carotenoids within the previous 6 months

Interventions	**Intervention:** • lutein 10mg or lutein 20mg or lutein 10mg and zeaxanthin 10mg (3 groups) (daily) NR people randomised (NR eyes) 80 (%) people followed-up (NR eyes) **Comparator:** NR people randomised (NR eyes)28 (%) people followed-up (NR eyes) **Duration**: 24 months **Similarity between intervention and comparator**: Quote "All the supplements were packaged identically with the same labels." But unclear how the placebo was made
Outcomes	**Primary:** • VFQ (Chinese version) **Secondary:** • not specifically reported but reported contrast sensitivity, visual acuity, MPOD, **Follow-up:** 24 weeks, 48 weeks and 24 months **Eyes**: unclear
Notes	**Source of funding**: Quote "The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Grant no. 81273063)." Declaration of interest: NR Date study conducted: : NR Trial registration number: NCT10528605 (registered retrospectively)

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "for randomization, the sequence was computer generated in a 1: 1: 1: 1 ratio within permuted blocks of size 8."

Allocation concealment (selection bias)	Low risk	Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 112 patients randomised. 4 excluded due to DNA. Remainder analysed
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: No access to trial protocol and trial was registered retrospectively.

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Bibliographic reference	**Veterans LAST study 2004** Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, Rudy D, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry 2004;75(4):216-30.
Methods	**Parallel group RCT** **Method of allocation**: coded bottles **Masking**: participant - yes; provider - yes; outcome – yes **Losses to follow-up**: 7 withdrew, 4 lost to follow-up, 3 died. Slightly lower % follow-up in group 2 (lutein/antioxidant) 80% compared with other 2 groups (lutein alone 86% placebo 87%).
Participants	**Country:** USA

	Number of people randomised: 90 (NR eyes) **Number of people followed-up**: 76 (84%) (NR eyes) **Average age (range)**: approximate 75 years **Percentage women**: 4% **Ethnic group**: NR **Baseline visual acuity**: average ranged from 0.279 to 0.445 logMAR by eye and treatment group **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria**: • atrophic AMD diagnosed by ophthalmoscopy • at least one visual abnormality reduced contrast sensitivity, photo-stress glare recovery deficit or deficit on Amsler grid • clear ocular media • free of any other ocular/systemic disease that could affect central or parafoveal macular visual function. **Exclusion criteria:** • cataract or retinal surgery within 6 months • photosensitising drugs • taken lutein supplements within the previous 6 months
Interventions	**Intervention**: • lutein 10 mg non-esterified lutein (FloraGlo from Kemin Foods International, Des Moines, Iowa) 29 people randomised (NR eyes) 25 (86%) people followed-up (NR eyes) • lutein plus additional antioxidants and nutrients (OcuPower, Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida) 30 people randomised (NR eyes) 24 (80%) people followed-up (NR eyes) **Comparator:** • placebo, maltodextrin

	31 people randomised (NR eyes) 27 (87%) people followed-up (NR eyes) **Duration**: 12 months Ocupower had a range of nutrients including lutein, vitamin A, beta-carotene, vitamins C, D3, E, B1, B2, B3, B5, B6, B12, folic acid, biotin, calcium, magnesium, iodine, zinc copper, manganese, selenium, chromium, molybdenum, lycopene, bilberry extract, alpha lipoic acid, N-acetyl cysteine, quercetin, rutin, citrus bioflavonoids, plant enzymes, black pepper extract, malic acid, taurine, L-glycine, L-glutathione, boron **Similarity between intervention and comparator**: Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food"
Outcomes	Primary: • macular pigment optical density Secondary: not specified The following clinical measurements were made: lens opacity; retinal images; Macular Pigment Optical Density (MPOD); visual acuity (Snellen) distance and near; glare testing; glare recovery; contrast sensitivity; VFQ-14 (activities of daily living, night driving, glare recovery symptoms); Amsler grid; self reported vision It was difficult to extract data on outcomes of relevance to this review: i.e. visual acuity and progression of AMD. Follow-up: 12 month Eyes: reported right and left eyes separately
Notes	**Source of funding**: Quote "This material is based on work supported by the DVA Medical Center, North Chicago, Illinois and the Department of Veteran's Affairs, Hines, Illinois." Quote "Grant sponsors are Kemin Foods, Inc. (Des Moines, Iowa); L/itacost.com, with its subsidiary Nutraceutical Sciences Institute (NSI: Boynton Beach, Florida); and Great Smokies Diagnostic Laboratory (Asheville, North Carolina). FloraGloB non-esterified lutein is a product of Kemin Foods. The FloraGloB lutein antioxidant supplement evaluated is known as OcuPower@, U.S. Patent #6,103,756-Wayne Gorsek, inventor; L/itacost.com assignee." Declaration of interest: NR Date study conducted: August 1999 to May 2001 Trial registration number: NR

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "... were randomly assigned to one of three capsule groups by consecutive random card-3-choice, allocation sequence" Page 217
Allocation concealment (selection bias)	Low risk	Quote "Nutraceutical Sciences Institute prepared the lutein capsules, the L/A capsules, and the P capsules and also maintained and concealed the blinding and four-digit allocation codes." Page 218 All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food.
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: Loss to follow-up 14/90: Lutein 10 mg group n = 29 • 1 person lost to follow-up • 1 person died • 2 other withdrawals

		Lutein 10 mg and antioxidant group n = 30 • 2 persons lost to follow-up • 4 other withdrawals Placebo group n = 31 • 1 persons lost to follow-up • 1 person died • 1 other withdrawals Members of placebo group removed from analysis due to the fact that they had taken lutein
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: Difficult to assess with the information available

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122 **Zinc supplements**

Bibliographic reference	**Newsome 1988** Newsome DA, Swartz M, Leone NC, Elston RC, Miller E. Oral zinc in macular degeneration. Archives of Ophthalmology 1988;106(2):192-8.
Methods	**Parallel group RCT** **Method of allocation**: computer-generated table of random numbers **Masking**: participant - yes; provider - yes; outcome – yes **Losses to follow-up**: 23 (10 treatment, 13 placebo)
Participants	**Country**: USA **Number of people randomised**: 174 (NR eyes) **Number (%) of people followed-up**: 151 (87%) (258 eyes) **Average age (range):** NR (42 to 89 years) **Percentage women**: 65%

	Baseline visual acuity: NR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria:** macular degeneration: clinically visible drusen with varying degrees of pigmentary change with visual acuity in 1 eye of 20/80 or better **Exclusion criteria:** cataract reducing vision more than one line; other known serious eye disease; diabetes mellitus; other known systematic/metabolic disease or congenital condition which might interfere with results
Interventions	**Intervention:** • zinc sulfate 200 mg (daily) 1 x 100mg twice daily 90 people randomised (NR eyes) 80 (89%) people followed-up (134 eyes) **Comparator:** • placebo 84 people randomised (NR eyes) 71 (85%) people followed-up (124 eyes) Duration: 1 to 2 years Similarity between intervention and comparator: Quote "Identical apprearing tablets containing lactose and fructose served as the placebo" Analyses were also stratified according to number of eyes per person.
Outcomes	Primary: not specified Secondary: not specified Outcomes reported in paper: • Pinhole corrected visual acuity using ETDRS charts • changes in visible pigment, drusen or atrophy from grading of macular photographs • adverse effects of zinc including copper deficiency anaemia

	Follow-up: 6, 12, 18 and 24 months Eyes: Some people had one eye enrolled in the study and some had two eyes Quote "To analyze the results of two eyes of the same participant, the individual eye data were averaged and that value was used"
Notes	**Source of funding**: Research Fund, Department of Veterinary Science, Utah State University, Logan; James L Shupe, DVM; Mary Katherine Peterson Foundation, Houston Declaration of interest: NR Date study conducted: NR Trial registration number: NR

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Subjects were randomly assigned [...] using a computer-generated table of random numbers."
Allocation concealment (selection bias)	Low risk	Quote "Subjects were randomly assigned to receive either zinc or placebo [...]. The individual who recorded the zinc-treated or placebo group assignment maintained personal control over the randomization sheet and participated in no other phases of the study. This individual also handed the study tablets to subjects. All other personnel were masked to the study."
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "All other personnel were masked to the study." Quote "Zinc sulfate was prepared as white tablets containing 100 mg of United States Pharmacopeia-graded material. Identical-appearing tablets containing lactose and fructose served as the placebo. All tablets were bottled in identical containers."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "All other personnel were masked to the study." Quote "Zinc sulfate was prepared as white tablets containing 100 mg of United States Pharmacopeia-graded material. Identical-appearing tablets containing lactose and fructose served as the placebo. All tablets were bottled in identical containers."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "All visual acuities were determined by one of two masked observers throughout the study" page 192

Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "Two independent observers masked as to patient identity,..."
Incomplete outcome data (attrition bias)	Low risk	A total of 90 subjects [...] were randomized to zinc and 84 subjects [...] to placebo. [.....]. A total of ten subjects were lost to follow-up from the zinc-treated group and 13 subjects from the placebo group. [...] This figure represents dropout rates of 11.1% and 15.4% from the zinc-treated and placebo groups, respectively page 193 Reasons for loss to follow-up zinc/placebo (page 194 table 1) • Stopped taking pills 5/6 • Started taking zinc 1/2 • Gastrointestinal symptoms 1/0 • Died 2/1 • Poor compliance 0/1 • Developed diabetes mellitus 0/1 • Unavailable 1/2
Selective reporting (reporting bias)	High risk	Other ocular functions assessed included ocular vision and photostress recover tests (These observations are being analysed and will be reported later)

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Bibliographic reference	**Stur 1996** Stur M, Tittl M, Reitner A, Meisinger V. Oral zinc and the second eye in age-related macular degeneration. Investigative Ophthalmology and Visual Science 1996;37(7):1225-35.
Methods	**Parallel group RCT** **Method of allocation**: sponsor prepared coded bottles **Masking**: participant - yes; provider - yes; outcome - yes **Losses to follow-up**: 6 withdrawn due to adverse gastrointestinal effects (4 treatment, 2 control); 14 withdrawn when developed neovascularisation (9 treatment, 5 control); 14 lost to follow-up (6 treatment, 8 control)
Participants	**Country**: Austria **Number of people randomised**: 112 (112 eyes) **Number (%) of people followed-up**: 92 (82%) (92 eyes); 78 (70%) (78 eyes) included the analyses because eyes that developed CNV were excluded

	Average age (range): 71 years (50 to NR) **Percentage women**: 57% **Ethnic group**: NR **Baseline visual acuity:** average 0.075 logMAR **Comorbidities affecting the eye**: NR **Percentage current smokers**: 21% **Inclusion criteria:** • exudative AMD in 1 eye (defined as angiographic evidence of classic or occult choroidal neovascularisation or RPE detachment) and early ARM with visual acuity 20/40 or better in other eye (early ARM: macular drusen with no angiographic evidence of exudative lesion) **Exclusion criteria:** • dense senile cataract • any other eye disease which could produce significant and permanent loss of visual acuity during follow-up • physical status that could prevent follow-up; history of serious systemic or metabolic disease
Interventions	**Intervention:** • zinc sulfate 200 mg (daily) 1 tablet 56 people randomised (56 eyes) NR (%) people followed-up but 37 (37 eyes) included in the analyses excluding eyes that developed CNV **Comparator:** • placebo 1 tablet people randomised (x eyes) NR (%) people followed-up but 41 (41 eyes) included in the analyses excluding eyes that developed CNV Duration: 24 months Similarity between intervention and comparator: Intervention was lemon flavoured effervescent tablet made of citric acid containing saccharine and sorbitol and placebo was as for treatment but without the zinc sulfate
Outcomes	**Primary:** not specified **Secondary**: not specified

	Outcomes reported in paper: Best-corrected LogMAR visual acuity measured using Bailey-Lovie chart; contrast sensitivity; incidence of choroidal neovascularisation; progression of disease (Wisconsin Age-related Maculopathy Grading System); copper deficiency anaemia **Follow-up**: 6, 12, 18 and 24 months Eyes: One eye per person, CNV in one eye and not in the fellow eye. The fellow eye was the "study eye"
Notes	A priori sample size estimate was 500 patients but trial stopped early because interim analysis showed no detectable trend Funders: Astra, Linz, Austria; Austrian Foundation for the Propagation of Scientific Research Source of funding: Quote "Supported in part by the Austrian Foundation for the Propagation of Scientific Research (Ostetreichischer Fonds zur Forderung der xuissenschaftlichen Forschung), Project 7215-MED." Quote "The authors thank the staff at Astra GmbH, Linz, Austria, for providing the coded doses of zinc sulfate and placebo." Declaration of interest: Quote "Proprietary interest category: N" Date study conducted: March 1990 to June 1992 Trial registration number: NR

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Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "This was a double-masked, randomized, placebo-controlled study conducted at a single center. The randomization between zinc and placebo was performed in a ratio 1:1" Page 1228 Judgement Comment: No details provided of method of sequence generation, however since coding provided by sponsor this is unlikely to be a source of bias
Allocation concealment (selection bias)	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group

		doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."

Incomplete outcome data (attrition bias)	High risk	Quote "One hundred twelve patients were enrolled between March 1, 1990 and June 30, 1992. Six patients (four in the treatment group, two in the placebo group) could not tolerate the medication because of gastrointestinal side effects and had to be withdrawn from the study. Fourteen patients did not return for the scheduled follow-up visits or decided to withdraw from the study because of personal reasons. The withdrawal of these 14 patients was not connected to any side effects of the study medication. The rest of the recruited patients (92 patients) returned for all required visits." Quote "During the treatment period, a CNV developed in the study eye in 14 patients (nine in the treatment group, five in the placebo group). Ten of these patients underwent laser treatment and were withdrawn from the study."
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

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Bibliographic reference	**Wang 2004** Wang H, Li RX, Wang MF. Effects of zinc and antioxidant on visual function of patients with age-related macular degeneration. Zhongguo Linchuant Kangfu 2004;8:1290-1.
Methods	**Parallel group RCT** **Method of allocation**: unknown **Masking**: participant - unknown; provider - unknown; outcome – unknown **Losses to follow-up**: unknown
Participants	**Country**: China **Number of people randomised**: 400 (400 eyes) **Number of people followed-up**: NR **Average age (range):** 65 years (52 to 76) **Percentage women**: 53% **Ethnic group**: NR **Baseline visual acuity:** NR

	Comorbidities affecting the eye: NR **Percentage current smokers**: NR
Interventions	**Intervention:** • zinc oxide 80 mg daily, vitamin C, vitamin E NR people randomised (NR eyes) NR (%) people followed-up (NR eyes) **Comparator:** • placebo NR people randomised (NR eyes) NR (%) people followed-up (NR eyes) Duration: 24 to 32 months Similarity between intervention and comparator: NR
Outcomes	Primary: not specified Secondary: not specified Outcomes: visual acuity, early and late AMD Follow-up: every 6 months for 24 to 32 months Eyes: one eye per person, worse eye was selected
Notes	Limited information available on this trial. AMD patients were stratified into early and late-stage disease Source of funding: NR Declaration of interest: NR Date study conducted: NR Trial registration number: NR

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)Visual acuity	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)Progression AMD	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)Visual acuity	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)Progression AMD	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Visual acuity was measured but not reported, possible because of non-significant results

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E.3 Diagnosis

E.3.1 Signs and symptoms of AMD

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

Bibliographic reference	Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012
Country/ies where the study carried out	Denmark
Aim of the study	The introduction of vascular endothelial growth factor inhibitors for the treatment of exudative age-related macular degeneration (AMD) has increased the referral rates of AMD patients with visual symptoms to treating centres considerably. However, a large proportion of the referred patients do not qualify for treatment implying that considerable resources could be saved if these patients could be identified on the basis of the clinical data available in the referring nonspecialized setting. This study sought to find the association between said clinical data and treatable choroidal neovascularisation.
Study type	Prospective cohort study
Study dates	Published 2012
Source of funding	VELUX foundation
Sample size	1,683 consecutive patients
Inclusion Criteria	All patients referred to the AMD clinic at the Department of Ophthalmology, Arhus University Hospital between 1 January 2007 and 31 October 2009.
Exclusion Criteria	None described
Diagnostic criteria	The patients underwent structured interviewing to record the time of occurrence and the duration of the following symptoms: blurred vision, central dark spot, metamorphopsia, micropsia, and dyschromatopsia.
Patient characteristics	Study did not report baseline characteristics for ethnic group, age, gender, visual acuity, refractive myopia, AMD disease stage, Comorbidities affecting the eye (e.g. cataracts) or other co-morbidities. Visual acuity (ETDRS steps ± SD) was 57.4 ± 16.7 in the treatment group and 63.1 ± 20.8 in the non-treatment group
Methods	The clinical examination consisted of a measurement of the visual acuity using ETDRS charts and fundoscopy of the retina using a 90-D lens to identify central macular oedema, retinal haemorrhages, and exudates. In all patients, an OCT scanning (Top-con 3D OCT-1000; Topcon Inc, Paramus, NJ, USA) was carried out. When macular oedema was present, a fluorescein angiography was performed using a Canon CF-1 angiography system. The angiography was analysed by a senior consultant to classify the patients as having classic, predominantly classic, minimally classic, or occult subretinal neovascularization, or

Bibliographic reference	**Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012**
	none of these alternatives. In case of discrepant opinions about the interpretation of the angiography, the opinion of the most experienced consultant in the clinic was followed. Treatable Neovascularisation: In cases with overt or suspected subretinal neovascularization, intravitreal injection of VEGF inhibitor was commenced. Patients with visual acuity below 0.05 and with significant preretinal fibrosis are excluded from treatment. In the remaining patients, OCT is performed to exclude patients with no signs of retinal oedema. The remaining patients are subjected to fluorescein angiography, and cases with early leakage because of overt or suspected subretinal neovascularization are included for treatment.
Results	Blurred Vision <table><tr><td></td><td>REFERENCE test result</td><td></td></tr><tr><td>INDEX test result</td><td>+ve for target condition</td><td>-ve for target condition</td></tr><tr><td>+ve for target condition</td><td>462</td><td>834</td></tr><tr><td>-ve for target condition</td><td>94</td><td>293</td></tr></table> Sensitivity = 0.831 Specificity = 0.260 PPV = 0.356 NPV = 0.757 Diagnostic accuracy = 0.449 Central Dark Spot <table><tr><td></td><td>REFERENCE test result</td><td></td></tr><tr><td>INDEX test result</td><td>+ve for target condition</td><td>-ve for target condition</td></tr><tr><td>+ve for target condition</td><td>257</td><td>360</td></tr><tr><td>-ve for target condition</td><td>299</td><td>767</td></tr></table> Sensitivity = 0.462 Specificity = 0.681 PPV = 0.417

Bibliographic reference	Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012

NPV = 0.720
Diagnostic accuracy =0.608

Metamorphosia

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	282	452
-ve for target condition	274	675

Sensitivity = 0.507
Specificity = 0.599
PPV = 0.384
NPV = 0.711
Diagnostic accuracy = 0.569

Micropsia

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	54	124
-ve for target condition	502	1003

Sensitivity = 0.097
Specificity = 0.890
PPV = 0.303
NPV = 0.666
Diagnostic accuracy = 0.628

Dyschromatopsia

Bibliographic reference	Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	102	128
-ve for target condition	454	999

Sensitivity = 0.183
Specificity = 0.886
PPV = 0.443
NPV = 0.688
Diagnostic accuracy = 0.654

Sudden Onset

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	200	310
-ve for target condition	356	817

Sensitivity = 0.360
Specificity = 0.725
PPV = 0.392
NPV = 0.697
Diagnostic accuracy = 0.604

Worsening of symptoms

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	343	606

Bibliographic reference	Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012
	-ve for target condition | 213 | 521 Sensitivity = 0.617 Specificity = 0.462 PPV = 0.361 NPV = 0.710 Diagnostic accuracy = 0.513
Limitations	QUADAS 2 diagnostic study checklist DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Consecutive Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: LOW B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW DOMAIN 2: INDEX TEST(S) A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? Unclear B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: HIGH: Unclear definitions DOMAIN 3: REFERENCE STANDARD Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (unlikely) Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW

Bibliographic reference	Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012
	B. Concerns regarding applicability Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: HIGH - People defined as not being treatable for neovascular AMD included those with visual acuity below 0.05 and with significant pre-retinal fibrosis, also the patients excluded from treatment in this study represented a heterogeneous group of fundus morphologies, including both atrophic AMD, pigment epithelial detachment alone, and exudative AMD with severe visual loss and/or signs of irreversible retinal damage. DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes (same flow of tests) Did patients receive the same reference standard? Yes (same flow of tests) Were all patients included in the analysis? Yes

E.3.2 Tools for triage, diagnosis and informed treatment

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

Bibliographic reference	**Cachulo,L., Silva,R., Fonseca,P., Pires,I., Carvajal-Gonzalez,S., Bernardes,R., Cunha-Vaz,J.G., Early markers of choroidal neovascularization in the fellow eye of patients with unilateral exudative age-related macular degeneration.Ophthalmologica, 225, 3, 144-149, 2011.**
Country/ies where the study carried out	USA
Study type	Prospective cohort study
Aim of the study	To identify morphological and/or functional early markers of choroidal neovascularization (CNV) development in fellow eyes of patients with exudative age-related macular degeneration (AMD).
Study dates	Not stated
Sources of funding	Not stated
Number of patients	62 patients
Inclusion criteria	Patients were older than 50 years of age Both gender Patients were able to give written consent to make the required visits and to follow instruction Patients had clinical diagnosis of wet AMD in one eye (non-study eye) and the presence of the following characteristics in the second eye (study eye): at least 5 or more intermediate (>63µm) or 1 large soft drusen (>125µm), and /or confluent drusen within 3,000µm of the foveal centre with or within pigmentary changes
Exclusion criteria	Patients had current or past history of a medical condition that would preclude scheduled study visits or completion of the study Patients had current or post history of an ophthalmic disease in the study eye (other than AMD) that would likely compromise the visual acuity of the study eye; Patient had clinical signs of myopic retinopathy or refractive power of >8dpt or funduscopic evidence of degenerative myopia; Patients had past history if intraocular surgery within 60 days prior to enrolling in the study Patients had evidence of past or present CNV in the study eye
Eligible participants characteristics	62 patients were enrolled in the study. 52 patients completed the 2-year follow up Mean age (SD): 76 (6) years No. of men: 26 (50%)

<table>
<tr><th>Bibliographic reference</th><th>Cachulo,L., Silva,R., Fonseca,P., Pires,I., Carvajal-Gonzalez,S., Bernardes,R., Cunha-Vaz,J.G., Early markers of choroidal neovascularization in the fellow eye of patients with unilateral exudative age-related macular degeneration.Ophthalmologica, 225, 3, 144-149, 2011.</th></tr>
<tr><td>Type of test</td><td>Indocyanine green angiography (ICG)
Optical coherence tomography (OCT)
Fundus autoflurescence (FAF)
Imaging and retinal leakage analysis (RLA)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography</td></tr>
<tr><td>Prevalence</td><td>33% of the 52 study eyes (17 eyes) were confirmed with CNV
<table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>ICG</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>9</td><td>7</td><td>16</td></tr>
<tr><td></td><td>Negative</td><td>8</td><td>28</td><td>36</td></tr>
<tr><td></td><td>Total</td><td>17</td><td>35</td><td>52</td></tr>
</table>
<table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>FAF</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>15</td><td>2</td><td>17</td></tr>
<tr><td></td><td>Negative</td><td>2</td><td>33</td><td>35</td></tr>
<tr><td></td><td>Total</td><td>17</td><td>35</td><td>52</td></tr>
</table>
<table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>RLA</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>13</td><td>8</td><td>21</td></tr>
<tr><td></td><td>Negative</td><td>1</td><td>27</td><td>28</td></tr>
<tr><td></td><td>Total</td><td>14 (as examination could not be processed in 3)</td><td>35</td><td>49</td></tr>
</table></td></tr>
<tr><td>Sensitivity</td><td>
<table>
<tr><td>ICG</td><td>52.9%, 95%CI 29.9 to 75.3%</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Cachulo,L., Silva,R., Fonseca,P., Pires,I., Carvajal-Gonzalez,S., Bernardes,R., Cunha-Vaz,J.G., Early markers of choroidal neovascularization in the fellow eye of patients with unilateral exudative age-related macular degeneration.Ophthalmologica, 225, 3, 144-149, 2011.
	FAF: 88.2%, 95%CI 69.8 to 98.4% OCT: - RLA: 92.8%, 95%CI 75.3 to 99.8%
Specificity	ICG: 80.0%, 95%CI 65.5 to 91.3% FAF: 94.3% 95%CI 84.7 to 99.3% OCT: - RLA: 77.1%, 95%CI 62.1 to 89.3%
Positive predictive values	ICG: 56.3%, 95%CI 32.3 to 78.7% FAF: 88.2%, 95%CI 69.8 to 98.4% OCT: - RLA: 61.9%, 95% CI 40.8 to 80.9%
Negative predictive values	ICG: 80.6%, 95%CI 70.0 to 89.4% FAF: 94.3%, 95%CI 84.7 to 99.3% OCT: - RLA: 96.4%, 95% CI 87.2 to 99.9%
Comments	Different imagings including OCT, ICG were evaluated for the development of CNV and the progression of early ARM to neovascular AMD Patient selection: Population eligiability was pre-defined (all included participants had a clinical diagnosis of wet AMD in one eye [non-study eye]). Patients satisfying the enrolment criteria completed the baseline/screening assessment and were follow-up for up to 24 months with repeated ophthalmic and imaging assessment performed at 6-month intervals. Patients developing CNV during the study were followed up for 6 months after the conversion to wet AMD and were treated at the discretion of the principlan investigator. Index test: blinding of index test was unclear. Reference standard: blinding of reference standard was unclear. Flow and timing: Patients were examined 6 months, but time intervals of tests were unclear. All patients included in the analysis.

<table>
<tr><th>Bibliographic reference</th><th>Cheung,C.M., Laude,A., Wong,W., Mathur,R., Chan,C.M., Wong,E., Wong,D., Wong,T.Y., Lim,T.H., 20151209 Improved specificity of polypoidal choroidal vasculopathy diagnosis using a modified everest criteria.Retina, 35, 7, 1375-1380, 2015</th></tr>
<tr><td>Country/ies where the study carried out</td><td>Singapore</td></tr>
<tr><td>Study type</td><td>Retrospective comparative study</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the performance of a modified EVEREST criteria using flash fundus camera-based ICGA, and to compare the sensitivity and specificity of individual and combinations of features within the EVEREST criteria with that subretinal focal hyperflurescene alone.</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>National Medical Research Council</td></tr>
<tr><td>Number of patients</td><td>230 patients</td></tr>
<tr><td>Inclusion criteria</td><td>Patients presenting with untreated exudative maculopathy (either typical neovascular AMD or PCV)</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Characteristics of diagnosed of polypoidal choroidal vasculopathy and typical age-related macular degeneration based on EVEREST criteria</td><td>
<table>
<tr><th></th><th>Polypoidal choroidal vasculopathy</th><th>Typical AMD</th></tr>
<tr><td>Number of eyes</td><td>131</td><td>110</td></tr>
<tr><td>Mean age (SD)</td><td>67.6 (8.8)</td><td>69.2 (10.0)</td></tr>
<tr><td>Percentage of men</td><td>64%</td><td>55%</td></tr>
<tr><td>Presenting vision, logMAR, mean (SD)</td><td>0.8 (0.6)</td><td>0.9 (0.6)</td></tr>
<tr><td>Fluorescein angiography</td><td></td><td></td></tr>
<tr><td>CNV less than 50% of lesion</td><td>39.7%</td><td>29.0%</td></tr>
<tr><td>CNV at least 50% of lesion</td><td></td><td></td></tr>
<tr><td>Classic/predominantly classic</td><td>21.5%</td><td>42.3%</td></tr>
<tr><td>Minimally classic/occult</td><td>78.5%</td><td>57.7%</td></tr>
</table>
</td></tr>
<tr><td>Type of test</td><td>Flash fundus camer-based ICGA
ICGA, applying modified EVEREST grading criteria: PCV diagnosis was made if, in addition to the presence of subretinal focal hyperfluorescence at least one of the following angiographic or clinical criteria was met (“additional” criteria):
branching vascular network
nodular appearance when viewed stereoscopically</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Cheung,C.M., Laude,A., Wong,W., Mathur,R., Chan,C.M., Wong,E., Wong,D., Wong,T.Y., Lim,T.H., 20151209 Improved specificity of polypoidal choroidal vasculopathy diagnosis using a modified everest criteria.Retina, 35, 7, 1375-1380, 2015</th></tr>
<tr><td></td><td>the presence of hypoflurescent halo
orange subretinal nodule on color photograph
association with massive submacular haemorrhage</td></tr>
<tr><td>Reference standard</td><td>Confocal scanning laser ophthalmscope-based ICGA
PCV diagnosis was made if, in addition to the presence of subretinal focal hyperfluorescence (“essential criterion”)</td></tr>
<tr><td>Prevalence</td><td>241 eyes were included in the study.
PCV was in 131 eyes (54%) and typical AMD was in 110 eyes (46%).
<table>
<tr><td></td><td></td><td>Essential criteria</td><td></td></tr>
<tr><td>Modified criteria</td><td></td><td>Positive</td><td>Negative</td></tr>
<tr><td></td><td>Positive</td><td>103</td><td>14</td></tr>
<tr><td></td><td>Negative</td><td>28</td><td>96</td></tr>
<tr><td></td><td></td><td>131</td><td>110</td></tr>
</table></td></tr>
<tr><td>Sensitivity</td><td>78.6%, 95%CI 71.2 to 85.2%</td></tr>
<tr><td>Specificity</td><td>87.3%, 95%CI 80.5 to 92.8%</td></tr>
<tr><td>Positive predictive values</td><td>88.0%, 95%CI 81.6 to 93.2%</td></tr>
<tr><td>Negative predictive values</td><td>77.4%, 95%CI 69.7 to 84.3%</td></tr>
<tr><td>Comments</td><td>This is a restrospective comparative study. The study reviewed colour fundus photograph, fluorescein angiography, and ICGA image from consecutive patients with untreated exudative maculopathy.
Patients selection: pateints were recruited from retinal clinics, but the inclusion/exclusion criteria were not reported in the study.
Indext test: Two independent retinal specialists graded imaging results, but masking between index test and reference standards were unclear.
Reference standards: Two independent retinal specialists graded imaging results, but masking between index test and reference standards were unclear.
Flow and timing: Time intervals between index test and reference standard were unclear.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Cheung C M. G; Yanagi Y ; Mohla A ; Lee S Y; Mathur R ; Chan C M; Yeo I ; Wong T Y. Characterization and differentiation of polypoidal choroidal vasculopathy using swept source optical coherence tomography angiography. Retina 2016</td></tr>
<tr><td>Country/ies where the study carried our</td><td>Singapore</td></tr>
<tr><td>Study type</td><td>Prospective cross sectional study</td></tr>
<tr><td>Aim of the study</td><td>To determine the correlation and agreement between swept-source optical coherence tomography angiography (SS-OCT-A) with fluorescein angiography (FA), indocyanine green angiography (ICGA) and spectral domain OCT (SD-OCT) in characterizing polypoidal choroidal vasculopathy (PCV) and in differentiating eyes with typical age-related macular degeneration (t-AMD).</td></tr>
<tr><td>Study dates</td><td>Published 2016</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Number of patients</td><td>86 eyes</td></tr>
<tr><td>Inclusion criteria</td><td>Patients presenting with untreated exudative maculopathy (either typical neovascular AMD or PCV)</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Characteristics of diagnosed of polypoidal choroidal vasculopathy and typical age-related macular degeneration based on EVEREST criteria</td><td>
<table>
<tr><td></td><td>Polypoidal choroidal vasculopathy</td><td>Typical AMD</td></tr>
<tr><td>Number of eyes</td><td>54</td><td>32</td></tr>
<tr><td>Mean age (SD)</td><td>68.9 (9.4)</td><td>74.8 (7.0)</td></tr>
<tr><td>Percentage of men</td><td>63%</td><td>59%</td></tr>
<tr><td>Treatment naïve, n(%)</td><td>17 (31.5%)</td><td>14 (43.8%)</td></tr>
<tr><td>ICGA, n (%)</td><td></td><td></td></tr>
<tr><td>Polypidl lesions</td><td>42 (77.8)</td><td>0</td></tr>
</table>
</td></tr>
<tr><td>Type of test</td><td>Swept-source optial coherence tomography angiography (OCT-A)</td></tr>
<tr><td>Reference standard</td><td>Indocyanine green aniogrpahy (ICGA)</td></tr>
<tr><td>Prevalence</td><td>86 eyes were included in the study.

<table>
<tr><td></td><td></td><td>ICGA</td><td></td><td>Total</td></tr>
<tr><td>OCT-A</td><td></td><td>Positive</td><td>Negative</td><td></td></tr>
<tr><td></td><td>Positive</td><td>17</td><td>9</td><td>26</td></tr>
<tr><td></td><td>Negative</td><td>25</td><td>35</td><td>60</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Cheung C M. G; Yanagi Y ; Mohla A ; Lee S Y; Mathur R ; Chan C M; Yeo I ; Wong T Y. Characterization and differentiation of polypoidal choroidal vasculopathy using swept source optical coherence tomography angiography. Retina 2016**
	<table><tr><td></td><td></td><td>42</td><td>44</td><td>86</td></tr></table>
Sensitivity	40.5%, 95%CI 26.3 to 55.5%
Specificity	81.4%, 95%CI 68.6 to 91.4%
Positive predictive values	68.0%, 95%CI 48.9 to 84.4%
Negative predictive values	58.3%, 95%CI 45.7 to 70.4%
Comments	Patient selection: prospectively a consecutive selection of patients with exudative AMD were recruited. Index test and reference standard: All patients had a standardized history,clinical examination and underwent fluoresce in angiography (FA) and ICGA. Swept-source optical coherence tomography angiography imaging was performed in all patients at the same visit as their conventional angiography,together withSD-OCT. Swept- source optical coherence tomography angiography images were evaluated by a retinal specialist(GC) independent of conventional angiography and masked to Diagnosis of AMD and PCV and FA/ICGA findings. Flow and timing: patients had their tests on the same visit.

Bibliographic reference	**de Carlo,T.E., Bonini Filho,M.A., Chin,A.T., Adhi,M., Ferrara,D., Baumal,C.R., Witkin,A.J., Reichel,E., Duker,J.S., Waheed,N.K., Spectral-domain optical coherence tomography angiography of choroidal neovascularization.Ophthalmology, 122, 6, 1228-1238, 2015**
Country/ies where the study carried out	USA
Study type	Retrospective cohort
Aim of the study	To describe the characteristics and the sensitivity and specificity of detection of choroidal neovascularization (CNV) on optical coherence tomography angiography (OCTA) using spectral-domain optical coherence tomography.
Study dates	2014
Sources of funding	Not reported
Number of patients	61 (a cohort of 24 patients who had suspected CNV underwent OCTA and FA)
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Eligible participants characteristics	Mean age, range: 64 years, 29 to 91 years Percentage of female: 50% (n=12)

Bibliographic reference	**de Carlo,T.E., Bonini Filho,M.A., Chin,A.T., Adhi,M., Ferrara,D., Baumal,C.R., Witkin,A.J., Reichel,E., Duker,J.S., Waheed,N.K., Spectral-domain optical coherence tomography angiography of choroidal neovascularization.Ophthalmology, 122, 6, 1228-1238, 2015**
Type of test	Optical coherence tomography
Reference standard	Fluorescein angiography
Prevalence	<table><tr><td></td><td></td><td>FA</td><td></td><td></td></tr><tr><td>SD-OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr><tr><td></td><td>Positive</td><td>4</td><td>2</td><td>6</td></tr><tr><td></td><td>Negative</td><td>4</td><td>20</td><td>24</td></tr><tr><td></td><td>Total</td><td>8</td><td>22</td><td>30 (eyes)</td></tr></table>
Sensitivity	50.0%, 95%CI 18.4 to 81.6%
Specificity	90.9%, 95%CI 76.2 to 98.8%
Positive predictive values	66.7%, 95%CI 28.4 to 94.7%
Negative predictive values	83.3%, 95%CI 66.4 to 95.0%
Comments	In the restropsective review, patients who underwent OCTA to evluate the sensitivity and specificity of detection of choroidal neovascularisation. Patient selection: all patients in whom CNV was identified on OCTA underwent further review of the medical records for underlying diagnosis. Detailed inclusion and exclusion criteria were not reported. Index test: The results of OCTA were evaluated independently by 2 trained readers Reference standard: FAs of the selected patients were evaluated independently from the OCTAs fro presences or absences of CNV. Flow and time: all selected patients had OCTA and FA on the same day.

Bibliographic reference	**De,Salvo G., Vaz-Pereira,S., Keane,P.A., Tufail,A., Liew,G., Sensitivity and specificity of spectral-domain optical coherence tomography in detecting idiopathic polypoidal choroidal vasculopathy.American Journal of Ophthalmology, 158, 6, 1228-1238, 2014**
Country/ies where the studies carried out	UK
Study type	Retrospective case-control study

<table>
<tr><th>Bibliographic reference</th><th>De,Salvo G., Vaz-Pereira,S., Keane,P.A., Tufail,A., Liew,G., Sensitivity and specificity of spectral-domain optical coherence tomography in detecting idiopathic polypoidal choroidal vasculopathy.American Journal of Ophthalmology, 158, 6, 1228-1238, 2014</th></tr>
<tr><td>Aim of the study</td><td>To evaluate the efficacy of spectral-domain optical coherence tomography (SD-OCT) compared with indocyanine green angiography (ICGA) in detecting idiopathic polypoidal choroidal vasculpathy (PCV) and in differentiating between PCV and occult choroidal neovascularization (CNV).</td></tr>
<tr><td>Study dates</td><td>January 2012 and December 2012</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Number of patients</td><td>44 patients (51 eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients have 1 or more pigment epithelial detachment (PEDs) in at least 1 eye.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with classic exudative age-related macular degeneration
Myopic CNV
Other secondary CNVs
Central serous chorioretinopathy (CSCR)</td></tr>
<tr><td>Eligible participants characteristics</td><td>Median age, range: 70 year, 48-95 years
Percentage of male: 32% (n=14)</td></tr>
<tr><td>Type of test</td><td>Spectral-domain optical coherence tomography (SD-OCT)</td></tr>
<tr><td>Reference standard</td><td>indocyanine green angiography (ICGA)</td></tr>
<tr><td>Prevalence</td><td>73% (n=32 patients)

<table><tr><td></td><td></td><td>ICGA</td><td></td><td></td></tr><tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr><tr><td></td><td>Positive</td><td>35</td><td>1</td><td>36</td></tr><tr><td></td><td>Negative</td><td>2</td><td>13</td><td>15</td></tr><tr><td>Total</td><td></td><td>37</td><td>14</td><td>51 (eyes)</td></tr></table></td></tr>
<tr><td>Sensitivity</td><td>94.6%, 95%CI 85.5 to 99.3%</td></tr>
<tr><td>Specificity</td><td>92.9%, 95%CI 75.3 to 99.8%</td></tr>
<tr><td>Positive predictive values</td><td>97.2%, 95%CI 90.0 to 99.9%</td></tr>
<tr><td>Negative predictive values</td><td>86.7%, 95%CI 66.1 to 98.2%</td></tr>
<tr><td>Comments</td><td>This is an observational case study evaluating the accuracy of OCT in detecting and differentiating PCV from occult CNV.</td></tr>
</table>

Bibliographic reference	De,Salvo G., Vaz-Pereira,S., Keane,P.A., Tufail,A., Liew,G., Sensitivity and specificity of spectral-domain optical coherence tomography in detecting idiopathic polypoidal choroidal vasculopathy.American Journal of Ophthalmology, 158, 6, 1228-1238, 2014
	Patient selection: The study reviewed 44 consecutive patients with 1 or more serous/hemorrhagic PED retrospectively. The study excluded patients with classic exudative AMD. Index test and reference standard: all patients underwent OCT, FFA and ICGA in both eyes. FFA and ICGA were reviewed by 2 authors masked to the results of the OCT grading. Disagreements were resolved by open adjusticatioon between the 2 authors. Flow and timing: Time interval between index test and reference standard was unclear.

Bibliographic reference	Do,D.V., Gower,E.W., Cassard,S.D., Boyer,D., Bressler,N.M., Bressler,S.B., Heier,J.S., Jefferys,J.L., Singerman,L.J., Solomon,S.D. Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC Study.Ophthalmology, 119, 4, 771-778, 2012
Country/ies where the study carried out	USA
Study type	Prospective cohort
Aim of the study	To determine the sensitivity of time domain optical coherence tomography (OCT) in detecting conversion to neovascular age-related macular degeneration n eyes with high risk for choroidal neovascularization(CNV), compared with detection using fluorescein angiography (FA) as the gold standard.
Study dates	2007
Sources of funding	Lincy Foundation to the Johns Hopkins University
Number of patients	98 patients enrolled (89 included)
Inclusion criteria	Patients aged 50 years and/over Patients have best-corrected ETDS visual acuity letter score≥65 Patients have neovascular AMD in the nonstudy eye Patients are absence of CNV in participants' study eyes confirmed on fluorescein angiography Patients have at least 1 large drusen(>125μm) and focal hyperpigmentation within 3600μ of the center of the macular Media are sufficiently clear to permit study imaging
Exclusion criteria	Patients are allergy to fluorescein dye Patients have advanced AMD with CNV in both eyes, confirmed on fluorescein angiography Patients have geographic atrophy which extends through the center of the macular in the participants' study eye Patients have macular disease other than AMD in their study eyes Patients had prior surgical or laser treatment to the macular in their study eye

<table>
<tr><th>Bibliographic reference</th><td>Do,D.V., Gower,E.W., Cassard,S.D., Boyer,D., Bressler,N.M., Bressler,S.B., Heier,J.S., Jefferys,J.L., Singerman,L.J., Solomon,S.D. Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC Study.Ophthalmology, 119, 4, 771-778, 2012</td></tr>
<tr><td>Eligible participants characteristics</td><td>
<table>
<tr><td></td><td>Included</td><td>Excluded</td></tr>
<tr><td>Median age, range</td><td>79.0, 58 to 91</td><td>78.0, 70 to 86</td></tr>
<tr><td>No. of male (%)</td><td>31 (36)</td><td>4 (36)</td></tr>
<tr><td>No. of White, not of Hispanic origin (%)</td><td>84 (97)</td><td>11 (100)</td></tr>
<tr><td>Current smokers</td><td>3 (3)</td><td>0</td></tr>
<tr><td>Never smokers</td><td>33 (38)</td><td>6 (55)</td></tr>
<tr><td>Median visual acuity in study eye, range</td><td>80, 66 to 95</td><td>84, 77 to 90</td></tr>
<tr><td>Median visual acuity in fellow eye, range</td><td>35, 0 to 84</td><td>39, 7 to 75</td></tr>
<tr><td>Cataract surgery in study eye (%)</td><td>26 (30)</td><td>4 (36)</td></tr>
</table>
</td></tr>
<tr><td>Type of test</td><td>Time-domain optical coherence tomography</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography</td></tr>
<tr><td>Prevalence</td><td>
<table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>9</td><td>32</td><td>41</td></tr>
<tr><td></td><td>Negative</td><td>6</td><td>40</td><td>46</td></tr>
<tr><td></td><td>Total</td><td>15</td><td>72</td><td>87</td></tr>
<tr><td>PHP</td><td>Positive</td><td>7</td><td>11</td><td>18</td></tr>
<tr><td></td><td>Negative</td><td>8</td><td>61</td><td>69</td></tr>
<tr><td></td><td>Total</td><td>15</td><td>72</td><td>87</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity</td><td>OCT: 60.0%, 95%CI 35.1 to 82.3%
PHP: 46.7%, 95%CI 23.0 to 71.1%</td></tr>
<tr><td>Specificity</td><td>OCT: 55.6%, 95%CI 44.0 to 66.8%
PHP: 84.7%, 95%CI 75.6 to 92.0%</td></tr>
</table>

Bibliographic reference	**Do,D.V., Gower,E.W., Cassard,S.D., Boyer,D., Bressler,N.M., Bressler,S.B., Heier,J.S., Jefferys,J.L., Singerman,L.J., Solomon,S.D. Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC Study.Ophthalmology, 119, 4, 771-778, 2012**
Positive predictive values	OCT: 22.0%, 95%CI 10.8 to 35.6% PHP: 38.9%, 95%CI 18.4 to 61.7%
Negative predictive values	OCT: 87.0%, 95%CI 75.9 to 94.9% PHP: 88.4%, 95%CI 79.9 to 92.8%
Comments	This study aimed to determine the sensitivity of OCT in detecting conversion to neovascular AMD in eye at risk of choroidal neovascular, compared with FA. Patient selection: a sample of 227 inviduals who had neovascular AMD in 1 eye (non-study eye) were included. Index test: The OCT were graded by 2 trained, maksed graders at the Reading centre. References standard: Am independent assessment of fluorescein leakage that could represent new onset CNV was performed by 2 trained, masked graders at the Reading Centre. A consensus grade was developed with input from the Reading Centre prinicipal investigator when unresolved discrepancies arose between the graders/ Flow and timing: Time intervals between index test and reference standard were unclear.

Bibliographic reference	**Gong Jingwen; Yu Suqin ; Gong Yuanyuan ; Wang Fenghua ; Sun Xiaodong. The Diagnostic Accuracy of Optical Coherence Tomography Angiography for Neovascular Age-Related Macular Degeneration: A Comparison with Fundus Fluorescein Angiography. Journal of ophthalmology 2016**
Country/ies where the study carried out	China
Study type	Retrospective case study
Aim of the study	To describe the morphological characteristics and efficacy of OCTA in detecting CNV in nAMD
Study dates	Published in 2016
Sources of funding	Health and Family Planning Commission of Zhejiang Province of China and major scientific and technological project of Science Technology Department of Zhejiang Province
Number of patients	53 patients (86 eyes)
Inclusion criteria	Patients aged 50 years and/over with clinical features of age-related maculopathey Patients have macular exudative signs on at least one of 2 imaging examiniation (FA or SD-OCT)
Exclusion criteria	Patients without OCTA or FA results available for analysis or the OCTA/FA not being performed within 7 days of each other Patients have advanced AMD with CNV in both eyes, confirmed on fluorescein angiography

<table>
<tr><th>Bibliographic reference</th><td>Gong Jingwen; Yu Suqin ; Gong Yuanyuan ; Wang Fenghua ; Sun Xiaodong. The Diagnostic Accuracy of Optical Coherence Tomography Angiography for Neovascular Age-Related Macular Degeneration: A Comparison with Fundus Fluorescein Angiography. Journal of ophthalmology 2016</td></tr>
<tr><td></td><td>Patients with CNV secondary to pathological myopia, angioid streaks, chorioretinitis, central serous chorioretinopathy, tumors, or trauma
Patients with media opacities, such as cataracts, preventing detailed imaging</td></tr>
<tr><td>Eligible participants characteristics</td><td><table>
<tr><td></td><td>Included</td></tr>
<tr><td>Median age, range</td><td>67 years, 50 to 85</td></tr>
<tr><td>No. of male (%)</td><td>33 (62.3)</td></tr>
</table></td></tr>
<tr><td>Type of test</td><td>Optical coherence tomography angiography</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography</td></tr>
<tr><td>Prevalence</td><td><table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>OCT-A</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>45</td><td>11</td><td>56</td></tr>
<tr><td></td><td>Negative</td><td>7</td><td>23</td><td>30</td></tr>
<tr><td></td><td>Total</td><td>52</td><td>34</td><td>86</td></tr>
</table></td></tr>
<tr><td>Sensitivity</td><td>OCTA: 86.5%, 95%CI 76.1 to 94.3%</td></tr>
<tr><td>Specificity</td><td>OCTA: 79.4%, 95%CI 64.5 to 91.0%</td></tr>
<tr><td>Positive predictive values</td><td>OCTA: 86.5%, 95%CI 76.1 to 94.3%</td></tr>
<tr><td>Negative predictive values</td><td>OCTA: 79.4%, 95%CI 64.5 to 91.0%</td></tr>
<tr><td>Comments</td><td>Patient selection: a review of consecutive patients with maculopathy who visited the study clinic.
Index test and reference standard: All the patients underwent a comprehensive eye examination, which included slitlamp biomicroscopy, color fundus photography, FA, spectraldomainOCT (SD-OCT), andOCTangiography. Two independent and trained readers evaluated each set of images (IR, FA, SD-OCT, and OCTA). The readers were blinded to any clinical patient information, such as the patient’s history, visual acuity, and which eye was the index eye, if not both. If there was disagreement between the two readers, a third ophthalmologist was asked to adjudicate.</td></tr>
</table>

Bibliographic reference	**Gong Jingwen; Yu Suqin ; Gong Yuanyuan ; Wang Fenghua ; Sun Xiaodong. The Diagnostic Accuracy of Optical Coherence Tomography Angiography for Neovascular Age-Related Macular Degeneration: A Comparison with Fundus Fluorescein Angiography. Journal of ophthalmology 2016**
	Flow and timing: patients whose OCTA/FA not being performed within 7 days of each other were excluded.

Bibliographic reference	**Lim,J.I., Labree,L., Nichols,T., Cardenas,I., Comparison of nonmydriatic digitized video fundus images with standard 35-mm slides to screen for and identify specific lesions of age-related macular degeneration.Retina (Philadelphia, Pa.)Retina, 22, 1, 59-64, 2002**
Country/ies where the study carried out	USA
Study type	Prospective case series
Aim of the study	To compare nonmydriatic digitized images obtained using a digital imaging system with 35-mm slide images for detecting specific findings of age-related macular degeneration and to evaluate its usefulness as a screening tool in detecting signs of AMD.
Study dates	Not reported
Sources of funding	The National Eye Institute and Research to Prevent blindness
Number of patients	17 patients (33 eyes)
Inclusion criteria	Patients were recruited in the study if they had diagnosis of AMD. Patients were 50 years or older Patients had one or more large drusen (>63µm), retinal pigment epithelial (RPE) change (mottling or atrophy) or disciform scar in at least one eye
Exclusion criteria	Not stated
Eligible participants characteristics	Median age, range: 79 years, 64-88 years
Type of test	Eligible patients underwent nonmydriatic digital fundus photography using a modified nonmydriatic, 45 degree video fundus camera for digital image capture.
Reference standard	Patients underwent mydriatic fundus photography using Zeiss 30-degree fundus camera. The 35-mm film images were processed, and the colour slides were labelled. The same retinal specialist then reviewed all images (digital and 35-mm slide)
Prevalence	Drusen

		Photo		
Digital		Positive	Negative	Total

Bibliographic reference	Lim,J.I., Labree,L., Nichols,T., Cardenas,I., Comparison of nonmydriatic digitized video fundus images with standard 35-mm slides to screen for and identify specific lesions of age-related macular degeneration.Retina (Philadelphia, Pa.)Retina, 22, 1, 59-64, 2002

	Positive	16	1	17
	Negative	9	7	16
	Total	25	8	33

CNV

		Photo		
Digital		Positive	Negative	Total
	Positive	3	0	3
	Negative	3	27	30
	Total	6	27	33

PED

		Photo		
Digital		Positive	Negative	Total
	Positive	1	0	1
	Negative	1	31	32
	Total	2	31	33

Sensitivity

	Sensitivity
Drusen	64.0%, 95%CI 44.7 to 81.2%
CNV	50.0%, 95%CI 16.7 to 83.3%
PED	50.0%, 95%CI 6.1 to 93.9%

Specificity

	Specificity
Drusen	87.5%, 95%CI 59.0 to 99.6%
CNV	98.2%, 95%CI 91.2 to 100%
PED	98.4%, 95%CI 92.3 to 100.0%

Positive predictive values

	PPV

Bibliographic reference	**Lim,J.I., Labree,L., Nichols,T., Cardenas,I., Comparison of nonmydriatic digitized video fundus images with standard 35-mm slides to screen for and identify specific lesions of age-related macular degeneration.Retina (Philadelphia, Pa.)Retina, 22, 1, 59-64, 2002**
	<table><tr><td>Drusen</td><td>94.1%, 95%CI 79.4 to 99.8%</td></tr><tr><td>CNV</td><td>87.5%, 95%CI 46.4 to 100%</td></tr><tr><td>PED</td><td>75.0%, 95%CI 14.7 to 100.0%</td></tr></table>
Negative predictive values	<table><tr><td></td><td>NPV</td></tr><tr><td>Drusen</td><td>43.8%, 95%CI 21.3 to 67.7%</td></tr><tr><td>CNV</td><td>88.7%, 95%CI 75.7 to 97.1%</td></tr><tr><td>PED</td><td>95.5%, 95%CI 86.3 to 99.7%</td></tr></table>
Comments	Patient selection: patients were recruited who met inclusion critieria including a patients having AMD who had one or more large drusen, RPE, or disciform scar in at least one eye. Index test and reference standard: eligible patients underwent nonmydriatic, digit fundus photography, a cerified ophthalmic photographer trained in the used of the nonmydriatic camera. After compleing the digital photographs, the patient's pupil was dilated. Then patient underwent mydriatic fundus photography. The film images were processed. Flow and time: Readings of the slide and the digitised images were sperpated by at least 2 days.

Bibliographic reference	**Maberley,D.A., Isbister,C., Mackenzie,P., Aralar,A. An evaluation of photographic screening for neovascular age-related macular degeneration.Eye, 19, 6, 611-616, 2005**
Country/ies where the study carried out	Canada
Study type	Cross sectional study
Aim of the study	To evaluate the utility of colour fundus photographs for identifying subjects with potentially treatable neovascular AMD.
Study dates	Jan 2002 to March 2002
Sources of funding	Not reported
Number of patients	74 eyes
Inclusion criteria	Patients who had been referred by general ophthalmologist with a diagnosis of "age-related macular degeneration".
Exclusion criteria	Not reported
Eligible participants characteristics	Not reported

Bibliographic reference	**Maberley,D.A., Isbister,C., Mackenzie,P., Aralar,A. An evaluation of photographic screening for neovascular age-related macular degeneration.Eye, 19, 6, 611-616, 2005**
Type of test	Colour fundus photography
Reference standard	Fluorescein angiography
Prevalence	Based on the consensus of the two retinal specialists, 46% (31) noevascular AMD was present, and 54% (43) of eyes displayed no evidence of neovascular AMD.

Reader A		FA		
CFP (colour image)		Positive	Negative	Total
	Positive	5	32	37
	Negative	36	1	37
	Total	41	33	74
CFP (stereo colour image)				
	Positive	8	33	41
	Negative	33	0	33
	Total	41	33	74
CFP (stereo colour image + clinical information				
	Positive	10	33	43
	Negative	31	0	31
	Total	41	33	74

Reader B		FA		
CFP (colour image)		Positive	Negative	Total
	Positive	3	31	34
	Negative	38	2	40
	Total	41	33	74

Bibliographic reference	Maberley,D.A., Isbister,C., Mackenzie,P., Aralar,A. An evaluation of photographic screening for neovascular age-related macular degeneration.Eye, 19, 6, 611-616, 2005

CFP (stereo colour image)				
	Positive	6	32	38
	Negative	35	1	36
	Total	41	33	74
CFP (stereo colour image + clinical information				
	Positive	9	33	42
	Negative	32	0	32
	Total	41	33	74

Sensitivity

	Sensitivity
Reader A	
Colour image	12.2%, 95%CI 4.2 to 23.7%
Stereo colour image	20.2%, 95%CI 9.7 to 33.5%
Stereo colour image +clinical information	25.0%, 95%CI 13.3 to 39.0%
Read B	
Colour image	7.3%, 95%CI 1.6 to 16.9%
Stereo colour image	14.6%, 95%CI 5.7 to 26.8%
Stereo colour image +clinical information	22.6%, 95%CI 11.5 to 36.2%

Specificity

	Specificity
Reader A	
Colour image	3.0%, 95%CI 0.1 to 10.9%
Stereo colour image	-
Stereo colour image +clinical information	-
Reader B	
Colour image	6.1%, 95%CI 0.7 to 16.2%

<table>
<tr><th>Bibliographic reference</th><th>Maberley,D.A., Isbister,C., Mackenzie,P., Aralar,A. An evaluation of photographic screening for neovascular age-related macular degeneration.Eye, 19, 6, 611-616, 2005</th></tr>
<tr><td></td><td>
<table>
<tr><td>Stereo colour image</td><td>3.0%, 95%CI 0.0 to 10.9%</td></tr>
<tr><td>Stereo colour image +clinical information</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Positive predictive values</td><td>
<table>
<tr><td></td><td>PPV</td></tr>
<tr><td>Reader A</td><td></td></tr>
<tr><td>Colour image</td><td>13.5%, 95%CI 4.7 to 26.1%</td></tr>
<tr><td>Stereo colour image</td><td>20.2%, 95%CI 9.7 to 33.5%</td></tr>
<tr><td>Stereo colour image +clinical information</td><td>23.8%, 95%CI 12.6 to 37.3%</td></tr>
<tr><td>Reader B</td><td></td></tr>
<tr><td>Colour image</td><td>8.8%, 95%CI 1.9 to 20.2%</td></tr>
<tr><td>Stereo colour image</td><td>15.8%, 95%CI 6.2 to 28.8%</td></tr>
<tr><td>Stereo colour image +clinical information</td><td>22.1%, 95%CI 11.2 to 35.4%</td></tr>
</table>
</td></tr>
<tr><td>Negative predictive values</td><td>
<table>
<tr><td></td><td>NPV</td></tr>
<tr><td>Reader A</td><td></td></tr>
<tr><td>Colour image</td><td>2.7%, 95%CI 0.1 to 9.7%</td></tr>
<tr><td>Stereo colour image</td><td>-</td></tr>
<tr><td>Stereo colour image +clinical information</td><td>-</td></tr>
<tr><td>Reader B</td><td></td></tr>
<tr><td>Colour image</td><td>5.0%, 95%CI 0.1 to 13.5%</td></tr>
<tr><td>Stereo colour image</td><td>2.8%, 95%CI 0.0 to 10.0%</td></tr>
<tr><td>Stereo colour image +clinical information</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Comments</td><td>Patient selection: patients were sent by general ophthalmologists with a diagnosis of age-related macular degeneration
Index test and reference standard: for each patient, both eyes were imaged by colour fundus photography and fluorescein angiography. The colour image readings were performed serially and independently by each specialist. The reader were required to predict which colour images would deomonstrated chorodial neovascularisation. A thoird retinal opinion was sought for grader disagree,emt pm the angiographic interpretation.</td></tr>
</table>

Bibliographic reference	**Maberley,D.A., Isbister,C., Mackenzie,P., Aralar,A. An evaluation of photographic screening for neovascular age-related macular degeneration.Eye, 19, 6, 611-616, 2005**
	Flow and timing: fluorescein aniograms taken at the same time as colour images were read by the two retinal speclaists at spate reading seesion.

Bibliographic reference	**Mathew,R., Pefkianaki,M., Kopsachilis,N., Brar,M., Richardson,M., Sivaprasad,S. Correlation of fundus fluorescein angiography and spectral-domain optical coherence tomography in identification of membrane subtypes in neovascular age-related macular degeneration.Ophthalmologica, 231, 3, 153-159, 2014**
Country/ies where the study carried out	UK
Study type	Retrospective cross sectional
Aim of the study	To assess the sensitivity and specificity of spectral-domain optical coherence tomography (SDOCT) for determinant of choroidal neovascularization subtypes in neovascular age-related macular degeneration (AMD) compared with fundus fluorescein angiography (FFA).
Study dates	Not reported
Sources of funding	Not reported
Number of patients	130 patients
Inclusion criteria	Patients initiated on ranibizumab therapy for neovascular AMD were selected from the respective AMD databases. Inclusion criteria were: eyes with subfoveal CNV due to neovascular AMD, of any lesion subtype, with lesion size of less than 12 disc areas and a clear media permitting OCT imaging with good signal strength.
Exclusion criteria	Patietns with CNV secondary to cause other than AMD, other retinal diseases in the study eye including diabetic retinopathy or hereditary retinal dystrophies were excluded. Eyes that presented with predominantly scar and blood that obscured identification of the CNV subtype were also excluded.
Eligible participants characteristics	No. of males: 36, 36% Mean age (SD): 75.6 (2.1) years
Type of test	Spectral-domain optical coherence tomography (SD-OCT)
Reference standard	Fundus fluorescein angiography (FFA)
Prevalence	On FFA, most of the CNV were occult types (62%) followed by RAP (20%0 and classic CNV (14%). Occult

		FFA		

Bibliographic reference	Mathew,R., Pefkianaki,M., Kopsachilis,N., Brar,M., Richardson,M., Sivaprasad,S. Correlation of fundus fluorescein angiography and spectral-domain optical coherence tomography in identification of membrane subtypes in neovascular age-related macular degeneration.Ophthalmologica, 231, 3, 153-159, 2014

OCT		Positive	Negative	Total
	Positive	75	10	85
	Negative	2	43	45
	Total	77	53	130

RAP

		FFA		
OCT		Positive	Negative	
	Positive	21	2	23
	Negative	5	102	107
	Total	26	104	130

Classic CNV

		FFA		
OCT		Positive	Negative	
	Positive	17	0	17
	Negative	5	108	113
	Total	22	108	130

PCV

		FFA		
OCT		Positive	Negative	
	Positive	5	0	5
	Negative	0	125	125
	Total	5	125	130

Sensitivity

	Sensitivity
Occult	97.3%, 95%CI 92.9 to 99.7%

Bibliographic reference	Mathew,R., Pefkianaki,M., Kopsachilis,N., Brar,M., Richardson,M., Sivaprasad,S. Correlation of fundus fluorescein angiography and spectral-domain optical coherence tomography in identification of membrane subtypes in neovascular age-related macular degeneration.Ophthalmologica, 231, 3, 153-159, 2014
	RAP: 80.8%, 95%CI 63.9 to 93.1% Classic CNV: 76.1%, 95%CI 57.1 to 90.8% PCV: 100%
Specificity	Occult: 81.1%, 95%CI 69.7 to 90.4% RAP: 98.1%, 95%CI 94.7 to 99.8% Classic CNV: 100% PCV: 100%
Positive predictive values	Occult: 88.2%, 95%CI 80.6 to 94.1% RAP: 91.3%, 95%CI 77.1 to 98.9% Classic CNV: 100% PCV: 100%
Negative predictive values	Occult: 95.6%, 95%CI 88.0 to 99.4% RAP: 95.3%, 95%CI 90.6 to 98.5% Classic CNV: 95.2%, 95%CI 90.6 to 98.3% PCV: 100%
Comments	Patient slection: this retrospective review included patients initiated on ranibizumab therapy for neovascular AMD. Index test and reference standard: Spectralis OCT scans of included patients were obtained. All patients underwent FFA at baseline. All SD-OCT images were assessed independently by two graders. Differences were adjudicated by the senior author (S.S.), after discussion. All anomymise images were evaluated by masked retina specialists. Flow and timing: time intervals between index test and reference standard were unclear.

<table>
<tr><th>Bibliographic reference</th><th>Mokwa,N.F., Ristau,T., Keane,P.A., Kirchhof,B., Sadda,S.R., Liakopoulos,S. Grading of Age-Related Macular Degeneration: Comparison between Color Fundus Photography, Fluorescein Angiography, and Spectral Domain Optical Coherence Tomography.Journal of ophthalmology, Vol 2013 (2013).</th></tr>
<tr><td>Country/ies where thte study carried out</td><td>Germany</td></tr>
<tr><td>Study type</td><td>Retrospective case control</td></tr>
<tr><td>Aim of the study</td><td>To compare FP, FA and SDOCT imaging regarding their sensitivity and specificity for detecting AMD, CNV, and CNV activity and to analyse whether SDOCT may have the potential to replace the other imaging techniques.</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>The Retinovit Foundation, Cologne, Germany</td></tr>
<tr><td>Number of patients</td><td>66 patients (120 eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>Eyes with early, intermediate, or late AMD as well as control cases were included. Control eyes were required to show no signs for AMD, but other chorioretinal diseases including CNV secondary to any other disease but AMD was allowed.</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Eligible participants characteristics</td><td>Not reported</td></tr>
<tr><td>Type of test</td><td>AMD: Fluorescein angiography, spectral-domain optical coherence tomography
CNV: Fundus photography, spectral-domain optical coherence tomography</td></tr>
<tr><td>Reference standard</td><td>AMD: Fundus photography
CNV: Fluorescein angiography</td></tr>
<tr><td>Prevalence</td><td>AMD
<table>
<tr><td></td><td></td><td>FP</td><td></td><td></td></tr>
<tr><td></td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td>FA</td><td>Positive</td><td>69</td><td>8</td><td>77</td></tr>
<tr><td></td><td>Negative</td><td>6</td><td>37</td><td>43</td></tr>
<tr><td>Total</td><td></td><td>75</td><td>45</td><td>120</td></tr>
</table>
<table>
<tr><td></td><td></td><td>FP</td><td></td><td></td></tr>
<tr><td></td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td>OCT</td><td>Positive</td><td>67</td><td>11</td><td>78</td></tr>
<tr><td></td><td>Negative</td><td>8</td><td>34</td><td>42</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Mokwa,N.F., Ristau,T., Keane,P.A., Kirchhof,B., Sadda,S.R., Liakopoulos,S. Grading of Age-Related Macular Degeneration: Comparison between Color Fundus Photography, Fluorescein Angiography, and Spectral Domain Optical Coherence Tomography.Journal of ophthalmology, Vol 2013 (2013).

Total		75	45	120

CNV

		FA		
		Positive	Negative	Total
FP	Positive	53	1	54
	Negative	15	51	66
Total		68	52	120

		FA		
		Positive	Negative	Total
OCT	Positive	64	1	65
	Negative	4	51	55
Total		68	52	120

Sensitivity		
AMD	Fluorescein angiography	92.0%, 95%CI 84.9 to 97.0%
	SD-optical coherence tomography	89.3%, 95%CI 81.5 to 95.2%
CNV	Fundus photography	77.9%, 95%CI 67.4 to 86.9%
	SD-optical coherence tomography	94.1%, 95%CI 87.4 to 98.4%
Specificity		
AMD	Fluorescein angiography	82.2%, 95%CI 70.0 to 91.8%
	SD-optical coherence tomography	75.6%, 95%CI 62.2 to 86.8%
CNV	Fundus photography	98.1%, 95%CI 93.0 to 99.9%
	SD-optical coherence tomography	98.1%, 95%CI 93.0 to 99.9%
Positive predictive values		
AMD	Fluorescein angiography	89.6%, 95%CI 81.9 to 95.3%
	SD-optical coherence tomography	86.9%, 95%CI 77.4 to 92.6%
CNV	Fundus photography	98.1%, 95%CI 93.2 to 99.9%
	SD-optical coherence tomography	98.4%, 95%CI 94.4 to 99.9%
Negative predictive values		

Bibliographic reference	**Mokwa,N.F., Ristau,T., Keane,P.A., Kirchhof,B., Sadda,S.R., Liakopoulos,S. Grading of Age-Related Macular Degeneration: Comparison between Color Fundus Photography, Fluorescein Angiography, and Spectral Domain Optical Coherence Tomography.Journal of ophthalmology, Vol 2013 (2013).**

AMD	Fluorescein angiography	86.0%, 95%CI 74.4 to 94.6%
	SD-optical coherence tomography	80.9%, 95%CI 67.9 to 91.2%
CNV	Fundus photography	77.2%, 95%CI 66.5 to 86.5%
	SD-optical coherence tomography	92.7%, 95%CI 84.6 to 97.9%

Comments	Patient selection: The European Genetic Database (EUGENDA), a database collecting AMD patients as well as healthy controls, was retrospectively reviewed, and and FP, FA,and SDOCT images of 120 eyes of 66 consecutive patients were randomly collected. Index test and reference standard: SDOCT images were acquired using the Spectralis SDOCT instrument. FA images were performed using the SpectralisHRAsystem. Images were independently analyzed by reading center graders at the Cologne Image ReadingCenter (CIRCL),which have been trained and certified in image interpretation of AMDpatients.Discrepancies between graders have been solved by open adjudication. During analysis of one imaging technique, the grader was masked to all other images and grading results of the patient. Flow and timing: To be eligible for this study, all imageshad to be performedonthe same day.

Bibliographic reference	**Padnick-Silver,L., Weinberg,A.B., Lafranco,F.P., Macsai,M.S. Pilot study for the detection of early exudative age-related macular degeneration with optical coherence tomography.Retina, 32, 6, 1045-1056, 2012**
Country/ies where the study carried out	USA
Study type	Prospective cohort study
Aim of the study	To investigate the ability of optical coherence tomography to detect early choroidal neovascularisation in age-related macular degeneration.
Study dates	Not stated
Sources of funding	The NorthShore University HealthSystem
Number of patients	79 patients
Inclusion criteria	Patients with bilateral AMD, who had developed unilateral exudative changes were enrolled in the study.
Exclusion criteria	Patients with other retinal disease in the eye with non exudative age-related macular degeneration were excluded from the study.

<table>
<tr><th>Bibliographic reference</th><th>Padnick-Silver,L., Weinberg,A.B., Lafranco,F.P., Macsai,M.S. Pilot study for the detection of early exudative age-related macular degeneration with optical coherence tomography.Retina, 32, 6, 1045-1056, 2012</th></tr>
<tr><td>Eligible participants characteristics</td><td>79 patients were enrolled in the study, and 62 patients were followed for the full 2 year or until the point of conversion to exudative AMD.

Mean age (SD): 79.7 (6.3)
Number of female: 55 (70%)
Mean visual acuity (SD): 0.27 (0.21) in the study eye and 1.4 (0.74) in the follow eye</td></tr>
<tr><td>Type of test</td><td>Optical coherence tomography</td></tr>
<tr><td>Reference standard</td><td>Fluorescence angiography</td></tr>
<tr><td>Prevalence</td><td>Of the 77 patients followed in this study, 15(19%) demonstrated exudative changes (as confirmed by FA) in their study eye.
<table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>12</td><td>4</td><td>16</td></tr>
<tr><td></td><td>Negative</td><td>3</td><td>58</td><td>61</td></tr>
<tr><td>Total</td><td></td><td>15</td><td>62</td><td>77</td></tr>
</table></td></tr>
<tr><td>Sensitivity</td><td>80.0%, 95%CI 57.2 to 95.3%</td></tr>
<tr><td>Specificity</td><td>93.5%, 95%CI 86.3 to 98.2%</td></tr>
<tr><td>Positive predictive values</td><td>75.0%, 95%CI 51.9 to 92.2%</td></tr>
<tr><td>Negative predictive values</td><td>95.1%, 95%CI 88.4 to 98.9%</td></tr>
<tr><td>Comments</td><td>Patient selection: Patients with bilateral AMD who had developed unilateral exudative changes were included in the study.
Index test and reference standard: patients were monitored at 3-month intervals over a period of 2 years. At each visit, patients underwent eye examination. If the examination raised suspicious of or demonstrated signes of EMA, an GA was perfomed as a standard care of measure. In these cases, patients also underwent OCT imaging as part of the study. Masking of index test and reference standard was unclear.
Flow and timing: If anigiography was negative for CNV, interim evaluation (OCT) and FA as requested by the physician) at 4-weeks to 6-weeks intervals were performed.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Pirbhai,A., Sheidow,T., Hooper,P. Prospective evaluation of digital non-stereo colour fundus photography as a screening tool in age-related macular degeneration. American journal of ophthalmology, 139, 3, 455-461, 2005</th></tr>
<tr><td>Country/ies where the study carried out</td><td>Ontario, Canada</td></tr>
<tr><td>Study type</td><td>Prospective case series</td></tr>
<tr><td>Aim of the study</td><td>To compare the expert evaluation of mydriatic, non-stereo digital colour fundus photographs with clinical examination and fluorescein angiography in identifying and classifying exudative age-related macular degeneration (AMD)</td></tr>
<tr><td>Study dates</td><td>September 2001 and June 2002</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Number of patients</td><td>118 patients (236 eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were seen in the AMD screening clinic</td></tr>
<tr><td>Exclusion criteria</td><td>Patients for whom fundus photographs were not available
Patients deemed not to require angiography or fundus photography on reference
Patients for whom the time between obtaining a fundus photograph and clinical examination was greater than 3 month
Patients seen in the AMD screening clinical for a condition other than AMD</td></tr>
<tr><td>Eligible participants characteristics</td><td>Median age, range: 79.2, 45 to 93 years</td></tr>
<tr><td>Type of test</td><td>Fundus photograph</td></tr>
<tr><td>Reference standard</td><td>Clinical examination (final clinical assessment for each eye was derived from information obtained from patient charts, including review of fluorescein angiograms).</td></tr>
<tr><td>Prevalence</td><td>The presence of specific lesion in age-related macular degeneration

RPE (retinal pigment epithelium) geographic atrophy
<table>
<tr><td></td><td></td><td>Clinical examination</td><td></td><td></td></tr>
<tr><td>FP</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>31</td><td>23</td><td>54</td></tr>
<tr><td></td><td>Negative</td><td>16</td><td>153</td><td>169</td></tr>
<tr><td>Total</td><td></td><td>47</td><td>176</td><td>223</td></tr>
</table>

PED (pigment epithelial detachment)</td></tr>
</table>

Bibliographic reference	Pirbhai,A., Sheidow,T., Hooper,P. Prospective evaluation of digital non-stereo colour fundus photography as a screening tool in age-related macular degeneration. American journal of ophthalmology, 139, 3, 455-461, 2005

		Clinical examination		
FP		Positive	Negative	Total
	Positive	8	12	20
	Negative	12	191	203
Total		20	203	223

CNVM (choroidal neovascular membrane)

		Clinical examination		
FP		Positive	Negative	Total
	Positive	99	16	115
	Negative	12	96	108
Total		111	112	223

Exudative age-related macular degeneration

		Clinical examination		
FP		Positive	Negative	Total
	Positive	69	29	98
	Negative	15	110	125
Total		84	139	223

Sensitivity

Exudative AMD	82.1%, 95%CI 73.3 to 89.5%
Presences of lesion in AMD	
RPE geographic atrophy	65.9%, 95%CI 51.9 to78.6%
PED	40.0%, 95%CI 20.3 to 61.6%
CNVM	89.2%, 95%CI 82.8 to 94.2

Bibliographic reference	Pirbhai,A., Sheidow,T., Hooper,P. Prospective evaluation of digital non-stereo colour fundus photography as a screening tool in age-related macular degeneration. American journal of ophthalmology, 139, 3, 455-461, 2005	
Specificity	Exudative AMD	79.1%, 95%CI 72.0 to 85.4%
	Presences of lesion in AMD	
	RPE geographic atrophy	86.9%, 95%CI 81.6 to 91.5%
	PED	94.1%, 95%CI 90.4 to 96.8%
	CNVM	85.7%, 95%CI 78.7 to 91.5%
Positive predictive values	Exudative AMD	70.4%, 95%CI 61.0 to 79.0%
	Presences of lesion in AMD	
	RPE geographic atrophy	57.4%, 95%CI 44.1 to70.2%
	PED	40.0% 95%CI 20.3 to 61.6%
	CNVM	86.1%, 95%CI 78.7 to 91.5%
Negative predictive values	Exudative AMD	88%, 95%CI 81.8 to 93.1%
	Presences of lesion in AMD	
	RPE geographic atrophy	90.5%, 95%CI 85.7 to 94.5%
	PED	94.1%, 95%CI 90.4 to 96.9%
	CNVM	88.9%, 95%CI 82.4 to 94.1%
Comments	Patient selection: patients seen in AMD screening clinic between Septermaber 2001 and June 2002. Index test and reference standard: Colour fundus photographys for each patient were randomly labeld before being read by a vitreoretinal surgeon. The readers was masked to other patient infomraiton and status of the fellow eye. Agreement between final clinical assessment and digital photography was calculated using a kappa coeffieicent. Flow and timing: Fundus photographs were taken at the time of fluorescein angiography, either berfore or after the clinicl visit.	

Bibliographic reference	Sallet,G., Lafaut,B.A., De Laey,J.J., Indocyanine green angiography and age-related serous pigment epithelial detachment.Graefes Archive for Clinical & Experimental Ophthalmology, 234, 1, 25-33, 1996
Country/ies where the study carried out	Belgium
Study type	Retrospective case
Aim of the study	To examine whether indocyanine green angiography (ICG-A) provides a better visualisation of choroidal circulation and of CNV than fluorescein angiography.

<table>
<tr><th>Bibliographic reference</th><th>Sallet,G., Lafaut,B.A., De Laey,J.J., Indocyanine green angiography and age-related serous pigment epithelial detachment.Graefes Archive for Clinical & Experimental Ophthalmology, 234, 1, 25-33, 1996</th></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>Supported by a grant form Les amis des Aveugles (Ghlin Belgium)</td></tr>
<tr><td>Number of patients</td><td>52 patients (58 eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients with age-related macular degeneration presenting a PED without classic CNV on fluorescein angiography
Evidence of CNV such as haemorrhage, exudate, regional masking on FA not related to hyperpigmentation, a notch at the edge of the PED and ill-defined hyperfluorescence with late diffusion
Serious PED of at least on disc diameter without signs of CNV on FA</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with other macular diseases associated with CNV and patients with absence of signs of ARMD in the fellow eyes</td></tr>
<tr><td>Eligible participants characteristics</td><td>Mean age, range: 72, 58 and 86 years.
Number of males: 25 (48%)</td></tr>
<tr><td>Type of test</td><td>Indocyanine green angiography (ICG-A)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography (FA)</td></tr>
<tr><td>Prevalence</td><td>
<table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>ICG-A</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>29</td><td>2</td><td>31</td></tr>
<tr><td></td><td>Negative</td><td>19</td><td>8</td><td>27</td></tr>
<tr><td>Total</td><td></td><td>48</td><td>10</td><td>58</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity</td><td>60.4%, 95%CI 46.4 to73.6%</td></tr>
<tr><td>Specificity</td><td>89.5%, 95%CI 72.7 to98.6%</td></tr>
<tr><td>Positive predictive values</td><td>93.5%, 95%CI 82.8 to 99.2%</td></tr>
<tr><td>Negative predictive values</td><td>47.2%, 95%CI 31.4 to 63.4%</td></tr>
<tr><td>Comments</td><td>Patient selection: patients with ARMD presenting a PED without classic CNV or FA were studied.
Index test and reference standard: ICG-A was perfomed following designed procedures. FA was also performed. Grading and masking of index test and reference standard were not described in the study.
Flow and timing: FA and ICG-A were performed on the same day.</td></tr>
</table>

Bibliographic reference	**Sandhu,S.S., Talks,S.J. Correlation of optical coherence tomography, with or without additional colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes.British Journal of Ophthalmology, 89, 8, 967-970, 2005**
Country/ies where the study carried out	UK
Study type	Prospective cross sectional
Aim of the study	To assess the diagnostic accuracy of optical coherence tomography (OCT), with/without colour funds photographs, in predicting fundus fluorescein angiography (FFA) findings in patients suspected of having choroidal neovascularisation (CNV).
Study dates	2002
Sources of funding	Not reported
Number of patients	118 patients (131 eyes) included in the analysis
Inclusion criteria	Patients with suspected choroidal neovascularisaiton
Exclusion criteria	Not reported
Eligible participants characteristics	Mean age (SD): 73.2 (13.7) years % of female: 57.6%
Type of test	Optical coherence tomography
Reference standard	Fundus fluorescein angiography (FFA)
Prevalence	CNV

		FFA		
OCT		Positive	Negative	Total
	Positive	81	16	97
	Negative	3	31	34
Total		84	47	131

		FFA		
OCT + stereo images (fundus)		Positive	Negative	Total
	Positive	79	5	84
	Negative	5	42	47

Bibliographic reference	**Sandhu,S.S., Talks,S.J. Correlation of optical coherence tomography, with or without additional colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes.British Journal of Ophthalmology, 89, 8, 967-970, 2005**
	Total: 84 / 47 / 131
Sensitivity	OCT alone: 96.4%, 95%CI 91.6 to 99.2% OCT with stereo imaged: 94.4%, 95%CI 88.1 to 98.0%
Specificity	OCT alone: 65.9%, 95%CI 52.0 to 78.6% OCT with stereo imaged: 89.3%, 95%CI 79.2 to 96.4%
Positive predictive values	OCT alone: 83.5%, 95%CI 75.5 to 90.2% OCT with stereo imaged: 94.0%, 95%CI 88.1 to 98.0%
Negative predictive values	OCT alone: 91.2%, 95%CI 79.8 to 98.1% OCT with stereo imaged: 89.4%, 95%CI 79.2 to 96.4%
Comments	Patient selection: patients presented with suspected CNV. Detailed inclusion and exclusion critiera were not reported in the study. Index test and reference standard: Imagings were reviewed by 2 independent observers, one assigning the OCT and then the OCT plus colour photography, the other the FFA. Each masked to the other's diagnositic classification and the clinicald disagnosis. Flow and timing: Time intervals of index tests and reference standard were unclear.

Bibliographic reference	**Talks,J., Koshy,Z., Chatzinikolas,K., Use of optical coherence tomography, fluorescein angiography and indocyanine green angiography in a screening clinic for wet age-related macular degeneration.British Journal of OphthalmologyBr.J.Ophthalmol., 91, 5, 600-601, 2007.**
Country/ies where the study carried out	UK
Study type	Retrospective audit
Aim of the study	To assess the utility of optical coherence tomography in a nurse-led, fast-track clinic for new age-related macular degeneration referrals, and to see how often indocyanine green angiography led to an additional diagnosis to that provided by fluorescein angiography.
Study dates	Not reported

<table>
<tr><th>Bibliographic reference</th><th>Talks,J., Koshy,Z., Chatzinikolas,K., Use of optical coherence tomography, fluorescein angiography and indocyanine green angiography in a screening clinic for wet age-related macular degeneration.British Journal of OphthalmologyBr.J.Ophthalmol., 91, 5, 600-601, 2007.</th></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Number of patients</td><td>111 patients</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were referred from optometrists and GPs with symptoms suggestive of wet AMD</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Eligible participants characteristics</td><td>Mean age, range: 84.6, 58 to 97 years
% of female: 60.4%</td></tr>
<tr><td>Type of test</td><td>OCT</td></tr>
<tr><td>Reference standard</td><td>Fundus fluorescein angiography
indocyanine green angiography</td></tr>
<tr><td>Prevalence</td><td>
<table>
<tr><td></td><td></td><td>FFA/ICG</td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td></tr>
<tr><td></td><td>Positive</td><td>93</td><td>12</td></tr>
<tr><td></td><td>Negative</td><td>0</td><td>23</td></tr>
<tr><td>Total</td><td></td><td>93</td><td>35</td></tr>
</table>
<table>
<tr><td></td><td></td><td>FFA/ICG</td><td></td></tr>
<tr><td>FFA</td><td></td><td>Positive</td><td>Negative</td></tr>
<tr><td></td><td>Positive</td><td>93</td><td>0</td></tr>
<tr><td></td><td>Negative</td><td>6</td><td>12</td></tr>
<tr><td>Total</td><td></td><td>99</td><td>12</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity</td><td>OCT: 100%
FFA: 93.5%, 95%CI 87.9 to 97.4%</td></tr>
<tr><td>Specificity</td><td>OCT: 65.0%, 95%CI 49.2 to 79.7%
FFA:100.0%</td></tr>
<tr><td>Positive predictive values</td><td>OCT: 88.2%, 95%CI 81.4 to 93.6%
FFA: 100.0%</td></tr>
<tr><td>Negative predictive values</td><td>OCT: 100%</td></tr>
</table>

Bibliographic reference	**Talks,J., Koshy,Z., Chatzinikolas,K., Use of optical coherence tomography, fluorescein angiography and indocyanine green angiography in a screening clinic for wet age-related macular degeneration.British Journal of OphthalmologyBr.J.Ophthalmol., 91, 5, 600-601, 2007.**
	FFA: 65.8%, 95%CI 43.7 to 84.7%
Comments	Patient selection: a selection of new patients referred wth wet AMD to a nurse-led, fast-tracl screening clinic. Index test and reference standard: patients underwent simultaneous FFA and ICGA. Masking of index test and reference standard were unclear. Flow and timing: patients underwent simultaneous FFA and ICGA.

Bibliographic reference	**Wilde,C., Patel,M., Lakshmanan,A., Amankwah,R., Dhar-Munshi,S., Amoaku,W., Medscape, The diagnostic accuracy of spectral-domain optical coherence tomography for neovascular age-related macular degeneration: a comparison with fundus fluorescein angiography.Eye, 29, 5, 602-610, 2015**
Country/ies where the study carried out	UK
Study type	Retrospective cross sectional
Aim of the study	To evaluate the diagnostic accuracy of spectral-domain optical coherence tomography (SD-OCT) for neovascular age-related macular degeneration (nAMD).
Study dates	February 2009 to February 2013
Sources of funding	The Macular Society UK
Number of patients	411 patients (822 eyes)
Inclusion criteria	Patients were over 50 years Patients were referred for suspected nAMD Patients had symptoms of reduced vision, metamorphopsia, or signs suggestive of nAMD
Exclusion criteria	All patients that had either no SD-OCT or FP/FFA available for analysis Patients whose imaging modality was deemed ungradable. If SD-OCT or FFA were not performed within 7 days of each other Patients with CNV secondary to angioid streaks or evidence of chorioretinitis
Eligible participants characteristics	Not reported
Type of test	Spectral-domain optical coherence tomography (SD-OCT)
Reference standard	Fundus fluorescein angiography (FFA)

<table>
<tr><th>Bibliographic reference</th><td>Wilde,C., Patel,M., Lakshmanan,A., Amankwah,R., Dhar-Munshi,S., Amoaku,W., Medscape, The diagnostic accuracy of spectral-domain optical coherence tomography for neovascular age-related macular degeneration: a comparison with fundus fluorescein angiography.Eye, 29, 5, 602-610, 2015</td></tr>
<tr><td>Prevalence</td><td>
<table>
<tr><td></td><td></td><td>FFA</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>231</td><td>47</td><td>278</td></tr>
<tr><td></td><td>Negative</td><td>0</td><td>198</td><td>198</td></tr>
<tr><td>Total</td><td></td><td>231</td><td>245</td><td>476</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity</td><td>100.0%</td></tr>
<tr><td>Specificity</td><td>80.6%, 95%CI 75.5 to 85.3%</td></tr>
<tr><td>Positive predictive values</td><td>83.0%, 95%CI 78.3 to 87.1%</td></tr>
<tr><td>Negative predictive values</td><td>100.0%</td></tr>
<tr><td>Comments</td><td>Patient selection: A consecutive patietsn who were referraed to a rapid access clinic over 4-year period. Patientswho may have had treatment 6 or more months previously with PDT or anti-VEGF but were thought to have new CNV were included.
Index test and reference standard: OCT and FA were performed. OCT images were reviewed without reference to the FFA. The grader was blind to any clinical patient information. Side by side independent grading took place withi immediate open discussion and adjudication. If there was disagrrement beween the two grading ophthamologists then adustification by a third ophthalmologist would take place.
Flow and timing: patients who had OCT or FFA were not performed within 7 days of each other were excluded.</td></tr>
</table>

E.4 Referral

E.4.1 Organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow-up people with suspected and confirmed AMD

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

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

RQ 24: How soon should people with neovascular AMD be diagnosed and treated after becoming symptomatic?

Bibliographic reference	**Muen Wisam J; Hewick Simon. Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study. 2011; JRSM Short Reports; 2(8): 2042-5333**
Country/ies where the study was carried out:	UK
Study type	Prospective study
Aim of the study	To assess the use and quality of referrals to a neovascular age-related macular degeneration clinic from optometrists using the standard rapid access referral form from the Royal College of Ophthamologists
Study dates	Referrals made between December 2006 and August 2009
Setting	Eye department at NHS Highlands Trust
Source of funding	Not reported
Sample size	54 rapid access referrals forms
Inclusion criteria	All patients referred to the eye department at NHS Highlands Trust using the RARF
Exclusion criteria	Not specified
Baseline characteristics	Not specified
Methods	Prospective data were gathered from all optometry referrals using the rapid access referral form(RARF), between the periods of December 2006 to August 2009. These were assessed for accuracy of history, clinical signs and final diagnosis as compared to a macula expert. The specific points recorded in the history were: Reduction of vision

Bibliographic reference	**Muen Wisam J; Hewick Simon. Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study. 2011; JRSM Short Reports; 2(8): 2042-5333**
	Distortion Central scotoma The clinical signs assessed were: Haemorrhage Exudates Drusen Subretinal fluid/macular oedema All patients were seen within 2 weeks of receipt of the referral. The optometrist history was taken from the RARF, and this was compared with the history obtained by the ophthammologists on the same three points.
Results	The overall agreement between the specialist and optometrist on all three history findings was 57.4%; The total number of patients with a correct diagnosis of neovascular AMD was 37% (n=20).

Diagnosis	Patients (n, %)
Exudative	20 (37.0)
Dry AMD	10 (18.5)
Branch retinal vein occlusion	4 (7.4)
Central serous retinopathy	4 (7.4)
Macular scar	3 (5.6)
Posterior vitreous detachment	2 (3.7)

Bibliographic reference	**Dobbelsteyn D ; McKee K ; Bearnes R D; Jayanetti S N; Persaud D D; Cruess A F; What percentage of patients presenting for routine eye examinations require referral for secondary care? A study of referrals from optometrists to ophthalmologists.2015; Clinical & Experimental Optometry; 98(3):214-17.**
Country/ies where the study was carried out	Nova Scotia, Canada:
Study type	Retrospective cohort case study
Aim of the study	To investigate the percentage of asymptomatic patients presenting for routine optometric eye examinations that have pathology or pathology-related risk factors warranting referral for ophthalmological consultation
Study dates	Patients presented for routine eye care between 2007 and 2010

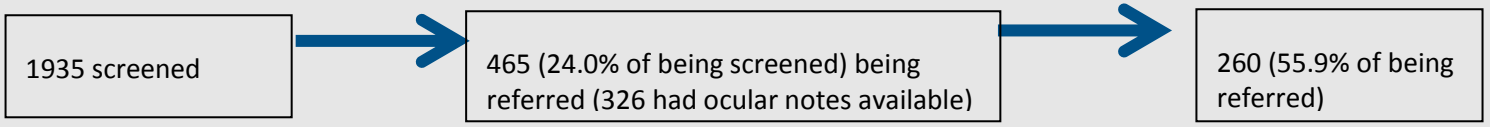
<table>
<tr><th>Bibliographic reference</th><td>Dobbelsteyn D ; McKee K ; Bearnes R D; Jayanetti S N; Persaud D D; Cruess A F; What percentage of patients presenting for routine eye examinations require referral for secondary care? A study of referrals from optometrists to ophthalmologists.2015; Clinical & Experimental Optometry; 98(3):214-17.</td></tr>
<tr><td>Setting</td><td>2 large multi-practitioner optometric clinics</td></tr>
<tr><td>Source of funding</td><td>Financial support of the Canadian optometric trust fund.</td></tr>
<tr><td>Sample size</td><td>23,330 individual patients were examined during study period.</td></tr>
<tr><td>Inclusion criteria</td><td>(i) The patient presented for routine optometric eye care during a specified period of time; (ii) the patient was found to have pathology (or showed enough risk of pathology) resulting in referral to an ophthalmologist; and (iii) a referral report was received from the consulting ophthalmologist stating the diagnosis and the treatment plan</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>A retrospectively review of patients files to indicate if patients were symptomatic or asymptomatic of the indicated pathology. Patient’s files were obtained at clinics through an electronic programme, which enabled the identification of patients meeting the inclusion criteria. Researchers then created a database including the patients’ ID, date of referral, clinical reasons for the referral, presence or absence of symptoms of pathology, diagnosis and treatment plan. Clinical reasons for referral were extracted from referral letters and sorted into 6 categories: AMD, cataract, glaucoma, diabetic, retinopathy, retinopathy and other.</td></tr>
<tr><td>Results</td><td>Referrals for symptomatic and asymptomatic patients
<table>
<tr><td></td><td>All referrals</td><td>symptomatic</td><td>asymptomatic</td><td>Total patients seen</td></tr>
<tr><td>Referrals for all ages</td><td>4,076</td><td>2,992</td><td>1,084</td><td>45,232</td></tr>
<tr><td>% of patients seen</td><td>9%</td><td>6.6%</td><td>2.4%</td><td></td></tr>
</table>
Reasons for referrals
<table>
<tr><td></td><td>Number of asymptomatic patients referred (total=1084) (%)</td><td>Number of symptomatic patients referred (total=2992) (%)</td><td>Relative risk (95%CI)</td></tr>
<tr><td>Retina</td><td>555 (51.2)</td><td>564 (18.8)</td><td>2.72 (2.47 to 2.98)</td></tr>
<tr><td>Glaucoma</td><td>307 (28.3)</td><td>199 (6.6)</td><td>4.26 (3.61 to 5.02)</td></tr>
<tr><td>Diabetic retinopathy</td><td>74 (6.8)</td><td>72 (2.4)</td><td>2.84 (2.07 to 3.89)</td></tr>
<tr><td>Other</td><td>67 (6.2)</td><td>991 (33.1)</td><td>0.19 (0.15 to 0.24)</td></tr>
<tr><td>Cataract</td><td>51 (4.7)</td><td>1,013 (33.8)</td><td>0.14 (0.11 to 0.18)</td></tr>
<tr><td>AMD</td><td>30 (2.7)</td><td>153 (5.1)</td><td>0.54 (0.37 to 0.80)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Azzolini C ; Torreggiani A ; Eandi C ; Donati S ; Oum M A; Vinciguerra R ; Bartalena L ; Tartaglia V. A teleconsultation network improves the efficacy of anti-VEGF therapy in retinal diseases. 2013. Journal of Telemedicine & Telecare; 19(8): 437-442.**
Country/ies where the study was carried out	Italy
Study type:	Cohort study
Aim of the study	To investigate the care of patients with age-related macular degeneration (AMD) managed via a physician-to-physician teleconsultation network for ophthalmology.
Study dates	June 2011 and December 2012.
Setting	10 cities across Italy, 11 groups of ophthalmologists, each group was based on retina centre located at a university or hospital
Source of funding	Not reported
Sample size	678 patients including 360 network patients and 318 control patients (consecutive undergoing usual care during the 3 months before the use of the network)
Inclusion criteria	Not specified
Exclusion criteria	Not specified
Baseline characteristics	Not specified
Methods	A longitudinal comparison of patient care in sites using the new telemedicine network, named as Reading Centre 2.0. The main components of the network are: • a central service, • a web accessible database, • storage and forwarding functions, • dedicated electronic medical records • short message service • email notification between physician, guaranteed privacy and confidentiality • a central help desk Main development in the software are: • application software for both computer and ipad/iphones • a grading system accounting for 5 variables providing key information about the risk of exudative AMD: age, visual acuity, Amsler test, macular haemorrhage and the status of second eye

<table>
<tr><th>Bibliographic reference</th><td>Azzolini C ; Torreggiani A ; Eandi C ; Donati S ; Oum M A; Vinciguerra R ; Bartalena L ; Tartaglia V. A teleconsultation network improves the efficacy of anti-VEGF therapy in retinal diseases. 2013. Journal of Telemedicine & Telecare; 19(8): 437-442.</td></tr>
<tr><td></td><td>• an interactive booking system to make an appointment directly with the Retina centre from outside with SMS notification for patients
• successive multiple masks for comparing images of the same electronic medical record during follow-up
• pop-up window to assist physicians and ensure correct data entry

A tablet computer (ipad) was given to each participant. Web consultation tests were carried out on site. After the initial meeting, the general ophthalmologist used the teleconsultation network for a trial period of 7-10 days to exchange clinical data with retina specialists from retina centres. After the trial period, the ophthalmologist began to exchange real data over the following 3-month period.
At the end of the 3 month period, the ophthalmologist at each site discussed the following results at a final audit meeting:
Degree of access to the network,
Acceptability of technology and medical efficacy</td></tr>
<tr><td>Results:</td><td>
<table>
<tr><td></td><td>Telemedicine network (n=360)</td><td>Usual care (n=318)</td><td>Effect (95%CI)</td></tr>
<tr><td>Visual acuity</td><td></td><td></td><td></td></tr>
<tr><td>First visit, log MAR (range)</td><td>0.29 (0.23 to 0.34)</td><td>0.29 (0.24 to 0.35)</td><td>0</td></tr>
<tr><td>Post-treatment</td><td>0.22 (0.18 to 0.25)</td><td>0.27 (0.23 to 0.32)</td><td>-0.05</td></tr>
<tr><td>Time from first visit to general ophthalmologist to treatment, mean days (SD)</td><td>5.5 (1.4)</td><td>28.7 (4.0)</td><td>-23.20 (-23.66 to -22.74)</td></tr>
</table>
</td></tr>
<tr><td>Notes</td><td>Not randomised trial (before-after study)</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Chasan J E; Delaune B ; Maa A Y; Lynch M G; Effect of a teleretinal screening program on eye care use and resources. 2014; JAMA Ophthalmology, 132 (9).; 1045-51.</td></tr>
<tr><td>Country/ies where the study was carried out</td><td>United State</td></tr>
<tr><td>Study type</td><td>Retrospective study</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the effect of a community-based diabetic teleretinal screening program on eye care use and resources</td></tr>
</table>

Bibliographic reference	**Chasan J E; Delaune B ; Maa A Y; Lynch M G; Effect of a teleretinal screening program on eye care use and resources. 2014; JAMA Ophthalmology, 132 (9).; 1045-51.**
Study dates	October 1, 2008, to March 31, 2009
Setting	Community based clinics
Source of funding	Not reported
Sample size	1935 underwent diabetic telerentinal screening in the primary care community-based clinics.
Inclusion criteria	Patients underwent diabetic telerentinal screening in the primary care community-based clinics and were referred for an ophthalmic examination in the eye clinic.
Exclusion criteria	Not specified
Baseline characteristics	Not reported
Methods	Clinical medical records were reviewed for a 2-year period after patients were referred from teleretinal screening. The following information was collected for analysis: patient demographics, referral and confirmatory diagnoses, ophthalmology clinic visits, diagnostic procedures, surgical procedures, medications, and spectacle prescriptions. Retinal cameras are used to capture images, which are remotely interpreted by an eye care professionals in a centralised reading centre.
Results	Between October 1 2008 to March 31 2009, a total of 1935 people underwent diabetic teleretinal screening in the primary care community-based clinical. Of those screened, 465 (24.0%) were referred to the eye clinic for an ophthalmic examination, 326 had ocular notes available (70.1% being referred) Of those referred, 260 (55.9%) underwent an ophthalmic examination within 2 years of the teleretinal screening.  Patients number by referral diagnoses Referral diagnoses / No. of patients (%) (total=465) Nonmacular diabetes retinopathy: 201 (43.2) Never-related disease: 143 (30.8) Lens or media opacity: 89 (19.1) Age-related macular degeneration: 60 (12.9)

Bibliographic reference	**Chasan J E; Delaune B ; Maa A Y; Lynch M G; Effect of a teleretinal screening program on eye care use and resources. 2014; JAMA Ophthalmology, 132 (9).; 1045-51.**
	<table><tr><td>Diabetic macular edema</td><td>26 (5.6)</td></tr><tr><td>other</td><td>67 (14.4)</td></tr><tr><td>unreadable</td><td>45 (9.7)</td></tr></table> Accuracy of telretinal screening in detecting diagnosis categories (n=326) <table><tr><td>Referral diagnoses</td><td>Sensitivity, %</td></tr><tr><td>Nonmacular diabetes retinopathy</td><td>81.2</td></tr><tr><td>Never-related disease</td><td>88.4</td></tr><tr><td>Lens or media opacity</td><td>56.0</td></tr><tr><td>Age-related macular degeneration</td><td>81.6</td></tr><tr><td>Diabetic macular edema</td><td>75.3</td></tr><tr><td>other</td><td>36.6</td></tr><tr><td>unreadable</td><td>73.6</td></tr></table>
Notes	The percentage of agreement of the teleretinal imaging programmer was calculated by comparing the referral diagnosis to the confirmation diagnosis. Sensitivity was calculated by dividing the total number of referral diagnosis confirmed by ophthalmic examination by number of diagnoses detected by ophthalmic examination. Study populations were not AMD specific.

Bibliographic reference	**Tschuor P ; Pilly B ; Venugopal D ; Gale R P. Optimising assessment intervals improves visual outcomes in ranibizumab-treated age-related neovascular degeneration: using the stability phase as a benchmark.2013. Graefes Archive for Clinical & Experimental Ophthalmology; 251 (10): 2327-30.**
Country/ies where the study was carried out	UK
Study type	Cohort study
Aim of the study	To observe visual acuity change in the stability phase when follow-up intervals are decreased in ranibizumab-treated neovascular age-related macular degeneration
Study dates	Data collected between October 2009 and December 2012

<table>
<tr><th>Bibliographic reference</th><td>Tschuor P ; Pilly B ; Venugopal D ; Gale R P. Optimising assessment intervals improves visual outcomes in ranibizumab-treated age-related neovascular degeneration: using the stability phase as a benchmark.2013. Graefes Archive for Clinical & Experimental Ophthalmology; 251 (10): 2327-30.</td></tr>
<tr><td>Setting</td><td>A base hospital to a community eye clinic</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>62 patients (72 treated eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were 50 years or over and have had a fluorescein angiogram confirmed diagnosis of nvAMD. In addition to this, the patients must have been in stability phrase of treatment, defined as the period following their 3 initial treatment with ranibizumab.</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Number of female (n=45); mean age, years=82.0</td></tr>
<tr><td>Methods</td><td>154 patients with nvAMD treated with intravitreal ranibizumab in routine clinical practice. Patients were transferred from a base hospital to a community eye clinic. Prior to transfer, the first 3 injection of ranibizumab were given at monthly intervals. However, following this, the follow-up interval could not be guaranteed to be monthly.
The patients must have attended at least 12 visits in the stability phrase consisting of 6 visits at the base hospital followed by 6 visits at the community eye centre. Both the base hospital and the community eye clinic used a “one-stop” mode enabling assessment and re-treatment to be performed at the same visit.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Community eye clinic (7 to 12 visits)</td><td>Base hospital (1 to 6 visits)</td><td>Effect (95%CI)</td></tr>
<tr><td>Mean follow-up time between each visit, days (range)</td><td>31.81 (21 to 139)</td><td>56.81 (21 to 288)</td><td>-25.0 (-30.48 to -19.52)</td></tr>
<tr><td>Mean BCVA , letters(SD)</td><td>55.7 (15.5)</td><td>54.5 (14.0)</td><td>1.20 (-4.00 to 6.40)</td></tr>
<tr><td>VA changes over 6 visits, letters</td><td>+4.6</td><td>-1.1</td><td>P<0.001</td></tr>
<tr><td>% of eyes had a gain of 15 letters (n)</td><td>12.5 (n=9)</td><td>1.3 (n=1)</td><td>9.00 (1.18 to 68.92)</td></tr>
<tr><td>% of eyes lost 15 letters (n)</td><td>4.1 (n=3)</td><td>9.5 (n=7)</td><td>0.43 (0.12 to 1.58)</td></tr>
<tr><td>Mean number of injections</td><td>3.39</td><td>3.69</td><td>-0.30 (-2.70 to 2.10)</td></tr>
<tr><td>Predicted mean number of injection</td><td>3.90</td><td>2.37</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Ghazala Fadi ; Hovan Marta ; Mahmood Sajjad. Improving treatment provision of Wet AMD with intravitreal ranibizumab 2013. BMJ Quality Improvement Reports; 2(1).</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>UK</td></tr>
<tr><td>Study type</td><td>Audit</td></tr>
<tr><td>Aim of the study</td><td>To identify improvement in visual acuity of patients treated for wet AMD following changes made to the appointment system, hospital macular treatment centre facility.</td></tr>
<tr><td>Study dates</td><td>2009-2011</td></tr>
<tr><td>Setting</td><td>Manchester Royal Eye hospital’s macular treatment centre (MTC)</td></tr>
<tr><td>Source of funding</td><td>not reported</td></tr>
<tr><td>Sample size</td><td>162 patients (2009); 53 (2010); 80 (2011)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients attending the AMD clinic</td></tr>
<tr><td>Exclusion criteria</td><td>not specified</td></tr>
<tr><td>Baseline characteristics</td><td>not reported</td></tr>
<tr><td>Methods</td><td>The study design was audit of patient treatment and visual measures and continuous re-audit to measure the impact of changes taken. Through regular re-audit it was possible to measure the effect of change made at the MTC on treatment time and the corresponding effect on the mean visual acuity.
<table>
<tr><th>Staffing capacity</th><th>Original</th><th>Improvement</th></tr>
<tr><td></td><td>Medical retinal consultants (3)
Ophthalmic fellows (2)
Specialist nurse (1)
Optometrist (1)
Imaging technician (1)</td><td>Medical retinal consultants (4)
Vitreo-retinal consultants (2)
Medical retinal fellows (4)
Vitreo-retinal fellows (2)
Associate specialist (2)</td></tr>
<tr><td>Number of treatment rooms</td><td>2</td><td>3</td></tr>
</table>

Other action plans were carried out between 2009 and 2011, including
Fast-track referral pathway into hospital eye service for wet AMD patients was implemented;
Application process for funding of ranibizumab injections from primary care trusts was streamlined so that no prior approval was required before commencing treatment;</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Ghazala Fadi ; Hovan Marta ; Mahmood Sajjad. Improving treatment provision of Wet AMD with intravitreal ranibizumab 2013. BMJ Quality Improvement Reports; 2(1).</td></tr>
<tr><td></td><td>With the agreement of hospital management, proposal changes to clinics templates were made and new protected slot became available for new patients to improve delay in initiation of treatment;
In order to ensure review intervals were being met, service capacity was increased through implementation of a training programme to involve optometrists in the assessment of patients;</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>2010 (n=53)</td><td>2011 (n=60)</td><td>Effect (95%CI)
(2011 vs 2010/2009) (n=53)</td></tr>
<tr><td>% of patients maintained vision</td><td>79% (n=42)</td><td>88% (n=53)</td><td>1.11 (0.94 to 1.45)</td></tr>
<tr><td>% of patients had a gain of 15 letters or more BCVA</td><td>6% (n=3)</td><td>20% (n=12)</td><td>3.53 (1.05 to 11.85)</td></tr>
<tr><td>VA changes, letters</td><td>-3.69</td><td>+2.72</td><td></td></tr>
<tr><td></td><td>2009 (n=100)</td><td>2011 (n=20)</td><td></td></tr>
<tr><td>% of patients being referred to 1st assessment within 1 week</td><td>28% (n=28)</td><td>60% (n=12)</td><td>2.14 (1.33 to 3.45)</td></tr>
<tr><td>Mean time interval between treatment decision to 1st treatment</td><td>70 days</td><td>15 days</td><td></td></tr>
</table>
</td></tr>
<tr><td>Notes</td><td>The majority of the changes that were made between 2009 and 2011 were implemented after the 2010 audit.</td></tr>
</table>

Bibliographic reference	**Goudie C; Lunt D; Reid S; Sanders S; Ophthalmic digital image transfer: benefit to triage, patient care and resource. 2014. Ophthalmic and physiological optics; 34(6): 628-35.**
Country/ies where the study was carried out:	UK
Study type	Retrospective study
Aim of the study	To quantity the effect of attaching digit image to ophthalmic referrals. In particular the effect of digital images on appointment priority, the need for an appointment and the disease categories involved.
Study dates	September 2010 to Jan 2011

<table>
<tr><th>Bibliographic reference</th><th>Goudie C; Lunt D; Reid S; Sanders S; Ophthalmic digital image transfer: benefit to triage, patient care and resource. 2014. Ophthalmic and physiological optics; 34(6): 628-35.</th></tr>
<tr><td>Setting</td><td>Ophthalmic referral centre, the Queen Margaret hospital, Dunfermline</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>358 consecutive electronic referrals with attached digital images. (794 consecutive electronic referrals without attached images were interrogated)</td></tr>
<tr><td>Inclusion criteria</td><td>All electronic referrals with or without attached image</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>All electronic referrals with and without images received from community optometry were reviewed and actioned on the day of receipt. When reviewed, the referring optometrist was sent an immediate email acknowledging receipt and outcome of referral.
Initial triage was performed by a specially trained team, consisting of 2 hospital optometrists and 3 specialist ophthalmic nurses.
Any referrals deemed urgent was reviewed by the on call consultant on the day, usually resulting in a patient appointment within 24hour. Non-urgent referral with images were collectedly reviewed at the end of the week by the consultant on call for the weekend. The decision not to see a patient was always made by the consultant, with a subsequent explanatory letter to patient, optometrist and general practitioner.</td></tr>
<tr><td>Results</td><td>Over 90% of referrals without attached imaged resulted in a hospital appointment, but there was no other data reported.

Referral pathway
<table>
<tr><td rowspan="3">Nurse led triage</td><td>On-call consultant</td><td>Urgent HES appointment, n=64 (18%)</td></tr>
<tr><td>On-call consultant/Consultant review</td><td>Routine HES appointment, n=170 (47%)</td></tr>
<tr><td>Consultant review</td><td>Discharge, n=122 (34%)</td></tr>
</table>

Relative risk between new nurse led triage and old referral=47%/90%=0.53 (95%CI 0.47 to 0.59)

Ophthalmological diagnosis given for optometry referrals vetted by the central ophthalmic electronic referral unit as “urgent”
<table>
<tr><th>Diagnosis</th><th>Number of referrals (total=64)</th></tr>
<tr><td>Wet macular pathology</td><td>28</td></tr>
<tr><td>Papilloedema</td><td>6</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Goudie C; Lunt D; Reid S; Sanders S; Ophthalmic digital image transfer: benefit to triage, patient care and resource. 2014. Ophthalmic and physiological optics; 34(6): 628-35.**
	Retinal detachment: 3 Central retinal vein occlusion: 2 Corneal pathology: 2 Macular haemorrhage: 2
Notes	Older referral pathway took between 2 and 32 weeks being referred to the hospital eye service; while new triage referral pathway takes less than 12 weeks. Not AMD specific clinic

Bibliographic reference	**Bo Li; Anne-Marie Powell; Philip L Hooper; Thomas G Sheidow. Prospective evaluation of teleophthalmology in screening and recurrent monitoring of neovascular age-related macular degeneration. A randomised clinical trial. 2015. JAMA Ophthalmol; 133 (2): 276-282.**
Country/ies where the study was carried out	Canada
Study type	Prospective randomised clinical trial
Aim of the study	To evaluate the use of teleophthalmology both in the initial screening and recurrence monitoring of neovascular AMD.
Study dates	November 2011 to November 2012
Setting	Retina service at the Ivey eye institute in London, Ontario, Canada
Source of funding	The Academic Health Science Centre Alternate Funding Plan from the Academic Medical Organisation of Southwestern Ontario.
Sample size	106 patients (106 eyes) enrolled for screening of nAMD, and 63 patients were enrolled in the monitoring of nAMD recurrence.
Inclusion criteria	Not specified
Exclusion criteria	Not specified
Baseline characteristics	Not specified
Methods	Teleophthalmology has the ability to provide localised communit-based evaluations, limiting patient travel and inconvenience. Teleophthalmologic screening program replied on store-forward approach where a series of digital images are obtained by a technician locally and electronically forwarded to a retinal specialist for grading and evaluation. Along with the digital image, a standard ophthalmic examination, including a short patient history, visual acuity and intraocular pressure measurement, can

Bibliographic reference	**Bo Li; Anne-Marie Powell; Philip L Hooper; Thomas G Sheidow. Prospective evaluation of teleophthalmology in screening and recurrent monitoring of neovascular age-related macular degeneration. A randomised clinical trial. 2015. JAMA Ophthalmol; 133 (2): 276-282.**

also be sent electronically to the retinal specialist. After reviewing the teleophthalmologic data set, any patient believed to require clinical assessment and treatment is then transferred to the nearest retinal specialist.

Patients with suspected neovascular AMD

The patients were randomised into routine screening or teleophthalmologic screening during the 1-year period.

Intervention (1T)	Control (1R)
Teleophthalomologic screening	Routine screening
Community-based stand-alone clinics operated by community and general ophthalmologists	Retinal specialists at the Ivey Eye Institute
In person assessment	Being assessed electronically by retinal specialists

Patients who previously treated for neovascular AMD

Patient who were previously treated for neovascular AMD and did not have evidence of disease activity at the time of enrolment (Jan 2010-November 2012)

Intervention (2T)	Control (2R)
Teleophthalmologic monitoring	Routine monitoring
Assessed and followed at the ocular health centre every 2 months	Regular appointment every 2 months
Patients data obtained at each visit were stored in the ocular health centre database and electronically sent to retinal specialist for formal evaluation of neovascular AMD reoccurrence. Patients were followed up at the OHC on a bimonthly if there was no evidence of disease reoccurance of neovascular AMD. Patients with evidence of neovascular AMD reoccurance based on teleophthalmologic data were recalled to the Eye institute for	In-person evaluation by a retinal specialist

Bibliographic reference	**Bo Li; Anne-Marie Powell; Philip L Hooper; Thomas G Sheidow. Prospective evaluation of teleophthalmology in screening and recurrent monitoring of neovascular age-related macular degeneration. A randomised clinical trial. 2015. JAMA Ophthalmol; 133 (2): 276-282.**
	treatment and continued to be followed up as needed
Results	

	Intervention (IT, n=52)	Control (1R, n=54)	Effect (95%CI)
Average time, referral to diagnostic imaging, days	22.5	18.0	4.5 (-2.80 to 11.80)
Time referral to treatment for patients being diagnosed with nAMD and required treatment, days	39.1	30.4	8.7 (-5.29 to 22.69)
	Intervention (2T, n=27)	Control (2R, n=36)	
Average time to recurrence, days	103.9	108.1	-4.2 (-47.77 to 39.15)
Average detection of disease recurrence to treatment time, days	13.6	0.04	13.5 (9.0 to 18.2)
BCVA at time of recurrence	20/154.2	20/155.2	
BCVA at the end of follow-up	20/184.8	20/180.7	

Bibliographic reference	**Markun Stefan, Dishy Avraham, Neuner-Jehle Stefan, Rosemann Thomas, Frei Anja. The Chronic care for wet age-related macular degeneration (CHARMED) study: a randomised controlled trial. 2015. Plos One**
Country/ies where the study was carried out	Switzerland
Study type	RCT
Aim of the study	To investigate the implementation of chronic care model to improve visual function and quality of live
Study dates	Study populations were recruited between April 2011 and Jan 2013, and being followed up for 12 months.
Source of funding	This study was supported by non-commercial foundation Zukunft Hausarzt, Zuricher.
Sample size	169 patients (190 eyes)

<table>
<tr><th>Bibliographic reference</th><th>Markun Stefan, Dishy Avraham, Neuner-Jehle Stefan, Rosemann Thomas, Frei Anja. The Chronic care for wet age-related macular degeneration (CHARMED) study: a randomised controlled trial. 2015. Plos One</th></tr>
<tr><td>Inclusion criteria</td><td>People aged 50 years or older, with wet AMD, who were eligible for therapy with anti-VEGF drugs, had a BCVA of at least 20 letters assessed with the ETDRS chart and provided written consent in study participant. In cases where both eye were affected by wet AMD both eyes were included and followed in the study</td></tr>
<tr><td>Exclusion criteria</td><td>Serious general or psychological illness (advance malignant diseases, severe depressive disorders or dementia) and insufficient German or French language skills (for completing the self-administrated questionnaire).</td></tr>
<tr><td>Baseline characteristics</td><td>Mean age 76.7 (SD=8.0) years; no. of females=107 (633%);</td></tr>
<tr><td>Methods</td><td>People were randomised either in intervention and control groups.
<table>
<tr><th>Intervention (chronic care model) group</th><th>Control group</th></tr>
<tr><td>Evidence based core elements of the chronic care model (CCM). Delivery of CCM was organised as followed: in every study site a practice assistant was assigned to be the “Chronic Care Coach” (CCC). The CCCs attended a one day training course comprising the instruction and materials to utilize as means to introduce the CCM core elements. The following elements were introduced:
Organisation of health care delivery system;
Self-management support;
Decision support;
Clinical information systems</td><td>No study specific intervention</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Markun Stefan, Dishy Avraham, Neuner-Jehle Stefan, Rosemann Thomas, Frei Anja. The Chronic care for wet age-related macular degeneration (CHARMED) study: a randomised controlled trial. 2015. Plos One**
Results	

	Intervention CCM (n=84)	Control (n=85)	Effect (95%CI)
Visual acuity			
Mean changes of ETDRS at 6 months	+0.3 (95%CI -3.4 to 4.0)	+2.7 (95%CI -1.0 to +6.4)	-2.40 (-12.65 to 7.85)
Mean changes of ETRDS at 12 months	-0.3 (95%CI -4.4 to +3.8)	+4.5 (95%CI +0.1 to +8.9)	-4.80 (-11.31 to 1.71)
NEI VFQ-25			
Score at 6 months	+2.1 (95%CI -0.4 to +4.6)	+2.4 (95%CI -0.3 to +5.1)	-0.30 (-3.89 to 3.29)
Score at 12 months	+3.4 (95%CI +1.1 to +5.7)	+1.3 (95%CI -1.2 to +3.8)	2.10 (-0.96 to 5.16)
Patients assessment of chronic illness care (PACIC) at 12 months	+0.6 (95%CI +0.1 to 1.0)	+0.6 (95%CI +0.2 to 1.0)	0
Number of ophthalmologist visits at 12 months, median (IQR)	12 (9 to 12)	12 (7 to 13)	

Notes	The study was stopped early due to recruitment difficulties. Open label study design (awareness of allocation in the intervention group)

Bibliographic reference	**Reeves Barmaby; Scott Lauren; Taylor Jodi; Harding Simon; Peto Tunde, Muldrew Alyson, Hogg Ruth; Wordsworth Sarah; Mills Nicola; O'Reilly Dermot; Rogers Chris; Chakravarthy. Effectiveness of community versus hospital eye service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual non-inferiority trial. 2016. BMJ Open.**
Country/ies where the study was carried out	UK
Study type	RCT
Aim of the study	To compare the ability of ophthalmologists versus optometrists to correctly classify retinal lesions due to neovascular age-related macular degeneration (nAMD).
Source of funding	The Queen's university Belfast. The ECHoES trial was funded through the rapid trials funding call advertised by the National Institute for Health Research Health Technology Assessment programme.
Sample size	155 healthcare professional including 62 ophthalmologists and 67 optometrists

<table>
<tr><th>Bibliographic reference</th><th>Reeves Barmaby; Scott Lauren; Taylor Jodi; Harding Simon; Peto Tunde, Muldrew Alyson, Hogg Ruth; Wordsworth Sarah; Mills Nicola; O'Reilly Dermot; Rogers Chris; Chakravarthy. Effectiveness of community versus hospital eye service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual non-inferiority trial. 2016. BMJ Open.</th></tr>
<tr><td>Inclusion criteria</td><td>Ophthalmologists were required to have 3 years' post-registration experience in ophthalmology, have passed the part 1 examination of the Royal College of Ophthalmologists or the Diploma in Ophthalmology or equivalent and have experience within the AMD service (no minimum duration specified).
Optometrists were required to be fully qualified, registered with the General Optical Council for at least 3 years and not be participating or have participated in any AMD shared care scheme.</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>A non-inferiority trial designed to emulate a parallel group design.
Decision about the reactivation status of lesions were made from vignettes, consisting of sets of retinal images (colour and spectral domain OCT) with accompanying clinical information, rather than by examining actual patients. Re-treatment decision-making on the basis of review of image, in the absence of the patient, is a strategy that is increasing being used by the HES to improve the efficiency of nAMD clinics.
A database consisting 288 vignettes was created from the clinical and image repository of a previously conducted trial (HTA ref: 07/36/01). The vignette consisted of a brief clinical summary that provided a patient's age, gender, cardiovascular health and smoking status; 2 sets of images comprising colour fundus and radial pattern spectral domain OCT from 2 separate visits with the corresponding visual acuity from each visit. The 2 sets of images were termed baseline and index, with the former from a visit when the lesion was quiescent and the latter from a visit when the lesion could have been either quiescent or reactivated.
All participants received the same training. Ophthalmologists and optometrists are qualified to detect retinal pathology, but optometrists may not have the skills to detect lesion reactivation. Eligible ophthalmologists may also not have been fully trained to detect lesion reactivation since doctors without specialist skills (grade ST1 and above) often staff retina clinics in the HES. There were 2 aspects of training. First, participants had to attend 2 online webinars; second, each participant had to assess a set of training vignettes and achieve a criterion level of performance.</td></tr>
<tr><td>Results</td><td>The primary outcome was correct classification of the activation status of the nAMD lesion characterised in the vignette at the index visit from the image and other information the vignette contained. Participants' classifications (reactivated, quiescent or suspicious) were judged against an expert reference standard.

<table>
<tr><td></td><td>Ophthalmologists</td><td>Optometrists</td><td>Effect RR (95%CI)</td></tr>
<tr><td>No. of correctly classified the nAMD lesion in the index images</td><td>1722/2016 (85.4%)</td><td>1702/2016 (84.4%)</td><td>1.01 (0.99 to 1.04)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Reeves Barmaby; Scott Lauren; Taylor Jodi; Harding Simon; Peto Tunde, Muldrew Alyson, Hogg Ruth; Wordsworth Sarah; Mills Nicola; O'Reilly Dermot; Rogers Chris; Chakravarthy. Effectiveness of community versus hospital eye service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual non-inferiority trial. 2016. BMJ Open.**

No. of correctly classified a vignette as reactivated	736/994 (74.0%)	795/994 (80.0%)	0.93 (0.88 to 0.97)
No. of correctly classified a vignette as quiescent/suspicious	986/1022 (96.5%)	907/1022 (88.7%)	1.09 (1.06 to 1.11)
Error occurred for the vignette that were classified as reactivated	62/994 (6.2%)	57/994 (5.7%)	1.09 (0.77 to 1.54)

Bibliographic reference	**Engman S, Edwards A, Barkri S. Administration of repeat intravitreal anti-VEGF drugs by retina specialists in an injection-only clinical for patients with exudative AMD: patient acceptance and safety. 2011. Ophthalmology 26(6): 380-86.**
Country/ies where the study was carried out	USA
Study type	Retrospective case review
Aim of the study	To examine patient acceptance and safety of repeated intravitreal injections of anti-VEGF agents for exudative AMD, by retina specialist, without an eye examination before every injection.
Source of funding	This study was supported by Research to prevent blindness and the central for translational science activities grant.
Sample size	110 patients (115 eyes)
Inclusion criteria	All intravitreal injections of bevacizumab and ranibizumab performed between June 2008 and May 2009 for the treatment of wet AMD.
Exclusion criteria	Not specified
Baseline characteristics	Not specified
Methods	Retrospective chart review. 115 eyes (110 patients) with exudative AMD underwent repeated intravitreal anti-VEGF injections with limited interval examination and diagnostic testing. Medication, laterality, number of injection cycles started and completed, number of injections per injection cycle, subjective visual changes, pre- and post-injection visual acuity (VA), pre- and post-injection intraocular pressure (IOP), nurse- and patient-initiated phone calls, emergency (non-scheduled) clinic visits, complications, new diagnoses, and patient complaints after each injection were recorded. The main outcome measures were complications and patient complaints.

<table>
<tr><th>Bibliographic reference</th><th>Engman S, Edwards A, Barkri S. Administration of repeat intravitreal anti-VEGF drugs by retina specialists in an injection-only clinical for patients with exudative AMD: patient acceptance and safety. 2011. Ophthalmology 26(6): 380-86.</th></tr>
<tr><td>Results</td><td>An injection clinic cycle is defined as the period of time from enrolment in the injection clinic until return for a full examination at the conclusion of the prescribed number of injections in the designated injection clinic.
A total number of intravitreal injections was 549 for 110 patients during a total of 175 injections clinic cycles. Of 549 injections were given at the clinical appointment at the time of enrolment, with remaining 396 given on subsequent visits to the designated injection clinic.
Patients were considered to have an “interrupted” injection circle cycle if they had a dilated examination at any time during an injection cycle prior to their scheduled post-injection clinical appointment.
<table>
<tr><td>Mean number of injection given per cycle (including injections given at the time of enrolment in the injection clinic)</td><td>Mean number of injection given in the designated injection clinic only (not including those given at the time of enrolment)</td></tr>
<tr><td>3.1</td><td>2.2</td></tr>
</table>
<table>
<tr><td rowspan="3">175 injection cycles(110 patients, 549 injections)</td><td>134 uninterrupted cycles (76.6%)</td><td>-</td></tr>
<tr><td rowspan="2">41 interrupted cycles (23.4%)</td><td>17 emergency visits</td></tr>
<tr><td>14 injection clinic evaluations</td></tr>
</table>
Of 175 injection cycles, cycles were more likely to be interrupted cycles compared to interrupted (RR=3.27, 95%CI 2.47 to 4.32)</td></tr>
</table>

Bibliographic reference	**Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.**
Country/ies where the study was carried out	Denmark
Study type	Systematic review
Aim of the study	This review searched the existing literature was to provide an overview of the experiences in non-physicians such as nurses are trained to give injections into the vitreous body of the eye for intravitreal therapy with vascular endothelial growth factor inhibitors against common eye diseases, e.g. age-related macular degeneration and diabetic retinopathy.
Source of funding	Not reported

<table>
<tr><th>Bibliographic reference</th><td>Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.</td></tr>
<tr><td>Sample size</td><td>5 included studies</td></tr>
<tr><td>Inclusion criteria</td><td>Studies had to address any outcome based on non-physician delivered intravitreal injection therapy.
Being non-physician was defined as the injecting personel not being a physician.</td></tr>
<tr><td>Exclusion criteria</td><td>Non-English studies
Case studies
Comments</td></tr>
<tr><td>Baseline characteristics</td><td>N/A</td></tr>
<tr><td>Methods</td><td>The study searched the literature using electronic bibliographic databases of PubMed, EMBASE, the Cochrane library, CINAHL and the Web of Science on 22 Septermber 2015.
The following search strategy (nurse OR orthoptists OR optometrist OR non-physicial) AND (intravitreal)
All references were screened by title and abstract by one author who excluded in irrelevant references, duplicates and studies not written in English. No date restrictins were applied.
All remaining references were retrieved in full-text. Full-text artciles were read for eligibility and data extraction by 2 authors, and reference for all included studied were read to find additional eligible studies.</td></tr>
<tr><td>Results</td><td>5 studies were included in the review.
All studies used nurses for non-physician intravitreal injections therapy.
<table>
<tr><th>Studies</th><th>Country</th><th>Design</th><th>Non-physician characteristics</th><th>Supervised injections, n</th><th>Injections</th><th>Prevalence of injection related AE, %</th><th>Patient satisfaction</th></tr>
<tr><td>DaCosta 2014</td><td>UK</td><td>Retrosective Cohort 2 yrs</td><td>3 nurses trained in 1 1-day course after which they observed practice</td><td>20</td><td>4,000</td><td>Endophthalmities: 0
Cataract: 0
Loss of central artery perfusion: 0
Uveitis: 0
Retinal detachment: 0
Vitreous haemorrhage: 0
Subconjunctival haemorrhage: 57</td><td>62% (31/50) patients were completedly satisfied (score 5/5); 38% (19/50) were satisfied (score 4/5)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.							
	Hasler 2015	Denark	Retrosective Cohort 5 yrs	4 nurses traing by vitreoretinal surgeons	8-10	12,542	Endophthalmities: 0.032	
	Michelotti 2014	UK	Retrosective Cohort 17mo	2 nurse and 1 senior nurse were trained and supervised by ophthammologist	200	3,355	Endophthalmities: 0 Retinal tear: 0 Uveitis: 0 Retinal detachment: 0 Vitreous haemorrhage: 0 Subconjunctival haemorrhage and corneal abrasion:3.6	Formal survey ongoing; no formal or informal patient complaints reported
	Simcock 2014	UK	Prosective Cohort 5.5 yrs	2 nurses practitioners trained 1-on-1 by a vitreoretinal surgeon	20	10,006	Endophthalmities: 0.40	
	Verma 2013	UK	Prosective Cohort 5mo	4 nurses with surgical backgrounds trained in a 1-day course	25	1,400	Endophthalmities: 0 Cataract: 0 Retinal detachment: 0 Exacerbation of blepharitis: 0.71 Corneal punctate epitheliopathy: 5.0 Subconjunctival haemorrhage:8.6	97% patients (1,351/1,400) gave pain score of 0-1 out of 5 (max); survey showed high levels of satisfaction.
Comments	1. Was an “a priori” design? it was unclear whether inclusion criteria were established before the conduct of the review; 2. Was there duplicate study selection and data extraction? all reference were screened by title and abstract by one author who exluded irrelevant references, duplications and studies not written in Engliish. Full text articles were read for eligibility and							

Bibliographic reference	**Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.**
	data extraction by 2 authors. The following search strategy (nurse OR orthoptists OR optometrist OR non-physicial) AND (intravitreal). 3. Was a comprehensive literature search performed? The search used the electronic bibliographic database of PubMed, EMBASE, the Cochrane Libraray, CINAHL and the web of science. 4. Was the status of publication used as as an inclusion crierion? non-English studies were excluded. 5. Was a list of studies (included and excluded) provided? Included studies were listed; 6. Were the characteristics of the included studies provided? Table 1 in the study summarised included studies. 7. Was the scientific quality of the included studies assessed and documented? Studies were included in a qualitative analysis to provide an overview of the existing literature. After reading the included studies, four topics were identified which we used to systematise the presentation of the review. Quality of included was not stated. 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? N/A 10. Was the likelihood of publication bias assessed? Not stated 11. Was the conflict of interest included? Yes Amstar score 3/11.
Notes	There was another systematic review (Li, Greenberg and Krzystolik 2015, nurse-administered intravitreal injections: a systematic review. Graefes Arch Clin Exp Ophthalmol 253: 1619-21), which included patients satisfaction as one of study outcomes.

Bibliographic reference	**Arias L ; Armada F ; Donate J ; Garcia-Arumi J ; Giralt J ; Pazos B ; Pinero A ; Martinez F ; Mondejar J J; Ortega I ; Zlateva G ; Buggage R . Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. 2009. Eye 23: 326-333.**
Country/ies where the study was carried out	Spain
Study type	Retrospective study
Aim of the study	To assess the impact on visual acuity of delays between diagnosis and treatment in patients with subfoveal neovascular age-related macular degeneration (NV-AMD) and to evaluate NV-AMD patients' emotional status before therapy initiation.
Setting	Patients registered in the Spanish national health system and referred to regional health centre for evaluation/treatment by a retinal specialist
Source of funding	The study was funded by Pfizer.

<table>
<tr><th>Bibliographic reference</th><th>Arias L ; Armada F ; Donate J ; Garcia-Arumi J ; Giralt J ; Pazos B ; Pinero A ; Martinez F ; Mondejar J J; Ortega I ; Zlateva G ; Buggage R . Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. 2009. Eye 23: 326-333.</th></tr>
<tr><td>Sample size</td><td>100</td></tr>
<tr><td>Inclusion criteria</td><td>Patients diagnosed with subfoveal neovascular AMD, aged 50 years or over, either gender with untreated AMD in one or both eyes were identified at the time diagnosis upon referral to a regional health centre for treatment. Patients were eligible for inclusion if they were capable of understanding and responding to study instruments and if they provided consent to participate.</td></tr>
<tr><td>Exclusion criteria</td><td>diagnosis of choroidal neovascularisation secondary to eye conditions other than AMD; participant or planned participation in any other clinical trial during the study period; or clinical or psychological conditions the effects of which might interfere with the collection or interpretation of study findings.</td></tr>
<tr><td>Baseline characteristics</td><td>Mean age (SD)=74.2 (7.9) years; no. of female=50 (50%); mean number of co-morbidities (SD)=2.2 (1.5);</td></tr>
<tr><td>Methods</td><td>This study included newly diagnosed NV-AMD patients registered in the Spanish national health system and referred to regional health centers for evaluation/treatment by a retinal specialist from 09/2005 to 03/2006. Records were reviewed and data abstracted at referring physicians' offices (diagnosis visit) and regional health centers (treatment visit). Treatment was at physicians' discretion. The Hospital Anxiety and Depression Scale was administered at the treatment visit (before therapy).</td></tr>
<tr><td>Results</td><td>The median time from the diagnosis visit to treatment visit was 2.3 months (95%CI 0.2 to 10.8).
50% patients received treatment within 2.3 months, 25% experience delays of > 2.3 to 4.2 months, and 25% had delays > 4.2 to 11.7 months.

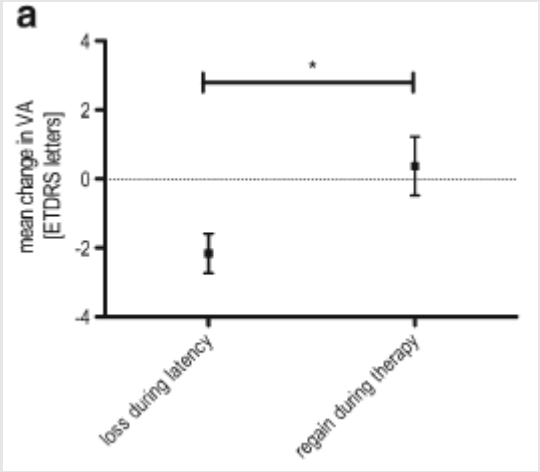
Correlation between months to treatment and mean change in visual acuity score (n=98)
<table>
<tr><th>Time to treatment</th><th>Change in visual acuity score, mean (SD)</th><th>Effect (95%CI)</th></tr>
<tr><td><1 months (n=29)</td><td>0.1 (0.4)</td><td>-</td></tr>
<tr><td>1 to 2 months (n=12)</td><td>0.2 (0.4)</td><td>0.10 (-0.17 to 0.37)</td></tr>
<tr><td>2 to 3 months (n=18)</td><td>0.4 (0.6)</td><td>0.30 (-0.01 to 0.61)</td></tr>
<tr><td>>3 months (n=39)</td><td>0.4 (0.9)</td><td>0.30 (-0.02 to 0.62)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Muether P S; Hermann M M; Koch K ; Fauser S . Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. 2011. Graefes Archive for Clinical & Experimental Ophthalmology; 249 (5): 633-37.</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Germany</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Muether P S; Hermann M M; Koch K ; Fauser S . Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. 2011. Graefes Archive for Clinical & Experimental Ophthalmology; 249 (5): 633-37.</td></tr>
<tr><td>Study type</td><td>Prospective non-randomised trial</td></tr>
<tr><td>Aim of the study</td><td>To evaluate changes in visual acuity and central retinal thickness over time, and their consequences for the patients concerned</td></tr>
<tr><td>Source of funding</td><td>The study was supported by the Koeln Fortune programme/Faculty of Medicine, University of Cologne</td></tr>
<tr><td>Sample size</td><td>90</td></tr>
<tr><td>Inclusion criteria</td><td>Neovascular AMD of all subtypes (occult, predominantly classic, minimally classic, classic, and retinal angiomatous proliferative lesions). Diagnosis was established by fluorescence and indocyanine green angiography at baseline</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with massive hemorrhages or advanced fibrosis were excluded. Further exclusion criteria included any previous CNV treatment, previous vitrectomy, central laser coagulation, peripheral laser coagulation within the last year, cataract surgery within the last 3 months, diabetic retinopathy, and progressive glaucoma.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>First treatment (n=69)</td><td>Recurrent treatment (n=21)</td></tr>
<tr><td>Mean age (SD)</td><td>77.7 (6.9)</td><td>77.0 (7.3)</td></tr>
<tr><td>VA at diagnosis, logMAR (SD)</td><td>0.62 (0.31)</td><td>0.44 (0.26)</td></tr>
<tr><td>VA at time of treatment, logMAR (SD)</td><td>0.60 (0.30)</td><td>0.47 (0.27)</td></tr>
<tr><td>Time from indication to treatment days (SD)</td><td>27.4 (25.2)</td><td>23.0 (13.7)</td></tr>
</table>
</td></tr>
<tr><td>Methods</td><td>Sixty-nine patients indicated for first-time ranibizumab treatment and 21 patients with necessary re-treatment were included in the study. Visual acuity and spectral domain optical coherence tomography (SD-OCT) central retinal thickness at the time of the indication examination were compared to values at the first-time treatment and during recurrent ranibizumab treatment.
First treatment: time between treatment indication and first injection.
Recurrent treatment: time between diagnosis of persistent or recurrent CNV activity and subsequent re-treatment indication and first re-injection.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td colspan="2">First treatment (n=69)</td><td></td><td colspan="2">Recurrent treatment (n=21)</td><td></td></tr>
<tr><td></td><td>Visual loss</td><td>No visual loss</td><td>Effect (95%CI)</td><td>Visual loss</td><td>No visual loss</td><td>Effect (95%CI)</td></tr>
<tr><td>No. of patients (%)</td><td>31 (44.9)</td><td>38 (55.1)</td><td>0.82 (0.58 to 1.14)</td><td>11 (52.4)</td><td>10 (47.6)</td><td>1.10 (0.60 to 2.02)</td></tr>
<tr><td>Time delays, days</td><td>31.6</td><td>24.0</td><td>MD=7.6 (1.07 to 14.13)</td><td>25.6</td><td>20.2</td><td>5.4 (-3.54 to 14.34)</td></tr>
<tr><td></td><td>Had a loss of more</td><td>No a loss of more than one</td><td></td><td>Had a loss of more than</td><td>No a loss of more than one</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Muether P S; Hermann M M; Koch K ; Fauser S . Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. 2011. Graefes Archive for Clinical & Experimental Ophthalmology; 249 (5): 633-37.						
		than one logMAR (equivalent to more than 5 ETDRS letters)	logMAR (equivalent to more than 5 ETDRS letters)		one logMAR (equivalent to more than 5 ETDRS letters)	logMAR (equivalent to more than 5 ETDRS letters)	
	No. of patients (%)	12 (17.4)	57 (82.6)	0.21 (0.12 to 0.36)	2 (9.5%)	19 (90.5)	0.11 (0.03 to 0.40)
	Time days, days	36.5	25.5	MD=11.0 (-0.27 to 22.27)	52.0	20.0	32.0 (10.05 to 53.93)

Bibliographic reference	Muether P S; Hoerster R ; Hermann M M; Kirchhof B ; Fauser. Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration. 2013. Graefes Archive for Clinical & Experimental Ophthalmology 251 (2): 453-58.
Country/ies where the study was carried out	Germany
Study type	Prospective interventional case series
Aim of the study	To investigate the efficacy of a monthly spectral domain optical coherence tomography (OCT) controlled PRN treatment regimen in clinical routine with the described delay between indication to treat and treatment.
Source of funding	The study was supported by the Koeln Fortune Programme, Faculty of Medicine, University of Cologne
Sample size	102
Inclusion criteria	Patients with primary diagnosis of exudative AMD based on fluorescein and indocyanine green angiography and SD-OCT were enrolled following informed consent. All patients received three initial consecutive monthly ranibizumab.
Exclusion criteria	Not specified
Baseline characteristics	102 patient enroled, and 89 patients were followed up for 12 months, and 83 were included in the analysis. Of those included in the analysis, mean age was 76.8 (SD=6.9). The CNV subtype was occult in 52 cases, minimally classic in 4 cases, predominantly classic in 5 cases, and classic in 12 cases
Methods	Eighty-nine patients with neovascular AMD were followed for 12 months. Early treatment diabetic retinopathy study (ETDRS) visual acuity (VA), Radner reading VA and spectral domain optical coherence tomography were performed monthly, with

Bibliographic reference	**Muether P S; Hoerster R ; Hermann M M; Kirchhof B ; Fauser. Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration. 2013. Graefes Archive for Clinical & Experimental Ophthalmology 251 (2): 453-58.**
	additional fluorescein angiography if needed. After an initial loading phase of three consecutive monthly intravitreal injections with ranibizumab, re-injections were performed when recurrent activity of choroidal neovascularization (CNV) was detected. Ranibizumab in Germany is only refunded by the health insurance company following a written request of the ophthalmologist including VA scores, FA and SD-OCT findings. Latency and approval of the request varies depending on the case and the insurance, as well as short-term surgical capacities for appointment of treatment. IN this study, latency between indicator for treatment and subsequent treatment was determined for every patients for the analysis.
Results	To determine the influence of latency between indication to treat and eventual treatment, the study analysed the loss of VA during latency and therapy period. During latency visual acuity decreased by -2.16 (SD=4.97) letter ETDRS. After conduction of the subsequent treatment series with 3 monthly injection, visual acuity recovered by +0.37 (SD=7.44) letter EDTRS. Thus recovery of ETDRS VA was significant lower than visual loss during latency period. 

Bibliographic reference	**Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.**
Country/ies where the study was carried out	Canada

Bibliographic reference	Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.
Study type	Prospective case series
Aim of the study	To determine whether a change in visual acuity occurred between time of initial (referral) diagnosis and the time of assessment and treatment by a retinal specialist.
Source of funding	The study was funded in part by Pfizer Global Pharmaceuticals, Pfizer Inc
Sample size	38
Inclusion criteria	Patients who presented with a newly diagnosis subfoveal CNV. Patients included in they had new-onset wet AMD, defined as acuity onset (<30 days) of visual loss, visual distortion, change in colour vision or development of central blurring of vision, in conjunction with angiographic evidence of subfoveal CNV.
Exclusion criteria	Patients were excluded of their CNV was not related to AMD.
Baseline characteristics	32 out of 38 enrolled patients included in the analysis. Included patietns had a mean age of 77 (SD=8.66), and 24 (75%) were female; 6% had purely classic membranes, 44% predominantly classic lesions, 19% minimally classic lesions and 31% occult CNV. Nearly all of the patients (94%) had evidence of macular degeneration in both eyes; most patients (72%) had the dry type in their contralateral eye.
Methods	A prospective pilot study of 38 consecutive AMD patients who presented with newly diagnosed subfoveal choroidal neovascularization was conducted in a tertiary care retinal practice. All eligible subjects underwent clinical examination and digital fluorescein angiography at the time of assessment by a retinal specialist. Correlations were performed to assess the association between continuous independent variables and any visual deterioration since initial diagnosis. Multivariate linear regression models with stepwise techniques were used to evaluate any association between visual progression and time elapsed, while controlling for potential clinical covariates.
Results	Conceptual model of AMD pathway

Bibliographic reference	**Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.**

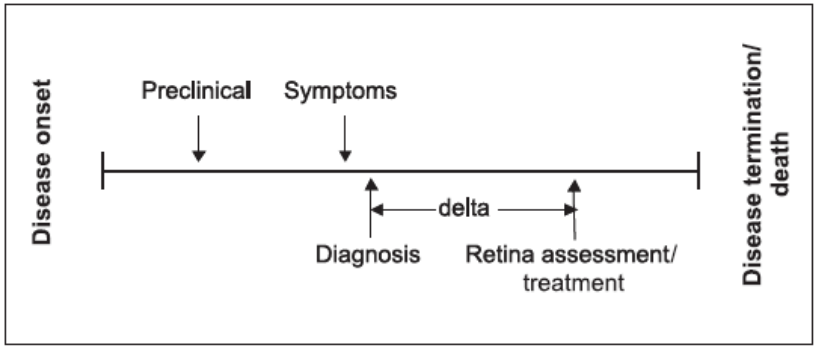
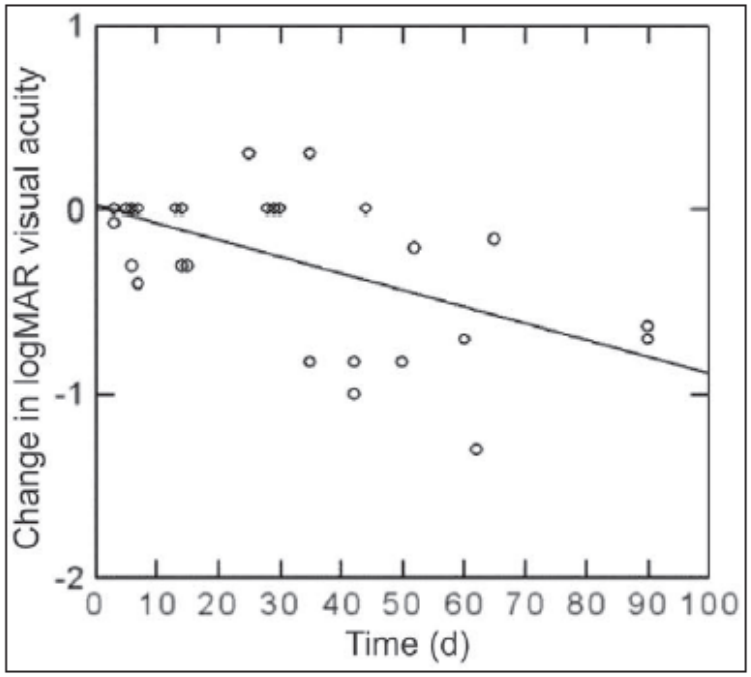


Fig. 1—Conceptual model of age-related macular degeneration (AMD).

The median time elapsed between initial diagnosis and referral assessment and treatment was 28 days; 14 (44%) of the subjects had some degree of visual loss, and 5 (16%) lost > 3 lines of distance visual acuity . Multivariate linear regression demonstrated that only time elapsed and lesion type based on fluorescein angiography were associated with progression of visual loss. Co-efficient for time elapsed=0.00674 (t=-4.148, 95%CI -0.010 to -0.003), p=0.000

Bibliographic reference	**Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.**
	 Fig. 2—Relation of degree of loss in visual acuity (calculated as the logarithm of the minimum angle of resolution [logMAR]) to time between initial diagnosis and specialist assessment and treatment.

Bibliographic reference	**Rauch R; Weingessel B; Maca S M; Vecs. Time to first treatment: the significance of early treatment of exudative age-related macular degeneration. 2012. Retina 32 (7): 1260-64.**
Country/ies where the study was carried out	Austria

Bibliographic reference	**Rauch R; Weingessel B; Maca S M; Vecs. Time to first treatment: the significance of early treatment of exudative age-related macular degeneration. 2012. Retina 32 (7): 1260-64.**
Study type	Retrospective case series
Aim of the study	To determine whether the duration of neovascular AMD, defined as the time elapsed between first symptoms and treatment, has an impact on the visual outcome after ranibizumab therapy.
Source of funding	Not reported
Sample size	45 patients
Inclusion criteria	Patients included when a subfoveal CNV showing activity of the disease was present, for instance, presence of retinal haemorrhage, intraretinal edema, subretinal fluid, or fibrovascular pigment epithelial detachment and fluorescein leakage during angiography. Furthermore, patients had to have received 2 ranibizumab injections at an interval of 4 weeks and had to be able to precisely state the onset and kind of visual symptoms (visual distortion, change in colour vision, or development of central blurring of vision)
Exclusion criteria	Patients were excluded from the study If the CNV was not subfoveal or not related to AMD, if they were not able to give precise information upon visual symptoms, or if they have received any other treatment than 2 injections of ranibizumab
Baseline characteristics	Mean age (SD)=76.9 (9.1) years; no. of female=33 (73%).
Methods	In the study, 45 patients with exudative age-related macular degeneration were split into 3 groups depending on the duration of visual symptoms--Group I: <1 month, Group II: 1 month to 6 months, and Group III: >6 months. Best-corrected visual acuity, clinical ophthalmologic examination, and central retinal thickness as measured by optical coherence tomography were recorded at baseline and 2 months later. Fluorescein angiography was performed at baseline. Treatment consisted of 2 intravitreal injections of 1.25 mg of ranibizumab at baseline and after 4 weeks. Non-parametric correlations were calculated using the Spearman rho test. For comparing differences in mean values and standard deviation of variables, a two-tailed t test was performed.
Results	

	Group 1 (duration symptoms <1m)	Group 2 (1-6m)	Group 3 (>6m)	Effect (G3-G1) (95%CI)
No. of patients	22	17	6	
Mean symptom duration, days (SD)	18 (9)	63.1 (21.3)	201 (14)	183 (171.18(-194.82)
Baseline VA, logMAR	0.4 (0.19)	0.31 (0.16)	0.09 (0.07)	-0.31 (-0.41 to 0.21)
VA after treatment, logMAR	0.49 (0.20)	0.38 (0.16)	0.16 (0.13)	-0.33 (- 0.46 to 0.20)

Bibliographic reference	**Rauch R; Weingessel B; Maca S M; Vecs. Time to first treatment: the significance of early treatment of exudative age-related macular degeneration. 2012. Retina 32 (7): 1260-64.**				
	Mean VA change from baseline to treatment	0.09	0.07	0.06	-0.03 (-0.05 to -0.01)
	Visual acuity by patients groups (symptom duration)				

Bibliographic reference	**Rasmussen A ; Brandi S ; Fuchs J ; Hansen L H; Lund-Andersen H ; Sander B ; Larsen M . Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Opthalmologica 93 (7), 2015.**
Country/ies where the study was carried out	Denmark
Study type	Retrospective case series
Aim of the study	To study the relation between the interval from diagnosis to initiation of intravitreal injection therapy and visual outcome in neovascular age-related macular degeneration (nAMD) and to report changes over time in fellow-eye status.
Study date	2007, 2009, 2011 and 2012
Source of funding	This study was supported by the VELUX Foundation, the Lundbeck Foundation and Glostrup Hospital.
Sample size	1099 people (1185 eyes)
Inclusion criteria	Patients aged≥50 years with active choroidal neovascularisation associated with AMD Patients had BCVA≥0.05 Patients' CNV involvied the foveal centra and absecen of extensive subretinal fibrosis
Exclusion criteria	Patients had previous PDT, retinal photocoagulation or intraocular pharmacotherapy Patients failed to complete the 3 monthly loading-phase injections Patients had missing data for baseline or 3 month BCVA
Baseline characteristics	Year (no.) / age median (IQR) / BCVA (confidence limit) 2007 (296) / 80 (10) / 0.23 (0.21-0.25) 2009 (267) / 80 (9) / 0.24 (0.22-0.26) 2011 (301) / 80 (10) / 0.23 (0.21-0.25) 2012 (321) / 79 (12) / 0.23 (0.21-0.26)
Methods	The retrospective analysis of a clinical database included all eligible patients who began intravitreal ranibizumab treatment for nAMD during the first 6 months of years 2007, 2009, 2011 and 2012. The periods were chosen to represent the first and the most recent year with full implantation of intravitreal VEGF inhibitor treatment for nAMD with arbitrarily chosen years in between and intervals between cohorts that were large enough to enhance contrast between clinical practices.

<table>
<tr><th>Bibliographic reference</th><th>Rasmussen A ; Brandi S ; Fuchs J ; Hansen L H; Lund-Andersen H ; Sander B ; Larsen M . Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Opthalmologica 93 (7), 2015.</th></tr>
<tr><td></td><td>The treatment protocol prescribed 3 initial 0.5mg ranibizuma injections at intervals of 4 weeks followed by a renvewed clinical exmainiation 1 month after the third injection.</td></tr>
<tr><td>Results</td><td>Time to treatment and mean ETDS letters gain
<table>
<tr><td>Year (no.)</td><td>Time to treatment, median (days)</td><td>Mean ETDRS letter gain in eyes with nAMD (confidence limits)</td><td>Mean ETDRS letter gain in fellow eyes with nAMD (confidence imits)</td></tr>
<tr><td>2007 (296)</td><td>16</td><td>2.6 (1.1 to 4.1)</td><td>5.1</td></tr>
<tr><td>2009 (267)</td><td>11</td><td>0.4 (-1.8 to 2.5)</td><td>4.3</td></tr>
<tr><td>2011 (301)</td><td>2</td><td>5.3 (3.6 to 7.0)</td><td>4.6</td></tr>
<tr><td>2012 (321)</td><td>1</td><td>6.3 (4.8 to 7.7)</td><td>4.8</td></tr>
</table>
<table>
<tr><td></td><td colspan="2">Time to treatment</td><td>Effect (95%CI)</td></tr>
<tr><td></td><td>13.5 days</td><td>1.5 days</td><td></td></tr>
<tr><td>Mean ETDRS letter giain (SD)</td><td>1.56 (15.42)</td><td>5.8 (14.12)</td><td>-4.24 (-5.93, -2.55)</td></tr>
</table></td></tr>
<tr><td>Notes</td><td>The estimated effect showed that 4 more letters lost of those waited longer to treatment. (4 letters differences for 12 days different time to treatment.</td></tr>
</table>

Bibliographic reference	**Real J P; Luna J D; Urrets-Zavalia J A; De Santis ; M O ; Palma S D; Granero G E. Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration. 2013. European Journal of Ophthalmology 23(6): 857-864.**
Country/ies where the study was carried out	Argentina
Study type	Retrospective cohort study
Aim of the study	To evaluate the impact on therapeutic effects and visual outcome of the different accessibilities to neovascular treatment.
Source of funding	No financial support was received for the study
	Sample size: 96 eyes (78 patients)

<table>
<tr><th>Bibliographic reference</th><td>Real J P; Luna J D; Urrets-Zavalia J A; De Santis ; M O ; Palma S D; Granero G E. Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration. 2013. European Journal of Ophthalmology 23(6): 857-864.</td></tr>
<tr><td></td><td>Inclusion criteria: patients aged over 50 years with treatment-naïve subfoveal choroidal neovascularisation secondary to neovascular AMD, confirmed by fluorescein angiogram (FA) or optical coherence tomography (OCT), who were managed within bevacizumab or ranibizumab in one of 3 opthalmologic centres.
Exclusion criteria: patients with CNV related to degeneration myopia, angioid streaks, chorioretinal inflammatory diseases, hereditary retinal disorderd, or central serous chorioretinopathy were excluded from the analysis, as well as those with CNV secondary to PCV ore RAP, or with a history of laser photocoagulation treatment, PDT, or prior intravitreal therapy. Patients who during the monitoring year had received a combined treatment with other drugs and/or surgical treatment that could have modified the VA were also excluded.
Baseline characteristics:
<table>
<tr><td></td><td>Bevacizumab (n=52 eyes, 41 patients)</td><td>Ranibizumab (n=44 eyes, 37 patients)</td><td>P value</td></tr>
<tr><td>Male, n(%)</td><td>17 (33)</td><td>17 (39)</td><td>0.66</td></tr>
<tr><td>Mean age, years (SD)</td><td>73.9 (9.28)</td><td>78.6 (6.76)</td><td><0.01</td></tr>
<tr><td>Occult CNV lesion</td><td>22 (44)</td><td>17 (13)</td><td>0.83</td></tr>
<tr><td>Classic CNV</td><td>19 (28)</td><td>18 (29)</td><td>0.68</td></tr>
<tr><td>VA≥20/40, n(%)</td><td>8 (15)</td><td>6 (13)</td><td>0.99</td></tr>
<tr><td>20/40 to 20/320</td><td>32 (62)</td><td>31 (70)</td><td>0.39</td></tr>
<tr><td>VA≤20/320</td><td>12 (23)</td><td>7 (16)</td><td>0.45</td></tr>
<tr><td>Mean VA, logMAR (SD)</td><td>0.79 (0.42)</td><td>0.77 (0.39)</td><td>0.8</td></tr>
</table></td></tr>
<tr><td>Methods</td><td>A retrospective analysis of the charts of 78 patients with previously untreated exudative AMD, who were treated with ranibizumab or bevacizumab between January 2009 and December 2011. The main outcomes measured included time delay and change in mean best-corrected visual acuity (BCVA) between diagnosis and treatment and mean BCVA change at 1-year follow-ups.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Bevacizumab (n=52 eyes, 41 patients)</td><td>Ranibizumab (n=44 eyes, 37 patients)</td><td>Effect (long delay vs short delay) (95%CI)</td></tr>
<tr><td>Average waiting time, days (SD)</td><td>36.06 (21.86)</td><td>153.80 (76.36)</td><td>117.74 (-143.24 to 92.24)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Real J P; Luna J D; Urrets-Zavalia J A; De Santis ; M O ; Palma S D; Granero G E. Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration. 2013. European Journal of Ophthalmology 23(6): 857-864.

Diagnostic confirmation time (elapsed time between baseline and diagnostic confirmation date)	19.21 (14.96)	28.4 (27.66)	9.19 (-0.83 to 19.21)
VA at baseline, logMAR (SD)	0.80 (0.43)	0.77 (0.39)	-0.03 (-0.21 0.15)
VA at diagnostic confirmation	0.91 (0.44)	1.03 (0.4)	0.12 (-0.07 to 0.31)
VA change between diagnosis and treatment, letter (SD)	-5.46 (9.90)	-13.01 (13.82)	-7.55 (-12.94 to -2.16)

Bibliographic reference	Lim J H; Wickremasinghe S S; Xie J ; Chauhan D S; Baird P N; Robman L D; Hageman G ; Guymer R H. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. 2012. American Journal of Ophthalmology 153 ($): 678-86.
Country/ies where the study was carried out	Australia
Study type	Prospective interventional case series
Aim of the study	To investigate the potential influences that affect visual acuity (VA) outcome in a clinic-based cohort of age-related macular degeneration (AMD) patients undergoing anti-vascular endothelial growth factor (anti-VEGF) treatment for choroidal neovascularization.
Source of funding	Publication of the study was funded by national health and medical research council.
Sample size	185 eyes of 185 patients
Inclusion criteria	Patients were over the age of 50 years and were diagnosed with subfoveal CNV secondary to AMD.
Exclusion criteria	The main exclusion criteria: 1) diagnosis of CNV secondary to other eye condition; 2) laser photocoagulation or PDT prior to anti-VEGF injections; 3) non white ancestry
Baseline characteristics	Not specified
Methods	Patients with subfoveal choroidal neovascularization (CNV) secondary to AMD were recruited. A detailed questionnaire was given to patients at time of enrollment, to collect information relating to demographics, history of visual symptoms, visual acuity (VA), and treatment scheduling. Delay from symptoms to treatment ("Treatment delay") was measured in terms of weeks and analyzed in tertiles. Information pertaining to treatment outcomes was collected over a 6-month period.
Results	

	Time delay: symptoms to treatment	

Bibliographic reference	Lim J H; Wickremasinghe S S; Xie J ; Chauhan D S; Baird P N; Robman L D; Hageman G ; Guymer R H. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. 2012. American Journal of Ophthalmology 153 ($): 678-86.

	Lowest tertile (<7 week) (n=55)	Middle tertile (7-21 weeks) (n=54)	Highest tertile (>21 weeks) (n=54)	Effect (highest vs lowest tertile) (95%CI)
No. of patients had a gain of more than 2 lines (%)	21 (38)	16 (30)	11 (20)	0.53 (0.29 to 1.00)
No. of patient had a gain or loss of less than 2 lines	28 (51)	30 (56)	36 (67)	1.31 (0.95 to 1.80)
No. of patients had a loss of more than 2 lines	6 (11)	8 (14)	7 (13)	1.19 (0.43 to 3.31)
	Time delay: diagnosis to treatment			
	Lowest tertile (<1 week) (n=84)	Middle tertile (1-3 weeks) (n=50)	Highest tertile (>3 weeks) (n=50)	
No. of patients had a gain of more than 2 lines (%)	24 (29)	17 (34)	11 (22)	0.77 (0.41 to 1.43)
No. of patient had a gain or loss of less than 2 lines	48 (57)	26 (52)	33 (66)	1.16 (0.88 to 1.52)
No. of patients had a loss of more than 2 lines	12 (14)	7 (14)	6 (12)	0.84 (0.34 to 2.10)

Bibliographic reference	Takahashi H ; Ohkubo Y ; Sato A ; Takezawa M ; Fujino Y ; Yanagi Y ; Kawashima H. Relationship between visual prognosis and delay of intravitreal injection of ranibizumab when treating agerelated macular degeneration. Retina 35 (7): 1331-38. 2015
Country/ies where the study was carried out	Janpan
Study type	Retrospective case
Aim of the study	In age-related macular degeneration, various factors in clinical practice cause delays to arise between the time exudative change is observed and the time antivascular endothelial growth factor drugs are actually injected. We investigated the influence of injection delay on prognosis.
Study date	Published in 2015

<table>
<tr><th>Bibliographic reference</th><th>Takahashi H ; Ohkubo Y ; Sato A ; Takezawa M ; Fujino Y ; Yanagi Y ; Kawashima H. Relationship between visual prognosis and delay of intravitreal injection of ranibizumab when treating agerelated macular degeneration. Retina 35 (7): 1331-38. 2015</th></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>50 people (50 eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were diagnosed with exudative AMD.
Patietns received PRN ranibizuma monotherapy for 1 year since exudative change as first noted.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients had injections of antiVEGF drugs other than ranibumab or receipt of PDT in the target eye
Patients had intraocular surgey to the target eye exluding cataract surgey performed in either 3 months before exudative change was first noted or in the 12 month follow-up period
Patients had a history of vitreous surgey such as vitreactomy or submacular surgey in the target eye
Patients had any intraocular, extraocular or periocular inflammation or infection affecting either eye
Patients had a history of uneitis in either eye</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Patient being treated in hospital A</td><td>Patient being treated in hospital B</td></tr>
<tr><td>Number</td><td>25</td><td>25</td></tr>
<tr><td>Mael, n(%)</td><td>12 (48)</td><td>17 (68)</td></tr>
<tr><td>Age, mean (SE) years</td><td>75.5 (1.6)</td><td>71.2 (1.6)</td></tr>
<tr><td>Initial BCVA (logMAR) Snellen</td><td>0.19 (20/31)</td><td>0.47 (20/59)</td></tr>
<tr><td>Mean injectin dealys, days</td><td>9</td><td>47</td></tr>
</table>
</td></tr>
<tr><td>Methods</td><td>The study retrospectively investigated BCVA on the date that exudative change was first noted as initial BCVA, BCVA after 1 year, number of injection per year, and mean and total delay in days from the time exudative change was observed until injection for each injection.
Four types of delay were categoried as follow:
1.Referal delay, the numerb of days between the date of AMD diagnosis at the preivous institution (if made) and the data of the first visit to the institution where the first IVR was performed;
2.Specialist outcome clinic appointment delay, the number of days between the date the patient fulfilled the injection criteria at the general outpatient clinic and the date they were examined at the specialist outpatient clinic;
3.Patient refusal delay, the number of days between the date the patient fulfilled the injection criteria at the specialist outpatient clinic and the date the actual injection was scheduled at which time the patient refused injection</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Takahashi H ; Ohkubo Y ; Sato A ; Takezawa M ; Fujino Y ; Yanagi Y ; Kawashima H. Relationship between visual prognosis and delay of intravitreal injection of ranibizumab when treating agerelated macular degeneration. Retina 35 (7): 1331-38. 2015</th></tr>
<tr><td></td><td>4. Appointment injection delay, all other delays.</td></tr>
<tr><td>Results</td><td>Predicted change in visual acuity is expressed by:
Change in visual acuity=0.000477-0.448 *(initial BCVA) + 0.00304 *(mean injection delay)

Expected visual acuity after 1 year for each patient’s VA at initial examiniation, and number of appointment waiting delays for intravitreal
<table>
<tr><td></td><td colspan="5">Mean administration delays (days)</td></tr>
<tr><td>Starting point BCVA</td><td>0</td><td>7</td><td>14</td><td>28</td><td>56</td></tr>
<tr><td>VA logMAR 1 Sneller 20/200</td><td>0.55
(0.55, 0.56)</td><td>0.57
(0.53-0.62)</td><td>0.59
(0.55-0.64)</td><td>0.64
(0.60-0.68)</td><td>0.72
(0.66-0.77)</td></tr>
<tr><td>VA logMAR 0.4 Sneller 20/50</td><td>0.22
(0.19-0.24)</td><td>0.24
(0.22-0.26)</td><td>0.26
(0.24-0.28)</td><td>0.31
(0.28-0.33)</td><td>0.39
(0.35-0.42)</td></tr>
<tr><td>VA logMAR 0.1, Sneller 20.25</td><td>0.05
(0.03-0.08)</td><td>0.08
(0.05-0.10)</td><td>0.10
(0.07-0.12)</td><td>0.14
(0.11-0.16)</td><td>0.22
(0.18-0.26)</td></tr>
</table></td></tr>
</table>

E.5 Non-pharmacological management

E.5.1 Psychological therapies

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

Bibliographic reference	**Birk,T., Hickl,S., Wahl,H.W., Miller,D., Kammerer,A., Holz,F., Becker,S., Volcker,H.E., Development and pilot evaluation of a psychosocial intervention program for patients with age-related macular degeneration, Gerontologist, 44, 836-843, 2004**
Country/ies where the study was carried out	Germany
Study type	Non-randomised controlled trial
Aim of the study	To develop and evaluate a psychosocial intervention program for ARMD patients.
Study dates	Published 2004
Source of funding	Unclear
Sample size	22 participants Intervention group - 14 Comparison group - 8
Inclusion criteria	Bilateral age-related macular degeneration as documented by the assessment of the ophthalmologists involved in the study. Remaining visual acuity in the better eye had to be less than 20/70, Between 60 and 80 years of age Living in a private household.
Exclusion criteria	Severe terminal illnesses, Major hearing loss (not corrected or correctable by a hearing aid) Major cognitive impairment
Patient characteristics	Age Intervention group: 73.1 years Comparison group: 72.6 years Gender (m) Intervention group: 5 Comparison group: 3

Bibliographic reference	**Birk,T., Hickl,S., Wahl,H.W., Miller,D., Kammerer,A., Holz,F., Becker,S., Volcker,H.E., Development and pilot evaluation of a psychosocial intervention program for patients with age-related macular degeneration, Gerontologist, 44, 836-843, 2004**
	The study did not report baseline characteristics for the following variables: Ethnic group Visual acuity Comorbidities affecting the eye (e.g. cataracts) Other co-morbidities (people with other sensory loss) Time since diagnosis of AMD Time since visual impairment due to AMD Disease stage
Details	Follow up was 7-9 weeks Positive and negative affect were assessed with the German version of the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS positive and negative affect subscales consist of 10 adjectives connoting positive and negative emotions. Interviewers asked participants to indicate on a 5-point scale, ranging from 0 (not at all) to 4 (very often), how frequently they had experienced each emotion during the past week. We divided the total scores by the number of items. Depressive symptoms were assessed with the short version (15 items) of the Geriatric Depression Scale (GDS) suggested by Sheik and Yesavage (1986). ADL–IADL ability was assessed using a slightly modified version of a scale taken from the Multilevel Assessment Instrument (MAI; Lawton, Moss, Fulcomer, & Kleban, 1982). The original scale was expanded to include four activities, which specifically addressed functional tasks that can be affected by vision loss (e.g., identifying coins and bills). The 18 items of this extended scale were assessed on a 4-point scale from 0 (performs task with no difficulty) to 3 (can perform task only with help) and summed them to create a total functional ability score (range 0–54). In addition, interviewers asked participants to rate their perceived autonomy on an 11-point Likert-type scale ranging from 0 (completely dependent) to 10 (completely independent). The Active Problem Orientation subscale from the Freiburger Fragebogen zur Krankheitsbewa¨ltigung, a standard German psycho-diagnostic instrument used to assess coping with illness (Muthny, 1989). This five-item measure addresses illness-related behaviours such as seeking information on diseases and treatments or making plans to proactively cope with illnesses. Each item is rated on 5-point Likert-type format from 1 (not at all) to 5 (very strong).
Interventions	There were six major modules to the intervention programme: In the first module, group trainers taught progressive muscle relaxation skills to reduce anxiety stress symptoms frequently found in patients with age-related macular degeneration. This technique can be learned in two sessions and can also be practiced outside of group sessions and upon completion of the intervention program. Attendees also received an audiocassette for home training.

Bibliographic reference	**Birk,T., Hickl,S., Wahl,H.W., Miller,D., Kammerer,A., Holz,F., Becker,S., Volcker,H.E., Development and pilot evaluation of a psychosocial intervention program for patients with age-related macular degeneration, Gerontologist, 44, 836-843, 2004**
	In the second module, exchange of personal experiences in dealing with age-related macular degeneration was addressed in order to exploit the potential of the group setting where patients could learn from one another's coping efforts and advice. The goal of this module was to strengthen a group atmosphere founded on mutual understanding, role-taking behaviour, and the providing of help. The third module focused on the links between thought, affect, and behaviour in order to underscore the close interdependence of these systems. The task of the group leaders in this module was to stimulate the reflection and to keep the group and individual discussion in the ''here and now.'' In the fourth module, the focus was on strategies toward making the most of available resources, improving the awareness of existing competencies, and developing sources of personal growth. For this purpose, the group leaders stimulated the attendees to actively imagine what kind of new plans of action would be possible for them and how they could enhance the probability of their own positive experiences. In the fifth module, systematic problem-solving strategies were taught in order to improve the general capacity of patients with age-related macular degeneration in the treatment group to deal with current and future problems in their personal lives. A major aspect of this classic cognitive-behaviour therapy was to circumscribe problems as clearly as possible and to concretely formulate new goals and respective problem-solving alternatives. In the sixth and final module, information on more practical issues in dealing with age-related macular such as learning more about available possibilities, home modification options, and the existence of self-help organizations was presented. Two group trainers with a strong background in clinical psychology ran the program.
Results	Mean differences and confidence intervals were calculated by the reviewer using the information provided within the study: Positive effect (mean change from T1-T2) Intervention group (n=14): -0.26 Comparison group (n=8): -0.14 Mean difference (95% CI): -0.12 (-0.58, 0.34) Negative effect (mean change from T1-T2) Intervention group (n=14): 0.1 Comparison group (n=8): -0.43 Mean difference (95% CI): 0.53 (0.13, 0.92) Depression (mean change from T1-T2)

Bibliographic reference	Birk,T., Hickl,S., Wahl,H.W., Miller,D., Kammerer,A., Holz,F., Becker,S., Volcker,H.E., Development and pilot evaluation of a psychosocial intervention program for patients with age-related macular degeneration, Gerontologist, 44, 836-843, 2004
	Intervention group (n=14): 1.4 Comparison group (n=8): -0.05 Mean difference (95% CI): 1.45 (0.01, 2.88) ADL-IADL (mean change from T1-T2) Intervention group (n=14): 1.3 Comparison group (n=8): -4.8 Mean difference (95% CI): 6.1 (1.31, 10.88) Perceived autonomy (mean change from T1-T2) Intervention group (n=14): -0.8 Comparison group (n=8): 1 Mean difference (95% CI): -1.8 (-3.56, -0.03) Active Problem Orientation Score (mean change from T1-T2) Intervention group (n=14): -1.4 Comparison group (n=8): 2.1 Mean difference (95% CI): -3.5 (-7.11, 0.11)
Overall Risk of Bias	Risk of bias assessed using the Cochrane risk of bias tool Overall risk of bias: High risk (not randomised, not blinded, unclear if significant difference between comparison groups, Other information: none Was the allocation sequence adequately generated? No Was allocation adequately concealed? No Was knowledge of the allocated intervention adequately prevented during the study? No Were incomplete outcome data adequately addressed?- No Are reports of the study free of suggestion of selective outcome reporting? Yes Was the study apparently free of other problems that could put it at a high risk of bias? Selection bias: Unclear if statistical difference found between those who took part in the trial and those who did not. The study did not report on the important baseline characteristics of Ethnic group, Visual acuity, Comorbidities affecting the eye (e.g. cataracts), Other co-morbidities (people with other sensory loss), Time since diagnosis of AMD, Time since visual impairment due to AMD, and Disease stage. Attrition bias: Unclear if statistical difference found between those who dropped out and those who remained. Large

Bibliographic reference	Birk,T., Hickl,S., Wahl,H.W., Miller,D., Kammerer,A., Holz,F., Becker,S., Volcker,H.E., Development and pilot evaluation of a psychosocial intervention program for patients with age-related macular degeneration, Gerontologist, 44, 836-843, 2004
	proportional drop out (5 in intervention group, 3 in comparison group) Performance bias: unclear if comparison groups received the same care apart from intervention studied although study reports that the comparison group did not receive any other psychological or psychosocial therapy during the course of the study.

Bibliographic reference	Brody,B.L., Roch-Levecq,A.C., Gamst,A.C., Maclean,K., Kaplan,R.M., Brown,S.I., Self-management of age-related macular degeneration and quality of life: a randomized controlled trial, Archives of Ophthalmology, 120, 1477-1483, 2002
Country/ies where the study was carried out	USA
Study type	Randomised controlled trial
Aim of the study	To assess the effectiveness of an age-related macular degeneration (AMD) self-management program, consisting of health education and enhancement of problem-solving skills, to improve quality of life as shown by measures of mood and function.
Study dates	Published 2002
Source of funding	National Eye Institute
Sample size	Participants were randomised to the following: 12-hour self-management program (n = 86) Series of 12 hours of tape-recorded health lectures (n = 74) Waiting list (n = 72)
Inclusion criteria	Diagnosis of AMD by an ophthalmologist and confirmed by fundus photographs Visual acuity of 20/60 or worse in the better eye and 20/100 or worse in the other eye with habitual correction (i.e. current glasses) No other unstable eye disease or vision loss due to other eye disease Age 60 years or older Adequate hearing, with a hearing aid if necessary, to complete the interview and to respond in normal conversation Physical ability to come to an interview if wheelchair access transportation was provided No cognitive impairment as assessed by the Orientation-Memory Concentration Test No current alcohol abuse as assessed by the Short Michigan Alcoholism Screening Test
Exclusion criteria	None

Bibliographic reference	Brody,B.L., Roch-Levecq,A.C., Gamst,A.C., Maclean,K., Kaplan,R.M., Brown,S.I., Self-management of age-related macular degeneration and quality of life: a randomized controlled trial, Archives of Ophthalmology, 120, 1477-1483, 2002
Patient characteristics	Ethnic group - not reported Age, mean ± SD Self-management group (n=86) - 80.73 ± 7.12 Tape recording group (n=74) - 81.21 ± 5.25 Wait list group (n=71) - 80.76 ± 5.75 Gender, M, % Self-management group (n=86) - 25 Tape recording group (n=74) - 25 Wait list group (n=71) - 28 Visual acuity (Snellen) Self-management group (n=86) - 20/537 Tape recording group (n=74) - 20/599 Wait list group (n=71) - 20/485 Comorbidities affecting the eye (e.g. cataracts) - not reported Other co-morbidities (people with other sensory loss) - not reported Time since diagnosis of AMD, months Self-management group (n=86)- 96.84 Tape recording group (n=74)- 92.93 Wait list group (n=71)- 100.30 Time since visual impairment due to AMD - not reported Disease stage - not reported

Bibliographic reference	**Brody,B.L., Roch-Levecq,A.C., Gamst,A.C., Maclean,K., Kaplan,R.M., Brown,S.I., Self-management of age-related macular degeneration and quality of life: a randomized controlled trial, Archives of Ophthalmology, 120, 1477-1483, 2002**
Details	Participants were randomly assigned to 1 of 3 groups: self-management, tape-recorded health education program, or to a waiting list (control group). Primary Outcome Measure The Profile of Mood States (POMS) was used to measure mood. This is a 65-item self-report inventory designed to assess emotional distress during the previous week. The participant responds to each item on a 5-point Likert scale, ranging from 0 = not at all to 4 = extremely. Scores can range from 0 to 232. Higher scores indicate higher levels of emotional distress. The POMS has been validated for use with older populations. Secondary Outcome Measures The National Eye Institute Visual Function Questionnaire (NEI-VFQ) was used to measure effects on everyday functioning. This is a multifaceted functional measure of health-related quality of life in relation to vision. The total score can range from 0 to 100, where 0 represents the worst possible functioning and 100 the best. Mediator Variables The following were studied as mediators of the effects of the self-management program on mood and function: Duke Social Support Index 11 item (DSSI-11). The DSSI-11 measures satisfaction with the frequency, content, and quality of support and social interaction with family and friends. Scores range from 0 to open-ended. Higher scores indicate greater perceived social support. Life Orientation Test–Revised (LOT-R). The LOT-R is a 10-item measure that assesses optimistic vs pessimistic life outlook. Scores range from 0 to 24. Higher scores indicate a more optimistic approach to life. Macular Degeneration Self-Efficacy Questionnaire (AMD-SEQ). As conceptualized in Bandura's social cognitive model, self-efficacy is a person's assessment of his or her abilities and encompasses the degree of certainty and underlying expectations about his or her ability to succeed in a given circumstance. Based on this theory, a self-efficacy questionnaire had been developed to address issues salient to AMD and shown to be reliable. The scale ranges from 1 to 100, with high scores indicating that participants feel very confident they can accomplish the task related to AMD vision loss described in the question (Higher scores indicate greater self-efficacy).
Interventions	Participants were randomly assigned to 1 of 3 groups: self-management, tape-recorded health education program, or to a waiting list (control group). The 6-week self-management program: 8 to 10 participants met weekly for 2-hour sessions led by an experienced professional in public health and behavioural medicine. Sessions incorporated 2 elements: didactic presentations and group problem-solving with guided practice. The didactic component was comprised of brief presentations and formal lectures by professionals in several fields, e.g., ophthalmology, rehabilitation, nutrition, exercise physiology, and low vision optometry. In the group problem-solving component, participants were guided through a hierarchy of behavioural challenges to improve problem-solving skills with the

<table>
<tr><th>Bibliographic reference</th><th>Brody,B.L., Roch-Levecq,A.C., Gamst,A.C., Maclean,K., Kaplan,R.M., Brown,S.I., Self-management of age-related macular degeneration and quality of life: a randomized controlled trial, Archives of Ophthalmology, 120, 1477-1483, 2002</th></tr>
<tr><td></td><td>support and experience of peers and professionals. The intervention was composed of both cognitive and behavioural components.
Cognitive components included information about the biological processes of AMD, suggestions of ways to maintain or increase activity levels, and hands-on demonstrations and discussions of available visual aids and services. Re-evaluation of perceived barriers to independence was encouraged, and positive challenges were provided from peers and group leaders.
Behavioural components included behavioural skills training in communicating with others about visual disability, handling a variety of challenges associated with AMD, and requesting assistance when needed. Modelled after successful psychosocial interventions with chronic disease, vignettes were presented to the group, covering various problems encountered by people with AMD. In addition, participants presented situations they had faced. Adaptive behaviours were modelled for the participants. A simple exercise program designed for this population was also incorporated into the program.
Tape recorded health-education
To control for the provision of educational information, which was the focus of the self-management program, the tape control consisted of a series of 12 hours of audiotapes of health lectures, which had been presented to the lay public, on AMD and healthy aging, to be listened to during a 6-week period. Subjects in the control condition were interviewed again 6 weeks after baseline interviews.
Waiting list
One further control group remained on a waiting list.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Baseline, mean (SD)</td><td>6-weeks, mean (SD)</td><td>Mean Difference</td></tr>
<tr><td>Profile of Mood States (POMS), total score</td><td></td><td></td><td></td></tr>
<tr><td>Self-management (n=86)</td><td>60.84 ± 29.69</td><td>53.75 ± 24.51</td><td>-7.09 ± 21.83
(95% CI, -15.39 to -1.21)</td></tr>
<tr><td>Control group (n=144)</td><td>54.86 ± 30.97</td><td>58.27 ± 34.17</td><td>3.41 ± 21.54
(95% CI, -2.39 to 9.21)</td></tr>
<tr><td>25-Item National Eye Institute- visual functioning (NEI-VFQ), total</td><td></td><td></td><td></td></tr>
<tr><td>Self-management (n=86)</td><td>59.72 ± 13.18</td><td>60.76 ± 12.69</td><td>1.02 ± 6.80
(95% CI -0.44 to 2.48)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Brody,B.L., Roch-Levecq,A.C., Gamst,A.C., Maclean,K., Kaplan,R.M., Brown,S.I., Self-management of age-related macular degeneration and quality of life: a randomized controlled trial, Archives of Ophthalmology, 120, 1477-1483, 2002			
	Control group (n=145)	58.80 ± 13.30	58.87 ± 13.23	0.07 ± 7.5 (95% CI -1.16 to 1.31)
	Age-related Macular Degeneration Self-Efficacy Scale, total score			
	Self-management (n=86)	70.89 ± 16.01	76.23 ± 13.56	5.34 ± 12.17 (95% CI 2.73 to 7.95)
	Control group (n=145)	71.60 ± 15.36	72.72 ± 15.77	1.12 ± 11.85 (95% CI, -0.82 to 3.07)

Depressed Participants at Baseline (as defined by SCID)

	Baseline, mean (SD)	6-weeks, mean (SD)	Mean Difference
Profile of Mood States (POMS), total score			
Self-management (n=20)	80.24 ± 25.34	65.10± 19.25	-15.41 ± 28.91 (–2867 to -1.61)
Control group (n=34)	65.77 ± 33.89	73.12 ± 40.51	7.35 ± 21.94 (-31 to 15.00)
25-Item National Eye Institute- visual functioning			
Self-management (n=20)	49.97+ 11.32	53.51 ± 11.60	3.58 ± 8.17 (-30 to 735)
Control group (n=34)	49.59 ± 13.61	47.94 ± 11.61	1.65 ± 8.53 (–4.62 to 1.33)

Non-depressed Participants at Baseline (as defined by SCID)

Bibliographic reference	**Brody,B.L., Roch-Levecq,A.C., Gamst,A.C., Maclean,K., Kaplan,R.M., Brown,S.I., Self-management of age-related macular degeneration and quality of life: a randomized controlled trial, Archives of Ophthalmology, 120, 1477-1483, 2002**

	Baseline, mean (SD)	6-weeks, mean (SD)	Mean Difference
Profile of Mood States (POMS), total score			
Self-management (n=66)	41.45±24.70	42.40 ± 23.57	0.94 ± 17.86 (–3.44 to 5.33)
Control group (n=110)	43.97 ± 28.32	43.42 ± 28.71	–0.55 ± 21.23 (–4.56 to 3.46)
25-Item National Eye Institute- visual functioning			
Self-management (n=66)	62.67 ± 12.32	62.94 ± 12.25	0.261±6.21 (–126 to 1.79)
Control group (n=110)	61.53 ± 12.00	62.17 ± 1.1.89	0.63±7.14 (-71 to 1.98)

Overall Risk of Bias	Risk of bias assessed using the Cochrane risk of bias tool Overall risk of bias: Initial randomisation was not stratified for presence of depression at initial outset (randomisation still intact however less powerful). Single masked study, however investigators were kept masked to the study allocation. The study reports "there were no differences in demographic or clinical characteristics in the potential participants who enrolled in the study and those who declined. The subjects who completed the study did not differ in demographic or clinical characteristics from those who dropped out." The study did not provide outcomes for two of its planned measures (the DSSI and LOT-R), only total scores were reported. In a post hoc decision, the study merged the two control groups. One which was given tape recording information and one which was put on a waiting list. This was because there was found to be no difference between the groups on either baseline or in the resulting change scores. Was the allocation sequence adequately generated? Yes Was allocation adequately concealed? Yes Was knowledge of the allocated intervention adequately prevented during the study? No Were incomplete outcome data adequately addressed?- Yes

Bibliographic reference	**Brody,B.L., Roch-Levecq,A.C., Gamst,A.C., Maclean,K., Kaplan,R.M., Brown,S.I., Self-management of age-related macular degeneration and quality of life: a randomized controlled trial, Archives of Ophthalmology, 120, 1477-1483, 2002**
	Are reports of the study free of suggestion of selective outcome reporting? No (but only with regard to the "mediator measures", as opposed to the primary outcome measures). Was the study apparently free of other problems that could put it at a high risk of bias? Unclear Other information- none

Bibliographic reference	**Brody,B.L., Roch-Levecq,A.C., Kaplan,R.M., Moutier,C.Y., Brown,S.I., Age-related macular degeneration: self-management and reduction of depressive symptoms in a randomized, controlled study, Journal of the American Geriatrics Society, 54, 1557-1562, 2006**
Country/ies where the study was carried out	USA
Study type	Randomised controlled trial
Aim of the study	To assess the effectiveness of a self-management program for age-related macular degeneration (AMD) in reducing depressive symptoms.
Study dates	Published 2006
Source of funding	Financed in part by grants from the National Eye Institute.
Sample size	Participants taken from the trial described in: Brody et al Self-management of age-related macular degeneration and quality of life: a randomized controlled trial (2002). A trial of 231 participants in the AMD self-management study. The present investigation focused on a subset of 32 depressed subjects who had been randomised to: An AMD self-management programme (n=12) One of two control groups (n=20)
Inclusion criteria	Subjects were included if at baseline they had met criteria from the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) for major or minor depressive disorder and had a score indicating significant depressive symptoms. Other inclusion criteria: Diagnosis of AMD by an ophthalmologist, confirmed using fundus photographs Visual acuity of 20/60 or worse in the better eye Visual acuity of 20/100 or worse in the worse eye With habitual correction (i.e. current glasses)
Exclusion criteria	Other unstable eye disease

Bibliographic reference	Brody,B.L., Roch-Levecq,A.C., Kaplan,R.M., Moutier,C.Y., Brown,S.I., Age-related macular degeneration: self-management and reduction of depressive symptoms in a randomized, controlled study, Journal of the American Geriatrics Society, 54, 1557-1562, 2006
	Vision loss due to other eye disease Aged 60 or older Cognitive impairment as assessed using the orientation-memory concentration test
Patient characteristics	Ethnic group: Not reported Age, y, mean ± SD Self-management group (n=12) - 81.2 ± 9.56 Tape recording group (n=8) - 81.9 ± 5.36 Wait list group (n=12) - 81.6 ± 7.10 Gender, M, % Self-management group (n=12) - 41.7% Tape recording group (n=8) - 25.0% Wait list group (n=12) - 33.3% Visual acuity, Snellen rating Self-management group (n=12) - 430 Tape recording group (n=8) - 350 Wait list group (n=12) - 335 Comorbidities affecting the eye - no detail given on type of co-morbidities Other co-morbidities (people with other sensory loss) - no further detail given on other co-morbidities Self-management group (n=12) - 91.7% Tape recording group (n=8) - 100% Wait list group (n=12) - 83.3% Time since diagnosis of AMD - not reported Time since visual impairment due to AMD (months)

Bibliographic reference	**Brody,B.L., Roch-Levecq,A.C., Kaplan,R.M., Moutier,C.Y., Brown,S.I., Age-related macular degeneration: self-management and reduction of depressive symptoms in a randomized, controlled study, Journal of the American Geriatrics Society, 54, 1557-1562, 2006**
	Self-management group (n=12) - 47.3 Tape recording group (n=8) - 41.0 Wait list group (n=12) - 64.0 Disease stage - not reported
Details	Participants were randomly assigned to 1 of 3 groups: self-management, tape-recorded health education program, or to a waiting list (control group). Primary Outcome Measure The Profile of Mood States (POMS) was used to measure mood. This is a 65-item self-report inventory designed to assess emotional distress during the previous week. The participant responds to each item on a 5-point Likert scale, ranging from 0 = not at all to 4 = extremely. Scores can range from 0 to 232. Higher scores indicate higher levels of emotional distress. The POMS has been validated for use with older populations. Secondary Outcome Measures The National Eye Institute Visual Function Questionnaire (NEI-VFQ) was used to measure effects on everyday functioning. This is a multifaceted functional measure of health-related quality of life in relation to vision. The total score can range from 0 to 100, where 0 represents the worst possible functioning and 100 the best. Mediator Variables The following were studied as mediators of the effects of the self-management program on mood and function: Duke Social Support Index 11 item (DSSI-11). The DSSI-11 measures satisfaction with the frequency, content, and quality of support and social interaction with family and friends. Scores range from 0 to open-ended. Higher scores indicate greater perceived social support. Life Orientation Test–Revised (LOT-R). The LOT-R is a 10-item measure that assesses optimistic vs pessimistic life outlook. Scores range from 0 to 24. Higher scores indicate a more optimistic approach to life. Macular Degeneration Self-Efficacy Questionnaire (AMD-SEQ). As conceptualized in Bandura's social cognitive model, self-efficacy is a person's assessment of his or her abilities and encompasses the degree of certainty and underlying expectations about his or her ability to succeed in a given circumstance. Based on this theory, a self-efficacy questionnaire had been developed to address issues salient to AMD and shown to be reliable. The scale ranges from 1 to 100, with high scores indicating that participants feel very confident they can accomplish the task related to AMD vision loss described in the question (Higher scores indicate greater self-efficacy).
Interventions	Participants were randomly assigned to 1 of 3 groups: self-management, tape-recorded health education program, or to a waiting list (control group). The 6-week self-management program:

<table>
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<tr><td></td><td>8 to 10 participants met weekly for 2-hour sessions led by an experienced professional in public health and behavioural medicine. Sessions incorporated 2 elements: didactic presentations and group problem-solving with guided practice. The didactic component was comprised of brief presentations and formal lectures by professionals in several fields, e.g. ophthalmology, rehabilitation, nutrition, exercise physiology, and low vision optometry. In the group problem-solving component, participants were guided through a hierarchy of behavioural challenges to improve problem-solving skills with the support and experience of peers and professionals. The intervention was composed of both cognitive and behavioural components.
Cognitive components included information about the biological processes of AMD, suggestions of ways to maintain or increase activity levels, and hands-on demonstrations and discussions of available visual aids and services. Re-evaluation of perceived barriers to independence was encouraged, and positive challenges were provided from peers and group leaders.
Behavioural components included behavioural skills training in communicating with others about visual disability, handling a variety of challenges associated with AMD, and requesting assistance when needed. Modelled after successful psychosocial interventions with chronic disease, vignettes were presented to the group, covering various problems encountered by people with AMD. In addition, participants presented situations they had faced. Adaptive behaviours were modelled for the participants. A simple exercise program designed for this population was also incorporated into the program.
Tape recorded health-education
To control for the provision of educational information, which was the focus of the self-management program, the tape control consisted of a series of 12 hours of audiotapes of health lectures, which had been presented to the lay public, on AMD and healthy aging, to be listened to during a 6-week period. Subjects in the control condition were interviewed again 6 weeks after baseline interviews.
Waiting list
One further control group remained on a waiting list.
Because at baseline, the randomisation resulted in no statistically significant differences between three groups on demographic and clinical characteristics, the two control groups were collapsed to become one (n=20).</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Baseline, mean (SD)</td><td>6-months, mean (SD)</td><td>Mean Difference</td></tr>
<tr><td>Geriatric Depression Scale, total score</td><td></td><td></td><td></td></tr>
<tr><td>Self-management (n=12)</td><td>7.50 ± 2.19</td><td>4.58 ± 2.42</td><td>-2.92 ± 3.26</td></tr>
<tr><td>Control group (n=20)</td><td>7.80 ± 2.35</td><td>6.80 ± 2.96</td><td>-1.00 ± 3.78</td></tr>
<tr><td>25-Item National Eye Institute- visual functioning</td><td></td><td></td><td></td></tr>
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Bibliographic reference	Brody,B.L., Roch-Levecq,A.C., Kaplan,R.M., Moutier,C.Y., Brown,S.I., Age-related macular degeneration: self-management and reduction of depressive symptoms in a randomized, controlled study, Journal of the American Geriatrics Society, 54, 1557-1562, 2006			
	Self-management (n=12)	44.82 ± 8.39	50.52 ± 10.04	5.70 ± 13.08
	Control group (n=20)	44.64 ± 14.56	47.98 ± 11.66	3.34 ± 18.65
	Age-related Macular Degeneration Self-Efficacy Scale, total score			
	Self-management (n=12)	55.76 ± 18.81	73.07 ± 13.75	17.31 ± 23.30
	Control group (n=20)	61.67 ± 14.84	65.62 ± 18.15	3.95 ± 23.44
	11-item Duke Social Support Index (social support), total score			
	Self-management (n=12)	29.16 ± 6.61	34.63 ± 9.29	5.47 ± 11.40
	Control group (n=20)	27.60 ± 8.76	27.35 ± 11.69	-0.25 ± 14.61
	Life Orientation Test- Revised (optimism), total score			
	Self-management (n=12)	10.25 ± 3.30	9.63 ± 2.54	-0.62 ± 4.16
	Control group (n=20)	9.40 ± 2.47	9.65 ± 2.73	0.25 ± 3.68
Overall Risk of Bias	Risk of bias assessed using the Cochrane risk of bias tool Overall risk of bias: Randomisation process was mostly described in another study. Initial randomisation was not stratified for presence of depression at initial outset (randomisation still intact however less powerful). Single masked study, however investigators were kept masked to the study allocation. The study reports "there were no differences in demographic or clinical characteristics in the potential participants who enrolled in the study and those who declined. The subjects who completed the study did not differ in demographic or clinical characteristics from those who dropped out." No apparent selective reporting of outcomes. In a post hoc decision, the study merged the two control groups. One which was given tape recording information and one which was put on a waiting list. This was because there was found to be no difference between the groups on either baseline or in the resulting change scores. Other information: This study reports a subset from a previously performed randomised controlled trial, but comparing the two studies it appears to have only included a proportion of the depressed population identified in the prior study. Unclear if the differences were systematic. If not randomisation may have been broken. Was the allocation sequence adequately generated? Yes Was allocation adequately concealed? Yes			

Bibliographic reference	**Brody,B.L., Roch-Levecq,A.C., Kaplan,R.M., Moutier,C.Y., Brown,S.I., Age-related macular degeneration: self-management and reduction of depressive symptoms in a randomized, controlled study, Journal of the American Geriatrics Society, 54, 1557-1562, 2006**
	Was knowledge of the allocated intervention adequately prevented during the study? No Were incomplete outcome data adequately addressed? Yes Are reports of the study free of suggestion of selective outcome reporting? Yes Was the study apparently free of other problems that could put it at a high risk of bias? Unclear

Bibliographic reference	**Rovner,B.W., Casten,R.J., Hegel,M.T., Leiby,B.E., Tasman,W.S., Preventing depression in age-related macular degeneration, Archives of General Psychiatry, 64, 886-892, 2007**
Country/ies where the study was carried out	USA
Study type	Randomised controlled trial
Aim of the study	To determine whether problem solving treatment can prevent depressive disorders in patients with recent vision loss.
Study dates	Published 2007
Source of funding	National Institute of Mental Health; National Eye Institute; Farber Institute for Neurosciences.
Sample size	206 participants: Problem-solving treatment group (n=105) Usual care (n=101)
Inclusion criteria	Older than 64 years Neovascular AMD in one eye diagnosed within the preceding 6 months, by FA Pre-existing AMD in the fellow eye
Exclusion criteria	DSM-IV–defined diagnoses of depressive disorders or current treatment for depression Cognitive impairment Confounding eye conditions
Patient characteristics	Ethnic group, white, % Problem solving treatment (n=105): 98.1 Usual care (n=101): 99.0 Age, mean (SD), y Problem solving treatment (n=105) - 81.3 (5.4)

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Leiby,B.E., Tasman,W.S., Preventing depression in age-related macular degeneration, Archives of General Psychiatry, 64, 886-892, 2007
	Usual care (n=101) - 81.0 Gender, female, % Problem solving treatment (n=105): 65.7 Usual care (n=101): 74.3 Visual acuity, mean (SD), best distance acuity, logMAR Problem solving treatment (n=105): 0.56 (0.33) Usual care (n=101): 0.64 (0.44) Comorbidities affecting the eye (e.g. cataracts) - not reported Hamilton Depression Rating Scale score Problem solving treatment (n=105): 2.10 (2.07) Usual care (n=101): 2.25 (2.36) Underwent previous depression treatment, % Problem solving treatment (n=105): 3.4 Usual care (n=101): 1.5 Time since diagnosis of AMD - not reported Time since visual impairment due to AMD - not reported Disease stage - all neovascular
Details	Follow up Follow up was 6-months Assessments Research nurses with extensive training in psychiatry and ophthalmology obtained informed consent and completed all assessments in subjects' homes.

Bibliographic reference	**Rovner,B.W., Casten,R.J., Hegel,M.T., Leiby,B.E., Tasman,W.S., Preventing depression in age-related macular degeneration, Archives of General Psychiatry, 64, 886-892, 2007**
	The primary outcome was a DSM-IV–defined diagnosis of major or minor depression. The research nurses administered the modified Schedule for Affective Disorders and Schizophrenia and the Structured Interview Guide for the Hamilton Depression Rating Scale (HDRS) to rule out depression at baseline, to obtain history of depression treatment, and to diagnose a depressive disorder at 2 and 6 months. Interrater reliability for nurse ratings was established (κ = 0.96). The 24-item HDRS was also used to quantify depressive symptoms. Possible scores ranged from 0 to 75, with higher scores indicating more severe depression. Scores less than 7 are considered normal.
Interventions	Problem-solving treatment A manual-driven psychological treatment that teaches problem-solving skills. It addresses negative perceptions that may interfere with finding practical solutions to problems and teaches the following problem-solving skills: (1) Defining problems (2) Establishing realistic goals (3) Generating, choosing, and implementing solutions (4) Evaluating outcomes Subjects are encouraged to use these skills routinely to develop practical compensatory strategies to achieve valued functional goals and thereby prevent depression. Problem-solving treatment–trained therapists (2 nurses and 1 master's-level counsellor) delivered 6 in-home PST sessions (45-60 minutes long) during 8 weeks to subjects randomized to PST. All therapists received extensive training, which included reviewing the PST treatment manual, watching training videotapes, and treating 5 practice patients. Usual care Subjects randomized to both PST and usual care continued to receive treatment as usual from their ophthalmologists or other health care providers. Usual care subjects were offered PST once the clinical trial was completed. During the trial, no subjects in either treatment group received outside specialty mental health treatment. There were no statistically significant differences in the proportions of subjects (PST vs usual care) who received low-vision rehabilitation, used optical devices, or were treated with antidepressant medications.
Results	

	2 MONTH FU			6-MONTH FU		
Measure	Problem solving (n=105)	Usual care (n=101)	Odds ratio (95% CI)	Problem solving	Usual care	Odds ratio (95% CI)
Depression, No (%)	11 (11.5)	23 (23.2)	0.39 (0.17-0.92)	20 (21.1)	26 (27.4)	0.65 (0.33-1.39)

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Leiby,B.E., Tasman,W.S., Preventing depression in age-related macular degeneration, Archives of General Psychiatry, 64, 886-892, 2007

No. of lost activities (%)	22 (23.2)	37 (37.4)	0.48 (0.25- 0.96)	29 (30.5)	42 (44.2)	0.53 (0.28-1.01)

	2 MONTH FU		6-MONTH FU	
Measure	Problem solving	Usual care	Problem solving	Usual care
Mean (SE) change in NEI VFQ-17 score	0.96 (7.97)	-1.35 (7.80)	-0.97 (8.88)	-2.45 (9.64)
Mean (SD) change in HDRS score	-0.35 (2.88)	-0.58 (2.96)	-1.03 (4.12)	-1.04 (4.32)

Overall Risk of Bias

Risk of bias assessed using the Cochrane risk of bias tool

Overall risk of bias: Moderate (single-blind and study did not report baseline characteristics of time since diagnosis of AMD and time since visual impairment due to AMD)

Was the allocation sequence adequately generated? Yes

Was allocation adequately concealed? Yes

Was knowledge of the allocated intervention adequately prevented during the study? No - single blind

Were incomplete outcome data adequately addressed? Yes

Are reports of the study free of suggestion of selective outcome reporting? Yes

Was the study apparently free of other problems that could put it at a high risk of bias? Selection bias: No statistical difference found between those who took part in the trial and those who did not. The study did not report on the important baseline characteristics of time since diagnosis and time since visual impairment. Attrition bias: no statistical difference found between those who dropped out and those who remained. Performance bias: unclear if comparison groups received the same care apart from intervention studied although there was no statistical difference for the number who received low-vision rehabilitation, used optical devices, or were treated with antidepressant medications between comparison groups.

Other information - none

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., Improving function in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 120, 1649-1655, 2013
Country/ies where the study was carried out	USA
Study type	Randomised controlled trial
Aim of the study	To compare the efficacy of problem-solving therapy (PST) with supportive therapy (ST) to improve targeted vision function in age-related macular degeneration (AMD).
Study dates	Published 2013
Source of funding	Supported by NEI grant
Sample size	241 participants: Problem solving treatment group: 121 Supportive therapy group: 120
Inclusion criteria	Age 65 years or older Bilateral AMD (neovascular and/or geographic atrophy) Visual acuity between 20/70 and 20/400 [inclusive; (best corrected)] in the better-seeing eye, and no lower acuity limit in the fellow eye Moderate difficulty in at least one valued vision-function goal (e.g., reading mail, attending social activities)
Exclusion criteria	Presence of uncontrolled glaucoma, diabetic retinopathy, or planned cataract surgery within 6 months Cognitive impairment on an abbreviated version of the Mini-Mental Status Examination (MM blind) that omits vision-dependent items Presence of a medical condition that would preclude participation Residence in a skilled nursing facility
Patient characteristics	Age (mean years, standard deviation) Problem solving treatment group (n=121): 82.7 (6.6) Supportive therapy group (n=120): 82.8 (7.3) Female (n, %) Problem solving treatment group (n=121): 82 (67.8) Supportive therapy group (n=120): 71 (59.2) Ethnicity, White (n, %)

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., Improving function in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 120, 1649-1655, 2013
	Problem solving treatment group (n=121): 120 (99.2) Supportive therapy group (n=120): 119 (99.2) Patient Health Questionnaire-9 (depression) Problem solving treatment group (n=121): 1.4 (2.7) Supportive therapy group (n=120): 1.2 (2.3) Number of resources/rehabilitative devices used Problem solving treatment group (n=121): 5.1 (3.3) Supportive therapy group (n=120): 4.7 (3.0) Chronic Disease Score (medical comorbidity) Problem solving treatment group (n=121): 5.5 (2.8) Supportive therapy group (n=120): 5.7 (3.1) Best eye, distance (logMAR) Problem solving treatment group (n=121): 0.58 (0.29) Supportive therapy group (n=120): 0.57 (0.28) Best eye, near (logMAR) Problem solving treatment group (n=121): 0.62 (0.25) Supportive therapy group (n=120): 0.62 (0.25) The study did not report baseline characteristics for: Time since diagnosis of AMD Time since visual impairment due to AMD Disease stage
Details	Follow up was 3 months and 6 months Primary outcome Vision function goals

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., Improving function in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 120, 1649-1655, 2013
	The Targeted Vision Function (TVF) goals that subjects valued but found difficult to achieve. To derive the TVF measure, at baseline subjects completed the Activities Inventory, which is a structured vision function questionnaire that asks patients to rate the value and difficulty of 48 vision function goals (e.g., daily meal preparation) and the tasks (e.g., seeing stove settings) that are required to achieve them. Higher average scores indicate greater disability. At each outcome assessment subjects again rated the difficulty of the same targeted goals and the average TVF score was calculated. In this way, TVF was targeted and tailored, measured in a standardized way, and allowed subjects to vary in the number of TVF goals they select at baseline. Secondary Outcomes The National Eye Institute Vision Function Questionaire-25 plus Supplement (NEI VFQ). This version of the NEI VFQ consists of 39 items that assess self-reported vision function and vision-related quality of life (QoL). The latter yields a multidimensional index of vision-related health comprised of social functioning (i.e., social interactions), mental health (i.e., worry, frustration), role difficulties (i.e., accomplishing less), and dependency (i.e., relying more on others) due to vision loss. Scores range from 0 to 100, with higher scores indicating better function. Vision Status Vision was assessed using a standardized battery of vision tests and standardized lighting to assess distance and near visual acuity, contrast sensitivity, and the size and location of central scotomas. Visual acuity was measured using the Lighthouse Ferris-Bailey Early Treatment Diabetes Retinopathy Study (ETDRS) chart at a distance of 10 feet. For near acuity the ETDRS chart calibrated for 40 cm was used. Physical Health Status The Chronic Disease Score, which provides an objective measure of medical comorbidity based on a weighted sum of medications taken for chronic illness was calculated. Higher scores indicate worse medical morbidity. Psychosocial Status To assess depression the Patient Health Questionnaire-9 was used, which yields a continuous measure of depression severity. Scores range from 0 to 27, with higher scores indicating worse depression. Control The Optimization in Primary and Secondary Control Scale (OPS) to assess subjects' control (i.e., coping) strategies. The OPS is divided into 4 control strategies, each comprised of 8 items rated from 0 ("never true") to 4 ("almost always true"), yielding a range of 0 to 32; higher scores indicate greater use of the particular strategy. Selective primary control refers to the investment of behavioural resources (i.e., time, effort, skills) to pursue a goal (e.g., "I do whatever I can to continue my everyday activities despite my vision problem."). Selective secondary control serves to maintain commitment to a goal in the face of obstacles (e.g., "I think how important it is to me to keep up my daily activities in spite of my vision problem."). Compensatory primary control refers to asking for help from others or using assistive devices (e.g., "If I'm having trouble doing something because of my vision problem, I look for a device or aid that will help get it done."). Compensatory

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., Improving function in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 120, 1649-1655, 2013
	secondary control refers to goal disengagement when goals become unattainable (e.g., “I can accept that there are things I can no longer do since I started having problems with my vision.”).
Interventions	Problem-Solving Therapy (PST) PST teaches problem-solving skills in a structured way to enable a patient to systematically identify his or her problems, generate alternative solutions for each problem, select the best solution, develop and conduct a plan, and evaluate whether the problem is solved. In this study, the PST therapist and subject discussed the functional problems caused by vision loss and used the following problem-solving steps to reduce the difficulty of vision-dependent tasks: 1) clarifying the problems associated with the task 2) establishing a realistic goal toward improvement of task performance 3) generating multiple solution alternatives 4) implementing decision-making guidelines 5) choosing the preferred solution(s) 6) implementing the preferred solutions(s) 7) evaluating the outcome The PST therapist helped subjects to develop feasible solutions and reviewed available rehabilitative services and devices to inform the process of generating solutions. The aim was to have subjects incorporate the problem-solving method of reasoning as a routine, often-recruited approach to solving future as well as current function-related problems. Control strategies ST is a structured, standardized, psychological treatment that controls for nonspecific treatment effects. ST resembles PST in all ways but for PST’s problem-solving skills training. Both interventions are based on written treatment manuals and similar in dose and intensity of attention (i.e. number and duration of sessions). ST is nondirective, supportive, and facilitates personal expression and conveys empathy, respect, and optimism (i.e. a general sense that things can get better). The ST therapist informs subjects that ST’s purpose is to explore the impact of vision loss on their lives. The goals were to facilitate and deepen knowledge of subjects’ life situations and their relationship to illness, disability, retirement, social isolation and vision loss. The ST therapists created an accepting, non-judgmental, empathic environment by using supportive statements, reflective listening, and empathic communications. In contrast to PST, there was no discussion of vision function goals, problem solving, or low vision rehabilitative strategies.
Results	Primary and Secondary Outcomes at Month 3 and Month 6

Treatment Group	Baseline (SD)	Month 3 (SD)	Month 6 (SD)
TVF			
PST (n=121)	2.71 (0.52)	2.18 (0.88)	2.18 (0.95)

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., Improving function in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 120, 1649-1655, 2013			
	ST (n=120)	2.73 (0.52)	2.14 (0.96)	2.15 (0.96)
	25.3			
	PST	0.69 (0.94)	0.99 (1.2)	0.93 (1.2)
	ST	0.70 (0.93)	1.02 (1.2)	0.92 (1.2)
	NEI-VFQ Total Score			
	PST	66.2 (14.3)	66.6 (14.9)	66.4 (16.7)
	ST	65.8 (14.2)	65.2 (16.2)	64.8 (17.4)
	NEI-VFQ QoL Social Functioning			
	PST	80.9 (22.3)	78.1 (22.8)	76.17 (25.1)
	ST	80.9 (23.9)	74.1 (25.6)	73.64 (28.0)
	NEI-VFQ QoL Mental Health			
	PST	60.3 (27.4)	66.9 (26.7)	68.0 (25.1)
	ST	56.8 (27.3)	60.9 (28.0)	62.5 (27.4)
	NEI-VFQ QoL Role Functioning			
	PST	57.8 (20.0)	57.1 (20.2)	56.9 (20.6)
	ST	55.7 (20.1)	58.3 (21.0)	57.6 (22.7)
	NEI-VFQ QoL Dependency			
	PST	70.0 (29.3)	73.0 (28.8)	72.6 (30.1)
	ST	66.6 (31.9)	65.6 (30.6)	66.5 (30.5)
	Control Strategies: Selective Primary Control			
	PST	22.4 (2.2)	21.5 (3.2)	21.1 (3.5)

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., Improving function in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 120, 1649-1655, 2013			
	ST	22.2 (2.6)	21.5 (3.3)	22.1 (2.7)
	Control Strategies: Compensatory Primary Control			
	PST	26.7 (6.1)	25.5 (6.6)	25.3 (6.4)
	ST	26.8 (6.0)	24.1 (6.7)	25.1 (6.3)
	Control strategies: Compensatory Secondary Control			
	PST	21.6 (4.1)	21.6 (4.0)	21.9 (4.8)
	ST	22.1 (3.8)	20.2 (4.6)	20.7 (4.9)
	Control Strategies: Selective Secondary Control			
	PST	30.0 (5.0)	29.0 (5.3)	28.6 (5.7)
	ST	30.1 (4.8)	28.3 (5.6)	28.5 (5.4)
Overall Risk of Bias	Risk of bias assessed using the Cochrane risk of bias tool Overall risk of bias: Moderate Other information: None Was the allocation sequence adequately generated? Yes Was allocation adequately concealed? Yes Was knowledge of the allocated intervention adequately prevented during the study? No (investigator "single" blind, the project director, statistician, and therapists were aware of treatment assignment) Were incomplete outcome data adequately addressed? Yes Are reports of the study free of suggestion of selective outcome reporting? Yes Was the study apparently free of other problems that could put it at a high risk of bias? Single masked study. Attrition: Unclear if differences in demographic or clinical characteristics in the potential participants who enrolled in the study and those who were lost to follow up, loss to follow up was relatively low. Groups did not appear to have received different treatment other than the intervention of interest. The study did not report baseline characteristics for: time since diagnosis of AMD, time since visual impairment due to AMD, disease stage.			

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., 20150326, Low vision depression prevention trial in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 121, 2204-2211, 2014
Country/ies where the study was carried out	USA
Study type	Randomised controlled trial
Aim of the study	To compare the efficacy of behaviour activation (BA) + low vision rehabilitation (LVR) with supportive therapy (ST) + LVR to prevent depressive disorders in patients with age-related macular degeneration (AMD).
Study dates	Published 2014
Source of funding	NEI grant
Sample size	188 participants were included: Behavioural activation plus low vision rehabilitation (n = 96) Supportive therapy plus low vision rehabilitation (n = 92)
Inclusion criteria	Age >65 years Bilateral AMD (either neovascular disease or geographic atrophy) Best-corrected visual acuity <20/70 in the better seeing eye >5 antiangiogenic injections if the better eye had neovascular disease, or no injections in the previous 3 months Moderate difficulty performing a valued vision-dependent activity Sub-threshold depressive symptoms, defined as a Patient Health Questionnaire-9 score of >5, or depressed mood or anhedonia several days per week.
Exclusion criteria	Ongoing or anticipated antiangiogenic treatment Current Diagnostic and Statistical Manual (DSM) IV-defined depressive disorder Uncontrolled glaucoma, diabetic retinopathy, corneal dystrophy, or anticipated cataract surgery Cognitive impairment on an abbreviated version of the Mini-Mental Status Examination that omits vision-dependent items.
Patient characteristics	Demographic Characteristics, Mean (SD) or N (%) Age (y) BA + LVR (n = 96): 85.2 (6.6) ST + LVR (n = 92): 82.7 (6.9) Sex (female) BA + LVR (n = 96): 70 (72.9%) ST + LVR (n = 92): 62 (67.4%)

Bibliographic reference	**Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., 20150326, Low vision depression prevention trial in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 121, 2204-2211, 2014**
	Chronic disease score BA + LVR (n = 96): 5.5 (3.0) ST + LVR (n = 92): 5.8 (2.8) Medical Outcomes Study BA + LVR (n = 96): 13.0 (4.3) ST + LVR (n = 92): 12.9 (4.0) Best eye distance acuity (logMAR) BA + LVR (n = 96): 0.68 (0.40) ST + LVR (n = 92): 0.65 (0.34) Worse eye distance acuity (logMAR) BA + LVR (n = 96): 1.36 (0.66) ST + LVR (n = 92): 1.39 (0.65) Previous anti-VEGF treatment BA + LVR (n = 96): 49 (51.0%) ST + LVR (n = 92): 42 (45.7%) Depressive symptoms (PHQ-9) BA + LVR (n = 96): 5.5 (2.5) ST + LVR (n = 92): 5.6 (2.2) Study did not report the following important baseline characteristics: Ethnic group Visual acuity Comorbidities affecting the eye Time since diagnosis of AMD Time since visual impairment due to AMD Disease stage
Details	Follow up was 4 months Outcomes

Bibliographic reference	Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., 20150326, Low vision depression prevention trial in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 121, 2204-2211, 2014
	Depression—DSM-IV diagnosis of major or minor depression based on the Patient Health Questionnaire-9 (PHQ-9).13 The PHQ-9 includes the 9 criteria that define DSM-IV diagnoses of depression and is valid in low-vision patients. Self-reported Functional Vision—Activities Inventory and the National Eye Institute Vision Function Questionaire-25 (NEI-VFQ) near and distance activities sub-scales. The Activities Inventory measures the ability to achieve general vision-dependent activity goals, and perform specific vision-dependent cognitive and motor tasks. The NEI-VFQ rates difficulty performing daily activities. Standardized scores range from 0 to 100, with higher scores indicating better function. Vision-Related Quality of Life—a latent variable comprised of the NEI-VFQ social functioning, mental health, role difficulties, and dependency subscales. Standardized scores range from 0 to 100 with higher scores indicating better life quality. Vision Status—Standardized measurement of distance and near visual acuity, contrast sensitivity, and the size and location of central scotomas. Physical Health Status—The Chronic Disease Score and the Medical Outcomes Study-6 (MOS-6). The Chronic Disease Score yields a weighted score based on medication use that reflects severity of medical comorbidity. The MOS-6 yields a global index of self-rated physical and mental health. Higher scores on both scales reflect worse health status. Personality—The Revised Neuroticism, Extroversion, Openness Five Factor Inventory was used to assess the personality traits of neuroticism, conscientiousness, and openness to experience. Higher scores reflect higher standing on a given trait. Behavioural Activation for Depression Scale— Measures engagement in social and occupational activities. Its 4 subscales tap activation, avoidance/rumination, work/school impairment, and social impairment. Scores range from 0 to 42; higher scores reflect worse functioning. Device Use—Subjects rated their frequency of use of various low vision aids (e.g., task lighting) and devices (e.g., magnifiers) to improve visual ability
Interventions	Low Vision Optometry - one of 5 community-based low vision optometrists evaluated and treated all subjects before randomization. The 2 clinic visits included assessment of vision function (e.g., visual acuity, refraction), and prescribing devices and providing instruction on their use. The study provided $350 to all subjects to purchase a basic set of optical devices. After these visits, subjects were randomized to BA, which was delivered by 1 of 5 occupational therapists, or ST, which was delivered by 1 of 3 masters-level therapists (e.g., social workers). BA+LVR - the occupational therapists delivered 6 in-home, 1-hour BA sessions over 8 weeks. Treatment emphasized the link between action, mood, and mastery, and promoted self-efficacy and social connection as ways to improve mood and function and counter self-defeating behaviours (e.g., social withdrawal). The occupational therapist suggested environmental modifications to improve function and, with the subject, developed action plans to accomplish valued personal and functional goals. The action plans drew on rehabilitation principles (e.g., breaking down tasks into manageable steps), were integrated into daily routines, and focused on increasing social activities and reducing vision-related task difficulty. The latter was accomplished by increasing magnification, improving lighting, highlighting objects with high-contrast tape, and simplifying routines.

Bibliographic reference	**Rovner,B.W., Casten,R.J., Hegel,M.T., Massof,R.W., Leiby,B.E., Ho,A.C., Tasman,W.S., 20150326, Low vision depression prevention trial in age-related macular degeneration: a randomized clinical trial, Ophthalmology, 121, 2204-2211, 2014**
	ST+LVR - supportive therapy therapists delivered 6 in-home, 1-hour sessions over 8 weeks to facilitate discussion of illness, disability, and vision loss. Treatment facilitated personal expression about vision loss and disability and, in this trial, controlled for the nonspecific effects of attention.
Results	Incident depressive disorder at 4 months follow up, n (%) BA + LVR (n = 96): 11 (12.6) ST + LVR (n = 92): 18 (23.7) Adjusted Relative Risk (CI) of incidence depressive disorder at 4 months: 0.51 (0.27–0.97)* Adjusted for: vision severity stratum, and baseline neuroticism, Patient Health Questionnaire-9, and Medical Outcomes Study-6 scores.
Overall Risk of Bias	Risk of bias assessed using the Cochrane risk of bias tool Overall risk of bias: Moderate Other information: None Was the allocation sequence adequately generated? Yes Was allocation adequately concealed? Yes Was knowledge of the allocated intervention adequately prevented during the study? No (investigator "single" blind) Were incomplete outcome data adequately addressed? Yes Are reports of the study free of suggestion of selective outcome reporting? Yes Was the study apparently free of other problems that could put it at a high risk of bias? Single masked study. Attrition: There were no differences between enrolled subjects and eligible patients who declined participation with regard to age, sex, or visual acuity. Loss to follow up was moderate and anticipated (10%). Those lost to follow up had higher baseline Chronic Disease Scores (i.e., worse medical status) and worse visual acuity than retained subjects but did not differ in PHQ-9 or MOS-6 scores. Groups did not appear to have received different treatment other than the intervention of interest. Selection bias: The study did not report baseline characteristics for: Ethnic group, Visual acuity, Comorbidities affecting the eye, Time since diagnosis of AMD, Time since visual impairment due to AMD and Disease stage. BA+LVR subjects were somewhat older and more often married, The BA+LVR subjects used a greater number of low vision devices+ than ST+LVR subjects (this could be a confounder or a treatment effect).

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

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

Bibliographic reference	**Cheong A M; Lovie-Kitchin J E; Bowers A R; Brown. Short-term in-office practice improves reading performance with stand magnifiers for people with AMD. Optometry and vision science 82(2). 2005**
Country/ies where the study was carried out	Australia
Study type	Comparison study
Aim of the study	To investigate the effect of home-based large print reading practice on reading performance when stand magnifiers (STMs) are first prescribed.
Study dates	Published in 2005
Source of funding	Supported by a Queensland University of Technology Postgraduate Research Scholarship.
Sample size	32 selected, and 25 included in the study
Length follow-up	Up to 20 weeks
Inclusion criteria	People with low vision because of AMD People whose monocular near visual acuity in the better eyes was equal to or better than 1.4logMAR (15 EDTRS letter, 6/150)
Exclusion criteria	Not reported
Patient characteristics	Age, mean (SD) years: 80.3 (4.4) Gender, M, %: not reported Distance visual acuity (logMAR): Control group: 0.18, Large print practice group (p1): .026, Large print with reduced field of view practice (p2): 0.30 Participants were generally in good health with no cognitive problem that might affect their compliance with home-training instructions.
Details	A full optometric examination was conducted for each participant before the experiment to ensure that his/her distance spectacle prescription provided best vision. Participants in practice groups were instructed to read large print book at home at least 10min.day for 2 weeks. Participants recorded on the large print book the number of pages read each day in an attempt to verify compliance with the reading practice.

Bibliographic reference	**Cheong A M; Lovie-Kitchin J E; Bowers A R; Brown. Short-term in-office practice improves reading performance with stand magnifiers for people with AMD. Optometry and vision science 82(2). 2005**
Intervention	Participants were assigned to one of 3 experimental groups according to age and near visual acuity to ensure that the distribution of these variables were not significant different among groups. Participants in the control group received no reading practice at home but repeated reading measure with and without STM's were taken in the laboratory at week 0,1, and 2 before the STM's were supplied for home use. Participants in the practice groups (P1 and P2) were instructed to do 10min/day of large print reading practice at home. P2 participants were additionally requested to read the large print through a restricted field of view. Repeated reading measure with and without STM's were taken in the laboratory at week 0,1, and 2 before the STM's were supplied for home use. The STM's were supplied at week 2 to all the participants for reading small print, at that point, large print reading practice ceased. Further reading measures with STM's were made at week 4,8 and 20.
Results	

	P1 (home training large print reading)	P2 (home training large print reading with additional request to read with a restrict field of view)	Control (no reading practice)	Effect (95%CI)	
Number of participants	10	9	6	P1 vs control	P2 vs control
Relative log reading rate (wpm), 2 weeks	0.08 (0.05, 0.12)	0.065 (0.03, 0.1)	0.025 (-0.02, 0.07)	0.06 (-0.06, 0.17)	0.04 (-0.07, 0.15)
Relative log reading rate (wpm), 8 weeks	0.12 (0.08, 0.16)	0.1 (0.06, 0.14)	0.08 (0.03, 0.13)	0.04 (-0.09, 0.17)	0.02 (-0.10, 0.14)
Relative log reading rate (wpm), 20 weeks	0.135 (0.08, 0.19)	0.05 (-0.01, 0.11)	0.06 (-0.01,0.13)	0.08 (-0.09, 0.25)	-0.01 (-0.19, 0.17)

Exponentials relative log reading rate, effect between treatment and control

	Effect (95%CI) MD

Bibliographic reference	Cheong A M; Lovie-Kitchin J E; Bowers A R; Brown. Short-term in-office practice improves reading performance with stand magnifiers for people with AMD. Optometry and vision science 82(2). 2005
	<table><tr><td></td><td>P1 vs control</td><td>P2 vs control</td></tr><tr><td>Relative log reading rate (wpm), 2 weeks</td><td>1.06 (0.94, 1.19)</td><td>1.04 (0.93, 1.16)</td></tr><tr><td>Relative log reading rate (wpm), 8 weeks</td><td>1.04 (0.40, 1.18)</td><td>1.02 (0.90, 1.15)</td></tr><tr><td>Relative log reading rate (wpm), 20 weeks</td><td>1.08 (0.91, 1.28)</td><td>0.99 (0.83, 1.18)</td></tr></table>
Missing data handling/loss to follow up	Not reported
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Unclear
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of	Unclear

Bibliographic reference	Cheong A M; Lovie-Kitchin J E; Bowers A R; Brown. Short-term in-office practice improves reading performance with stand magnifiers for people with AMD. Optometry and vision science 82(2). 2005
selective outcome reporting?	

Bibliographic reference	Eklund K ; Sonn U ; Dahlin-Ivanoff S. Long-term evaluation of a health education programme for elderly persons with visual impairment. A randomized study. Disability & Rehabilitation 26 (7), 2004.
Country/ies where the study was carried out	Sweden
Study type	RCT
Aim of the study	To investigate the impact of the health education programme on perceived security in the performance of daily activities.
Study dates	Published in 2004
Source of funding	Not reported
Sample size	229 participants, and 98 person dropout
Length follow-up	28 months
Inclusion criteria	People aged 65 years or older Living at home Diagnosed with AMD A distance VA of better eye with BCVA no lower than 0.1 (VA was tested with a letter chart graded 0.1 to 1.0 at distance of 5 m with the person's own glasses and with best refraction).
Exclusion criteria	Not reported
Patient characteristics	Age, mean (SD) years: 78 Gender, M, %: 26% Visual acuity: 0.3 (range 1.0-0.1) Participants living alone, %: 60% Participants receiving public transportation service: 37% Participants receiving social service: 18% Participants reported perceived good health: 86%

Bibliographic reference	Eklund K ; Sonn U ; Dahlin-Ivanoff S. Long-term evaluation of a health education programme for elderly persons with visual impairment. A randomized study. Disability & Rehabilitation 26 (7), 2004.
Details	The participants were randomly assigned, according a random number table, either to the health education programme, or to an individual intervention programme that was standard at the low vision clinic. The occupational therapists that collected the data were not blinded to the composition of the groups but were not involved in the programme. Assessment at baseline at the 28 months follow-up were made when participants attended the low vision clinic. The study procedure did not differ between the programs. Independent registered occupational therapists interviewed the participants according to a structured protocol that consisted of questions about marital status, living arrangements, social service, and health problems. An assessment of perceived security in performing daily occupations also was completed; details about this assessment follow in the next section. An optometrist made the optical evaluation during the visit. Visual acuity was tested with a letter chart (Monoyer-Granström, Kifa), graded .1 to 1.0 at a distance of 5 m, with the person's own eyeglasses and with best refraction. The instrument for measuring the primary outcome—perceived security in performing daily occupations was developed for the purpose of evaluating the health education program. The instrument is a questionnaire that consists 29 items divided into 7 performance areas: Meals, self-care and care of clothing, communication, cleaning, mobility, shopping, and financial management. Perceived confidence in performing each task is rated on a 4-point ordinal scale (very insecure, insecure, quite secure, secure). The participants completed the questionnaire after instructions from the occupational therapists.
Intervention	Intervention with the health education program. Groups of 4 to 6 participated in the health education program for a total of 20 formed consecutively during the study period. The intervention period for each group was 8 weeks, and the groups met once a week for 2 hr. The groups were led by occupational therapists, and each group always had the same leader. The therapists were experienced in leading groups and trained in the methodology and theoretical foundations of the program before the start of the study. The occupational therapist provided information and skills training based on the occupational categories and guided and encouraged the participants in the learning process. Other health professionals, such as an ophthalmologist, an optometrist, a low vision therapist, and a light expert, were invited to give information. The information and the skills training were derived from strategies elderly persons with age-related macular degeneration use to continue to perform daily occupations. The strategies were presented within the program as a problem-solving model, and the participants were taught to use the model as a way of thinking when performing daily occupations. A booklet containing the information given by health professionals as well as information about occupational categories was used in the health education program. The participants were asked to prepare themselves before participating in the sessions by reading relevant chapters and formulating questions. Individual intervention programme

Bibliographic reference	**Eklund K ; Sonn U ; Dahlin-Ivanoff S. Long-term evaluation of a health education programme for elderly persons with visual impairment. A randomized study. Disability & Rehabilitation 26 (7), 2004.**
	The individual intervention program was the standard intervention for the target group at the low vision clinics. The participants were provided with optical aids with the aim to improve reading and near and distance viewing. Hand and stand magnifiers as well as eyeglasses for reading were prescribed. The participants were given information about the disease if they requested it. The individual intervention measures were carried out by an occupational therapist with special training in low vision. The individual intervention typically included one to two 1-hr sessions at the clinic, with follow-up phone calls over a 4-week period.
Results	

	Relative position (95%CI)		Relative variance	
	Health education programme	Individual education programme	Health education programme	Individual education programme
Median	0.25 (-0.09, 0.47)	-0.14 (-0.32, 0.15)	0.16 (0.04, 0.32)	0.1 (0.05, 0.46)

	Significant difference in perceived security in performance daily activities between groups	Non-significant difference in perceived security in performance daily activities between groups
Meal	pouring coffee/tea for yourself	Finding food on the plate
	finding utensils and supplies in cabinets	Finding things on the table while eating
	measuring ingredients for making coffee	Slicing bread
	determining if vegetables are clear	
	managing the knobs on the stove	
	determining if the dishes are clear	

Bibliographic reference	Eklund K ; Sonn U ; Dahlin-Ivanoff S. Long-term evaluation of a health education programme for elderly persons with visual impairment. A randomized study. Disability & Rehabilitation 26 (7), 2004.		
	Self-care and care of clothing	cutting/filing your nails	Treading a needle and sewing on a button
		discovering if your clothes are stained	
	Communication	writing a memo to yourself	Reading an article in your newspaper
			Following the news on your TV
			Dialling on your phone
	Clean	dusting your apartment	Vacuuming your apartment
	Mobility	going to your local shop	
		using a pedestrian traffic light crossing	
		distinguishing irregularity in the street	
	Financial management	Knowing your turn in the queue	Reading a bank statement
		Filing in a withdrawal form	
	Shopping		Finding your way in your local shop
			Picking the right product

Bibliographic reference	Eklund K ; Sonn U ; Dahlin-Ivanoff S. Long-term evaluation of a health education programme for elderly persons with visual impairment. A randomized study. Disability & Rehabilitation 26 (7), 2004.
	<table><tr><td></td><td></td><td>Knowing the price on the products</td></tr><tr><td></td><td></td><td>Managing money and paying</td></tr><tr><td></td><td>Relative position (RP), intervention group=0.27 (0.10, 0.43) Individual group=-0.15 (-0.31, 0)</td><td></td></tr></table>
Missing data handling/loss to follow up	98 drop out from the participations
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Masking technique was not applied
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Drop outs did not differ from the participants at baseline
Are reports of the study free of suggestion of selective outcome reporting?	Yes
Other	There was an early publication on this trial reporting 4 month follow up (Dahlin Ivanoff 2002).

Bibliographic reference	Eklund K ; Sjostrand J ; Dahlin-Ivanoff S. A randomized controlled trial of a health-promotion programme and its effect on ADL dependence and self-reported health problems for the elderly visually impaired. Scandinavian Journal of Occupational Therapy 15 (2): 68-74. 2008.
Country/ies where the study was carried out	Sweden
Study type	RCT
Aim of the study	To compare the differences between an activity-based health promotion programme and an individual programme concerning their effect on activities of daily living (ADL) dependence and self-reported health.
Study dates	Published in 2008
Source of funding	Not reported
Sample size	229 participated, 81 lost to follow-up, and 131 included in the analysis
Length follow-up	28 months
Inclusion criteria	People with AMD as the primary diagnosis People with a distance visual acuity of the better than with best correction ≥0.1 65 years or older Living at home Being capable of participation in group discussion
Exclusion criteria	Not reported
Patient characteristics	Age, mean (SD) years: 78 Gender, M, %: 26% Visual acuity: 0.3 (range 1.0-0.1) Participants living alone, %: 60% Participants receiving public transportation service: 37% Participants receiving social service: 18% Participants reported perceived good health: 86%
Details	The participants were randomly assigned, according a random number table, either to the health promotion programme, or to an individual intervention programme that was standard at the low vision clinic.

<table>
<tr><th>Bibliographic reference</th><th>Eklund K ; Sjostrand J ; Dahlin-Ivanoff S. A randomized controlled trial of a health-promotion programme and its effect on ADL dependence and self-reported health problems for the elderly visually impaired. Scandinavian Journal of Occupational Therapy 15 (2): 68-74. 2008.</th></tr>
<tr><td></td><td>The occupational therapists that collected the data were not blinded to the composition of the groups but were not involved in the programme.</td></tr>
<tr><td>Intervention</td><td>The health-promotion programme
This programme was carried out with groups of 4 to 6 persons. A total of 20 formed consecutively during the study period.
The intervention period for each group was 8 weeks, and the groups met once a week for 2 hr.
The content of the programme included 8 occupation themes:
Self-care; meals; communications, orientation and mobility; food preparation; shopping; financial management, and cleaning.

Health professional such as ophthalmologist, optician, low vision therapies and a lightening expert provided information. The optician also prescribed glasses. Occupational therapists led the groups, and each group had the same leader.

Individual intervention programme
The individual intervention program was the standard intervention for the target group at the low vision clinics. Magnifiers and reading glasses were prescribed and introduced at the clinic and were taken home directly for practice application. Information about lighting, mainly for reading was provided. If requested, the participants also received information about the disease. The individual programme measures were carried out by occupational therapies with special training in low vision. The individual intervention typically included one to two 1-hr sessions at the clinic, with follow-up phone calls over a 2-4-week period. An optician therapists prescribed glasses and the occupational therapists prescribed low-vision aids.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Baseline</td><td></td><td>28 months</td><td></td><td>Effect (95%CI), at 28 months</td></tr>
<tr><td></td><td>Health promotion programme (n=62)</td><td>Individual programme (n=69)</td><td>Health promotion programme (n=62)</td><td>Individual programme (n=69)</td><td></td></tr>
<tr><td>ADL step, n(%)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>0</td><td>26 (42)</td><td>33 (48)</td><td>24 (39)</td><td>15 (22)</td><td>1.78 (1.03, 3.08)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Eklund K ; Sjostrand J ; Dahlin-Ivanoff S. A randomized controlled trial of a health-promotion programme and its effect on ADL dependence and self-reported health problems for the elderly visually impaired. Scandinavian Journal of Occupational Therapy 15 (2): 68-74. 2008.					
	1	19 (31)	18 (26)	14 (23)	15 (22)	1.04 (0.55, 1.97)
	2	8 (13)	5 (7)	8 (13)	16 (23)	0.56 (0.26, 1.21)
	3	7(11)	10 (15)	9 (15)	13 (19)	0.77 (0.35, 1.68)
	4	2 (3)	3 (4)	4 (7)	5 (7)	0.89 (0.25, 3.17)
	5			2 (3)	2 (3)	1.11 (0.16, 7.67)
	6			1 (2)	1 (1)	1.11 (0.07, 17.42)
	7				0 (0)	
	8				1 (1)	
	9				1 (1)	
	General health (SF-36)					
	Excellent	13 (21)	10 (15)	6 (10)	1 (1)	6.68 (0.83, 53.93)
	Poor/fairly poor	41 (66)	48 (70)	42 (68)	40 (58)	1.17 (0.90, 1.52)
	Bad	5 (8)	10 (15)	13 (21)	26 (38)	0.56 (0.31, 0.98)

Bibliographic reference	Eklund K ; Sjostrand J ; Dahlin-Ivanoff S. A randomized controlled trial of a health-promotion programme and its effect on ADL dependence and self-reported health problems for the elderly visually impaired. Scandinavian Journal of Occupational Therapy 15 (2): 68-74. 2008.					
	Health problems					
	0	8 (13)	5 (7)	7 (11)	1 (1)	7.79 (0.99, 61.55)
	1-2	32 (52)	38 (55)	42 (68)	40 (58)	1.17 (0.90, 1.52)
	3-4	15 (25)	20 (29)	12 (19)	21 (30)	0.64 (0.34, 1.18)
	5 or more	7(11)	6 (9)	1 (2)	7 (10)	0.16 (0.02, 1.26)
	Visual acuity					
	1.0-0.8	2 (3)	0	2 (3)	2 (3)	1.11 (0.16, 7.67)
	0.7-0.5	9 (15)	18 (26)	4 (6)	8 (12)	0.56 (0.18, 1.76)
	0.4-0.2	40 (65)	41 (59)	23 (37)	28 (41)	0.91 (0.59, 1.41)
	0.1	10 (16)	10 (15)	14 ((23)	16 (23)	0.97 (0.52, 1.83)
	Finger counting			19 (31)	14 (20)	1.51 (0.83, 2.75)
Missing data handling/loss to follow up	81 lost to follow-up					
Was allocation adequately concealed?	Unclear					

Bibliographic reference	Eklund K ; Sjostrand J ; Dahlin-Ivanoff S. A randomized controlled trial of a health-promotion programme and its effect on ADL dependence and self-reported health problems for the elderly visually impaired. Scandinavian Journal of Occupational Therapy 15 (2): 68-74. 2008.
Was knowledge of the allocated intervention adequately prevented during the study?	Masking technique was not applied
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Drop outs did not differ from the participants at baseline
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Parodi M B; Toto L ; Mastropasqua L ; Depollo M ; Ravalico G. Prismatic correction in patients affected by age-related macular degeneration. Clinical Rehabilitation 18 (7): 828-32. 2004
Country/ies where the study was carried out	Italy
Study type	RCT
Aim of the study	To evaluate the effectiveness and the tolerance of prismatic correction in improving visual function in patients affected by advanced AMD
Study dates	Published in 2004
Source of funding	Not reported
Sample size	28
Length follow-up	Up to 360 days
Inclusion criteria	People with advanced AMD, presented with bilateral exudative AMD at an advanced stage Visual acuity better than 6/19

<table>
<tr><th>Bibliographic reference</th><td>Parodi M B; Toto L ; Mastropasqua L ; Depollo M ; Ravalico G. Prismatic correction in patients affected by age-related macular degeneration. Clinical Rehabilitation 18 (7): 828-32. 2004</td></tr>
<tr><td></td><td>Stable visual acuity for at least one year
Being able to consent their participation</td></tr>
<tr><td>Exclusion criteria</td><td>Presence of any other ocular disease able to impair visual function;
Presence of disorder causing choroidal neovascularisation other than AMD;
Previous laser photocoagulation</td></tr>
<tr><td>Patient characteristics</td><td>Age, mean (SD) years: treatment group: 72 years; control group: 71 years

Gender, M, %: not reported

Visual acuity (logMAR): treatment group: 1.06 logMAR; control group:1.06 logMAR</td></tr>
<tr><td>Details</td><td>The variation of visual acuity during the study period was evaluated using the analysis of variance for repeated measurement.</td></tr>
<tr><td>Intervention</td><td>Patients were randomly assigned to the treatment or control group, following a computer generated list using a block randomisation.
The treatment group received spectacles providing prismatic correction. A prism of low power (4-7 prismatic dioptres) placed in front of the better eyes was rotated to the position of clearest vision.
Visual acuity in control group was assessed in the same way, using the best optical correction (without prismatic correction) that had been prescribed at baseline.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>VA (logMAR)</td><td>Prismatic correction (n=14)</td><td>Control (without prismatic correction) (n=14)</td><td>Effect (95%CI)</td></tr>
<tr><td>Baseline</td><td>1.062857 (1.01, 1.10)</td><td>1.084285714 (1.02, 1.13)</td><td>-0.02 (-0.16, 0.12)</td></tr>
<tr><td>1 day</td><td>0.89 (0.81,0.91)</td><td>1.08 (1.01, 1.13)</td><td>-0.19 (-0.34, -0.04)</td></tr>
<tr><td>90 days</td><td>0.80 (0.77,0.85)</td><td>1.12 (1.09,1.14)</td><td>-0.32 (-0.41, -0.23)</td></tr>
<tr><td>180 days</td><td>0.71 (0.68, 0.79)</td><td>1.10 (1.08, 1.13)</td><td>-0.39 (-0.51, -0.27)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Parodi M B; Toto L ; Mastropasqua L ; Depollo M ; Ravalico G. Prismatic correction in patients affected by age-related macular degeneration. Clinical Rehabilitation 18 (7): 828-32. 2004**
	360 days | 0.69 (0.65, 0.73) | 1.09 (1.02,1.10) | -0.40 (-0.52, -0.28)
Missing data handling/loss to follow up	2 participants in treatment groups lost to follow-up
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Unclear
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	**Reeves B C; Harper R A; Russell W B. Enhanced low vision rehabilitation for people with age related macular degeneration: a randomised controlled trial. British Journal of Ophthalmology 88 (11): 1443-9. 2004**
Country/ies where the study was carried out	UK
Study type	RCT
Aim of the study	To compare the effectiveness of three models of low vision rehabilitation for people with age related macular degeneration (AMD) referred for low vision rehabilitation (LVR): (a) an enhanced low vision rehabilitation model (ELVR) including supplementary home based low vision rehabilitation; (b) conventional low vision rehabilitation (CLVR) based in a hospital clinic;

Bibliographic reference	Reeves B C; Harper R A; Russell W B. Enhanced low vision rehabilitation for people with age related macular degeneration: a randomised controlled trial. British Journal of Ophthalmology 88 (11): 1443-9. 2004
	(c) CLVR with home visits that did not include rehabilitation (CELVR), intended to act as a control for the additional contact time with ELVR.
Study dates	Published in 2004
Source of funding	The trial was funded by North West Regional Health Authority (research grant RDO/18/39); Manchester Royal Eye Hospital General Research endowment fund.
Sample size	226 randomised, and 194 completed trial
Length follow-up	12 months
Inclusion criteria	People were eligible for the trial if they were newly referred to the low vision clinic at Manchester Royal Eye Hospital with a primary diagnosis of AMD. Participants had to have Snellen visual acuity worse than 6/18 (.0.5 logMAR) in both eyes and equal to or better than 1/60 ((1.8 logMAR) in the ‘‘better’’ eye.
Exclusion criteria	People were ineligible if they were living in a residential or nursing home, were suffering from mental illness or dementia, or were not proficient in English.
Patient characteristics	Age, median (IQR) years: CLVR group: 81 (77-84) years; ELVR group: 80 (76-85) years; CELVR group: 83 (78-86) years Gender, M, % CLVR group: 37%; ELVR group: 36%; CELVR group: 28% Living alone, % CLVR group: 42%; ELVR group: 52%; CELVR group: 60% Median distance visual acuity (logMAR): CLVR group: 0.81 (0.48-1.00); ELVR group: 0.90 (0.56-1.08); CELVR group: 0.62 (0.44-1.00)
Details	Participants allocated to CLVR received a clinical low vision assessment at the hospital provided by a team of qualified optometrists, a dispensing optician, and a limited number of preregistration optometrists working under supervision. As a pragmatic trial, assessments were carried out as part of standard hospital care for people referred to the low vision clinic. While general guidelines were suggested, practitioners did not have to adhere to a strict assessment protocol, although they were asked to complete data sheets requesting information on diagnosis, co-morbidity, visual requirements, unaided vision, performance with existing LVAs (if any), refraction, corrected acuities, contrast sensitivity, and performance with new LVAs.

Bibliographic reference	Reeves B C; Harper R A; Russell W B. Enhanced low vision rehabilitation for people with age related macular degeneration: a randomised controlled trial. British Journal of Ophthalmology 88 (11): 1443-9. 2004
	Participants allocated to ELVR received all components of CLVR but, in addition, received additional low vision training at home. A rehabilitation officer, with specific training in the rehabilitation of people with visual impairment and 5 years' experience in this role, provided the home visits. Participants allocated to CELVR also received all components of CLVR but, in addition, were visited at home by one of four community care workers from Age Concern. Community care workers do not have training about visual impairment or any formal training in low vision. Hence, they did not provide any specific LVR. The community care workers did not have any formal link with the hospital through a reporting system and did not visit the low vision clinic.
Intervention	Conventional low vision rehabilitation (CLVR) Check a patient's understanding of the diagnosis and prognosis Discuss needs/visual requirements and set initial goals Assess vision (including sight test and near acuities) Re-appraise goals Demonstrate specific LVAs Explain use and handling of prescribed LVAs Advise about lighting and other methods of enhancing vision Provide large print literature about diagnosis, vision enhancement, use of LVAs and other services Refer to other services where necessary (e.g., to a hospital support worker) Arrange for follow ups, usually at 3 months with additional appointments being offered if necessary Enhanced low vision rehabilitation (ELVR) As for conventional LVR, plus up to three home visits (at approximately 2 weeks, 4–8 weeks, and at 4–6 months after the first low vision assessment) by a trained rehabilitation officer to: advise on use of LVA(s): assess patterns of LVA use (e.g., tasks attempted, frequency and duration of use) and difficulties experienced in using LVAs; demonstrate and supply alternative or additional LVAs, if appropriate; provide wider patient support—e.g., direct patients to relevant support and welfare services Controlled for additional contact time in enhanced low vision rehabilitation (CELVR) As for conventional LVR, plus up to three home visits (at approximately 2 weeks, 4–8 weeks, and at 4–6 months after the first low vision assessment) by a community care worker to: discuss ability to cope with daily activities

Bibliographic reference	Reeves B C; Harper R A; Russell W B. Enhanced low vision rehabilitation for people with age related macular degeneration: a randomised controlled trial. British Journal of Ophthalmology 88 (11): 1443-9. 2004
	discuss ability to take part in leisure activities discuss other problems or topics raised by participant
Results	

	Enhanced low vision rehabilitation (ELVR)	Controlled for additional contact time in enhanced low vision rehabilitation (CELVR)	Conventional low vision rehabilitation (CLVR)	Effect (95%CI) ELVR vs CLVR	Effect (95%CI) CELVR vs CLVR
At 12 month					
No.	64	70	60		
Vision specific QoL (VCM), median (IQR)	2.2 (1.7, 3.0)	2.3 (1.5, 2.9)	2.4 (1.8,3.1)	0.06 (-0.17, 0.30)	-0.05 (-0.29, 0.18)
SF-36 (physical health), median (IQR)	26 (14,40)	28 (17,41)	38 (24,44)	-6.05 (-10.2, -1.91)	-2.27 (-6.29, 1.76)
SF-36 (mental health), median (IQR)	53 (41,57)	53 (45,57)	52 (43,59)	-4.04 (-7.44, -0.65)	-1.48 (-4.69, 1.73)
Nottingham adjustment scale (NAC)					
Locus of control	18 (14,20)	18 (16,20)	18 (14,20)	-0.42 (-1.68, 0.83)	0.02 (-1.21, 1.25)
Acceptance	36 (29,42)	38 (29,42)	38 (27,41)	-0.36 (-3.04,2.32)	0.36 (-2.24, 2.97)

Bibliographic reference	Reeves B C; Harper R A; Russell W B. Enhanced low vision rehabilitation for people with age related macular degeneration: a randomised controlled trial. British Journal of Ophthalmology 88 (11): 1443-9. 2004					
	Attitude	20 (17,24)	19 (17,25)	20 (15,23)	0.22 (-1.34, 1.77)	0.25 (-1.27, 1.77)
	Self-efficacy	28 (23,34)	29 (24,34)	28(24,33)	-0.44 (-2.88, 2.00)	0.44 (-1.91, 2.79)
	Manchester low vision questionnaire (MLVQ)					
	Self rated restriction score	0.6 (0.4, 0.7)	0.4 (0.3,0.6)	0.6 (0.4, 0.70)	0.04 (-0.02, 0.11)	-0 (-0.06, 0.06)
	Using at least one low vision aid, n(%)	58 (90.6%)	67 (95.7%)	57 (95.5%)	0.95 (0.87, 1.05)	1.01 (0.93, 1.09)
	Using low vision aid daily, n(%)	47 (73.4%)	51 (72.9%)	42 (70.0%)	1.05 (0.84, 1.31)	1.04 (0.84, 1.30)
	Using low vision aid for≥5 minutes, n(%)	22 (34.4%)	16 (22.9%)	18 (30.0%)	1.15 (0.69, 1.92)	0.76 (0.43, 1.36)
	Measured task performance, no. (%)					
	Read one or both use by dates	39 (61.9%)	54 (77.1%)	39 (66.1%)	0.94 (0.72, 1.23)	1.19 (0.95, 1.49)
	Read drug name	30 (46.9%)	43 (61.4%)	32 (55.2%)	0.88 (0.62, 1.25)	1.15 (0.85, 1.56)
Missing data handling/loss to follow up	32 lost to follow-up of 3 groups					
Was allocation adequately concealed?	Allocation codes were generated by computer before the start of the study by BCR (who took no part in recruitment, data collection, or the care of patients) and were concealed in sealed opaque envelopes.					
Was knowledge of the allocated intervention	Allocation codes were generated by computer before the start of the study by BCR (who took no part in recruitment, data collection, or the care of patients) and were concealed in sealed opaque envelopes.					

Bibliographic reference	Reeves B C; Harper R A; Russell W B. Enhanced low vision rehabilitation for people with age related macular degeneration: a randomised controlled trial. British Journal of Ophthalmology 88 (11): 1443-9. 2004
adequately prevented during the study?	Eligible people were told about the study and were invited to participate by a large print letter. Those who agreed to participate gave written informed consent. At recruitment, an appointment was made for the initial home visit. RAH then randomised the participant by opening the next sealed envelope, keeping the allocation secret from the researcher who measured outcomes (WBR).
Was the allocation sequence adequately generated?	Allocation was randomised and blocked using blocks of unequal length
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Smith H J; Dickinson C M; Cacho I ; Reeves B C; Harper R A. A randomized controlled trial to determine the effectiveness of prism spectacles for patients with age-related macular degeneration. Archives of Ophthalmology 123 (8): 1042-50. 2005.
Country/ies where the study was carried out	UK
Study type	RCT
Aim of the study	To determine the effectiveness of prism spectacle in people with AMD by relocating the retinal image.
Study dates	Published in 2005
Source of funding	Supported by the Health Foundation, London
Sample size	225 people
Inclusion criteria	People with bilateral AMD People with visual acuity of at least 1/60 but no better than 6/18 in the better seeing eye Free of mental illness, dementia, and severe physical limitations Proficient in English and literate

<table>
<tr><th>Bibliographic reference</th><th>Smith H J; Dickinson C M; Cacho I ; Reeves B C; Harper R A. A randomized controlled trial to determine the effectiveness of prism spectacles for patients with age-related macular degeneration. Archives of Ophthalmology 123 (8): 1042-50. 2005.</th></tr>
<tr><td></td><td>Not a resident in a hospital or a nursing home</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Patient characteristics</td><td>Age, median (IQR) year:
Custom group: 81 (77-85) years; Standard group: 81 (77-85) years; Placebo: 81 (76-86) years

Gender, M, %:
Custom group: 36%; Standard group: 32%; Placebo: 38%

Median visual acuity better eye, logMAR (IQR):
Custom group: 0.82 (0.62-1.12); Standard group: 0.92 (0.63-1.19); Placebo group: 1.00 (0.66-1.00)

Living alone, %
Custom group: 56%; Standard group: 51%; Placebo: 53%</td></tr>
<tr><td>Details</td><td>Participants were allocated to groups using computer generated randomisation codes prepared in advance by one of researchers. Randomisation and the ordering of spectacles were performed by a principal investigator who had no contact with participants during the study. Participants were recruited by the trial optometrist and another investigator collected all outcome data at baseline and follow-up.</td></tr>
<tr><td>Intervention</td><td>Participants received 1 of the following 3 types of test spectacles:
Custom, incorporating bilateral prisms to match participants’ preferred power and base direction.
Standard, incorporating standard bilateral prisms (6 prism dioptres base up for logMAR VA of 0.48-1.00 and 10 prism dioptres base up for logMAR VA of 1.02-1.68.
Placebo, consisting of spectacles matched in weight and thickness to prism spectacles but without prism.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Custom prisms group</th><th>Standard prisms group</th><th>Placebo</th><th>Effect1 (95%CI) Custom vs placebo</th><th>Effect (95%CI) Standard vs placebo</th></tr>
<tr><td>No. of participants, 3 months follow-up</td><td>70</td><td>75</td><td>80</td><td></td><td></td></tr>
<tr><td>logMAR, ETDRS (SD)</td><td>0.88 (0.32)</td><td>0.89 (0.32)</td><td>0.95 (0.32)</td><td>-0.02 (-0.07, 0.02)</td><td>-0.02 (-0.06, 0.03)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Smith H J; Dickinson C M; Cacho I ; Reeves B C; Harper R A. A randomized controlled trial to determine the effectiveness of prism spectacles for patients with age-related macular degeneration. Archives of Ophthalmology 123 (8): 1042-50. 2005.
	logMAR, critical print size: 1.45 (0.26) | 1.45 (0.26) | 1.50 (0.24) | -0.04 (-0.10, 0.03) | -0.05 (-0.11, 0.01) Words per minutes: 73 (54) | 74 (53) | 67 (52) | -2.70 (-10.35, 4.96) | 1.39 (-6.09, 8.87) NEI-VFQ 25, self-assessed visual function: 53 (16) | 54 (17) | 53 (15) | 1.25 (-1.98, 4.47) | 0.29 (-2.90, 3.49) Manchester low vision questionnaire, part 1observed task performance: 36 (12) | 36 (14) | 36 (12) | -0.72 (-2.30, 0.87) | 0.45 (-1.11, 2.01) Manchester low vision questionnaire, part 2, activities of daily living: 28 (4) | 28 (5) | 29 (4) | -0.14 (-0.67, 0.39) | -0.07 (-0.59, 0.45) Observed performance dependent on vision (OPTV): 48 (19) | 50 (22) | 49 (17) | -1.44 (-4.47, 1.59) | 1.84 (-1.14, 4.81) Activities of daily living (ADL): 46 (20) | 49 (20) | 48 (17) | -0.56 (-3.08, 1.97) | -0.10 (-2.59, 2.39) Adjusted mean differences (using ANCOVA)
Missing data handling/loss to follow up	18 lost to follow-up
Was allocation adequately concealed?	Yes
Was knowledge of the allocated intervention adequately prevented during the study?	Yes
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that	Yes

Bibliographic reference	Smith H J; Dickinson C M; Cacho I ; Reeves B C; Harper R A. A randomized controlled trial to determine the effectiveness of prism spectacles for patients with age-related macular degeneration. Archives of Ophthalmology 123 (8): 1042-50. 2005.
could put it at a high risk of bias?	
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Vukicevic Meri and Fitzmaurice Kerry. Eccentric viewing training in the home environment: can it improve the performance of activities of daily living? Journal of visual impairment & blindness 103 (5): 277-289. 2009.
Country/ies where the study was carried out	Australia
Study type	RCT
Aim of the study	To investigate the impact of eccentric viewing on near acuity and self-care activities of daily living from the point of view of a clinician working in the field of low vision.
Study dates	Published in 2009
Source of funding	Not reported
Sample size	48
Length follow-up	8 weeks
Inclusion criteria	People in good general health, aged 60 years and older People with a visual acuity of 20/200 (1.0 logMAR unit) (equivalent to 6/60) People with a diagnosis of AMD
Exclusion criteria	People were excluded if they had secondary ocular pathologies that affected their vision. People with a diagnosis of dementia People had received previous training in eccentric viewing
Patient characteristics	Age, mean (SD) years: Treatment group: 82.4 (4.9); Control group: 81.4 (7.9) Gender, M, %:

<table>
<tr><th>Bibliographic reference</th><td>Vukicevic Meri and Fitzmaurice Kerry. Eccentric viewing training in the home environment: can it improve the performance of activities of daily living? Journal of visual impairment & blindness 103 (5): 277-289. 2009.</td></tr>
<tr><td></td><td>Treatment group: 16.7%; Control group: 41.7%)

Distance visual acuity (logMAR):
Treatment group: 1.15 (0.17); Control group: 1.17 (0.22)

Mean schooling completed (in years)
Treatment group: 9.92 (2.02); Control group: 9.38 (1.2)</td></tr>
<tr><td>Details</td><td>All the data collection, assessment and rehabilitation training were conducted in the participants' homes. Training in eccentric viewing is commonly conducted as part of a home visit by clinicians of low vision agencies in Australia, and an additional purpose of providing in-home training was to decrease the amount of traveling required by the participants.
Training in eccentric viewing was conducted using the EccVue computer programme presented on a laptop personal computer.</td></tr>
<tr><td>Intervention</td><td>Participants were sequentially allocated to either an eccentric viewing group or a non-intervention group. The participants were told that they would be allocated to a study group but were not told to which group they were assigned.
The eccentric viewing group received 8 training sessions in eccentric viewing. The number of training sessions was chosen based on the basis of data from a pilot study.
The non-intervention group was a control group that received a weekly telephone call of 15 or fewer minutes for the duration of study in which they received support but no rehabilitation advice.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Eccentric viewing group (n=24)</td><td>Control group (n=24)</td><td>Effect (95%CI)</td></tr>
<tr><td>Mean near visual acuity logMAR (SD)</td><td>1.0 (0.18)</td><td>1.40 (0.17)</td><td>-0.38 (-0.47, -0.29)</td></tr>
<tr><td>Activities of daily living (MLVAI)</td><td>31.58 (3.88)</td><td>25.33 (4.98)</td><td>6.25 (3.72, 8.78)</td></tr>
</table>
</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>All completed study</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Unclear</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>Unclear</td></tr>
</table>

Bibliographic reference	Vukicevic Meri and Fitzmaurice Kerry. Eccentric viewing training in the home environment: can it improve the performance of activities of daily living? Journal of visual impairment & blindness 103 (5): 277-289. 2009.
adequately prevented during the study?	
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Unclear
Were incomplete outcome data adequately addressed?	N/A
Are reports of the study free of suggestion of selective outcome reporting?	Unclear

Bibliographic reference	Vukicevic Meri and Fitzmaurice Kerry. Rehabilitation strategies used to ameliorate the impact of centre field loss. Visual impairment research 7: 79-84. 2005.
Country/ies where the study was carried out	Australia
Study type	RCT
Aim of the study	To compare the impact of 3 interventions (eccentric viewing, magnification, and combined intervention) upon near print size and the performance of daily living task.
Study dates	Published in 2005
Source of funding	Not reported
Sample size	58
Length follow-up	8 weeks
Inclusion criteria	People aged 50 years or older People were legally blind according to Australian Social Security classifications, which equates to a level of visual acuity of 6/60 (20/200) or worse due to AMD.
Exclusion criteria	People were secondary ocular pathology or diagnosed with dementia.
Patient characteristics	Age, mean (SD) years: 82 years

<table>
<tr><th>Bibliographic reference</th><td>Vukicevic Meri and Fitzmaurice Kerry. Rehabilitation strategies used to ameliorate the impact of centre field loss. Visual impairment research 7: 79-84. 2005.</td></tr>
<tr><td></td><td>Gender, M, %: 33.7% (n=19)</td></tr>
<tr><td>Details</td><td>N/A</td></tr>
<tr><td>Intervention</td><td>Participants were randomly allocated into one of 4 age-matched groups:
Group 1: eccentric viewing received 8 training session in eccentric viewing using the “EccVue” computer programme;
Group 2: combination group received 8 training sessions in eccentric viewing using “EccVue” and assessment and instruction in the use of magnification;
Group 3: Magnification group received assessment and up to 3 instruction sessions in the use of magnification which telephone contact from the researcher to the equivalent to the 8 eccentric viewing session;
Group 4: a non-intervention group that received a weekly phone call for the 8 weeks of the study, each lasting no more than 15 minutes.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Eccentric viewing</td><td>Magnification</td><td>Combination (eccentric viewing + magnification)</td><td>Non-intervention</td></tr>
<tr><td>Number of participants</td><td>22</td><td>12</td><td>12</td><td>12</td></tr>
<tr><td>Near visual acuity</td><td></td><td></td><td></td><td></td></tr>
<tr><td>ADL score, part A</td><td>35.2</td><td>45.3</td><td>45.1</td><td>30</td></tr>
<tr><td>ADL score, part A change from baseline</td><td>5.2</td><td>12.8</td><td>16.6</td><td>0</td></tr>
<tr><td>ADL score, part B</td><td>30</td><td>24</td><td>31</td><td>26</td></tr>
<tr><td>ADL score, part B change from baseline</td><td>6</td><td>1</td><td>5</td><td>-1</td></tr>
</table>
Percentage of people had their goals achieved.
<table>
<tr><td></td><td>Eccentric viewing</td><td>Magnification</td><td>Combination (eccentric viewing + magnification)</td><td>Non-intervention</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Vukicevic Meri and Fitzmaurice Kerry. Rehabilitation strategies used to ameliorate the impact of centre field loss. Visual impairment research 7: 79-84. 2005.				
	Number of participants	22	12	12	12
	% of people reported goals achieved	74%	55%	71%	0
Missing data handling/loss to follow up	N/A				
Was allocation adequately concealed?	Unclear				
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear				
Was the allocation sequence adequately generated?	Unclear				
Was the study apparently free of other problems that could put it at a high risk of bias?	Unclear				
Were incomplete outcome data adequately addressed?	Unclear				
Are reports of the study free of suggestion of selective outcome reporting?	Unclear				

E.6 Pharmacological management

E.6.1 Anti-angiogentic therapies for the treatment of late AMD (wet active)

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

RQ18: What is the effectiveness of different frequencies of administration of antiangiogenic therapies for the treatment of late AMD (wet active)?

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

Photodynamic therapy for late age-related macular degeneration (wet active)

<table>
<tr><td>Bibliographic reference</td><td>TAP 1999
Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: One-year results of 2 randomized clinical trials - TAP report 1. Archives of Ophthalmology 1999;117(10):1329-45.</td></tr>
<tr><td>Methods</td><td>Randomised controlled trial: one eye per patient was randomised in a 2:1 (treatment: control) ratio</td></tr>
<tr><td>Participants</td><td>609 people with subfoveal CNV lesions caused by AMD with evidence of classic CNV and best corrected acuity of approximately 20/40 to 20/200</td></tr>
<tr><td>Interventions</td><td>Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose.
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>PDT (verteporfin)</td><td>Placebo (5%dextrose water)</td></tr>
<tr><td>Frequency of follow-up</td><td>Every 3 months</td><td>Every 3 months</td></tr>
</table></td></tr>
<tr><td>Outcomes</td><td>Visual acuity at 12 and 24 months.</td></tr>
</table>

Results

Visual acuity (12 months)

	PDT (n=402)	Placebo (n=207)	RR (95%CI)
Gain of ≥15 letters, n(%)	24	5	2.47 (0.96, 6.38)
Loss of ≥15 letters	156	111	0.72 (0.61, 0.86)
No change	87 (21.6)	34 (16.4)	1.32 (0.92, 1.89)

Adverse events (12 months)

	PDT (n=402)	Placebo (n=207)	RR (95%CI)
Visual disturbance	71 (17.7)	24 (11.6)	1.52 (0.99, 2.34)
Vitreous haemorrhage	4 (1.0)	1 (0.5)	2.06 (0.23, 18.31)
Injection site adverse event	54 (13.4)	7 (3.4)	3.97 (1.84, 8.57)
Allergic reactions	5 (1.2)	7 (3.4)	0.37 (0.12, 1.14)
Photosensitivity reactions	12 (3.0)	0	12.90 (0.77, 216.85)

Notes

One session PDT (or placebo), then followed up every 3 months, repeated treatment if there is leakage.

Risk of bias	Authors' judgement	Description
Adequate sequence generation?	Yes	"Random assignments were prepared by the statistical department of CIBA Vision Corp. Sealed envelopes with random assignments were prepared by the Quality Assurance Department within QLT PhotoTherapeutics Inc (Vancouver, British Columbia), which maintained independence from any other function of the trials." TAP report 1, page 1331
Allocation concealment?	Yes	"The allocation of verteporfin therapy or placebo was recorded on a randomization log that was stored in a locked cabinet with both opened and unopened randomization envelopes at each clinical center." TAP report 1, page 1331
Blinding? All outcomes	Yes	"The study coordinator aware of the treatment assignment and anyone else who might assist in the setup of verteporfin or placebo solutions were trained to make every reasonable attempt to maintain masking of the ophthalmologist, patient, vision examiner, and Photograph Reading Centre personnel. The verteporfin and placebo solutions were different colours (green vs colourless). All verteporfin and

		placebo solutions as well as the intravenous tubing were covered entirely with foil so that the patient and treating ophthalmologist were masked during the infusion. The ophthalmologist remained masked while administering the light since the fundus appearance during treatment does not change in any way to indicate verteporfin or placebo treatment. On the materials submitted to them, the Photograph Reading Centre graders did not have any information to indicate that verteporfin or placebo was administered. The marked hypofluorescence within a treated area noted within 1 week after verteporfin therapy in phase 1 and 2 studies is not readily apparent 3 months after treatment. Therefore, this hypofluorescence was not judged to be a likely source of potential unmasking of the graders evaluating photographs obtained at least 3 months after verteporfin therapy. Clinic monitors also had no access to information that would indicate treatment assignment. There were no known instances of unmasking of the vision examiners or Photograph Reading Centre graders. Only 2 patients who noted a green solution following extravasation of drug were likely unmasked. Treating ophthalmologists, but not the patients, were unmasked in 4 additional cases. In 2 of these cases, fluorescein angiography was obtained within 1 week after treatment to evaluate severe visual acuity decrease and showed hypofluorescence typical for verteporfin therapy. In another case the ophthalmologist noted the green verteporfin leaking onto the cover over the intravenous solution, and in 1 additional case, the ophthalmologist became unmasked prior to a vitrectomy for a subretinal hemorrhage; the patient had been assigned to placebo." TAP report 1, page 1331
Incomplete outcome data addressed? 12 month follow up	Yes	Follow-up good and equal between both groups. 94% of patients within each group completed the month 12 follow-up examination. 379/402 in verteporfin group and 194/207 in placebo group. TAP report 1, figure 1, page 1335
Incomplete outcome data addressed? 24 month follow up	Yes	Follow-up equal between both groups. 351/402 (87%) of patients PDT group completed the month 24 follow-up examination compared to 178/207 (86%) of placebo group. TAP report 2, figure 1, page 201
Free of selective reporting?	Unclear	Unlikely for primary analysis of treatment versus control but possible for subgoup analyses by lesion type. No mention of proposed subgroup analyses in power statement and discussion suggests exploratory analysis of data eg. "To explore these subgroup findings further, visual acuity distributions (Figure 9), mean change in contrast sensitivity (Table 6), and angiographic outcomes (Table 6) at the month 12 examination were evaluated, based on lesion components noted at baseline. The lesion components at baseline affected the magnitude of the treatment benefit with respect to the visual acuity distributions." TAP report 1, page 1340.

		The protocol for this study was not independently published prior to this first report of results but contact with the communicating author provided an assertion that subgoup analyses were planned a priori.

Bibliographic reference	**VIM 2005** Azab M, Boyer DS, Bressler NM, Bressler SB, Cihelkova I, Hao Y, et al. Visudyne in Minimally Classic Choroidal Neovascularization Study Group. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration. Archives of Ophthalmology 2005;123(4):448-57.
Methods	Randomised controlled trial: One eye of each patient was enrolled. No information on allocation concealment is provided but double masking is described. Participants were randomised to Verteporfin or placebo in a 2:1. Patients were also randomised 1:1 into two groups of fluence, reduced and standard in which the reduced group had less intense illumination of the photodynamic dye as it passed through the neovascular membrane.
Participants	117 patients with minimally classic CNV due to AMD.
Interventions	Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose. Participants in the placebo and treatment groups were also randomised to Standard Fluence (SF) intensity of illumination equivalent to a light dose of 50 Joules per square centimetre and a Reduced Fluence (RF) equivalent to 25 Joules per square centimetre.
Outcomes	Visual acuity at 12 and 24 months. Acute severe visual acuity loss.

Results

Visual acuity (12 months)

	PDT (n=36)	Placebo (n=38)	RR/MD (95%CI)
Gain of ≥15 letters, n(%)	1 (3)	0	3.16 (0.13, 75.20)
Loss of ≥15 letters	10 (28)	18 (47)	0.59 (0.31, 1.09)
No change	5 (14)	9 (24)	0.59 (0.22, 1.59)
Mean changes in letters	-9.0	-13.5	4.5

Visual acuity (24 months)

	PDT (n=32)	Placebo (n=37)	RR/MD (95%CI)
Gain of ≥15 letters, n(%)	3 (9)	1 (3)	3.47 (0.38, 31.72)
Loss of ≥15 letters	17 (5.3)	23 (62.2)	0.85 (0.57, 1.29)
No change	4 (12.5)	5 (13.5)	0.92 (0.27, 3.15)
Mean changes in letters	-16.0	-21.0	5.0

Adverse events (12 months)

	PDT (n=36)	Placebo (n=38)	RR (95%CI)
Vision disturbance	5 (13)	4 (10)	1.32 (0.38, 4.53)
Infusion-related pain	6 (15)	1 (3)	6.33 (0.80, 50.06)
Injection site event	2 (5)	4(10)	0.53 (0.10, 2.71)

Notes

Risk of bias	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Patients were randomly assigned to 1 of 2 fluence groups; at the same time, patients were randomly assigned to received verteporfin therapy or placebo." Main report published Archives of Ophthalmology 2005, page 450

Allocation concealment?	Yes	Allocation concealment not specifically mentioned but probably adequate as was well dealt with in all the other studies from this group.“All study participants and outcome assessors, including vision examiners, photographers, ophthalmologists, Photograph Reading Center personnel and clinic monitors, were masked to the treatment assignment.” Main report published Archives of Ophthalmology 2005, page 450
Blinding? All outcomes	Yes	“All study participants and outcome assessors, including vision examiners, photographers, ophthalmologists, Photograph reading Center personnel and clinic monitors, were masked to the treatment assignment. The ophthalmologist responsible for applying the laser light was not masked to the fluence rate because the treating ophthalmologist was responsible for the light fluence rate being applied to the study participant’s retina. Only the study coordinators and any other person who might assist in the setup of verteporfin or placebo solutions were aware of the treatment assignment with respect to verteporfin or placebo; these individuals were trained to make every reasonable attempt to maintain masking of participating patients and all other study personnel. However treatment assignment was unmasked for a total of 3 patients. Investigators were unmasked to the treatment assignment of 2 patients. One patient was identified by the Reading Center as having a predominantly classic lesion at the initial visit; the other was identified by the Reading Center as having a predominantly classic lesion at the 6-week examination. In both cases the treating ophthalmologist believed that verteporfin therapy should not be delayed until the next scheduled visit. A third patient was inadvertently unmasked to the sponsor by the study coordinator at the site were the patient was being treated because the coordinator asked the sponsor what the site should do with the reconstituted vial of verteorfin, thus indirectly and inadvertently revealing the treatment assignment for a particular randomisation number. The success of masking otherwise was not evaluated formally" Main report published Archives of Ophthalmology 2005, page 450.
Incomplete outcome data addressed? 12 month follow up	Yes	Follow-up good and equal between groups. 38/40 (95%) of placebo group seen at 12 months compared to 36/38 (95%) of reduced fluence group and 36/39 (92%) of the standard fluence group. Main report published Archives of Ophthalmology 2005, figure 1, page 451
Incomplete outcome data addressed? 24 month follow up	Unclear	Follow-up a little lower in the treatment groups. 37/40 (93%) of placebo group seen at 24 months compared to 34/38 (89%) of reduced fluence group and 32/39 (82%) of the standard fluence group. Main report published Archives of Ophthalmology 2005, figure 1, page 451
Free of selective reporting?	Unclear	Primary outcome specified but secondary outcomes less clearly specified. Main outcome of interest to this review reported

Bibliographic reference	**VIO 2007** Kaiser PK. Visudyne in Occult CNV (VIO) study group. Verteporfin PDT for subfoveal occult CNV in AMD: two-year results of a randomized trial. Current Medical Research and Opinion 2009;25(8):1853-60.
Methods	2-year randomized, placebo-controlled, double-masked, multi-centre, Phase III study of the treatment of occult with no classic subfoveal CNV lesions secondary to AMD using Visudyne therapy compared with placebo.
Participants	364 people over 50 years with occult but no classic CNV due to AMD enrolled at 43 centres in North America randomised 2:1 active versus placebo treatment. The VIO study was to confirm the treatment effect shown in patients with occult CNV and evidence of recent disease progression in the VIP AMD study. Most of the patients in VIP AMD study had occult with no classic CNV (258 of 339 patients: 76%). Nevertheless, VIO study included a more restricted patient population who showed a greater treatment benefit in the VIP AMD study."
Interventions	Visudyne administered as a 10 minute intravenous infusion followed 15 minutes after the start of the infusion by light application of 600mW/cm2 for 83 seconds (dose of 50J/cm2). Treatments maybe repeated every 3 months in the event of recurrent neovascularisation up to a maximum of 4 treatments in a year. No information is provided in the report about how the double masked placebo intervention was delivered.
Outcomes	"Four co-primary analyses of the patients' responder rates were planned: proportion of patients who lose, at Month 12 and at Month 24, fewer than 15 letters (<3 lines) and fewer than 30 letters (<6 lines) of best-corrected visual acuity in the study eye from baseline."

Results

Visual acuity (12 months)

	PDT (n=244)	Placebo (n=120)	RR (95%CI)
Loss of ≥30 letters, n(%)	39 (16)	20 (17)	0.96 (0.59, 1.57)
Loss of ≥15 letters	90 (37)	54 (45)	0.82 (0.63, 1.06)
Loss <5 letters	98 (40)	36 (30)	1.34 (0.98. 1.83)

Visual acuity (24 months)

	PDT (n=244)	Placebo (n=120)	RR (95%CI)
Loss of ≥30 letters, n(%)	56 (23)	30(25)	0.92 (0.62, 1.35)
Loss of ≥15 letters	115(47)	64(53)	0.88 (0.71, 1.09)
Loss <5 letters	86 (35)	26 (22)	1.63 (1.11, 2.38)

Adverse event

	PDT (n=244)	Placebo (n=120)	RR (95%CI)
Visual disturbance	67 (28)	29 (24)	1.14 (0.78, 1.66)
Acute severe VA decrease	4 (2)	1 (0.8)	1.97 (0.22, 17.41)
Injection-site adverse events	13 (5)	3 (3)	2.13 (0.62, 7.34)
Infusion-related pain	25 (10)	0	25.19 (1.55, 410.23)
Allergic reaction	5 (2)	5 (4)	0.49 (0.15, 1.67)
Photosensitivity reactions	1 (0.4)	1 (0.8)	0.49 (0.03, 7.80)

Notes

Trial was sponsored by Novartis Pharma AG and QLT Inc (see http://clinicaltrials.gov/ct2/show/NCT00121407?term=NCT00121407&rank=1).

Risk of bias	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Patients were randomly assigned to verteporfin or placebo in a 2 : 1 ratio". Patients and methods page 1854. .
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	"All study participants and outcome assessors were masked to the treatment assignment" Patients and methods page 1854.

Incomplete outcome data addressed? 12 month follow up	Yes	At 12 months 219/244 (90%) verteporfin and 111/364 (93%) placebo group given visual acuity assessment. Figure 1, page 1856. Missing data were imputed using last observation carried forward.
Incomplete outcome data addressed? 24 month follow up	Yes	"At month 24, 198/244 patients (81%) in the verteporfin group and 108/120 (90%) patients in the placebo group had a VA assessment (Figure 1)." Results page 1855 Missing data were imputed using last observation carried forward. Increased death rate in intervention arm attributed to chance alone.
Free of selective reporting?	Unclear	No prior publication of trial protocol

Bibliographic reference	**VIP 2001** Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization - Verteporfin in Photodynamic Therapy Report 2. American Journal of Ophthalmology 2001;131(5):541-60.
Methods	Randomised controlled trial: one eye per patient was enrolled. Randomisation in sealed envelopes stratified by clinical centre.
Participants	339 people with subfoveal CNV caused by AMD
Interventions	Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose.
Outcomes	Visual acuity at 12 and 24 months. Secondary outcomes include contrast sensitivity and changes in angiographic outcomes.

Results

Visual acuity (12 months)

	PDT (n=166)	Placebo (n=92)	RR (95%CI)
Gain of ≥15 letters, n(%)	5 (3)	2 (2)	1.39 (0.27, 7.00)
Loss of ≥15 letters	85	51	0.92 (0.73, 1.17)
No change	36 (22)	15 (16)	1.33 (0.77, 2.30)

Visual acuity (24 months)

	PDT (n=166)	Placebo (n=92)	RR (95%CI)
Gain of ≥15 letters, n(%)	8 (5)	1 (1)	4.43 (0.56, 34.90)
Loss of ≥15 letters	91	63	0.80 (0.66, 0.97)
No change	25 (15)	14 (15)	0.99 (0.54, 1.81)

Adverse events

	PDT (n=166)	Placebo (n=92)	RR (95%CI)
Severe vision decrease within 7 days	10 (4.4)	0	11.69 (0.69, 197.32)
Visual disturbance	94 (42)	26 (23)	2.00 (1.41, 2.85)
Injection site adverse	18 (8)	6 (5)	1.66 (0.68, 4.04)
Infusion-related back pain	5 (2.2)	0	
Allergic reaction	3 (1)	3 (3)	0.55 (0.11, 2.69)
Photosensitivity reactions	1 (<1)	1 (1)	0.55 (0.04, 8.76)

Notes

Randomised 2:1 to verteporfin treatment.

Risk of bias	Authors' judgement	Description
Adequate sequence generation?	Yes	"Random assignments were prepared by Statprobe (Ann Arbor, MI). Statprobe also prepared sealed envelopes with random assignments and distributed them to the clinical centers. Patients were randomized in a ratio of 2:1 to verteporfin treatment or placebo (to gather more safety data on patients receiving verteporfin), with only one eye of a patient to be randomized. For cases in which an enrolling ophthalmologist believed that both eyes of a patient were eligible, the patient and ophthalmologist chose which eye would be enrolled in the study. Randomization was stratified by clinical center. Separate groups of color-coded envelopes were used to distinguish patients

		participating in the VIP Trial with pathologic myopia from those with AMD. A study coordinator was instructed to open the sealed envelope only after a patient was judged to meet all of the eligibility criteria and only after the enrolling ophthalmologist and the patient agreed to the patient's participation in the trial. Treatment was to begin the same day that the treatment assignment was revealed by opening the envelope." VIP report number 1, page 843
Allocation concealment?	Yes	See above
Blinding? All outcomes	Yes	"Masking was carried out in a manner identical to procedures followed in the TAP Investigation.7 All patients were to remain masked until all of them had completed the month 24 examination and the data collection and entry was completed." VIP report number 1, page 843 referring to TAP report number 1 (see risk of bias table for TAP study).
Incomplete outcome data addressed? 12 month follow up	Yes	Follow-up good and similar between treatment groups. 210/225 (93%) in verteporfin group and 104/114 (91%) seen in placebo group at 12 months. VIP report number 2, figure 1, page 548.
Incomplete outcome data addressed? 24 month follow up	Yes	Follow-up good and similar between treatment groups. 193/225 (86%) in verteporfin group and 99/114 (87%) seen in placebo group at 24 months. VIP report number 2, figure 1, page 548.
Free of selective reporting?	Yes	Usual vision and clinical outcomes reported and report suggests these were decided a priori.

Anti-vascular endothelial growth factor for late age-related macular degeneration (wet active)

Bevacizumab vs control

Bibliographic reference	**ABC 2010** Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ 2010;340:c2459.
Methods	**Number randomized** (total and per group): 131 participants randomly assigned to study treatment; 65 to intravitreal bevacizumab and 66 to 'standard treatment'. Standard treatment included intravitreal pegaptanib injections (n = 38), PDT with verteporfin (n = 16), or sham injection (n = 12) **Exclusions after randomization**: none **Number analysed (total and per group):** 131 total participants; 65 bevacizumab and 66 standard treatment **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: bevacizumab group: 1 participant died; standard treatment group: 3 participants withdrew from the trial and chose to have alternative treatment and 1 participant withdrew due to pain of treatment **Compliance**: limited information given: "more than 90% of patients in each group (overall 96%) were receiving treatment at the last treatment visit (48 weeks) and were followed up to week 54"

	Intention to treat analysis: yes, using last observation carried forward for 1 participant in bevacizumab group and 4 in standard treatment group **Reported power calculation**: yes; sample of 130 participants to provide power of 82% to detect or rule out a difference of 25% to 67% in outcome rates at P < 0.05 **Study design comment**: 'standard treatment' was not uniform; it was decided for each participant before randomization based on eligibility for NHS coverage of treatments at the time
Participants	**Country**: UK (London, England) **Age**: mean in bevacizumab group was 79 years and in standard treatment group was 81 years **Gender** (percent): 80/131 (61%) women and 51/131 (39%) men **Inclusion criteria**: age 50 years or older; primary subfoveal CNV lesion in study eye secondary to AMD; occult CNV lesions required evidence of "disease progression", based on deteriorating VA, sub- or intraretinal blood, or increase in lesion size; evidence of central macular thickening assessed using OCT; lesion in study eye with total size < 12 optic disc areas for minimally classic or occult lesions; area of fibrosis < 25% of the total lesion area; area of subretinal blood less than 50% of total lesion area; no more than 5400 microns in greater linear dimension for predominantly classic lesions; BCVA of 20/40 to 20/320 on ETDRS chart; no permanent structural damage to central fovea **Exclusion criteria**: surgery or other treatment in study eye; participation in any other clinical trial of antiangiogenic agents or (within previous month) of investigational drugs; primarily hemorrhagic lesion; coexisting ocular disease; premenopausal women not using adequate contraception; current treatment for active systemic infection; history of cardiac events (myocardial infarction, unstable angina) or cerebrovascular event in preceding 6 months; history of allergy to fluorescein; inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analysed and graded; inability to comply with study or follow up procedures **Equivalence of baseline characteristics**: yes **Diagnoses in participants**: 3/4 (75% of bevacizumab group and 76% of standard treatment group) had "minimally classic-occult" CNV; remainder of participants had predominantly classic CNV
Interventions	**Intervention 1**: Bevacizumab: three initial injections every 6 weeks (1.25 mg in 0.05 mL per injection). "After the first three injections, investigators masked to treatment allocation used standardized criteria to decide whether to give further injections... Patients could therefore receive between three and nine injections over a total of 54 weeks." PRN after first 3 injections. 1. ...patients randomized to bevacizumab received sham treatments [sham injections] if they did not require intravitreal treatment at that visit (weeks 18 to 48), according to standardized criteria for retreatment." 2. Participants who were randomized to bevacizumab in whom the usual treatment would have been photodynamic therapy...received placebo photodynamic therapy.

Intervention 2: Standard treatment group: one of three treatment options decided for each participant before randomization based on eligibility for NHS coverage of treatments.

1. Intravitreal pegaptanib injections (0.3 mg to 0.09 mL) intravitreal every 6 weeks for a year, "nine injections in 54 weeks."
2. Verteporfin photodynamic therapy with sham intravitreal injection, "patients received initial treatment at baseline, with further treatment based on criteria outlined in the pivotal phase III studies."
3. Sham intravitreal injection every 6 weeks for a year.

	Intervention 1	**Intervention 2 (standard care)**		
Agent	Bevacizumab	Pegatanib	Verteporfin PDT	Sham PDT
Dose	1.25mg	0.3mg		
Frequency	Every 6 weeks for 3 injections	Every 6 weeks for 1 year	One treatment at baseline, with further treatment based on study criteria	Sham injection every 6 weeks for a year
	PRN after first 3 injections. ...patients randomized to bevacizumab received sham treatments [sham injections] if they did not require intravitreal treatment at that visit (weeks 18 to 48), according to standardized criteria for retreatment." Participants who were randomized to bevacizumab in whom the usual treatment would have been			

	photodynamic therapy...received placebo photodynamic therapy.			

Follow up: Planned length: 54 weeks; Actual length: 96% followed to week 54
Frequency of assessments for retreatment: 6-week intervals

Outcomes

Primary outcome, as defined: proportion of participants gaining 15 letters or more of BCVA at 1 year (54 weeks), as measured on an ETDRS chart
Secondary outcomes, as defined: proportions of participants gaining 10 letters or more of BCVA at 6 months and 1 year (54 weeks) and proportions of participants gaining 5 letters or more of BCVA at 6 months and 1 year (54 weeks) as measured on an ETDRS chart; proportion with stable vision (defined as loss of < 15 letters); mean change in VA at 12 months; mean change in macular thickness from baseline to 6- and 12-month examinations; contrast sensitivity (Pelli-Robson charts), unspecified outcome definition and time; reading ability (maximum reading speed, critical print size and reading acuity) using Minnesota Reading cards, unspecified outcome definition and time
Adverse events
Intervals at which outcomes assessed: 1 week (safety visit), 6, 12, 18, 24, 30, 36, 42, 48 weeks (treatment or assessment for treatment), 1 year (54 weeks)

Results

Visual acuity

	Bevacizumab (n=65)	Standard care (n=66)	RR (95%CI)
Gain of ≥15 letters, n(%)	21 (32)	2 (3)	10.66 (2.60, 43.64)
Gain of ≥10 letters, n(%)	30 (46)	5 (8)	6.09 (2.52, 14.73)
Loss of <15	59 (91)	44 (67)	1.36 (1.13, 1.64)

On average, visual acuity of patients treated with bevacizumab increased by 6.3 letters at 6 weeks after the first treatment, and increased slightly further over time to a gain of 6.6 letters 6 weeks after the final loading phase of 3 injections (week 18) and to 7.0 letters by 54 weeks.
In contrast, patients in standard care group had an average loss in visual acuity at each 6 weekly follow-up visits, with a mean of 9.4 letters by 54 weeks.

Adverse event

	Bevacizumab (n=65)	Standard care (n=66)	RR (95%CI)
Uveitis	2	1	2.03 (0.19, 21.85)
Ocular inflammation	8	4	2.03 (0.64, 6.42)
Myocardial infarction	1	0	
Death (vascular cause)	1	0	

Notes

Full study name: The Avastin® (Bevacizumab) for Choroidal Neovascularization (ABC) Trial
Type of study: published
Funding sources: special trustees of Moorfields Eye Hospital; Department of Health through an award by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology; additional support from the National Eye Research Centre, Bristol
Declarations of interest: "The authors who work at Moorfields Eye Hospital have no financial gain from this endeavour, and no patents or patent applications with regard to bevacizumab are owned by the authors or Moorfields Pharmaceuticals."; "The pharmaceutical division at Moorfields (Moorfields Pharmaceuticals) is involved in the repackaging of bevacizumab for intraocular use for sale to other institutions."; various authors reported being on advisory boards for Novartis, Pfizer, GSK, MSD, and/or Allergan; receiving research grants for investigator sponsored trials, money, travel grants, and/or lecture fees from Novartis; and/or being a shareholder of a software company that has business links with Novartis and Pfizer
Study period: August 2006 to November 2008 (enrolment Aug 2006 to November 2007)
Reported subgroup analyses: by type of neovascular lesion (minimally classic/occult; predominantly classic); type of standard treatment
Contacting study investigators: trial authors contacted; no additional information provided for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were allocated to treatment groups by minimisation—a dynamic process.
Allocation concealment (selection bias)	Low risk	The trial manager telephoned the clinical trials unit to obtain a treatment allocation.

Masking of participants (performance bias)	Low risk	To maintain masking, patients randomized to bevacizumab received sham treatments if they did not require intravitreal treatment at that visit. Participants also received placebo PDT therapy if in the bevacizumab group; "care was taken to ensure that the intravenous infusion pump and line were covered as the active verteporfin solution is green while the placebo infusion is a clear solution."
Masking of study personnel (performance bias)	Low risk	Treating physicians were not masked; however, "investigators masked to treatment allocation used standardised criteria to decide whether to give further injections" in the bevacizumab group.
Masking of outcome assessment (detection bias)	Low risk	We assured outcome assessors were masked to treatment allocation by the use of a standard operating procedure that kept the outcome assessors out of contact with treating physicians and unable to obtain access to the treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Four participants in the standard treatment group and one participant in the bevacizumab group were without 54-week VA outcome data. Intent-to-treat analysis was followed using last observation carried forward for missing data.
Selective reporting (reporting bias)	Unclear risk	Study outcomes were published in a design and methods paper. We identified published results for these outcomes with the exception of outcomes related to reading ability (maximum reading speed, critical print size and reading acuity).
Other bias	Low risk	The standard therapy group did not receive the same intervention (PDT, pegaptanib injection, or sham injection).

Bibliographic reference	**Sacu 2009** Sacu S, Michels S, Prager F, Weigert G, Dunavoelgyi R, Geitzenauer W, et al. Randomised clinical trial of intravitreal Avastin® vs photodynamic therapy and intravitreal triamcinolone: long-term results. Eye 2009;23(12):2223-7.
Methods	**Number randomized (total and per group):** 28 participants randomly assigned to study treatment; 14 in bevacizumab group and 14 in PDT + IVTA group **Exclusions after randomization**: none **Number analysed (total and per group**): 28 total participants; 14 in bevacizumab group and 14 in PDT + IVTA group **Unit of analysis:** individuals (one study eye per participant) **Losses to follow up**: one participant in PDT + IVTA group did not complete 6 or 12 month visits **Compliance**: not reported; no participant was excluded up to 12 months **Intention to treat analysis**: yes, although the paper does not state how data were imputed for the participant missing the 6 and 12 month follow-up visits in the PDT + IVTA group

<table>
<tr><td></td><td>Reported power calculation: yes, sample of 14 participants per group for power of 80%
Study design comment: bevacizumab group had more follow-up visits than the PDT + IVTA group</td></tr>
<tr><td>Participants</td><td>Country: Vienna, Austria
Age: mean 78 years (range 58 to 88)
Gender (percent): 19/28 women (68%) and 9/28 men (32%)
Inclusion criteria: participants with neovascular AMD of any lesion type; lesion smaller than four disc areas; no prior treatment for neovascular AMD; VA of 20/40 to 20/800
Exclusion criteria: participants with a history of thromboembolic events within the past 3 months and predictable need for ocular surgery
Equivalence of baseline characteristics: yes
Diagnoses in participants: neovascular AMD</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1 mg intravitreal bevacizumab injections; after 3 initial injections at monthly intervals re-treatment was based on OCT findings only (evidence of persistent or recurrent intra- or subretinal fluid); participants seen at monthly intervals
Intervention 2: standard verteporfin PDT plus same day 4 mg intravitreal triamcinolone acetonide; re-treatment at 3 months if there was evidence of leakage by fluorescein angiography
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Verteporfin PDT plus intravitreal triamcinolone acetonide (same day)</td></tr>
<tr><td>Dose</td><td>1 mg</td><td>Standard PDT, 4 mg triamcinolone</td></tr>
<tr><td>Frequency (interval)</td><td>Monthly</td><td></td></tr>
<tr><td></td><td>After 3 initial injections at monthly intervals re-treatment was based on OCT findings only</td><td>Re-treatment at 3 months if there was evidence of leakage by fluorescein angiography</td></tr>
</table>
Length of follow up: Planned: 12 months; Actual: 12 months</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: change in mean visual acuity
Secondary outcomes, as reported: change in mean 1 mm central retinal thickness; BCVA; StratusOCT; fluorescein angiography; indocyanine green angiography; microperimetry
Adverse events
Intervals at which outcomes assessed: baseline, months 1, 3, 6, and 12</td></tr>
</table>

Results	**Visual acuity** <table><tr><th></th><th>Bevacizumab (n=14)</th><th>PDT + IVTA (n=14)</th><th>RR (95% CI)</th></tr><tr><td>Gain ≥15 letters , n(%)</td><td>4 (29)</td><td>1 (7)</td><td>4.00 (0.51, 31.46)</td></tr><tr><td>Gain <15 letters (0-14), n(%)</td><td>7</td><td>4</td><td>1.75 (0.66, 4.66)</td></tr><tr><td>Loss <15 letters, n(%)</td><td>3</td><td>7</td><td>0.43 (0.14, 1.33)</td></tr><tr><td>Loss ≥ 15 letters</td><td>0</td><td>2</td><td>0.20 (0.01, 3.82)</td></tr></table> Mean VA in bevacizumab treated eyes improved from 50 letters at baseline to 58 letters at month 12; changes of mean VA in the PDT+IVTA-treated eyes were 46 letters at baseline to 43 letters at month 12.
Notes	**Type of study**: published **Funding sources**: not reported **Declarations of interest**: one investigator reported being "an owner of the patent on the use of green porphyrins in neovasculature of the eye under the guidelines of the Wellman Laboratories of Photomedicine, Harvard Medical School, Boston, MA, USA" **Study period**: not reported **Reported subgroup analyses**: none **Contacting study investigators**: trial authors contacted and contributed information for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"In our study we used computer generated randomized scheme and the allocation concealment methods was used (central coordinating centre)" (email communication with Dr Stefan Sacu, dated 19 May 2012).
Allocation concealment (selection bias)	Low risk	"In our study we used computer generated randomized scheme and the allocation concealment methods was used (central coordinating centre)" (email communication with Dr Stefan Sacu, dated 19 May 2012).
Masking of participants (performance bias)	Low risk	"Open label"; participants could not be masked to treatment groups.
Masking of study personnel (performance bias)	High risk	"Open label"; physicians were not masked to treatment groups.
Masking of outcome assessment (detection bias)	High risk	"Patients in the PDT + IVTA groups had characteristic post-treatment hypofluorescence within the area of the PDT treatment spot..."

Incomplete outcome data (attrition bias)	High risk	Intent-to-treat analysis was followed.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Low risk	None observed

Rnibizumba vs control

Ranibizumab vs PDT

Bibliographic reference	**ANCHOR 2006** Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim R, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. New England Journal of Medicine 2006;355(14):1432-44.
Methods	**Number randomized (total and per group):** 423 participants randomly assigned to study treatment; 140 to 0.3 mg ranibizumab, 140 to 0.5 mg ranibizumab, and 143 to verteporfin PDT **Exclusions after randomization**: 3 participants in the 0.3 mg ranibizumab group did not receive treatment after randomization, one because of participant's decision and two based on physician's decision **Number analyzed (total and per group):** 422 total participants; 140 in 0.3 mg ranibizumab group, 139 in 0.5 mg ranibizumab group, and 143 in verteporfin PDT group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 10 in 0.3 mg ranibizumab group, 5 in 0.5 mg ranibizumab group, and 10 in verteporfin PDT group; reasons included death, adverse events, loss to follow up, participant's decision, physician's decision and participant non-compliance **Compliance**: limited information given: "more than 90% of patients in each group (91.5% overall) were receiving treatment at 12 months" **Intention to treat analysis**: yes, using last observation carried forward for missing data Reported power calculation: yes, sample of 426 participants to provide power of 96% to detect or rule out differences in proportion of participants losing less than 15 letters at 12 months assuming 67% of participants in the PDT control arm and 84% in the ranibizumab arms will have that outcome (? ? 0.05). **Study design comment**: randomization stratified by study center and baseline visual acuity
Participants	**Country:** USA, France, Germany, Hungary, Czech Republic, and Australia (83 study centers) **Age**: mean (range) was 77 years (54 to 97) in 0.3 ranibizumab group, 76 years (54 to 93) in 0.5 mg ranibizumab group, and 78 years (53 to 95) in verteporfin PDT group

<table>
<tr><td></td><td>Gender (percent): 211/423 (50%) women and 212/423 (50%) men
Inclusion criteria: age 50 years or older; subfoveal CNV lesion secondary to AMD determined independently based on fluorescein angiography and fundus photography to be predominantly classic in composition and suitable for treatment with verteporfin PDT; ≥ 5400 microns in greater linear dimension; BCVA of 20/40 to 20/320 Snellen using equivalent ETDRS charts; no permanent structural damage to central fovea; participants with juxta- or extrafoveal photocoagulation in the study eye more than 1 month prior to day 0 and prior verteporfin PDT in the non-study eye more than 7 days before study day 0 were included
Exclusion criteria: surgery or other treatment in study eye; treatment with verteporfin PDT in the non-study eye less than 7 days preceding study day 0; participation in any other clinical trial of antiangiogenic agents or (within previous month) of investigational drugs; subretinal hemorrhage in study eye 50% or more of lesion area; subfoveal fibrosis or atrophy in study eye; coexisting ocular disease; premenopausal women not using adequate contraception; current treatment for active systemic infection; history of other disease, metabolic dysfunction, or physical examination or laboratory finding giving reasonable suspicion of a condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or place the participant at a high risk for complications; history of allergy to fluorescein; inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded; inability to comply with study or follow-up procedures
Equivalence of baseline characteristics: a slightly higher percentage of participants in 0.3 mg ranibizumab group were aged 75-84 years (60% compared with 45.7% in 0.5 mg group and 51.7% in verteporfin PDT group)
Diagnoses in participants: 410/423 (97%) had predominantly classic CNV (> 95% of each treatment group); 12/423 (3%) had minimally classic CNV; and 1/423 (0.2%) had occult with no classic CNV</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 0.3 mg ranibizumab monthly intravitreal injections plus sham verteporfin PDT (intravenous infusion of saline followed by laser irradiation of macula), need for retreatment based on assessment of fluorescein angiograms at 3-month intervals
Intervention 2: 0.5 mg ranibizumab monthly intravitreal injections plus sham verteporfin PDT when needed for retreatment, as above
Intervention 3: sham intravitreal injection plus active verteporfin PDT (laser irradiation of macula following intravenous administration of verteporfin)
Ranibizumab was injected into the study eye at monthly intervals (ranging from 23 to 37 days) for a total of 12 injections in the first year beginning on day 0. Either verteporfin or sham verteporfin PDT was administered on day 0 and then if needed on the basis of investigators' evaluation of angiography at months 3, 6, 9, or 12.
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention 3</th></tr>
<tr><td>Agent</td><td>Ranibizumab +sham PDT</td><td>Ranibizumab + sham PDT</td><td>PDT + sham injection</td></tr>
</table></td></tr>
</table>

Dose	0.3mg	0.5mg	
Frequency	Monthly	Monthly	
			administered on day 0 and then if needed on the basis of investigators' evaluation of angiography at months 3, 6, 9, or 12

Follow up: Planned length: 2 years; Actual length: 2 years
Frequency of assessments for retreatment: 3-month intervals for PDT and sham PDT

Outcomes

Primary outcome, as defined: proportion of participants losing fewer than 15 letters from baseline visual acuity in the study eye at 12 months
Secondary outcomes reported: proportion of participants gaining 15 letters or more from baseline; proportion of participants with a Snellen equivalent of 20/40 or better; proportion of participants with a Snellen equivalent of 20/200 or worse; mean change from baseline (letters over time); mean change from baseline to month 12 in the size of the classic CNV component and total area of leakage from CNV
Exploratory efficacy endpoints: loss of 30 letters or more of visual acuity, mean changes in area of CNV and area of the entire lesion
Safety assessments: IOP measurement before and 50 to 70 minutes after each study treatment, ocular and non-ocular adverse events, changes and abnormalities in clinical laboratory parameters and vital signs, and immunoreactivity to ranibizumab
Quality-of-life indicators
Intervals at which outcomes were assessed: "at regularly scheduled study visits," 12 and 24 months, angiography evaluation was performed at months 3, 6, 9, 12

Results

Visual acuity (at 12 month follow-up)

	0.3mg ranibizumab (n=140)	0.5mg ranibizumab (n=140)	PDT (n=143)
Gain of ≥15 letters, n(%)	50 (35.7)	56 (40.3)	8 (5.6)
Loss of <15 letters	132 (94.3)	135 (96.4)	92 (64.3)
Loss ≥30 letters	0	0	19 (13.3)

Visual acuity (24 months)

	0.3mg ranibizumab (n=140)	0.5mg ranibizumab (n=140)	PDT (n=143)
Gain of ≥15 letters, n(%)	48 (34.3)	57 (41.0)	9 (6.3)
Loss of <15 letters	126 (90.0)	125 (89.9)	94 (65.7)
Loss ≥30 letters	2 (1.4)	0	23 (16.1)

Adverse event (24 months)

	0.3mg ranibizumab (n=140)	0.5mg ranibizumab (n=140)	PDT (n=143)
Presumed endophthalmitis, no.	0	3	0
Rhegmatogenous retinal detachment	1	2	0
Vitreous haemorrhage	0	2	0
Ocular inflammation	8	14	1
Cataract	23	27	15
Treatment-emergent hypertension	13	17	23
Arterial thromboembolic event (nonfatal)	4	5	4
Death (vascular & nonvascular)	5	3	5
Non-ocular haemorrhage	16	16	8

Notes

Full study name: Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) Trial
Type of study: published
Funding sources: Genentech, USA and Novartis Pharma, Switzerland

	Declarations of interest: several authors reported having received consulting fees from Genentech, Eyetech, Novartis, Allergan, Alcon, Thea, Alimera, Oxigene, Genzyme, iScience, ISTA, Regeneron, Theragenics, VisionCare, and/or Jerini; lecture fees from Genentech, Eyetech, Novartis, Allergan, Pfizer, Alcon, Thea, and/or Jerini; grant support from Alcon, Acuity Pharmaceuticals, Allergan, Alimera, Eyetech, Pfizer Novartis, Genentech, Eli Lilly, Oxigene, or the Diabetic Retinopathy Clinical Research network; and/or having an equity interest in Pfizer or being full-time employees of Genentech, holding an equity interest in the company, and having received stock options. **Study period**: May 2003 to September 2006 **Reported subgroup analyses**: analyses of visual acuity outcome by baseline age, visual acuity, and CNV lesion type reported and specified as retrospective analyses in Kaiser 2007 (referenced under ANCHOR 2006)Contacting study investigators: trial authors were contacted and contributed information for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A dynamic randomization method was used, stratified by study centre and visual acuity scores on day 0 (< 45 letters vs >= 45 letters). "Dynamic randomization, a generalization of the hierarchical method proposed by Signorini, et al. (1993)" (email communication with Genentech, dated 24 October 2007)
Allocation concealment (selection bias)	Low risk	"A centralized IVRS was used to conduct the randomization. Participants, study site personnel, and Sponsors' personnel were masked to the treatment assignment throughout the study, except for the injecting physician, designated unmasked site personnel, and Sponsors' drug accountability monitors." (email communication with Genentech, dated 24 October 2007)
Masking of participants (performance bias)	Low risk	"To maintain masking, patients who had received saline as well as those who had received verteporfin were instructed to follow exposure-to-light-precautions after PDT administration according to the verteporfin package insert." "An empty, needle-less syringe was used for sham injections, with pressure applied to the anesthetized and prepared eye at the site of a typical intravitreal injection. Pre- and post-injection procedures (described previously) were identical for ranibizumab and sham injections."
Masking of study personnel (performance bias)	Low risk	"The "injecting" ophthalmologist administering the study treatments was unmasked. All other study site personnel (except those assisting with study treatment administration), patients, and central reading centre personnel were masked to treatment assignment."
Masking of outcome assessment (detection bias)	Low risk	"Double masking of treatment assignment necessitated at least two investigators per study site: an unmasked "injecting" ophthalmologist to administer the study treatments and a masked "evaluating" ophthalmologist to perform study assessments."

Incomplete outcome data (attrition bias)	Low risk	"Efficacy analyses were performed on an intent-to-treat basis (including all randomized patients and according to the treatment group to which they were assigned) using a last-observation-carried-forward method to impute missing data (primary analysis) and using observed data (exploratory sensitivity analysis)."
Selective reporting (reporting bias)	Low risk	We did not have access to the protocol. However, primary and secondary outcomes reported to the FDA were reported in the publication with no changes.
Other bias	Unclear risk	Sponsored by Genentech and Novartis Pharma.

Bibliographic reference	**LAPTOP 2013** Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, and Negi A. 2013. "Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results". American Journal of Ophthalmology 156(4):644-51.
Study details	**Country/ies:** Japan
	Study type: Phase IV RCT
	Aim of the study: To compare the vision-improving effect of ranibizumab and PDT
	Study dates: study recruitment between July 2009 and June2011
	Sources of funding: supported by in part by the Japan Society for the Promotion of Science
Participants	**Sample size:** 93: 47 PDT, 46 ranibizumab
	Inclusion Criteria: Patients aged older than 50 years with treatment-naïve PCV. PCV was diagnosed based on the presence of polypoidal lesion depicted with IGA. Only 1 eye per patient was included in the study.
	Exclusion Criteria: VA better than 0.6, greatest linear dimension greater than 5400µm, refractive error greater than 6 diopters, or axial length long than 26.5mm. The presence of past AMD or central serous chorinopathy, rentinal vascular disease, glaucoma, angioid streaks, presumed ocular histoplasmosis, history of radiation therapy, or history of ocular surgery other than phacoemulsification

Bibliographic reference

LAPTOP 2013

Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, and Negi A. 2013. "Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results". American Journal of Ophthalmology 156(4):644-51.

Baseline characteristics

	Photodynamic therapy (n=47)	Ranibizumab (n=46)	P values
Mean age, year (SD)	75.0 (8.0)	75.4 (6.9)	0.80
% of female (n)	15 (31.9)	18 (39.1)	
BCVA (logMAR unit (SD)	0.57 (0.31)	0.48 (0.27)	0.12
BCVA Snellen equivalence, n(%)			
≤0.1 (20/200)	7 (14.9)	5 (10.9)	
>0.1 (20/200 but <0.5 (20/40)	24 (51.1)	24 (52.2)	
≥0.5 (20/40)	16 (34.0)	17 (37.0)	

Methods

Study visits and procedures:
Patients were randomised in a1:1 ratio to either vertiporfin PDT (6mg/m^2) or ranibizumab monotherapy (0.5mg). As the initial treatment, patients in PDT group underwent verteporfin injection and laser irradiation. Patients in the ranibizumab group underwent 3 monthly ranibizumab injection.
After the initial treatment, repeat treatment was applied as need (pro re nata)

Intervention 1: vertiporfin PDT

Intervention 2: ranibizumab

Outcomes: primary outcome: the proportion of patients in each group gaining or losing logMAR of more than 0.2 at 24 months; secondary outcome: central retinal thickness and the outer border of the retinal pigment epithelium measure with OCT.

Analyses: Chi-square test was used to compare the percentage of patients with gained, unchanged or lost VA. Two-way repeated-measures analysis of variance was used to investigate the difference in mean VA or CRT.

Length of follow up: 12 months

Results

	Photodynamic therapy (n=47)	Ranibizumab (n=46)	Effect (relative risk, 95%CI)

Bibliographic reference	**LAPTOP 2013** Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, and Negi A. 2013. "Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results". American Journal of Ophthalmology 156(4):644-51.		
	Change in logMAR, n(%)		
	No change	15 (31.9)	20 (43.5)	
	Decrease			
	≥0.1 but <0.2 unit (equivalent to more than 1 line but fewer than 2 lines=more than 5 letters fewer than 10 letter)	4 (8.5)	1 (2.2)	
	≥0.2 but <0.3 unit	0 (0)	1 (2.2)	
	Fewer than 15 letters	4 (8.5)	2 (4.3)	1.96 (0.38 to 10.17)
	≥0.3 but <0.4 unit	8 (17.0)	3 (6.5)	
	≥0.4 but <0.5 unit	1 (2.1)	0 (0)	
	≥0.5 but <0.6 unit	2 (4.3)	0 (0)	
	≥0.6 unit	2 (4.3)	0 (0)	
	15 letters or more loss	15 (31.9)	4 (8.6)	3.67 (1.32 to 10.23)
	30 letters or more loss	2 (4.3)	0 (0)	
	Increase			
	≥0.6 unit (30 letters or more)	2 (4.3)	1 (2.2)	1.96 (0.18 to 20.85)
	≥0.5 but <0.6 unit	1 (2.1)	0(0)	
	≥0.4 but <0.5 unit	0(0)	2(4.3)	
	≥0.3 but <0.4 unit	2 (4.3)	5 (10.9)	
	15 letters or more gain	5 (10.6)	8 (17.4)	0.61 (0.22, 1.73)
	≥0.2 but <0.3 unit	3 (6.4)	5(10.9)	
	≥0.1 but <0.2 unit	7(14.9)	8(17.4)	
	Less than 15 letters gain	10 (21.3)	13 (28.3)	0.75 (0.37 to 1.54)

Bibliographic reference	**LAPTOP 2013** Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, and Negi A. 2013. "Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results". American Journal of Ophthalmology 156(4):644-51.
	Missing data handling/loss to follow up: 4 patients did not complete the initial 3-month treatment
Comments	**Was allocation adequately concealed?**
	Was knowledge of the allocated intervention adequately prevented during the study? unclear
	Was the allocation sequence adequately generated? unclear
	Was the study apparently free of other problems that could put it at a high risk of bias? None observed
	Were incomplete outcome data adequately addressed? "We excluded patients who did not complete the initial 3-month follow-up from final analysis. For the rest of the patients, we applied intention-to-treat analysis policy.
	Are reports of the study free of suggestion of selective outcome reporting? Results were reported for primary and secondary outcomes specified in the Methods section

Ranibizumab vs sham

Bibliographic reference	**MARINA 2006** Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006;355(14):1419-31.
Methods	**Number randomized (total and per group):** 716 participants randomly assigned to study treatment; 238 to 0.3 mg ranibizumab group, 240 to 0.5 mg ranibizumab group, and 238 to sham injection group **Exclusions after randomization**: none **Number analysed (total and per group):** all 716 participants; 238 to 0.3 mg ranibizumab group, 240 to 0.5 mg ranibizumab group, and 238 to sham injection group **Unit of analysis**: individuals (one study eye per participant)

	Losses to follow up: 52 participants did not complete 12 months: 12 in the 0.3 mg ranibizumab group, 14 in the 0.5 mg ranibizumab group, and 26 in the sham injection group. Reasons included death, adverse events, loss to follow up, participant's decision, physician's decision, participant non-compliance, and need for other therapeutic intervention. **Compliance**: "more than 90% of patients in each treatment group remained in the study at 12 months, and approximately 80 to 90% remained at 24 months" **Intention to treat analysis:** yes, using last observation carried forward for missing data **Reported power calculation**: yes, sample of 720 participants for power of 95% **Study design comment**: following primary analyses of the study at one year and with recommendation of the data monitoring committee, the study protocol was amended to offer treatment with 0.5 mg ranibizumab to participants still being followed in the sham control group. The study protocol was amended four months into the study to allow photodynamic therapy for active minimally classic or occult with no classic lesions that were no larger than 4 disc areas in size and accompanied by a 20-letter or greater loss from baseline visual acuity confirmed at consecutive study visits. When photodynamic therapy was used, the scheduled study treatment was postponed until the next scheduled monthly study visit
Participants	**Country:** USA **Age**: range 52 to 95 years; mean was 77 years in each of the three treatment groups **Gender (percent**): 464/716 (65%) women and 252/716 (35%) men **Inclusion criteria:** age 50 years or older; active primary or recurrent subfoveal lesions with CNV secondary to AMD defined as: (1) exhibiting at least a 10% increase in lesion size determined by comparing a fluorescein angiogram performed within 1 month preceding study day 0 with a fluorescein angiogram performed within 6 months preceding study day 0, (2) resulting in a visual acuity loss of greater than 1 Snellen line any time within the prior 6 months, or (3) subretinal hemorrhage associated with CNV within 1 month preceding study day 0; total area of CNV encompassed within the lesion at least 50% of the total lesion area; total lesion area of 12 disc areas or less in size; best-corrected visual acuity of 20/40 to 20/320 (Snellen equivalent on ETDRS chart). Participants with lesions with an occult CNV component were included, but for participants with concomitant classic CNV, the area of classic CNV must have been less than 50% of the total lesion size. **Exclusion criteria:** prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy in the study eye; previous participation in a clinical trial involving antiangiogenic drugs; treatment with verteporfin in the non-study eye less than 7 days preceding study day 0; previous intravitreal drug delivery or subfoveal focal laser photocoagulation in the study eye; laser photocoagulation in the study eye within 1 month preceding study day 0; history of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in study eye; participation in any studies of investigational drugs within 1 month preceding study day 0; subretinal hemorrhage in study eye involving center of the fovea if the size of hemorrhage is either 50 % or more of the total lesion area or 1 or more disc areas in size;

subfoveal fibrosis or atrophy in study eye; CNV in either eye due to other causes; retinal pigment epithelia tear involving the macula in the study eye
Equivalence of baseline characteristics: yes
Diagnoses in participants: 1/716 (0.1%) had predominantly classic CNV; 264/716 (37%) had minimally classic CNV; and 451/716 (63%) had occult with no classic CNV

Interventions

Intervention 1: 0.3 mg ranibizumab intravitreal injection monthly for 2 years
Intervention 2: 0.5 mg ranibizumab intravitreal injection monthly for 2 years
Intervention 3: sham injection monthly for 2 years
In all intervention groups, verteporfin photodynamic therapy for the study eye was allowed if the choroidal neovascularization converted to a predominantly classic pattern.

	Intervention 1	**Intervention 2**	**Intervention3**
Agent	Ranibizumab	Ranibizumab	Sham injection
Dose	0.3 mg	0.5mg	-
Frequency	Monthly for2 years	Monthly for 2 years	Monthly for 2 years
	verteporfin photodynamic therapy for the study eye was allowed if the choroidal neovascularization converted to a predominantly classic pattern		

Length of follow up: Planned: 2 years; Actual: 2 years

Results

Visual acuity (12 months)

	0.3mg ranibizumab (n=238)	0.5mg ranibizumab (n=240)	Sham injection(n=238)
Gain of ≥15 letters, n(%)	59 (24.8)	81 (33.8)	12 (5.0)
Loss of <15 letters	225 (94.5)	227 (94.6)	148 (62.2)

Visual acuity (24 months)

	0.3mg ranibizumab (n=238)	0.5mg ranibizumab (n=240)	Sham injection (n=238)
Gain of ≥15 letters, n(%)	62 (26.1)	80 (33.3)	9 (3.8)
Loss of <15 letters	219 (92.0)	216 (90.0)	127 (52.9)

Adverse events (24 months)

		0.3mg ranibizumab (n=238)	0.5mg ranibizumab (n=240)	Sham injection (n=238)
	Presumed endophthalmitis, no.	2	3	0
	Rhegmatogenous retinal detachment	0	0	1
	Vitreous haemorrhage	1	1	2
	Ocular inflammation	40	50	30
	Cataract	37	37	37
	Treatment-emergent hypertension	41	39	38
	Arterial thromboembolic event (nonfatal)	9	9	6
	Death (vascular & nonvascular)	5	6	6
	Non-ocular haemorrhage	25	26	15
Outcomes	**Primary outcomes**, as defined: proportion of participants who lost fewer than 15 letters from baseline visual acuity in study eye at 12 months **Secondary outcomes**, as defined: proportion of participants who gained 15 letters or more from baseline, proportion of participants with a Snellen equivalent of 20/200 or worse, and mean change from baseline (letters over time); mean change from baseline to month 12 in the size of the classic CNV component and total area of leakage from CNV **Exploratory efficacy end points**: proportion of participants with visual acuity 20/40 or better, and 20/20 at 12 and 24 months (Snellen equivalent), total area of and change from baseline CNV lesion, area of leakageAdverse events, including ocular and non-ocular adverse events and proportion of participants developing immunoreactivity to ranibizumab, intraocular inflammation, and IOP **Safety assessments**: IOP measurement 60 minutes after each injection, incidence and severity of ocular and non-ocular adverse events, changes and abnormalities in clinical laboratory parameters and vital signs, and immunoreactivity to ranibizumab **Intervals at which outcomes assessed**: 12 and 24 months			
Notes	**Full study name**: Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration			

	Type of study: published **Funding sources**: Genentech, USA and Novartis Pharma, Switzerland **Declarations of interest**: various authors reported having received consulting fees from Genentech, Eyetech, Novartis Ophthalmics, Novartis, QLT, Alcon Laboratories, Pfizer, Regeneron, Theragenics, VisionCare, Protein Design Labs, Allergan, BioAxone, Tanox, Genaera, Jerini, Oxigene, Quark, Genzyme, iScience, ISTA, and Athenagen; lecture fees from Genentech, Eyetech, Pfizer, Jerini, Allergan, and Novartis Ophthalmics; grant support from Genentech, Novartis, Eyetech, Pfizer, Theragenics, and Genaera and Alcon Laboratories; and/or equity interest in Pfizer and/ or being employees of Genentech and owning Genentech stock **Study period**: enrolment March 2003 to December 2003 Reported subgroup analyses: by baseline lesion (4 or fewer optic-disk areas; more than 4), type of lesion (minimally classic; occult with no classic), and baseline VA (less than 55 letters; 55 or more letters) **Contacting study investigators**: trial authors contacted and contributed information for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly assigned in a 1:1:1 ratio, using a dynamic randomization algorithm, to receive ranibizumab (LUCENTIS®, Genentech, Inc., South San Francisco, CA) 0.3 or 0.5 mg or a sham injection monthly (30±7 days) for 2 years (24 injections). Randomization was stratified by baseline visual acuity score (<55 letters [approximately worse than 20/80] vs. ≥ 55 letters) at day 0, by choroidal neovascularization subtype (minimally classic or occult with no classic), and by study centre."
Allocation concealment (selection bias)	Low risk	"A centralized interactive voice response system (IVRS) was used to handle the randomization" (email communication with Genentech, dated 24 October 2007).
Masking of participants (performance bias)	Low risk	"All other study site personnel (except those assisting with injections), patients, and central reading centre personnel were masked to treatment assignment."
Masking of study personnel (performance bias)	Low risk	"Masking of treatment assignment required at least two investigators per study site: an evaluating physician (masked to treatment assignment), and an injecting physician (unmasked regarding ranibizumab or sham treatment but masked to ranibizumab dose)."
Masking of outcome assessment (detection bias)	Low risk	"All other study site personnel (except those assisting with injections), patients, and central reading centre personnel were masked to treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	"Efficacy analyses were performed on an intent-to-treat basis (all randomized patients) using a last observation carried forward method to handle missing data."

Selective reporting (reporting bias)	Low risk	We did not have access to the protocol. We matched all outcomes reported in publications with those reported to the FDA.
Other bias	Unclear risk	Sponsored by Genentech and Novartis Pharma. The study authors disclosed financial interests and/or were paid consultants, employees, and/or shareholders of the funding companies.

Bibliographic reference	**Pier 2008** Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. American Journal of Ophthalmology 2008;145(2):239-48.
Methods	**Number randomized (total and per group**): 184 participants randomly assigned to study treatment; 60 to 0.3 mg ranibizumab, 61 to 0.5 mg ranibizumab, and 63 to sham injection **Exclusions after randomization**: one participant in the 0.3 mg ranibizumab group withdrew from the study prior to receiving first treatment and was excluded **Number analyzed (total and per group):** 183 participants; 59 in the 0.3 mg ranibizumab, 61 in the 0.5 mg ranibizumab, and 63 in the sham injection group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 13 participants did not complete 12 months: 1 in the 0.3 mg ranibizumab group, 2 in the 0.5 mg ranibizumab group, and 8 in the sham injection group. Reasons included participant's decision, participant non-compliance, and need for other therapeutic intervention. **Compliance:** "...treatment compliance was good in the ranibizumab groups, with 85% or more of subjects receiving each scheduled injection. In the sham group, 27% of subjects permanently discontinued treatment before month 12, most often because the subject's condition mandated another therapeutic intervention." **Intention to treat analysis (Y/N**): yes, using last observation carried forward for missing data **Reported power calculation**: yes, sample of 180 participants for power of 90% **Study design comment:** following reports of other clinical trials, the study protocol was amended (February 2006) to offer treatment with 0.5 mg ranibizumab to participants in the sham control group who had completed 12 months of follow up and were still being followed. The study protocol was amended again (August 2006) to switch participants in the 0.3 mg ranibizumab group to receive 0.5 mg ranibizumab, to change assessments for all participants from quarterly to monthly after month 12, and to allow treatment with ranibizumab in the fellow eyes.
Participants	**Country**: USA (43 study centres) **Age**: range 54 to 94 years; mean was 79 years in each ranibizumab treatment group and 78 years in the sham injection group

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Gender (percent): 110/184 (60%) women and 74/184 (40%) men
Inclusion criteria: age 50 years or older; primary or recurrent subfoveal CNV secondary to AMD, with total CNV area (classic plus occult CNV) 50% or more of the total lesion area and total lesion size 12 or fewer disc areas; best-corrected visual acuity of 20/40 to 20/320 (Snellen equivalent on ETDRS chart). participants with minimally classic or occult with no classic CNV were included if they had 10% or more increase in lesion size between one and six months prior to day 0, one or fewer Snellen line (or equivalent) VA loss within the prior six months, or CNV-associated subretinal hemorrhage within one month before day zero.
Exclusion criteria: prior treatment with verteporfin photodynamic therapy, external-beam radiation therapy, transpupillary thermotherapy, or subfoveal laser photocoagulation (or juxtafoveal or extrafoveal laser photocoagulation within one month before day zero); subretinal hemorrhage in the study eye involving the center of the fovea, if the size of the hemorrhage is either 50% or more of the total lesion area or one or more disk areas in size; previous inclusion in antiangiogenic drug trial; prior treatment with photodynamic therapy in non-study eye within seven days before day zero.
Equivalence of baseline characteristics: yes
Diagnoses in participants: 35/184 (19%) had predominantly classic CNV; 69/184 (38%) had minimally classic CNV; 79/184 (43%) had occult with no classic CNV; and 1/184 (< 1%) could not be classified
</td></tr>
<tr><td>Interventions</td><td>
Intervention 1: 0.3 mg ranibizumab intravitreal injection every month for first three doses (day 0, months one and two), followed by doses every three months (months 5, 8, 11, 14, 17, 20, and 23)
Intervention 2: 0.5 mg ranibizumab intravitreal injection every month for first three doses (day 0, months one and two), followed by doses every three months (months 5, 8, 11, 14, 17, 20, and 23)
Intervention 3: sham injection every month for first three doses (day 0, months one and two), followed by doses every three months (months 5, 8, 11, 14, 17, 20, and 23)
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td><td>Intervention 3</td></tr>
<tr><td>Agent</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Sham injection</td></tr>
<tr><td>Dose</td><td>0.3 mg</td><td>0.5 mg</td><td>-</td></tr>
<tr><td>Frequency</td><td>Monthly</td><td>Monthly</td><td>monthly</td></tr>
<tr><td></td><td colspan="3">All interventions had monthly injection for first 3 doses, followed by doses every 3 months.</td></tr>
</table>
Length of follow up: Planned: 2 years; Actual: 2 years
</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)</td></tr>
</table>

	0.3mg ranibizumab (n=60)	0.5mg ranibizumab (n=61)	Sham injection (n=63)
Gain of ≥15 letters, n(%)	7 (11.7)	8 (13.1)	6 (9.5)
Loss of <15 letters	50 (83.3)	55 (90.2)	31 (49.2)

Adverse event (12 months)

	0.3mg ranibizumab (59)	0.5mg ranibizumab (n=61)	Sham injection (n=63)
Ocular haemorrhage	2	0	2
Macular odema	1	0	2
Ocular inflammation	4	2	3
Cataract	3	4	4
Hypertension	4	6	5

Outcomes

Primary outcomes, as defined: mean change from baseline to 12 months in visual acuity score
Secondary outcomes, as defined: proportion of participants losing 15 letters or fewer from baseline; proportion of participants gaining 15 letters or greater from baseline; proportion of participants with a Snellen equivalent of 20/200 or worse; mean change from baseline in the near activities, distance activities, and vision-specific dependency NEI VFQ-25 subscales; and mean change from baseline in total area of CNV and total area of leakage from CNV (based on central reading center assessment)
Exploratory efficacy end points: proportion of participants who had lost 30 letters or fewer from baseline VA at 12 months; mean change in visual acuity score from baseline to three months; mean change in visual acuity score from three months to 12 months
Adverse events
Safety assessments: incidence and severity of ocular and non-ocular adverse events, changes in vital signs, incidence of positive serum antibodies to ranibizumab, IOP measurement 60 minutes after each injection
Intervals at which outcomes assessed: injection visits at day 0 and months 1, 2, 3, 8, 11, 14, 17, 20, and 23; clinic visits at months 3, 12, and 24

Notes

Full study name: A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration
Type of study: published
Funding sources: Genentech, USA and Novartis Pharma, Switzerland

	Declarations of interest: various authors reported receiving consulting fees from Genentech, Novartis, OSI/Eyetech, Eyetech/Pfizer, Novartis, and Alcon; lecture fees from Genentech, Novartis, OSI/Eyetech, Eyetech/Pfizer; and grant support from Genentech, Novartis, Alcon, Allergan, Acuity, OSI/Eyetech, and Eyetech/Pfizer; holding Pfizer stock; and/or being an employee and/or stockholder of Genentech **Study period**: enrolment 7 September 2004 to 16 March 2005 **Reported subgroup analyses**: post hoc analysis of lesion size and composition (Brown 2013) **Contacting study investigators**: trial authors contacted and contributed information for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a dynamic randomization algorithm, subjects were randomly assigned 1:1:1 to receive 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections. Randomization was stratified by VA score at day zero (≤54 letters [approximately worse than 20/80] vs ≥55 letters [approximately 20/80 or better], CNV type (minimally classic vs occult with no classic vs predominantly classic CNV), and study center."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported. Study investigators were contacted, but could not provide additional information (email communication with Dr Regillo, dated 16 May 2012).
Masking of participants (performance bias)	Low risk	"All other study site personnel (other than those assisting with study treatment administration), central reading center personnel, and the subjects were masked to treatment assignment." "For the sham-injected control group, an empty syringe without a needle was used, with pressure applied to the anesthetized and antiseptically prepared eye at the site of a typical intravitreal injection. Pre- and post-injection procedures were identical for all group." "No subjects were unmasked to their original treatment assignment as a result of these protocol amendments."
Masking of study personnel (performance bias)	Low risk	"To achieve double-masking of treatment assignment, at least two investigators participate at each study site: an 'injecting' ophthalmologist unmasked to treatment assignment (ranibizumab vs sham) but masked to ranibizumab dose, and a masked 'evaluating' ophthalmologist for efficacy and safety assessments."
Masking of outcome assessment (detection bias)	Low risk	"To achieve double-masking of treatment assignment, at least two investigators participate at each study site: an 'injecting' ophthalmologist unmasked to treatment assignment (ranibizumab vs sham) but masked to ranibizumab dose, and a masked 'evaluating' ophthalmologist for efficacy and safety assessments. All other study site personnel (other than those assisting with study

		treatment administration), central reading center personnel, and the subjects were masked to treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	"Efficacy analyses used the intent-to-treat approach and included all subjects as randomized. Missing values were imputed using the last-observation-carried-forward method."
Selective reporting (reporting bias)	Low risk	Results were reported for primary and secondary outcomes specified in the Methods section.
Other bias	Unclear risk	Sponsored by Genentech and Novartis Pharma. The study authors disclosed financial interests and/or were paid consultants, employees, and/or shareholders of the funding companies.

Bevacizumab vs ranibizumab

Bibliographic reference	**Biswas 2011** Biswas P, Sengupta S, Choudhary R, Home S, Paul A, Sinha S. Comparative role of intravitreal ranibizumab versus bevacizumab in choroidal neovascular membrane in age-related macular degeneration. Indian Journal of Ophthalmology 2011;59(3):191-6.
Methods	**Number randomized (total and per group):** 120 participants randomly assigned to study treatment; 60 in bevacizumab group and 60 in ranibizumab group **Exclusions after randomization**: none **Number analyzed (total and per group**): 104 total participants who completed 18 months of follow up; 50 in bevacizumab group and 54 in ranibizumab group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 16 participants by 18 months: reasons for losses to follow up not reported (ten in bevacizumab group, six in ranibizumab group) **Compliance**: 104/120 participants completed the 18-month study **Intention to treat analysis**: no, 16 participants enrolled and randomized were not included in analysis **Reported power calculation:** no; "aimed to enroll a total of 120 patients...this number was arrived at by the investigators after considering the sample size of the available literature of relevant studies" **Study design comment:** see 'Risk of bias' table regarding randomization logistics
Participants	**Country**: two study centers in Kolkata, India **Age**: not reported for 120 enrolled participants (mean 64.4 years in analyzed bevacizumab group; mean 63.5 years in analyzed ranibizumab group) **Gender (percent**): not reported for 120 enrolled participants (28/50 (56%) men and 22/50 (44%) women in analyzed bevacizumab group; 22/54 (41%) men and 32/54 (59%) women for analyzed ranibizumab group)

<table>
<tr><td></td><td>Inclusion criteria: age 50 years or older; presence of subfoveal or juxtafoveal CNV of any type; active leakage pattern; baseline BCVA between 35 and 70 ETDRS letters; baseline central macular thickness greater than or equal to 250 ?m, as measured by OCT
Exclusion criteria: previous treatment for CNV in either eye; macular scarring; any coexisting other ocular disease or pathology; monocular patients; history of ocular surgery within six months of enrolment; history of cerebrovascular accident and myocardial infarction
Equivalence of baseline characteristics: gender imbalance between analysed groups
Diagnoses in participants: all with subfoveal or juxtafoveal CNV; 22/50 participants with occult CNV in bevacizumab group and 24/54 participants with occult CNV in ranibizumab group</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg intravitreal bevacizumab every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.5 mg intravitreal ranibizumab every month for first three months; re-treatment afterwards based on OCT or VA changes
<table>
<tr><td></td><td>Intervention1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>monthly</td><td>monthly</td></tr>
<tr><td></td><td colspan="2">Treatment for first 3 months, and re-treatment afterwards based on OCT or VA changes</td></tr>
</table>
Length of follow up: Planned: 18 months; Actual: 18 months</td></tr>
<tr><td>Outcomes</td><td>Primary outcomes, as defined: "changes in BCVA and CMT from baseline (month 0) to month 18"
Secondary outcomes, as reported: blood pressure measurements; reports of unusual extremity pain
Adverse events
Intervals at which outcome assessed: monthly through 18 months</td></tr>
</table>

Results

Visual acuity (18 months)

	Bevacizumab (n=50)	Ranibizumab (n=54)	RR (95%CI)
Gain more than 5 letters, n(%)	16 (32)	18 (33)	0.96 (0.55, 1.67)
Loss more than 5 letters	4 (8)	6 (11)	0.72 (0.22, 2.40)
Maintain within +/- 5 letters	30 (60)	30 (56)	1.08 (0.78, 1.50)

Number of injections

	Bevacizumab (n=50)	Ranibizumab (n=54)
Mean number of injections	4.3	5.6

Notes

Type of study: published
Funding sources: reported "nil"
Declarations of interest: "none declared"
Study period: April 2007 to April 2009
Reported subgroup analyses: for participants with predominantly classic CNV
Contacting study investigators: trial authors contacted; no additional information provided for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using random numbers tables, 60 numbers were randomly picked up from 1 to 120 and assigned to group A while the remaining sixty numbers were assigned to group B."
Allocation concealment (selection bias)	Unclear risk	"...randomization of the 120 numbers into two groups was done before initiation of enrolment itself. Upon initiation of enrollment, the patients were numbered sequentially based on the serial order of enrolment in the study. Depending on the enrolment number, the patients were automatically assigned to either group A or B based on the prior randomization of number 1-120 into two equal groups using random number tables."
Masking of participants (performance bias)	Unclear risk	Masking of participants not reported.

Masking of study personnel (performance bias)	Low risk	“The injections were given...by the investigators, who were blinded to the type of injection."
Masking of outcome assessment (detection bias)	Low risk	"All assessors were masked to the group of patient they were following up."
Incomplete outcome data (attrition bias)	Unclear risk	Sixteen (13%) participants lost to follow up were excluded from the analyses; 10 in the bevacizumab group and 6 in the ranibizumab group.
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial registration was identified for this study. Outcomes were reported for stated outcomes in the methods section of the published report; however, only P values were reported for between-group comparisons and no standard deviation or variance measures were reported for continuous outcomes.
Other bias	Low risk	None observed

Bibliographic reference	**CATT 2011** CATT Research Group; Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2011;364(20):1897-908.
Methods	**Number randomized (total and per group):** 1208 participants randomly assigned to study treatment; number of participants randomized per group not reported **Exclusions after randomization**: one study center (23 participants) was excluded due to protocol violations **Number analyzed (total and per group):** 1105 total participants; 265 in bevacizumab monthly group, 284 in ranibizumab monthly group, 271 in bevacizumab as needed group, and 285 in ranibizumab as needed group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 80 total participants: 21 in bevacizumab monthly group (4 died and 17 with missing data), 17 in ranibizumab monthly group (4 died and 13 with missing data), 29 in bevacizumab as needed group (11 died and 18 with missing data), 13 in ranibizumab as needed group (5 died and 8 with missing data) **Compliance**: limited information given: mean of 11.9 treatments given for bevacizumab monthly group and mean of 11.7 treatments given for ranibizumab monthly group **Intention to treat analysis**: no, 103 participants enrolled and randomized were not included in the analyses **Reported power calculation:** yes, sample of 277 participants per group for power of 90% **Study design comment:** non-inferiority design, four arms, six pairwise comparisons planned; at one year, participants in the monthly dose treatment groups were re-randomized to either continue with monthly injections or switch to as needed injections of the same treatment drug

Participants	**Country**: USA **Age**: mean was 80 years in bevacizumab monthly group, 79 years in ranibizumab monthly group, 79 years in bevacizumab as needed group, and 78 years in ranibizumab as needed group **Gender (percent):** 732/1185 (61.8%) women and 453/1185 (38.2%) men **Inclusion criteria**: age 50 years or older; one study eye per participant with untreated active CNV due to AMD (based on presence of leakage as seen by fluorescein angiography and of fluid as seen by OCT); VA of 20/25 to 20/320 on electronic visual-acuity testing **Exclusion criteria**: fibrosis or atrophy in center of fovea in the study eye; CNV in either eye due to other causes; retinal pigment epithelial tear involving the macula; any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention or contribute to VA loss during the 3 year follow-up period; active or recent (within 4 weeks) intraocular inflammation; current vitreous hemorrhage in the study eye; history of rhegmatogenous retinal detachment or macular hole; active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis; spherical equivalent > 8 diopters; intraocular surgery (including cataract surgery) in the study eye within 2 months; uncontrolled glaucoma; participants unable to be photographed to document CNV due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV; premenopausal women not using adequate contraception; pregnancy or lactation; history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications; current treatment for active systemic infection; uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders; history of recurrent significant infections or bacterial infections; inability to comply with study or follow-up procedures **Equivalence of baseline characteristics**: a slightly higher percentage of participants in bevacizumab monthly group had history of transient ischemic attack (8.7% compared with 4% in ranibizumab monthly group, 4% in ranibizumab as needed group, and 6.3% in bevacizumab as needed group) **Diagnoses in participants**: 688/1185 (58%) had active neovascular AMD with CNV in foveal center; 315/1185 (27%) had fluid in foveal center; 93/1185 (8%) had hemorrhage in foveal center; 71/1185 (6%) had other foveal center involvement; and 18/1185 (1.5%) had no CNV or not possible to grade
Interventions	**Intervention 1**: 1.25 mg per 0.05 ml intravitreal bevacizumab injections on a fixed schedule of every 4 weeks for 1 year, at 1 year, re-randomization to bevacizumab every 4 weeks or as needed **Intervention 2**: 0.5 mg intravitreal ranibizumab injections on a fixed schedule of every 4 weeks for 1 year, at 1 year, re-randomization to ranibizumab every 4 weeks or as needed **Intervention 3**: 1.25 mg intravitreal bevacizumab as needed for 2 years

Intervention 4: 0.5 mg intravitreal ranibizumab as needed for 2 years

	Intervention 1	**Intervention 2**	**Intervention3**	**Intervention4**
Agent	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab
Dose	1.25mg	0.5mg	1.25mg	0.5mg
Frequency	Every 4 weeks for 1 year, re-randomization to bevacizumab every 4 weeks or as needed	Every 4 weeks for 1 year, re-randomization to ranibizumab every 4 weeks or as needed	As needed for 2 years	As needed for 2 years

Length of follow up:
Planned: 12 months for primary analysis; 24 months for secondary analyses, with modifications to two intervention arms as described above
Actual: 12 months for primary analysis; 24 months for secondary analyses

Outcomes

Primary outcome, as defined: change in visual acuity from baseline at 12 months with a non-inferiority margin of 5 letters
Secondary outcomes: proportion of eyes with 15-letter change, number of injections, OCT measured change in foveal thickness, change in lesion size on OCT and also on fluorescein angiography, incidence of ocular and systemic adverse events, and annual drug cost
Intervals at which outcomes were assessed: weeks 4, 12, 24, 36, 52 during first year for visual acuity; weeks 4, 8, 12, 24, 52 for changes on OCT

Results

Visual acuity (12 months)

	Bevacizumab PRN (n=271)	Ranibizumab PRN (n=285)	Bevacizumab monthly (n=265)	Ranibizumab monthly (n=284)
Gain of ≥15 letters, n(%)	76 (28.0)	71 (24.9)	83 (31.1)	97 (34.2)
Loss of ≥15 letters	23 (8.5)	13 (4.6)	16 (6.0)	16 (5.6)
Change between less 15 letters loss and gain	172	201	166	171

Visual acuity (24 months, patients treated with the same dosing regimen)

	Bevacizumab PRN (n=251)	Ranibizumab PRN (n=264)	Bevacizumab monthly (n=129)	Ranibizumab monthly (n=134)
Gain of ≥15 letters, n(%)	71 (28.3)	81 (30.7)	41 (31.8)	44 (32.8)
Loss of ≥15 letters	29 (11.6)	19 (7.2)	10 (7.8)	9 (6.7)
Change between less 15 letters loss and gain	172	201	166	171

Adverse event after enrolment (12 months)

	Bevacizumab PRN (n=300)	Ranibizumab PRN (n=298)	Bevacizumab monthly (n=286)	Ranibizumab monthly (n=301)
Endophthalmitis	0	0	4 (1.4)	2 (0.7)
Death any cause	11 (3.7)	5 (1.7)	4 (1.4)	4 (1.3)
Nonfatal myocardial infarction	1 (0.3)	3 (1.0)	2 (0.7)	2 (0.7)
Nonfatal stroke	2 (0.7)	1 (0.3)	2 (0.7)	2 (0.7)
Cardiac disorder	13 (4.3)	12 (4.0)	16 (5.60)	10 (3.3)
Infection	18 (6.0)	12 (4.0)	11 (3.8)	6 (2.0)

Gastrointenstinal disorder	9 (3.0)	2 (0.7)	6 (2.1)	3 (1.0)
1 or more serious systemic event	77 (25.7)	61 (20.5)	64 (22.4)	53 (17.6)

Adverse event within 2 years of enrolment

	Bevacizumab (n=586)	Ranibizumab (n=599)
Endophthalmitis	7 (1.2)	4 (0.7)
Death any cause	36 (6.1)	32 (5.3)
Nonfatal myocardial infarction	7 (1.2)	9 (1.5)
Nonfatal stroke	8 (1.4)	8 (1.3)
Cardiac disorder	62 (10.6)	45 (7.5)
Infection	54 (9.2)	41 (6.8)
Gastrointenstinal disorder	28 (4.8)	11 (1.8)
1 or more serious systemic event	234 (39.9)	190 (31.7)

Number of injections (one year)

	Bevacizumab PRN (n=300)	Ranibizumab PRN (n=298)	MD (95%CI)
Mean number of injections (SD)	7.7 (3.5)	6.9 (3.0)	0.80 (0.28, 1.32)

Notes

Full study name: Comparison of Age-related macular degeneration Treatment Trials
Type of study: published
Funding: National Eye Institute, National Institutes of Health, US
Declarations of interest: one investigator reported receiving consulting fees from GlaxoSmithKline and another consulting fees from Neurotech and SurModics
Study period: accrual February 2008 through December 2009; follow up through December 2011 **Reported subgroup analyses**: none, but risk factors for 2-year VA outcomes have been reported (Ying 2015 under CATT 2011)
Contacting study investigators: trial authors not contacted as data were available in published reports

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to 1 of 4 study groups. Randomization schedules were stratified according to clinical center with the use of a permuted-block method with randomly chosen block sizes."
Allocation concealment (selection bias)	Low risk	Web-based data entry system was used to allocate participants to treatment groups.
Masking of participants (performance bias)	Unclear risk	Initially, participants were masked to which drug they received, but not to the treatment schedule. The study investigators noted that "insurance and billing documents specified ranibizumab but not study-supplied bevacizumab. Therefore, patients may have learned or deduced their assigned drug from these financial documents."
Masking of study personnel (performance bias)	Low risk	Physicians were masked to drug but not to injection schedule. Physicians were uninvolved in visual acuity testing and in secondary outcome assessments.
Masking of outcome assessment (detection bias)	Low risk	Electronic Visual Acuity system (computerized testing) was used for primary outcome. Retinal center personnel were masked. Adverse event reporting was unmasked, but medical monitor who evaluated serious adverse events was masked.
Incomplete outcome data (attrition bias)	Unclear risk	103/1208 (8.5%) participants randomized were not included in the one-year analysis. At two years, outcomes were not available for all participants by their originally assigned treatment groups.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes, specified a priori, for 1 year follow up were reported.
Other bias	Low risk	None reported

Bibliographic reference	**GEFAL 2013** Kodjikian L, Souied EH, Mimoun G, Mauget-Faysse M, Behar-Cohen F, Decullier E, et al. Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: Results from the GEFAL noninferiority randomized trial. Ophthalmology 2013;120(11):2300-9.
Methods	**Number randomized (total and per group**): 501 participants randomly assigned to study treatment; 255 in bevacizumab group and 246 in ranibizumab group **Exclusions after randomization:** 16 participants excluded because they received no injection (9 in bevacizumab group and 7 in ranibizumab group)

	Number analyzed (total and per group): 485 participants (246 in bevacizumab group and 239 in ranibizumab group) for safety analysis at one year; 404 participants (207 in bevacizumab group and 197 in ranibizumab group) for analysis on visual acuity at one year; most data analyzed for 374 participants (191 in bevacizumab group and 183 in ranibizumab group) with available baseline BCVA data, at least 10 months follow up, and did not have major deviations from the study protocol **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 81 total participants: 39 in bevacizumab group and 42 in ranibizumab group; additional 30 participants (16 in bevacizumab group and 14 in ranibizumab group) excluded from most analyses due to protocol violations **Compliance**: 374/501 participants completed the study without major protocol violations **Intention to treat analysis**: no, not all participants enrolled and randomized were included in the analyses **Reported power calculation**: yes, sample of 200 participants per group for power of 90% to detect 15 letters changes in BCVA **Study design comment:** non-inferiority design
Participants	**Country**: France (38 study centers) **Age**: mean age for 374 participants without major protocol violations was 79 years **Gender (percent**): 248/374 (66%) women and 126/374 (34%) men **Inclusion criteria**: age 50 years or older; active subfoveal neovascular AMD (one study eye eligible in bilateral cases); lesion size < 12 disk areas; recent development of lesion in cases of occult neovessels; BCVA of 20/32 to 20/320 on ETDRS scale **Exclusion criteria**: subretinal hemorrhage reaching foveal center and > 50% of the lesion area; fibrosis or atrophy in center of fovea in the study eye; CNV of other pathogenesis; retinal pigment epithelial tear reaching the macula; previous or current treatment with intravitreal anti-VEGF therapy; history of treatment 3 months prior or intraocular surgery 2 months prior to first study injection; history of photocoagulation or intravitreal medical device in the study eye; ocular or periocular infection; intraocular inflammation; diabetic retinopathy; history of autoimmune or idiopathic uveitis; IOP ? 25 mmHg with topical hypotensive therapy; aphakia or lack of lens capsule in the study eye; known illness or condition requiring intraocular surgery within 12 months; known hypersensitivity to study drugs or allergy to agents used for ocular testing; uncontrolled arterial hypertension; history of treatment with systemic bevacizumab; premenopausal women not using adequate contraception; involvement in another clinical study; not part of French national health insurance program **Equivalence of baseline characteristics**: yes **Diagnoses in participants:** 354/374 (95%) had intraretinal and/or subretinal fluid on OCT

<table>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg in 0.05 ml intravitreal bevacizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.50 mg intravitreal ranibizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
<table><tr><td></td><td>Intervention1</td><td>Intervention2</td></tr><tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td></tr><tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr><tr><td>Frequency</td><td>Monthly for 3 months</td><td>Monthly for 3 months</td></tr><tr><td></td><td colspan="2">Retreatment after initial 3 doses afterwards based on OCT or VA changes</td></tr></table>
Length of follow up: Planned: 1 year; Actual: 1 year</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: mean change in BCVA at 1 year (at least 10 months after inclusion), as measured on an ETDRS chart
Secondary outcomes, as defined in published reports: visual acuity outcomes at 1 year: BCVA, change in BCVA, proportion with gain of ≥15 letters, proportion with loss of ≥15 letters, proportion with gain of ≥5 letters, proportion with loss of ≥5 letters; change in CNV area between the baseline and final evaluations; presence of intraretinal and/or subretinal fluid; presence of pigment epithelial detachment; central subfield macular thickness; change in central subfield macular thickness; dye leakage on angiogram; number of injections; model of OCT equipment; adverse events
Secondary outcomes, as defined in trial registry: efficacy of treatments at 1 year; proportions of ocular and systemic adverse events at 1 year; average number of injections and time before re-injection during 1 year; drug profiles in blood and aqueous humor of a subset of 20 participants at 3 months; medico-economic impact of treatments at 1 year
Intervals at which outcomes were assessed: monthly through 12 months</td></tr>
</table>

Results

Visual acuity (12 months)

	Bevacizumab (n=191)	Ranibizumab (n=183)	RR (95%CI)
Gain of ≥15 letters	39 (20.4)	39 (21.3)	0.96 (0.65, 1.42)
Loss of ≥15 letters	40 (20.9)	45 (24.6)	0.85 (0.59, 1.24)
Gain or loss less than 15 letters	135	126	1.03 (0.90, 1.17)

Adverse events (12 months)

	Bevacizumab (n=191)	Ranibizumab (n=183)	RR (95%CI)
Endophthalmitis	0	1	0.32 (0.01, 7.79)
Vitreous haemorrhage	0	1	0.32 (0.01, 7.79)
Death	2	3	0.64 (0.11, 3.78)
Myocardial infarction	1	1	0.96 (0.06, 15.20)
Cardiac disorder	2	5	0.38 (0.08, 1.95)
Infection	4	2	1.92 (0.36, 10.34)
Gastrointestinal disorder	3	5	0.57 (0.14, 2.37)
With at least 1 serious adverse events	31	29	1.02 (0.64, 1.63)

Number of injections (12 months)

	Bevacizumab (n=191)	Ranibizumab (n=183)	MD (95%CI)
Mean number of injections (SD)	6.8 (2.7)	6.5 (2.4)	0.30 (-0.22, 0.82)
13.1% of patients in both groups did no need additional injections. 4.2% and 1.6% patients treated with bevacizumab and ranibizumab required monthly treatment (12 injections, p=0.14)			

Notes

Full study name: Groupe d'Etude Français Avastin versus Lucentis dans la DMLA néovasculaire
Type of study: published
Funding sources: French Ministry of Health (Programme Hospitalier de Recherche Clinique National 2008); the French Health Insurance System co-financed the study and funded study drugs

	Declarations of interest: four authors declared disclosures as principal investigators for trials sponsored by Novartis, Bausch & Lomb, Théa, and Alcon; serving on advisory boards for Alcon, Allergan, Bayer, Bausch & Lomb, Novartis, and Théa; receiving lecture fees from Alcon, Allergan, Bayer, Bausch & Lomb, Heidelberg Engineering, the Krys group, Novartis, Théa, and Zeiss; receiving consulting fees from Novartis, Bayer, and Allergan; or receiving honoraria from Novartis, Bayer, and Allergan; the other four authors declared no conflicts of interests **Study period**: random enrollment 24 June 2009 to 9 November 2011 **Reported subgroup analyses**: none **Contacting study investigators**: trial authors contacted and contributed information for this review

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomization was stratified by center and visual acuity (threshold: 20/100). Local hospital pharmacies were responsible for randomizing patients in each center using pre-established lists.'"
Allocation concealment (selection bias)	Low risk	Hospital pharmacy used to conceal treatment assignments prior to participant enrollment and randomization (email communication with Dr Kodjikian, dated 7 August 2014).
Masking of participants (performance bias)	Low risk	"Identical syringes were masked and delivered by local hospital pharmacies after aseptic preparation in authorized, centralized drug-preparation units, using vials of Avastin 100 mg/ml and Lucentis 10 mg/ml." "The main strength of the GEFAL trial is that the study remained effectively double-masked, unlike CATT in which some participants received billing information and IVAN in which the masking differed between centers (some treating teams were aware of treatment allocation)."
Masking of study personnel (performance bias)	Low risk	"Identical syringes were masked and delivered by local hospital pharmacies after aseptic preparation in authorized, centralized drug-preparation units, using vials of Avastin 100 mg/ml and Lucentis 10 mg/ml." "The main strength of the GEFAL trial is that the study remained effectively double-masked, unlike CATT in which some participants received billing information and IVAN in which the masking differed between centers (some treating teams were aware of treatment allocation)."
Masking of outcome assessment (detection bias)	Low risk	Only the pharmacists who prepared the syringes knew about the randomization assignments; ophthalmologists, study coordinators, and all outcome assessors were masked like participants (email communication with Dr Kodjikian, dated 7 August 2014).
Incomplete outcome data (attrition bias)	Unclear risk	16/501 (3%) participants randomized were not included in any analysis; most analyses reported did not include 127/501 (25%) of participants.

Selective reporting (reporting bias)	Unclear risk	Differences in outcomes between the trial registration and published one-year results papers included: 1) secondary visual acuity and morphology outcomes were specified clearly in the paper, but described only as 'efficacy of treatments' in the trial registration;2) the published paper included model of OCT equipment as outcome, whereas the trial registration did not; and 3) the trial registration included time before re-injection during one year, drug profiles in blood and aqueous humor of a subset of 20 participants at 3 months, and medico-economic impact of treatments as outcomes, whereas the published paper did not.
Other bias	Low risk	None observed

Bibliographic reference	**IVAN 2013** Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA; on behalf of the IVAN study investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013;382(9900):1258-67.
Methods	**Number randomized (total and per group):** Drug randomization: 628 total participants; 305 to bevacizumab group and 323 to ranibizumab group **Regimen randomization**: 294/305 in bevacizumab group and 312/323 in ranibizumab group completed first three injections and were randomized to continue or discontinue treatment: 149 continued bevacizumab; 145 discontinued bevacizumab; 157 continued ranibizumab; and 155 discontinued ranibizumab **Exclusions after randomization**: 18 participants did not receive treatment and were excluded after randomization to drug treatment (9 in bevacizumab group and 9 in ranibizumab group) **Number analyzed (total and per group):** at one year follow up: 561 total participants at one year; 136 in continued bevacizumab group; 138 in discontinued bevacizumab group; 141 in continued ranibizumab group; and 146 in discontinued ranibizumab group at two years follow up: 525 total participants at one year; 127 in continued bevacizumab group; 127 in discontinued bevacizumab group; 134 in continued ranibizumab group; and 137 in discontinued ranibizumab group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up:**

	at one year follow up: 49 total participants: 4 participants receiving treatment withdrew prior to completing third injection (2 in bevacizumab group and 2 in ranibizumab group); 45 participants randomized to regimen groups exited trial before one year (13 in continued bevacizumab group; 7 in discontinued bevacizumab group; 16 in continued ranibizumab group; and 9 in discontinued ranibizumab group) at two years follow up: 85 total participants: 5 participants receiving treatment withdrew prior to completing third injection (3 in bevacizumab group and 2 in ranibizumab group); 80 participants randomized to regimen groups exited trial before two years (21 in continued bevacizumab group; 18 in discontinued bevacizumab group; 23 in continued ranibizumab group; and 18 in discontinued ranibizumab group) **Compliance**: the wrong study drug was administered twice during the first year; at one year follow up: adherence was 6576/6699 (98%) scheduled injections received at two years follow up: adherence was 12761/14640 (87%) scheduled injections received **Intention to treat analysis**: no, 67 participants enrolled and randomized were not included in the analyses at one year and 103 at two years **Reported power calculation**: yes, sample of 600 participants per group for power of 90% to detect non-inferiority **Study design comment**: non-inferiority design; 2 x 2 factorial design – randomization in two stages: first randomized to drug treatment (bevacizumab or ranibizumab), then to treatment regimen (continue monthly injections or discontinue monthly injections and switch to as needed injections given in three month cycles); results reported only as bevacizumab versus ranibizumab and continuous versus discontinuous
Participants	**Country**: UK (23 study centers) **Age**: mean age for 610 participants receiving treatment was 78 years **Gender (percent):** 366/610 (60%) women and 244/610 (40%) men **Inclusion criteria**: age 50 years or older; previously untreated neovascular AMD in study eye with any component of the neovascular lesion (CNV, blood, serous pigment epithelial detachment, elevated blocked fluorescence) involving the center of the fovea, confirmed by fluorescein angiography; best-corrected VA of 25 letters or greater on the ETDRS chart (measured at 1 m) **Exclusion criteria**: neovascular lesion of 50% or more fibrosis or blood; more than 12 disc diameters; argon laser treatment in study eye within 6 months; presence of thick blood involving the center of the fovea; presence of other active ocular disease causing concurrent vision loss; myopia 8 or more diopters; previous treatment with PDT or a VEGF inhibitor in study eye; women pregnant, lactating, or of child-bearing potential; men with a spouse or partner of child-bearing potential **Equivalence of baseline characteristics**: yes

<table>
<tr><td></td><td>Diagnoses in participants: 301/610 (58%) had neovascular AMD with CNV in foveal center; 308/610 (54%) had fluid in foveal center; 90/610 (16%) had hemorrhage in foveal center; 75/610 (13%) had other foveal center involvement; and 15/610 (3%) had no CNV or not possible to grade</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg in 0.05 ml intravitreal bevacizumab injected monthly for two years
Intervention 2: 0.5 mg intravitreal ranibizumab injected monthly for two years
Intervention 3: after first 3 monthly 1.25 mg intravitreal bevacizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
Intervention 4: after first 3 monthly 0.5 mg intravitreal ranibizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
<table>
<tr><td></td><td>Intervention1</td><td>Intervention2</td><td>Intervention3</td><td>Intervention4</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td colspan="2">Monthly for 2 years
Monthly for 2 years</td><td colspan="2">Initial 3 doses monthly, then treatment was givens as needed in cycles of 3 monthly dosee</td></tr>
</table>

Follow up: Planned length: 2 years; Actual length: 2 years
Frequency of follow-up assessments: monthly</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: best-corrected distance visual acuity measured as ETDRS letters at two years
Secondary outcomes, as defined in protocol: at 1 year and 2 years follow up - frequencies of adverse effects of treatment; generic and vision-specific health-related quality of life; treatment satisfaction; cumulative resource use/cost and cost-effectiveness; clinical measures of vision (contrast sensitivity measured with Pelli-Robson charts, near visual acuity measured by Bailey-Love near reading cards, and reading speed measured with Belfast reading charts); lesion morphology (fluorescein angiography and OCT); distance visual acuity at one year; survival free from treatment failure
Exploratory analysis: association between serum markers and cardiovascular serious adverse events
Intervals at which outcomes were assessed: monthly through 24 months; various data were collected at every visit depending on assessment schedule and regimen group</td></tr>
</table>

Results

Visual acuity (12 months)

	Bevacizumab monthly (n=134)	Bevacizumab PRN (n=136)	Ranibizumab monthly (n=140)	Ranibizumab PRN (n=143)
Gain of ≥ 15 letters, no.	19	25	36	29
Loss of ≥15 letters	7	5	6	6
Gain or loss less than 15 letters	108	106	98	108
BCVA, letters (SD)	4.4 (13.2)	5.1 (11.4)	7.8 (14.2)	5.1 (10.4)

Visual acuity (24 months)

	Bevacizumab monthly (n=126)	Bevacizumab PRN (n=123)	Ranibizumab monthly (n=133)	Ranibizumab PRN (n=135)
Gain of ≥ 15 letters, no.	24	17	41	22
Loss of ≥15 letters	12	11	8	15
Gain or loss less than 15 letters	90	95	84	98
BCVA, letters (SD)	3.6 (15.2)	4.5 (11.5)	7.3 (15.2)	2.6 (14.4)

Notes

Full study name: alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation
Type of study: published
Funding sources: National Institute for Health Research Health Technology Assessment program, UK
Declarations of interest: various authors reported being principal investigators of trials sponsored by Novartis; attending and being remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and/or Bausch and Lomb; being employed by institution that has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and/or Pfizer; receiving honoraria from Novartis for lecture and/or teaching fees from Janssen-Cilag
Study period: random enrollment 27 March 2008 to 15 October 2010
Reported subgroup analyses: 3 genetic polymorphisms (Lotery 2013)
Contacting study investigators: trial authors not contacted as data were available in published reports

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	"Randomized allocations were computer generated by a third party in blocks and stratified by center." "Randomisation was stratified by centre and was blocked to ensure roughly equal numbers of participants per group within a centre."
Allocation concealment (selection bias)	Low risk	"Research teams at sites recruited participants, and accessed a password-protected website to randomize participants. Allocations were concealed until participants' eligibility and identities were confirmed." "Allocations were computer generated and concealed with an internet-based system (Sealed Envelope, London, UK). Staff in participating centres accessed the website and, on entering information to confirm a participant's identity and eligibility, were provided with the unique study number."
Masking of participants (performance bias)	Low risk	From study protocol: "Participants, clinicians and trial personnel will be masked to the VEGF inhibitor to which a participant is assigned." "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Masking of study personnel (performance bias)	Low risk	"We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments." From study protocol:"We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Masking of outcome assessment (detection bias)	Low risk	"We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments." From study protocol: "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Incomplete outcome data (attrition bias)	Unclear risk	67/628 (11%) participants randomized were not included in the one-year analysis; 111/628 (18%) participants randomized were not included in the two-year analysis.
Selective reporting (reporting bias)	Unclear risk	Differences between the protocol and published one-year and two-year results papers included: 1) two secondary outcomes in the protocol were not listed in paper: treatment satisfaction and survival free from treatment failure; and

		2) exploratory (serum) analysis in protocol upgraded to a secondary outcome in paper.
Other bias	Low risk	None observed

Bibliographic reference	**LUCAS 2015** Berg K, Pedersen TR, Sandvik L, Bragadottir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and extend protocol. Ophthalmology 2015;122(1):146-52
Methods	**Number randomized (total and per group):** 441 participants randomly assigned to study treatment; 220 in bevacizumab group and 221 in ranibizumab group **Exclusions after randomization**: 10 total participants; 7 in the bevacizumab group and 3 in the ranibizumab group. "All 9 patients from 1 study center were excluded becasue of serious protocol violations, and 1 patient was excluded after a serious retinal and viteous hemmorhage . . . " **Number analyzed (total and per group**): 371 total participants; 184 in bevacizumab group and 187 in ranibizumab group **Unit of analysis:** individuals (one study eye per participant) **Losses to follow up**: none, but 60 excluded from analysis (29 in the bevacizumab group and 31 in the ranibizumab group), including 11 total participants who died **Compliance**: 371/441 participants completed the study per protocol **Intention to treat analysis:** no, 70 participants enrolled and randomized were not included in analysis **Reported power calculation:** yes, 181 participants per arm to provide 80% power to detect or rule out a difference in visual acuity outcome, assuming a 10% dropout rate **Study design comment:** non-inferiority design using margin of 5 letters on ETDRS chart
Participants	**Country**: 10 clinical centers in Norway **Age**: mean 78.7 years in bevacizumab group and 78.0 in ranibizumab group **Gender (percent):** 140/431 (32.5%) men and 291/431 (67.5%) women **Inclusion criteria**: age 50 years or older; previously untreated active neovascular AMD in study eye; BCVA in study eye between 20/25 and 20/120, measured at 4 meters using an ETDRS "standardized viewer" **Exclusion criteria**: "Pigment epithelial detachments with no associated intraretinal or subretinal edema and lesions comprising more than 50% blood or fibrosis were excluded." **Equivalence of baseline characteristics:** more participants in the ranibizumab group had a history of myocardial infarction **Diagnoses in participants**: neovascular AMD; 86% had CNV under the foveal center

<table>
<tr><td>Interventions</td><td>
Intervention 1: 1.25 mg per 0.05 ml intravitreal bevacizumab injections every 4 weeks until no signs of active AMD were found based on OCT and biomicroscopic fundus examination, followed by the "treat and extend" protocol
Intervention 2: 0.5 mg intravitreal ranibizumab injections every 4 weeks, followed by the "treat and extend" protocol
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks until no signs of active AMD (based on OCT), followed by treat and extend protocol</td><td>Every 4 weeks, followed by the treat and extended protocol</td></tr>
</table>

The "treat and extend" protocol for each treatment group specified that whenever a new injection was given, the "period" (interval) to the next injection was to be extended by 2 weeks up to a maximum interval of 12 weeks. Whenever recurrent neovascularization was treated, the interval was shortened by 2 weeks until the lesion was inactive. Interval extension was then restarted to a maximum of 2 weeks less than when the recurrence was observed,
Follow up: Planned length: 24 months; Actual length: 12 months
Frequency of follow-up assessments: 4-week intervals, modified by 2-week increases or decreases, as described above
</td></tr>
<tr><td>Outcomes</td><td>
Primary outcome, as defined: "change in BCVA at 1 year as measured on the ETDRS visual acuity chart"
Secondary outcomes, as defined: "number of injections, change in CRT as measured with OCT, and change in lesion size as measured on FA"
Safety outcome: occurrence of arteriothrombotic events
Intervals at which outcomes were assessed: unclear, but presumably whenever participant was assessed for the need for retreatment
</td></tr>
<tr><td>Results</td><td>
Visual acuity (12 months)
<table>
<tr><td></td><td>Bevacizumab (n=184)</td><td>Ranibizumab (n=187)</td><td>RR (95%CI)</td></tr>
<tr><td>Gain of ≥ 15 letters, n (%)</td><td>47 (25.5)</td><td>50 (26.7)</td><td>0.96 (0.68, 1.35)</td></tr>
<tr><td>Loss of ≥ 15 letters</td><td>7 (3.8)</td><td>8 (4.3)</td><td>0.89 (0.33, 2.40)</td></tr>
<tr><td>Gain or loss of less than 15 letters</td><td>130</td><td>129</td><td>1.02 (0.90, 1.17)</td></tr>
</table>

Adverse event within 1 year of recruitment (12 months)
</td></tr>
</table>

	Bevacizumab (n=220)	Ranibizumab (n=221)	RR (95%CI)
Macular haemorrhage	2	0	5.02 (0.24, 104.02)
Death any cause	4	7	0.57 (0.17, 1.93)
Nonfatal myocardial infarction	0	6	0.08 (0.00, 1.36)
Nonfatal stroke	2	3	0.67 (0.11, 3.97)
Cardiac disorder	5	14	0.36 (0.13, 0.98)
Infection	4	5	0.80 (0.22, 2.95)
Gastrointestinal disorder	5	5	1.00 (0.29, 3.42)
≥1serious systematic event	37	45	0.83 (0.56, 1.22)

Number of injections (12 months)

	Bevacizumab (n=184)	Ranibizumab (n=187)	MD (95%CI)
Mean number of injections (SD)	8.9 (2.6)	8.0 (2.3)	0.90 (0.40, 1.40)

Notes

Full study name: Lucentic Compared to Avastin Study
Type of study: published
Funding sources: Oslo University Hospital, Oslo, Norway
Declarations of interest: "The funding organization had no role in the design of the study but aided in the conduct of the study and data management." One author had participated in an advisory board meeting for another anti-VEGF agent for Bayer.
Study period: random enrolment March 2009 to July 2012
Reported subgroup analyses: none
Contacting study investigators: pending

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated by a third party at the Norwegian University of Science and Technology, Trondheim . . . with the use of the block method and stratification by centre."

Allocation concealment (selection bias)	Low risk	The drugs were allocated by unmasked study nurses who were also responsible for aseptic filling of a syringe with the assigned study drug. The identical syringes, regardless of which drug was given, were filled by these nurses behind a screen. The syringe was then presented directly to the treating ophthalmologist."
Masking of participants (performance bias)	Low risk	"the patient, the treating ophthalmologist, and the assisting nurse were masked to the drug at all times."
Masking of study personnel (performance bias)	Low risk	"These study nurses were not involved in any other patient-related activities in the study."
Masking of outcome assessment (detection bias)	Low risk	"Ophthalmic nurses, who also were masked to the drug and patient records, tested the ETDRS visual acuity."
Incomplete outcome data (attrition bias)	Unclear risk	About 15% of participants were missing 12-month outcome data, compared to 10% assumed in sample size calculation.
Selective reporting (reporting bias)	Low risk	All outcomes specified were reported.
Other bias	Low risk	No other bias identified

Bibliographic reference	**MANTA 2013** Krebs I, Schmetterer L, Boltz A, Told R, Vécsei-Marlovits V, Egger S, et al. A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. British Journal of Ophthalmology 2013;97(3):266-71.
Methods	**Number randomized (total and per group):** 321 participants randomly assigned to study treatment; number per group not reported **Exclusions after randomization**: 4 participants (3 due to receiving the wrong drug and 1 because the participant received prior treatment and was not eligible) **Number analyzed (total and per group):** 317 total participants; 154 in bevacizumab group and 163 in ranibizumab group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 69 participants: reasons for losses to follow up not reported (33 in bevacizumab group, 36 in ranibizumab group) **Compliance**: 248/317 participants completed the study **Intention to treat analysis:** no, 4 participants enrolled and randomized were not included in analysis; data imputed using last-observation-carried-forward method for 69 participants lost to follow up

<table>
<tr><td></td><td>Reported power calculation: yes, sample of 320 participants for power of 95%
Study design comment: non-inferiority design</td></tr>
<tr><td>Participants</td><td>Country: 10 clinical centers in Austria
Age: mean 76.7 years in bevacizumab group and 77.6 years in ranibizumab group
Gender (percent): 115/317 (36.3%) men and 202/317 (63.7%) women
Inclusion criteria: age 50 years or older; active primary or recurrent subfoveal lesion with CNV, measured by fluorescein angiography or OCT; BCVA in study eye between 20/40 to 20/320, measured by ETDRS charts
Exclusion criteria: previous treatment for CNV or AMD; prior treatment with any intravitreal drug or verteporfin PDT in study eye; prior treatment with systemic bevacizumab; prior treatment with any intravitreal drug or verteporfin PDT in non-study eye within 3 months; laser photocoagulation in study eye within 1 month; participation in another clinical trial within 1 month; subfoveal fibrosis or atrophy > 50% in study eye; CNV in either eye due other causes than AMD; RPE tear involving macula of study eye; history of uncontrolled glaucoma or concurrent intraocular condition in study eye; pregnancy; allergy to fluorescein; inability to comply with study procedures
Equivalence of baseline characteristics: yes
Diagnoses in participants: active primary or recurrent subfoveal CNV</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg per 0.05 ml intravitreal bevacizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.5 mg intravitreal ranibizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months; retreatment based on OCT or VA changes</td><td>Monthly for 3 months, retreatment based on OCT or VA changes</td></tr>
</table>
Length of follow up: Planned: 12 months; Actual: 12 months</td></tr>
<tr><td>Outcomes</td><td>Primary outcomes, as defined: "mean change in BCVA between baseline and 1 year"
Secondary outcomes, as reported: Kaplan-Meier proportions of the gain of 15 letters of vision, gain of 5 letters of vision, loss of 5 letters of vision, loss of 15 letters of vision; lesion size, assessed by fluorescein angiography; number of retreatments; and retinal thickness, assessed by OCT
Adverse events</td></tr>
</table>

Intervals at which outcome assessed: monthly through 12 months

Results

Visual acuity (12 months)

	Bevacizumab (n=154)	Ranibizumab (n=163)	RR (95%CI)
Gain of ≥15 letters, n	36	35	1.09 (0.72, 1.64)
Loss of ≥15 letters	8	10	0.85 (0.34, 2.09)
Gain or loss less than 15 letters	110	118	0.99 (0.86, 1.13)

Adverse event (12 months)

	Bevacizumab (n=154)	Ranibizumab (n=163)	RR (95%CI)
Total no. of patients reported AE	19	15	1.34 (0.71, 2.54)
Death	3	2	1.59 (0.27, 9.37)
Vascular disorder	5	3	1.76 (0.43, 7.26)
Infection	3	3	1.06 (0.22, 5.16)

Number of re-treatment (12 months)

	Bevacizumab (n=154)	Ranibizumab (n=163)	MD (95%CI)
Mean number (SD)	6.1 (2.8)	5.8 (2.7)	0.30 (-0.31, 0.91)
During the observation, 6 patients required treatment also in the fellow eye (4 in the ranibizumab group, 2 in the bevacizumab group).			

Notes

Full study name: A Randomized Observer and Subject Masked Trial Comparing the Visual Outcome After Treatment With Ranibizumab or Bevacizumab in Patients With Neovascular Age-related Macular Degeneration Multicenter Anti VEGF Trial in Austria
Type of study: published
Funding sources: Austrian ophthalmologic society; the Ludwig Boltzmann Institute of Retinology and Biomicroscopic Lasersurgery; the participating study center sitesDeclarations of interest: authors reported no competing interests
Study period: not reported
Reported subgroup analyses: none
Contacting study investigators: trial authors contacted; no additional information provided for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was stratified according to the clinical centre using a permuted block method with a fixed block size of 20."
Allocation concealment (selection bias)	Low risk	"Eligible patients were randomized in a 1:1 ratio to one of two groups by members of the Department of Clinical Pharmacology, Medical University of Vienna, which was otherwise not involved in the study.
Masking of participants (performance bias)	Low risk	"All other personnel and the patients were masked to treatment assignment."
Masking of study personnel (performance bias)	Low risk	"The evaluating physician was masked to treatment assignment, whereas the injecting physician was not involved in the collection of data."
Masking of outcome assessment (detection bias)	Low risk	"The evaluating physician was masked to treatment assignment, whereas the injecting physician was not involved in the collection of data."
Incomplete outcome data (attrition bias)	Unclear risk	There were 4/321 (1.2%) participants excluded from the study. At 12 months, 69 participants did not have outcome data; last-observation-carried-forward method was used to impute missing data for these 69 participants.
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes were reported.
Other bias	Low risk	None observed

The BRAMD study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016
Country/ies	Netherlands
Study type	RCT
Aim of the study	To compare the effectiveness of bevacizumab and ranibizumab in the treatment of exudative age-related macular degeneration (AMD). Design: Multicentre, randomized, controlled, double-masked clinical trial in 327 patients.
Study dates	Published 2016
Sources of funding	This study was funded by the Netherlands organisation for health research and development. This study was supported by Dutch health insurance companies.
Sample size	327

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016
Inclusion Criteria	Patients 60 years of age or higher. Patients with primary or recurrent sub-, juxta- or extrafoveal CNV secondary to AMD, including those with RAP, that may benefit from anti-VEGF treatment in the opinion of the investigator. Patients with primary or recurrent sub-, juxta- or extrafoveal CNV secondary to AMD, including those with RAP, that may benefit from anti-VEGF treatment in the opinion of the investigator. The total area of CNV (including both classic and occult components) encompassed within the lesion must be more or equal to 30% of the total lesion area. The total lesion area should be < 12 disc areas. A best corrected visual acuity (BCVA) score between 78 and 20 letters (approximately 0,63–0,05 Snellen equivalent) in the study eye.
Exclusion Criteria	Ocular treatment with anti-angiogenic drugs in the last 2 months or Triamcinolone in the last 6 months. Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within one month preceding Baseline. Patients with angioid streaks or precursors of CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia. Spherical equivalent of refractive error in the study eye demonstrating more than– 8 dioptres of myopia. Cataract extraction within three months preceding Baseline IOP >25 mm Hg Active intraocular inflammation in the study eye. Vitreous haemorrhage obscuring view of the posterior pole in the study eye. Presence of a retinal pigment epithelial tear involving the macula in the study eye. Subretinal haemorrhage in the study eye if the size of the haemorrhage is > 70% of the lesion Subfoveal fibrosis or atrophy in the study eye. History of hypersensitivity or allergy to fluorescein. Inability to obtain fundus photographs, fluorescein angiograms or OCT's of sufficient quality to be analyzed and graded by the Central Reading Centre. Systemic disease with a life expectancy shorter than the duration of the study. Inability to adhere to the protocol with regard to injection and follow-up visits. Legally incompetent adult Refusal to give written informed consent

Bibliographic reference	**Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016**
Baseline characteristics	

	Bevacizumab (n=161)	Ranibizumab (n=166)	All (n=327)
Mean age (SD)	79 (7)	78 (7)	78 (7)
Male: n (%)	72 (45%)	73 (44%)	145 (44%)
Caucasuan: n(%)	158 (98%)	163 (98%)	321 (98%)
Mean BCVA (SD)	60 (13)	60 (14)	60 (13)
BCVA≤52 letters: n (%)	42 (26%)	43 (26%)	85 (26%)
Active CNV: n(%)	161 (100%)	165 (99.9%)	326 (99.9%)
Predominiantly classic CNV, n(%)	44 (28%)	41 (26%)	85 (27%)
Minimally classic CNV: n (%)	18 (12%)	33 (21%)	51 (16%)
Occult CNV, n(%)	93 (60%)	84 (53%)	177 (57%)
EQ-5D state score (SD)	6.2 (1.2)	6.4 (1.3)	6.3 (1.3)

Study visits and procedures	Participants were allocated to one of two study arms: monthly injections (window, 30 ± 7 days) with 1.25 mg of bevacizumab or with 0.5 mg ranibizumab. The commercially available formulations of bevacizumab and ranibizumab were used and both were prepared for injection by aspiration in a Kendall monoject syringe in an aseptic manufacturing facility to ensure masking for everybody taking part in the study, apart from the pharmacists. Syringes were only labelled with the patient identification number. Prepared syringes were kept at 4°Celsius and injections were given not later than 24 hours after preparation. Participants attended monthly for a protocolized BCVA measurement, SD-OCT (3D and cross scans) and intravitreal injection with the allocated drug. Besides the identical syringes masking was also ensured by the fact that the ophthalmologists who performed the injections did not take part in interpretation of any data or patient assessment. The patient was labelled as a poor-responder and treatment was changed to the other drug, if at any visit after the third injection there was a drop in BCVA of more than 10 letters compared to baseline and there was clear evidence of active CNV or leakage by qualitative SD-OCT and/or FA assessment or at least two of the following signs of leakage on OCT; central retinal thickening >300 micron (CRT), intraretinal cysts or subretinal fluid any time after the third injection. The choice for CRT > 300 micron was based on the assumption that this would be more than two standard deviations above the mean CRT of a healthy retina in all three the devices used (see also

<table>
<tr><th>Bibliographic reference</th><th>Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016</th></tr>
<tr><td></td><td>below). FA and a standardized full ophthalmic examination were done at baseline, 4 months and exit visit.</td></tr>
<tr><td>Intervention</td><td>intravitreal bevacizumab 1.25mg monthly</td></tr>
<tr><td>Comparator</td><td>Intravitreal ranibizumab 0.5mg monthly</td></tr>
<tr><td>Outcomes</td><td>Primary outcome:
Change in best-corrected visual acuity
Secondary outcome:
Proportoin of people with a loss of BCVA less than 15 letters from baseline at 12 months (responders)
Proportion of patients with a loss or a gian of BCVA less than 15 letters from basedlin at 12 months (stabilizers)
Proportion of people with 15 letters loss or more BCVA from baseline at 12 months (losers)
Proportion of drpouts befire the final 12 months assessment
Proportion of switcher after the third injection
Adverse event</td></tr>
<tr><td>Analyses</td><td>Non-inferiority is assumed if the difference between both groups is 4 letters or less using a onesided t-test with a significance level of 0.05.
We performed intention-to-treat (ITT) analysis. When patients did not complete the study, their last available BCVA-score was used as the BCVA-score at visit 14 (last-observation-carried-forward). Further, to minimize the risk of false claiming non-inferiority we used the BCVA at the moment of switch for patients who were switched to the other treatment.
The mean BCVA-change per treatment group was calculated.
Covariance analysis of the BCVA-change was used with treatment as fixed factor and baseline BCVA-score as covariate.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Result</td><td>Visual acuity
<table>
<tr><td></td><td>Bevacizumab (n=161)</td><td>Ranibizumab (n=166)</td><td>Effect (95%CI)</td></tr>
<tr><td>Best-corrected visual acuity changes (ETDRS letter score), all patients</td><td>5.1 (14.1)</td><td>6.4 (12.2)</td><td>-1.30 (-4.16, 1.56)</td></tr>
<tr><td>Best-corrected visual acuity changes (ETDRS letter</td><td>6.64 (12.8)</td><td>7.11 (11.6)</td><td>-0.47 (-3.12, 2.18)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016

score), excluded patients switched the agents (n=17)			
Best-corrected visual acuity changes (ETDRS letter score), treatment naïve (n=284)	6.06 (13.67)	6.82 (12.63)	-0.76 (-3.82,2.30)
N, % of people had a gain of ≥15 letters	39, 24%	32, 19%	1.25 (0.83, 1.89)
N, % of people had a loss of ≥15 letters	18, 11%	8, 5%	2.31 (1.03, 5.15)
N, % of people had a loss or gain of <15 letters	105, 65%	126, 76%	0.85 (0.74, 0.98)
N, % of people drop out	34, 21%	28 (17%)	1.24 (0.79, 1.95)

Adverse event

	Bevacizumab (n=161)	Ranibizumab (n=166)	Effect (95%CI)
Occurance of SAEs	34	37	0.94 (0.62, 1.42)
1Death due to SAE	1	1	1.02 (0.06, 16.24)
Life-threathening conditions	1	2	0.51 (0.05, 5.60)
Hosptialisation	30	32	0.96 (0.61, 1.50)
Severe permanent damange	1	0	3.07 (0.13, 74.90)
No relation to study medication	32	35	0.94 (0.61, 1.44)

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016

Improbable relation to study medication	1	1	1.02 (0.06, 16.24)
MedDRA system organ class			
Cardiact disorder	4	6	0.68 (0.20, 2.38)
Infection	4	4	1.02 (0.26, 4.03)
Nervous system disorder	3	1	3.07 (0.32, 29.25)
Injury or procedural complication	5	1	5.12 (0.61, 43.38)
Benigh or malignant neoplasm	2	3	0.68 (0.12, 4.03)
Surgerical or medical procedure	13	16	0.83 (0.41, 1.68)
Gastrointestinal disorder	2	2	1.02 (0.15, 7.19)
Any other system organ class	18	17	1.08 (0.58, 2.03)

Missing data handling/loss to follow up	21% patients in bevacizumab and 17% patients in ranibizumab dropped out in the study.
Was allocation adequately concealed?	The randomization list was imported into the data management system Oracle Clinical. Upon randomization of a patient, an automatized email notification containing the allocation result was sent to the site's pharmacy keeping the investigator and trial personnel blinded from treatment allocation.
Was knowledge of the allocated intervention adequately prevented during the study?	Upon randomization of a patient, an automatized email notification containing the allocation result was sent to the site's pharmacy keeping the investigator and trial personnel blinded from treatment allocation.
Was the allocation sequence adequately generated?	Yes

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	**Subramanian 2010** Subramanian ML, Abedi G, Ness S, Ahmed E, Fenberg M, Daly MK, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial. Eye 2010;24(11):1708-15.
Methods	**Number randomized (total and per group**): 28 participants randomly assigned to study treatment; 20 in bevacizumab group and 8 in ranibizumab group **Exclusions after randomization**: none **Number analyzed (total and per group):** 22 total participants; 15 in bevacizumab group and 7 in ranibizumab group **Unit of analysis:** individuals (one study eye per participant) **Losses to follow up**: six participants: three participants voluntarily dropped out (two in bevacizumab group, one in ranibizumab group); one participant relocated (in bevacizumab group); and two participants died (both in bevacizumab group) **Compliance**: 22/28 participants completed the study **Intention to treat analysis:** no, six participants enrolled and randomized were not included in analysis **Reported power calculation:** yes, 79% power for sample size of 135 participants using 2:1 randomization ratio **Study design comment:** although the target sample size was 135, only 28 participants were evaluated
Participants	**Country:** Boston, MA, USA **Age:** not reported for 28 enrolled participants (mean 78 years for analyzed bevacizumab group; mean 80 years for analyzed ranibizumab group)

<table>
<tr><td></td><td>Gender (percent): not reported for 28 enrolled participants (all men for analyzed bevacizumab group; 6 men and 1 woman for analyzed ranibizumab group)
Inclusion criteria: age 50 years or older; presence of symptomatic CNV, confirmed by intravenous fluorescein angiogram and optical coherence tomography as affecting the foveal centre; ability to provide informed consent; willing to commit to regular clinic appointments and follow-up; original protocol specified baseline VA between 20/40 and 20/200, later amended to include all baseline VAs equal to or better than 20/400
Exclusion criteria: previous treatment for wet AMD within the past year; presence of subretinal hemorrhage greater than 50% of the size of the lesion on fluorescein angiography, presence of advanced glaucoma; any coexisting macular disease causing decreased vision; history of malignant or uncontrolled hypertension; intraocular inflammation; history of thromboembolic phenomena; inability to provide informed consent; participation in another concurrent ophthalmic clinical trial
Equivalence of baseline characteristics: yes
Diagnoses in participants: AMD</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 0.05 ml intravitreal bevacizumab injection (concentration not reported) every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.05 ml intravitreal ranibizumab injection (concentration not reported) every month for first three months; re-treatment afterwards based on OCT or VA changes
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>-</td><td>-</td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months; retreatment based on OCT or VA changes</td><td>Monthly for 3 months, retreatment based on OCT or VA changes</td></tr>
</table>
Length of follow up: Planned: 12 months; Actual: 12 months</td></tr>
<tr><td>Outcomes</td><td>Primary outcomes, as defined: visual acuity
Secondary outcomes, as reported: central foveal thickness by OCT, total number of injections; blood pressure measurements
Adverse events
Intervals at which outcome assessed: one week after injections to assess adverse events; and monthly through 12 months</td></tr>
</table>

Results	**Visual acuity (12 months)** **Number of injections (12 months)**
Notes	**Type of study:** published **Funding sources**: Veterans Affairs Boston Healthcare System, USA **Declarations of interest:** "The authors declare no conflict of interest" **Study period:** April 2007 to February 2009 **Reported subgroup analyses**: none **Contacting study investigators**: trial authors contacted and contributed information for this review

	Bevacizumab (n=15)	Ranibizumab (n=7)	RR (95%CI)
Gain of ≥15 letters, n	5	1	2.33 (0.33, 16.41)
Loss of ≥15 letters	0	1	0.17 (0.01, 3.65)
Gain or loss less than 15 letters	10	5	0.93 (0.52, 1.68)

	Bevacizumab (n=15)	Ranibizumab (n=7)
Median (range)	7 (3,8)	4 (3,6)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were enrolled by a 2:1 randomization to either the bevacizumab (2) or the ranibizumab (1) arm of the study." Study investigators were contacted, but could not provide additional information as to how the sequence was generated (email communication with Dr Subramanian, dated 16 May 2012).
Allocation concealment (selection bias)	Low risk	"The Research Pharmacist at the [Veterans Affairs] Hospital Pharmacy was responsible for randomization" and "all subjects were assigned a study number."
Masking of participants (performance bias)	Low risk	Reported as "double-blind"; identical syringes were used to administer agents, and study personnel in contact with participants were all masked.
Masking of study personnel (performance bias)	Low risk	"To obtain blinding of treatment assignments, the Research Pharmacist at the [Veterans Affairs] Hospital Pharmacy was responsible for randomization, tracking and ensuring the correct study drug was administered to each patient at each visit, and dispensing the same volume of each drug in identical 1 ml syringes."

Masking of outcome assessment (detection bias)	Low risk	"To obtain blinding of treatment assignments, the Research Pharmacist at the [Veterans Affairs] Hospital Pharmacy was responsible for randomization, tracking and ensuring the correct study drug was administered to each patient at each visit, and dispensing the same volume of each drug in identical 1 ml syringes."
Incomplete outcome data (attrition bias)	Unclear risk	Six of 28 (21%) participants enrolled were not included in the analysis: three voluntarily dropped out; one relocated; and two died.
Selective reporting (reporting bias)	Low risk	Primary outcomes were reported; however, the clinical trials register record for this trial but not the published reports specified quality of life as an outcome.
Other bias	Low risk	None observed

Aflibercept vs ranibizumab

Bibliographic reference	**VIEW 1** Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119(12):2537-48.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomly assigned**: 1217 total participants (1217 eyes) • 304 in the aflibercept 0.5 mg every 4 weeks group • 304 in the aflibercept 2.0 mg every 4 weeks group • 303 in the aflibercept 2.0 mg every 8 weeks group • 306 in the ranibizumab group **Exclusions after randomization**: Full analysis: 7 total participants • 3 in the aflibercept 0.5 mg every 4 weeks group, 0 in the aflibercept 2.0 mg every 4 weeks group, 2 in the aflibercept 2.0 mg every 8 weeks group, and 2 in the ranibizumab group Safety analysis: 2 total participants (both in the ranibizumab group) **Losses to follow-up:** 103 participants discontinued treatment at 1-year follow-up • 30 in the aflibercept 0.5 mg every 4 weeks group • 16 in the aflibercept 2.0 mg every 4 weeks group • 30 in the aflibercept 2.0 mg every 8 weeks group • 27 in the ranibizumab group **Number analysed:**

	Full analysis - 1210 total participants at 1-year follow-up 301 in the aflibercept 0.5 mg every 4 weeks group 304 in the aflibercept 2.0 mg every 4 weeks group, 301 in the aflibercept 2.0 mg every 8 weeks group 304 in the ranibizumab group Safety analysis - 1215 total participants at 1-year follow-up 304 in the aflibercept 0.5 mg every 4 weeks group 304 in the aflibercept 2.0 mg every 4 weeks group 303 in the aflibercept 2.0 mg every 8 weeks group 304 in the ranibizumab group **Unit of analysis:** individual (1 study eye per participant) **How were missing data handled?** missing values imputed using last observation carried forward approach **Power calculation:** none reported
Participants	**Country**: United States and Canada (154 study sites) **Mean age** (range not reported): 78 years in the aflibercept 0.5 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 8 weeks group, and 78 years in the ranibizumab group **Gender**: 134 men (44.5%) and 167 women (55.5%) in the aflibercept 0.5 mg every 4 weeks group, 110 men (36.2%) and 194 women (63.8%) in the aflibercept 2.0 mg every 4 weeks group, 123 men (40.9%) and 178 women (59.1%) in the aflibercept 2.0 mg every 8 weeks group, and 132 men (43.4%) and 172 women (56.6%) in the ranibizumab group **Inclusion criteria:** 50 years of age or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or smaller) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent **Exclusion criteria:** prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis, scleromalacia; presence of other ocular conditions such as uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye **Equivalence of baseline characteristics:** yes; "Baseline demographics and disease characteristics were evenly balanced among all treatment groups"

<table>
<tr><td>Interventions</td><td>
Intervention 1: intravitreal aflibercept 0.5 mg every 4 weeks
Intervention 2: intravitreal aflibercept 2.0 mg every 4 weeks
Intervention 3: intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial doses at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8)
Intervention 4: intravitreal ranibizumab 0.5 mg every 4 weeks

<table>
<tr><th></th><th>Intervention1</th><th>Intervention2</th><th>Intervention3</th><th>Intervention4</th></tr>
<tr><td>Agent</td><td>aflibercept</td><td>aflibercept</td><td>aflibercept</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 4 weeks</td><td>Every 8 weeks after 3 initial doses, sham injections were given at the interim 4-week visits after week8</td><td>Every 4 weeks</td></tr>
</table>

Length of follow-up: 1 year for primary end point; dosing for all groups changed to as needed (PRN) after 1 year and follow-up at 2 years from baseline
</td></tr>
<tr><td>Outcomes</td><td>
Primary outcome, as defined in study reports: "proportion of patients maintaining vision at week 52 (losing < 15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart)"
Secondary outcomes, as defined in study reports: change in BCVA, proportion gaining ≥ 15 letters, change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid as assessed by OCT, mean number of intravitreal injections, adverse events
Intervals at which outcomes assessed: every 4 weeks through 96 weeks; week 1 after first treatment for safety assessment; weeks 12, 24, 36, and 52 for the NEI-VFQ-25 assessment
</td></tr>
<tr><td>Results</td><td>
Visual acuity (52 weeks)
<table>
<tr><td></td><td>Aflibercept 0.5mg monthly (n=301)</td><td>Aflibercept 2.0mg monthly (n=304)</td><td>Aflibercept 2.0mg bi-monthly (n=301)</td><td>Ranibizumab 0.5mg monthly (n=304)</td></tr>
</table>
</td></tr>
</table>

Loss of <15 letters, n(%)	286(95)	289 (95.1)	284 (94.4)	285 (93.8)
Gain of ≥15 letters	75 (24.9)	114 (37.5)	92 (30.6)	94 (30.9)
Loss of ≥15 letters	15	15	17	19

Adverse event (52 weeks)

	Aflibercept 0.5mg monthly (n=304)	Aflibercept 2.0mg monthly (n=304)	Aflibercept 2.0mg bi-monthly (n=303)	Ranibizumab 0.5mg monthly (n=304)
Endophthalmitis	0	3	0	3
VA reduced	2	1	0	2
Retinal hemogghage	0	0	2	2
≥ 1 ocular SAE	6	7	3	10
Nonfatal myocardial infarction	4	1	1	4
Nonfatal stroke	2	1	1	0

Notes

Type of study reports: published journal articles; clinical trial registration

Funding sources: "Sponsored by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer HealthCare, Berlin Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript"

Disclosures of interest: "J.S.H. is a consultant to and has received research funding from Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, and Regeneron Pharmaceuticals. He has also received travel support from Regeneron Pharmaceuticals. D.M.B. is a consultant to Alimera, Allergan, Bayer, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, and Thrombogenics and has received research funding from Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, and Thrombogenics. He has also received travel support from Regeneron Pharmaceuticals and lecture fees from Genentech. V.C. is a consultant to Alimera and Bayer and has received research funding from Alcon, Allergan, Bayer, Novartis, and Pfizer. He is an advisory board member for Allergan and Novartis and has also received travel support from Bayer. J.-F.K. is a consultant to Alcon, Bayer, and Thea and an advisory board member for Allergan, Bayer, and Novartis. He has received travel support from

	Regeneron Pharmaceuticals. P.K.K. is a consultant to Bayer, Genentech, Novartis, and Regeneron Pharmaceuticals. He has received research funding from Regeneron Pharmaceuticals. Q.D.N. is a consultant to Bausch & Lomb and Santen and has received research funding from Genentech, Novartis, and Pfizer. B.K. has received travel support from Bayer. A.H. is a consultant to Alcon, Allergan, Centocor, Johnson & Johnson, Neovista, Merck, Ophthotech, Oraya, Paloma, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Thrombogenics. He has received research funding and lecture fees from Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Second Sight. Y.O. is a consultant to Alcon and Bayer and has received travel support from Bayer. G.D.Y., N.S., R.V., A.J.B., and Y.S. are employees of Regeneron Pharmaceuticals. M.A., G.G., B.S., and R.S. are employees of Bayer HealthCare. C.S.'s institution has received payments from the Medical University of Vienna for data monitoring/reviewing and statistical analysis. U.S.-E. is a consultant to Alcon, Allergan, Bayer HealthCare, and Novartis, and an advisory board member for Alcon and Novartis. She has received travel support from Bayer HealthCare and lecture fees from Bayer HealthCare and Novartis" **Study period**: July 2007 to September 2010 **Subgroup analyses**: none reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was unclear. "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system"
Allocation concealment (selection bias)	Low risk	Central randomization: "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system"
Masking of participants and personnel (performance bias)	Low risk	"Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging"
Masking of outcome assessment (detection bias)	Low risk	"A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment"

Incomplete outcome data (attrition bias)	Low risk	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 91.1% to 96.4% of participants per treatment group completed 52 weeks of follow-up
Selective reporting (reporting bias)	Low risk	The study was registered at clinicaltrials.gov; intended outcomes were reported
Other bias	High risk	Many authors are employees of, consultants to, or have received research funding from Regeneron Pharmaceuticals, which manufactures aflibercept and participated in the design of the trial, collected and analyzed data, and prepared the study reports

Bibliographic reference	**VIEW 2** Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119(12):2537-48.
Methods	**Study design:** parallel-group randomized controlled trial **Number randomly assigned**: 1240 total participants (1240 eyes) 311 in the aflibercept 0.5 mg every 4 weeks group 313 in the aflibercept 2.0 mg every 4 weeks group 313 in the aflibercept 2.0 mg every 8 weeks group 303 in the ranibizumab group **Exclusions after randomization:** Full analysis - 38 total participants: 15 in the aflibercept 0.5 mg every 4 weeks group 4 in the aflibercept 2.0 mg every 4 weeks group 7 in the aflibercept 2.0 mg every 8 weeks group 12 in the ranibizumab group Safety analysis - 36 total participants: 14 in the aflibercept 0.5 mg every 4 weeks group 4 in the aflibercept 2.0 mg every 4 weeks group 6 in the aflibercept 2.0 mg every 8 weeks group 12 in the ranibizumab group **Losses to follow-up:** 148 participants discontinued treatment at 1-year follow-up 45 in the aflibercept 0.5 mg every 4 weeks group 37 in the aflibercept 2.0 mg every 4 weeks group

	33 in the aflibercept 2.0 mg every 8 weeks group 33 in the ranibizumab group **Number analyzed:** Full analysis - 1202 total participants at 1-year follow-up 296 in the aflibercept 0.5 mg every 4 weeks group 309 in the aflibercept 2.0 mg every 4 weeks group 306 in the aflibercept 2.0 mg every 8 weeks group 291 in the ranibizumab group Safety analysis - 1204 total participants at 1-year follow-up 297 in the aflibercept 0.5 mg every 4 weeks group 309 in the aflibercept 2.0 mg every 4 weeks group 307 in the aflibercept 2.0 mg every 8 weeks group 291 in the ranibizumab group **Unit of analysis:** individual (1 study eye per participant) **How were missing data handled**? missing values imputed using last observation carried forward approach **Power calculation**: none reported
Participants	**Country:** Argentina; Australia; Austria; Brazil; Belgium; Colombia; Czech Republic; France; Germany; Hungary; India; Israel; Italy; Japan; Latvia; Mexico; Netherlands; Poland; Portugal; South Korea; Singapore; Slovakia; Spain; Sweden; Switzerland; United Kingdom (172 study sites) **Mean age** (range not reported): 75 years in the aflibercept 0.5 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 8 weeks group, and 73 years in the ranibizumab group **Gender:** 149 men (50.3%) and 147 women (49.7%) in the aflibercept 0.5 mg every 4 weeks group, 133 men (43.0%) and 176 women (57.0%) in the aflibercept 2.0 mg every 4 weeks group, 131 men (42.8%) and 175 women (57.2%) in the aflibercept 2.0 mg every 8 weeks group, and 122 men (41.9%) and 169 women (58.1%) in the ranibizumab group **Inclusion criteria:** 50 years or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or fewer) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent **Exclusion criteria**: prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis, scleromalacia; presence of other ocular conditions such as

<table>
<tr><td></td><td>uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye
Equivalence of baseline characteristics: yes; "Baseline demographics and disease characteristics were evenly balanced among all treatment groups"</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal aflibercept 0.5 mg every 4 weeks
Intervention 2: intravitreal aflibercept 2.0 mg every 4 weeks
Intervention 3: intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial doses at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8)
Intervention 4: intravitreal ranibizumab 0.5 mg every 4 weeks
<table>
<tr><td></td><td>Intervention1</td><td>Intervention2</td><td>Intervention3</td><td>Intervention4</td></tr>
<tr><td>Agent</td><td>aflibercept</td><td>aflibercept</td><td>aflibercept</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 4 weeks</td><td>Every 8 weeks after 3 initial doses, sham injections were given at the interim 4-weeks visits after week8</td><td>Every 4 weeks</td></tr>
</table>
Length of follow-up: 1 year for primary end point; dosing for all groups changed to as needed (PRN) after 1 year and follow-up at 2 years from baseline</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined in study reports: "proportion of patients maintaining vision at week 52 (losing < 15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart)"
Secondary outcomes, as defined in study reports: change in BCVA and anatomic measures, proportion gaining ≥ 15 letters, change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid as assessed by OCT, mean number of intravitreal injections, adverse events
Intervals at which outcomes assessed: every 4 weeks through 96 weeks; week 1 after first treatment for safety assessment; weeks 12, 24, 36, and 52 for the NEI-VFQ-25 assessment</td></tr>
</table>

Results

Visual acuity (52 weeks)

	Aflibercept 0.5mg monthly (n=296)	Aflibercept 2.0mg monthly (n=309)	Aflibercept 2.0mg bi-monthly (n=306)	Ranibizumab 0.5mg monthly (n=291)
Loss of <15 letters, n(%)	282 (95.3)	292 (94.5)	292 (94.5)	276 (94.8)
Gain of ≥15 letters	103 (34.8)	91 (29.4)	96 (31.4)	99 (34.0)
Loss of ≥15 letters	14	17	14	15

Adverse event (52 weeks)

	Aflibercept 0.5mg monthly (n=297)	Aflibercept 2.0mg monthly (n=309)	Aflibercept 2.0mg bi-monthly (n=307)	Ranibizumab 0.5mg monthly (n=291)
Endophthalmitis	0	0	0	0
VA reduced	1	1	5	1
Retinal hemogghage	1	1	2	1
≥ 1 ocular SAE	5	6	9	9
Nonfatal myocardial infarction	2	2	5	2
Nonfatal stroke	1	1	2	2

Notes

Type of study reports: published journal articles; clinical trial registration
Funding sources: "Sponsored by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer HealthCare, Berlin Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript"
Disclosures of interest: "J.S.H. is a consultant to and has received research funding from Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, and Regeneron Pharmaceuticals. He has also received travel support from Regeneron Pharmaceuticals. D.M.B. is a consultant to Alimera, Allergan, Bayer, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, and Thrombogenics and has received research funding from Alcon, Alimera, Allergan, Eli

	Lilly, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, and Thrombogenics. He has also received travel support from Regeneron Pharmaceuticals and lecture fees from Genentech. V.C. is a consultant to Alimera and Bayer and has received research funding from Alcon, Allergan, Bayer, Novartis, and Pfizer. He is an advisory board member for Allergan and Novartis and has also received travel support from Bayer. J.-F.K. is a consultant to Alcon, Bayer, and Thea and an advisory board member for Allergan, Bayer, and Novartis. He has received travel support from Regeneron Pharmaceuticals. P.K.K. is a consultant to Bayer, Genentech, Novartis, and Regeneron Pharmaceuticals. He has received research funding from Regeneron Pharmaceuticals. Q.D.N. is a consultant to Bausch & Lomb and Santen and has received research funding from Genentech, Novartis, and Pfizer. B.K. has received travel support from Bayer. A.H. is a consultant to Alcon, Allergan, Centocor, Johnson & Johnson, Neovista, Merck, Ophthotech, Oraya, Paloma, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Thrombogenics. He has received research funding and lecture fees from Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Second Sight. Y.O. is a consultant to Alcon and Bayer and has received travel support from Bayer. G.D.Y., N.S., R.V., A.J.B., and Y.S. are employees of Regeneron Pharmaceuticals. M.A., G.G., B.S., and R.S. are employees of Bayer HealthCare. C.S.'s institution has received payments from the Medical University of Vienna for data monitoring/reviewing and statistical analysis. U.S.-E. is a consultant to Alcon, Allergan, Bayer HealthCare, and Novartis, and an advisory board member for Alcon and Novartis. She has received travel support from Bayer HealthCare and lecture fees from Bayer HealthCare and Novartis" **Study period**: March 2008 to September 2010 **Subgroup analyses**: yes; Japanese subgroup

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was unclear. "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system"
Allocation concealment (selection bias)	Low risk	Central randomization: "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system"
Masking of participants and personnel (performance bias)	Low risk	"Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging"

Masking of outcome assessment (detection bias)	Low risk	"A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment"
Incomplete outcome data (attrition bias)	Low risk	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 88.1% to 91.1% of participants per treatment group completed 52 weeks of follow-up
Selective reporting (reporting bias)	Low risk	Study was registered at clinicaltrials.gov; intended outcomes were reported
Other bias	High risk	Many authors are employees of, consultants to, or have received research funding from Regeneron Pharmaceuticals, which manufactures aflibercept and participated in the design of the trial, collected and analyzed data, and prepared the study reports

The Yuzawa study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	**Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015**
Country/ies	VIEW1 (154 sites in the USA and Canada); VIEW 2 (172 sites in Europe, the Middle East, Asia-Pacific region and Latin America)
Study type	RCT
Aim of the study	To evaluate the effect of intravitreal aflibercept injection on visual function in wet age-related macular degeneration (AMD)
Study dates	Published 2015
Sources of funding	Medical writing support was funded by Bayer Parma AG
Sample size	2419
Inclusion Criteria	50 years of age or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or smaller) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent
Exclusion Criteria	Prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis,

Bibliographic reference	**Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015**
	scleromalacia; presence of other ocular conditions such as uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye
Baseline characteristics	

	VIEW 1		VIEW2	
	Aflibercept (2mg, q8)	Ranibizumab (0.5mg,q4)	Aflibercept (2mg, q8)	Ranibizumab (2mg, q4)
No.	301	304	306	291
Mean age (SD)	77.9 (8.4)	78.2 (7.6)	73.8 (8.6)	73.0 (9.0)
Male: n (%)	123 (40.9)	132 (43.4)	131 (42.8)	12 (41.9)
Race, White: n(%)	287 (95.3)	296 (97.4)	217 (70.9)	213 (73.2)
Mean BCVA in study eye (SD)	55.7 (12.8)	54.0 (13.4)	51.6 (13.9)	53.8 (13.5)
NEI-VFQ25 score				
No. reported	293	303	306	291
Composite score	69.6 (16.8)	71.8 (17.2)	71.3 (19.1)	72.9 (19.1)
Subscale score				
General vision	59.4 (17.2)	60.0 (17.4)	56.1 (16.5)	57.0 (17.0)
Near activies	61.2 (21.4)	62.8 (22.6)	60.9 (26.4)	63.7 (25.5)
Distance activies	65.3 (22.3)	69.1 (22.7)	70.6 (25.7)	70.8 (27.1)
Metal health	57.5 (25.6)	62.0 (25.4)	60.5 (27.6)	62.6 (26.5)
Social functioning	82.6 (21.8)	85.0 (19.5)	83.1 (22.8)	85.4 (22.1)
Dependency	73.3 (24.9)	75.3 (27.0)	76.7 (28.8)	80.0 (28.8)
Role difficulities	64.8 (25.0)	66.3 (27.8)	60.3 (31.5)	64.1 (31.2)
Driving	55.8 (30.3)	58.0 (30.5)	55.4 (36.3)	57.7 (35.3)
Colour vision	85.1 (22.2)	88.7 (19.0)	89.7 (20.2)	90.1 (19.8)
Peripheral vision	76.1 (23.5)	77.3 (23.3)	79.1 (25.8)	81.0 (24.2)
Ocular pain	82.4 (18.1)	84.5 (18.2)	84.0 (20.0)	82.4 (21.0)

Bibliographic reference	**Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015**
	General health | 65.2 (22.5) | 64.2 (21.6) | 49.5 (21.2) | 50.2 (21.1)
Study visits and procedures	Patients were randomized in a 1:1:1:1ratio to1of3 intravitreal aflibercept dosing regimens(0.5q4 or 2.0mgevery4weeks;2.0mg every 8weeks[2q8]) or t oranibizumab 0.5q4; All treatment groups received injections of the assigned drug at weeks 0,4,and 8(sham injections were given to the intravitreal aflibercept 2q8 group at each interim visit after the initial 3 injections to maintain masking). The study eye in those with bilateral wet AMD was the worse-seeing eye. If VA was similar in both eyes, additional criteria were specified to determine the study eye.The fellow eye could be treated outside of the study according to the prevailing standard of care.
Intervention	Intravitreal aflibercept 2.0mg every 4 weeks, 2.0mg every 8 weeks, or 0.5mg every 4 weeks.
Comparator	Intravitreal ranibizumab 0.5mg every 4 weeks.
Outcomes	The NEIVFQ-25 assessments were conducted by trained interviewers who were masked to treatment arm assignment.The NEI VFQ-25 was administered at the following time points: screening (visit1) and weeks 12, 24, 36 and 52. InVIEW1, the instrument was administered by telephone; inVIEW2, it was administered face to face.The NEIVFQ-25 scores were calculated according to standard scoring protocols published by the instrument's developers.28 In both studies, mean change from baseline to week52 in composite score was a secondary efficacy outcome and mean change from baseline to week 52 in subscale scores was an exploratoryefficacy outcome measure.
Analyses	All planned analyses were performed in the full analysis set population (subjects who received any study medication and had at least 1 post baseline assessment) separately for each study (protocol specified). One additional analysis was performed in the pooled data set that compared mean change from baseline with week 52 in composite and subscale scores, in subgroups of patients, based on the status of the heterolateral eye. Missing data were imputed using last observation carried forward; descriptive statistics reported here are mean and standard deviation. Sensitivity analyse susing observed cases were performed to assess the robustness of the analysis.
Length of follow up	52 weeks
Result	**Mean change NEI-VFQ from baseline to week 52** **Mean change in NEI-VFQ25 composite socre by clinical reponse** **VIEW 1** Mean change in composite score, no. | | | | Aflibercept, | Raibizumab | Effect, RR (95%CI)

Bibliographic reference	Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015

	2.0mg, q8 (no. of people) (total=293)	0.5mg, q4 (no. of people) (total=304)	
Loss of >5 EDTRS letters	-2.3 (34 people)	-2.5 (32 people)	1.10 (0.70, 1.73)
Change of ≥5 and ≤ 5 EDTRS letters	1.5 (73 people)	3.8 (63 people)	2.10 (0.89, 1.61)
Gain of >5 EDTRS letters	7.2 (192 people)	8.5 (192 people)	1.03 (0.92, 1.17)

VIEW 2

	Mean change in composite score, no.		
	Aflibercept, 2.0mg, q8 (no. of people) (total=306)	Raibizumab 0.5mg, q4 (no. of people) (total=291)	Effect, RR (95%CI)
Loss of >5 EDTRS letters	-1.9 (38 people)	-0.1 (40 people)	0.90 (0.60, 1.37)
Change of ≥5 and ≤ 5 EDTRS letters	4.8 (72 people)	2.0 (70 people)	0.98 (0.73, 1.30)
Gain of >5 EDTRS letters	7.1 (182 people)	7.0 (190people)	0.90 (0.80, 1.03)

Mean change in NEI-VFQ25 subscale score

VIEW1

	Aflibercept (2.0mg, q8)	Ranibizumab (0.5mg, q4)	Effect, MD (95%CI)
No. (at basline)	293	303	

Bibliographic reference	Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015

General vision	10.1 (19.0)	9.5 (18.8)	0.60 (-2.44, 3.64)
Near activies	6.1 (19.0)	7.2 (23.1)	-1.10 (-4.74, 2.54)
Distance activies	6.2 (21.8)	2.5 (23.1)	3.70 (0.10, 7.30)
Metal health	10.1 (24.1)	9.8 (21.8)	0.30 (-3.39, 3.99)
Social functioning	2.6 (22.1)	3.0 (20.0)	-0.40 (-3.85, 3.05)
Dependency	3.4 (22.9)	5.4 (22.6)	-2.00 (-5.65, 1.65)
Role difficulities	7.1 (26.7)	5.8 (29.3)	1.30 (-3.20, 5.80)
Driving	2.2 (24.4)	0.1 (22.0)	2.10 (-1.63, 5.83)
Colour vision	0.6 (22.3)	1.9 (19.1)	-1.30 (-4.64, 2.04)
Peripheral vision	4.4 (23.9)	5.5 (25.3)	-1.10 (-5.05, 2.85)
Ocular pain	1.2 (20.0)	1.3 (17.7)	-0.10 (-3.14, 2.94)
General health	-4.9 (22.1)	-3.6 (20.4)	-1.30 (-4.72, 2.12)

VIEW 2

	Aflibercept (2.0mg, q8)	Ranibizumab (0.5mg, q4)	Effect (95%CI)
No. (at basline)	306	291	
General vision	9.1 (17.0)	9.5 (18.1)	-0.40 (-3.22, 2.42)
Near activies	7.0 (21.3)	7.2 (21.1)	-0.20 (-3.60, 3.20)
Distance activies	4.3 (21.8)	7.6 (21.6)	-3.30 (-6.78, 0.18)
Metal health	10.4 (22.0)	11.2 (23.9)	-0.80 (-4.49, 2.89)
Social functioning	1.5(19.9)	4.9 (20.0)	-3.40 (-6.60, -0.20)
Dependency	4.1 (25.2)	4.5 (25.5)	-0.40 (-4.47, 3.67)
Role difficulities	7.8 (24.1)	6.9 (29.9)	0.90 (-3.47, 5.27)
Driving	1.0 (24.0)	0.1 (23.2)	0.90 (-2.89,4.69)
Colour vision	0.4 (21.2)	3.1(18.2)	-2.70 (-5.86, 0.46)
Peripheral vision	2.5 (25.7)	3.1 (26.2)	-0.60 (-4.77, 3.57)

Bibliographic reference	Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015
	<table><tr><td>Ocular pain</td><td>3.1 (19.4)</td><td>5.1 (22.7)</td><td>-2.00 (-5.40,1.40)</td></tr><tr><td>General health</td><td>1.5 (19.0)</td><td>0.8 (20.6)</td><td>0.70 (-2.48, 3.88)</td></tr></table>
Missing data handling/loss to follow up	Missing data were imputed using last observation carried forward; descriptive statistics reported here are mean and standard deviation. Sensitivity analyse susing observed cases were performed to assess the robustness of the analysis.
Was allocation adequately concealed?	Central randomization: “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Was knowledge of the allocated intervention adequately prevented during the study?	“Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging”
Was the allocation sequence adequately generated?	The method of random sequence generation was unclear. “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes
Were incomplete outcome data adequately addressed?	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 88.1% to 91.1% of participants per treatment group completed 52 weeks of follow-up
Are reports of the study free of suggestion of selective outcome reporting?	Study was registered at clinicaltrials.gov; intended outcomes were reported

Effectiveness of treatment frequency of antiangiogenic therapies

Regular frequencies (routine injections)

Bibliographic reference	Lushchyk 2013 Lushchyk T, Amarakoon S, Martinez-Ciriano JP, Born LI, Baarsma GS, Missotten T. Bevacizumab in age-related macular degeneration: A randomized controlled trial on the effect of injections every 4 weeks, 6 weeks and 8 weeks. Acta Ophthalmologica 2013;91(6):e456-61.

Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** 191 total participants; 64 in the every 8 weeks group; 63 in the every 6 weeks group; 64 in the every 4 weeks group **Exclusions after randomization**: 2 participants due to lack of evidence of choroidal neovascularization **Number analyzed (total and per group):** 54 in the every 8 weeks group; 57 in the every 6 weeks group; 46 in the every 4 weeks group for efficacy analysis **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**: 18 (28.1%) in the IVB every 4 weeks group; 6 (9.5%) in the IVB every 6 weeks group; 10 (15.6%) in the IVB every 8 weeks group **Intention to treat analysis:** no, participants with missing data excluded from analyses **Power calculation**: Yes; 80% **Study design comment**: single center trial
Participants	**Country**: Netherlands **Mean age:** 77 years **Gender (percent):** male 18(28.1%) and female 46(71.9%) in the IVB every 4 weeks group; male 25(39.7%) and female 38(60.3%) in the IVB every 6 weeks group; male 21(32.8%) and female 43(67.2%) in the IVB every 8 weeks group **Inclusion criteria**: 65 years of age or older; visual acuity of 20/200 to 20 /20 (Snellen equivalent) assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts; previously untreated active choroidal neovascularization due to ARMD; presence of active leakage to establish active choroidal neovascularization defined as a leakage observed using fluorescein angiography (FA) and indocyanine green (ICG) angiography, and the presence of fluid, observed using spectral-domain optical coherence tomography (OCT), located either below the retina or below the retinal pigment epithelium **Exclusion criteria:** other significant ocular disorders affecting visual; allergy to either FA or ICG dye injections was known; patients with immunocompromised or patients with an ocular surgery planned during the 1-year follow-up period; patients who used coumarin derivatives at the time of inclusion and patients who experienced clinically significant cerebrovascular accident or myocardial infarction in the 6 months prior to planned inclusion **Equivalence of baseline characteristics**: Yes

Interventions

Intervention 1: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05-ml solution) every 4 weeks
Intervention 2: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05-ml solution) every 6 weeks
Intervention 3: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05-ml solution) every 8 weeks

	Intervention 1	**Intervention 2**	**Intervention3**
Agent	Bevacizumab	Bevacizumab	Bevacizumab
Dose	1.25mg	1.25mg	1.25mg
Frequency	Every 4 weeks	Every 6 weeks	Every 8 weeks

Follow-up: 1 year
Frequency of assessments for retreatment: every 12 weeks in addition to regular injection visits

Outcomes

Primary outcome, as defined: best-corrected visual acuity (BCVA)
Secondary outcomes, as defined: fluid and foveal thickness on spectral-domain OCT
Adverse events: Yes
Intervals at which outcome assessed: every 12 weeks

Results

Visual acuity (12 months)

	Bevacizumab (n=46)	Bevacizumab (n=57)	Bevacizumab (n=54)
Dose	1.25mg	1.25mg	1.25mg
Frequency	Every 4 weeks	Every 6 weeks	Every 8 weeks
Gain of ≥15 letters, n (%)	6 (13.0)	8 (14.1)	7 (13.0)
Loss of ≥15 letters	3 (6.5)	6 (10.5)	0 (0)
Gain or loss of less than 15 letters	37	43	47

Adverse event

	Bevacizumab (n=64)	Bevacizumab (n=63)	Bevacizumab (n=64)
Dose	1.25mg	1.25mg	1.25mg
Frequency	Every 4 weeks	Every 6 weeks	Every 8 weeks
Total SAEs, no	9	4	9
Atherothrombotic event	2	1	1
Endophthalmitis	1	0	0

	Death from vascular cause	2	1	0

Notes	**Full study name**: not reported **Trial registration**: NTR117 **Funding sources:** not reported **Declarations of interest**: not reported **Study period:** June 2008 to March 2011 **Subgroup analyses:** none reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Masking of participants and personnel (performance bias)	High risk	This study was “open-label” study.
Masking of outcome assessment (detection bias)	High risk	This study was “open-label” study.
Incomplete outcome data (attrition bias)	High risk	Although this paper claimed that intention-to-treat analysis was followed, 34 (17.8%) participants [18 (28.1%) in the IVB every 4 weeks group; 6 (9.5%) in the IVB every 6 weeks group; 10 (15.6%) in the IVB every 8 weeks group] were not included in the final efficacy analysis.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the final report.
Other bias	Unclear risk	Funding sources and declarations of interest were not reported.

Bibliographic reference	**NATTB 2013**

<table>
<tr><td></td><td>Li X, Hu Y, Sun X, Zhang J, Zhang M, Neovascular Age-Related Macular Degeneration Treatment Trial Using Bevacizumab (NATTB). Bevacizumab for neovascular age-related macular degeneration in China. Ophthalmology 2012;119(10):2087-93.</td></tr>
<tr><td>Methods</td><td>Study design: cluster randomized controlled trial
Number randomized (total and per group): 13 centers, 185 participants in total; 91 in the intervention 1; 94 in the intervention 2
Exclusions after randomization: none reported
Number analyzed (total and per group): 79 eyes (86.8%) in the intervention 1; 82 eyes (87.2%) in the intervention 2
Unit of analysis: individual (one study eye per participant)
Losses to follow up: not reported
Intention to treat analysis: no
Power calculation: none reported
Study design comment: none reported</td></tr>
<tr><td>Participants</td><td>Country: China
Age(mean ± SD): median 67 years in the intervention 1; median 70 years in the intervention 2
Gender (percent): male 60(65.9%) and female 31(34.4%) in the intervention 1; male 62(66.0%) and female 32(34.0%) in the intervention 2
Inclusion criteria: age of 50 years or more; previously untreated active choroidal neovascularization (determined by the presence of leakage, as seen on fluorescein angiography, and by the presence of fluid, as seen on OCT, located either within or under the neurosensory retina or under the retinal pigment epithelium) resulting from AMD; a lesion area of 12 disc areas or less, and best-corrected visual acuity between 5 and 73 letters using the Early Treatment Diabetic Retinopathy Study charts
Exclusion criteria: presence of a macular scar, choroidal neovascularization not resulting from AMD, and polypoidal choroidal vasculopathy
Equivalence of baseline characteristics: Yes</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05ml solution) every 6 weeks for 8 injections
Intervention 2: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05ml solution) every 6 weeks for the first 3 injections, followed by injections every 12 weeks for the last 2 injections
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td></tr>
</table>
</td></tr>
</table>

Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections	

Follow-up: 48 weeks
Frequency of assessments for retreatment: not reported

Outcomes

Primary outcome, as defined: mean change in visual acuity
Secondary outcomes, as defined: proportion of patients with a change in visual acuity of 15 letters or more; the number of injections; the change in central retinal thickness on OCT,; the incidence of ocular and systemic adverse events; and annual drug cost
Adverse events: Yes
Intervals at which outcome assessed: every 6 weeks

Results

Visual acuity (12 months)

	Bevacizumab (n=79)	Bevacizumab (n=82)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections	
Gain of ≥15 letters, no.	35	33	1.10 (0.77, 1.58)
Loss of ≥15 letters	3	5	0.62 (0.15, 2.52)
Gain or loss between 14 letters	41	44	0.97 (0.72, 1.30)

Adverse event after enrolment (12 months)

	Bevacizumab (n=91)	Bevacizumab (n=94)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections	

Sterile inflammation, n(%)	17 (18.7)	9 (9.6)	1.95 (0.92, 4.15)
Headache	4 (4.4)	1 (1.1)	4.13 (0.47, 36.27)

Number of injections (48 weeks)

Agent	Bevacizumab (n=79)	Bevacizumab (n=82)
Dose	1.25mg	1.25mg
Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections
Mean number of injections (SD not reported)	7.86	4.89

Notes	**Full study name**: Bevacizumab for Neovascular Age-related Macular Degeneration in China **Trial registration:** NCT01306591 **Funding sources:** "Supported by the National Key Technology Research and Development Program in the 11th Five-Year Plan of China (no. 2006BAI02B05)." **Declarations of interest**: "The author(s) have no proprietary or commercial interest in any materials discussed in this article" **Study period:** January 2008 to January 2010 **Subgroup analyses**: none reported	
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants (performance bias)	High risk	This study was "open-label" study
Masking of outcome assessment (detection bias)	Low risk	"Visual acuity examiners and imaging technicians were unaware of study group assignment"

		"A medical monitor who was unaware of study group assignments reviewed all adverse event data."; masking of other outcome assessors was not reported
Incomplete outcome data (attrition bias)	High risk	24(13.0%) participants[12(13.2%) in the IVB every 6 weeks group; 12(12.8%) in the IVB every 6 weeks followed by every 12 weeks group] were not included in the final efficacy analysis
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the final report
Other bias	Low risk	none

Bibliographic reference	Schmidt-Erfurth Ursula, Eldem B, Guymer R, Korobelnik J F, Schlingermann R, Axer-Siegel R, Wiedemann P, Simader C, Gekkieva M, Weichsellberge A. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration. The American Academy of Ophthalmology 2010. (EXCITE)
Methods	**Study design**: randomised, double-masked, active-controlled multicentre study **Number randomized (total and per group):** 353 patients randomised for treatment including 120 patients in 0.3mg quarterly treatment arm; 118 patients in 0.5mg quarterly treatment arm; and 115 patients in 0.3mg monthly treatment arm. **Exclusions after randomization**: none **Number analyzed (total and per group):** 120 patients in 0.3mg quarterly treatment arm; 118 patients in 0.5mg quarterly treatment arm; and 115 patients in 0.3mg monthly treatment arm for efficacy analysis **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**: 14 (11.7%) in 0.3mg quarterly treatment arm; 23(19.5%) in 0.5mg quarterly treatment arm; 12 (10.4%) in 0.3mg monthly treatment arm **Intention to treat analysis:** Yes **Power calculation**: Yes; 87% **Study design comment**: multi-center trial
Participants	**Country**: 16 European countries. **Mean age:** 75.3 (SD=7.56) years **Gender (percent):** male 50(41.7%) and female 70(58.3%) in the 0.3mg quarterly treatment arm; male 45(38.1%) and female 73(61.9%) in 0.5mg quarterly treatment arm; male 49(42.6%) and female 66(57.4%) in the 0.3mg monthly treatment arm

<table>
<tr><td></td><td>Inclusion criteria: ≥50 years of age or older; primary or recurrent subfoveal CNV secondary to AMD, with predominantly, classic, minimally classic, or occult (with no classic component) lesions. BCVA score between 73 and 24 letters (appropriately 20/40 to 20/320 Snellen equivalent).
Exclusion criteria: BCVA score of <34 letters in both eyes; previous treatment or participation in a clinical trial (for either eye) with antiangiogenic drugs; use of any other investigational drugs at the time of screening, or within 30 days or 5 half-lives of screening; prior treatment in the study eye with
verteporfin, external-beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy, or transpupillary thermotherapy; operative intervention for AMD in the past in the study eye; laser
photocoagulation in the study eye within 1 month preceding baseline; angioid streaks or precursors of CNV in either eye due to other causes; clinically significant subretinal haemorrhage in the study eye that involved the foveal center; or any other significant clinical condition detrimental to the study outcome.
Equivalence of baseline characteristics: Yes</td></tr>
<tr><td>Interventions</td><td>Eligible patients were randomly assigned in a 1:1:1 ratio to any of the following 3 double-masked treatment arms : loading doses of 3 initial monthly intravitreal injections of 0.3 mg (intervention 1)or 0.5 mg (intervention 2) ranibizumab followed by quarterly injections of the respective doses at months 5, 8, and 11 (i.e., a total of 6 injections) or 0.3 mg ranibizumab administered monthly from baseline to month 11 (arm C, active control) (i.e., a total of 12 injections).
Intervention 1: intravitreal ranibizumab (0.3 mg) quarterly
Intervention 2: intravitreal ranibizumab (0.5 mg) quarterly
Intervention 3: intravitreal ranibizumab (0.3 mg) monthly
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention3</th></tr>
<tr><td>Agent</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>0.3mg</td><td>0.5mg</td><td>0.3mg</td></tr>
<tr><td>Frequency</td><td>quarterly</td><td>quarterly</td><td>monthly</td></tr>
</table>
Follow-up: 1 year
Frequency of assessments for retreatment: monthly</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: best-corrected visual acuity (BCVA)
Secondary outcomes, as defined: fluid and foveal thickness on spectral-domain OCT
Adverse events: Yes
Intervals at which outcome assessed: Monthly</td></tr>
</table>

Results

Visual acuity (12 months) (intent to treat)

	Ranibizumab (n=120)	Ranibizumab (n=118)	Ranbiziumab (n=115)
Dose	0.3mg	0.5mg	0.3mg
Frequency	quarterly	quarterly	monthly
Gain of ≥15 letters, n (%)	17 (14.2)	21 (17.8)	33 (28.7)
Lost <15 letters, n(%)	112(93.3)	108(91.5)	109(94.8)
Mean change, letter (SD)	4.0 (14.88)	2.8 (13.78)	8.0 (11.27)

Adverse event

	Ranibizumab (n=120)	Ranibizumab (n=118)	Ranbiziumab (n=115)
Dose	0.3mg	0.5mg	0.3mg
Frequency	quarterly	quarterly	monthly
Eye pain	22(18.3)	14(11.9)	24(20.9)
Conjunctival haemorrhage	23(19.2)	19(16.1)	12(10.4)
Reduced VA	16(13.3)	19(16.1)	9(7.8)
Increased intraocular pressure >10 mmHg	6(5.0)	7(5.9)	17(14.8)
Non-ocular, nasopharyngitis	11(9.2)	4(3.4)	8(7.0)
Non-ocular, hypertension	10(8.3)	6(5.1)	8(7.0)

Notes

Full study name: not reported
Trial registration: NCT00275821
Funding sources: Novertis Pharma, AG, Switzerland
Declarations of interest: not reported
Study period: Jan 2006 to Feb 2011
Subgroup analyses: none reported

Comments

Missing data handling/loss to follow up: 304 patients completed the study including 106 (88.3%) in the ranibizumab 0.3mg quarterly, 95(80.5%) in ranibizumab 0.5mg quarternly, and 103 (89.6%) in the ranibizumab 0.3mg monthly. ITT analysis was reported.

	Was allocation adequately concealed? unclear
	Was knowledge of the allocated intervention adequately prevented during the study? unclear
	Was the allocation sequence adequately generated? unclear
	Was the study apparently free of other problems that could put it at a high risk of bias? None observed
	Were incomplete outcome data adequately addressed? The primary end point was analysed for both per protocol and intent-to-treat (ITT) population. The PP population was a subset of the ITT population and included patients who had an assessment for BCVA at month 12 and with no major study protocol deviation. The ITT population comprised all randomised patients.
	Are reports of the study free of suggestion of selective outcome reporting? Results were reported for primary and secondary outcomes specified in the Methods section

Bibliographic reference	**VIEW 2** Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119(12):2537-48.
Methods	**Study design:** parallel-group randomized controlled trial **Number randomly assigned**: 2457 total participants (2457 eyes) · 615 in the aflibercept 0.5 mg every 4 weeks group · 617 in the aflibercept 2.0 mg every 4 weeks group · 616 in the aflibercept 2.0 mg every 8 weeks group · 609 in the ranibizumab group **Exclusions after randomization:** Full analysis - 45 total participants: · 18 in the aflibercept 0.5 mg every 4 weeks group · 4 in the aflibercept 2.0 mg every 4 weeks group · 9 in the aflibercept 2.0 mg every 8 weeks group · 14 in the ranibizumab group **Safety analysis - 38 total participants:** · 14 in the aflibercept 0.5 mg every 4 weeks group · 4 in the aflibercept 2.0 mg every 4 weeks group

	· 6 in the aflibercept 2.0 mg every 8 weeks group · 14 in the ranibizumab group **Losses to follow-up:** 251 participants discontinued treatment at 1-year follow-up · 75 in the aflibercept 0.5 mg every 4 weeks group · 53 in the aflibercept 2.0 mg every 4 weeks group · 63 in the aflibercept 2.0 mg every 8 weeks group · 60 in the ranibizumab group **Number analyzed:** Full analysis - 2412 total participants at 1-year follow-up · 597 in the aflibercept 0.5 mg every 4 weeks group · 613 in the aflibercept 2.0 mg every 4 weeks group · 607 in the aflibercept 2.0 mg every 8 weeks group · 595 in the ranibizumab group Safety analysis - 2419 total participants at 1-year follow-up · 601 in the aflibercept 0.5 mg every 4 weeks group · 613 in the aflibercept 2.0 mg every 4 weeks group · 610 in the aflibercept 2.0 mg every 8 weeks group · 595 in the ranibizumab group **Unit of analysis:** individual (1 study eye per participant) **How were missing data handled**? missing values imputed using last observation carried forward approach **Power calculation**: none reported
Participants	**Country:** Argentina; Australia; Austria; Brazil; Belgium; Colombia; Czech Republic; France; Germany; Hungary; India; Israel; Italy; Japan; Latvia; Mexico; Netherlands; Poland; Portugal; South Korea; Singapore; Slovakia; Spain; Sweden; Switzerland; United Kingdom (172 study sites) **Mean age** (range not reported): 78 years in the aflibercept 0.5 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 8 weeks group, and 78 years in the ranibizumab group and 75 years in the aflibercept 0.5 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 8 weeks group, and 73 years in the ranibizumab group **Gender:** 134 men (44.5%) and 167 women (55.5%) in the aflibercept 0.5 mg every 4 weeks group, 110 men (36.2%) and 194 women (63.8%) in the aflibercept 2.0 mg every 4 weeks group, 123 men (40.9%) and 178 women (59.1%) in the aflibercept 2.0 mg every 8 weeks group, and 132 men (43.4%) and 172 women (56.6%) in the ranibizumab group and 149 men (50.3%) and 147 women (49.7%) in the aflibercept 0.5 mg every 4 weeks group, 133 men (43.0%) and 176

<table>
<tr><td></td><td>women (57.0%) in the aflibercept 2.0 mg every 4 weeks group, 131 men (42.8%) and 175 women (57.2%) in the aflibercept 2.0 mg every 8 weeks group, and 122 men (41.9%) and 169 women (58.1%) in the ranibizumab group
Inclusion criteria: 50 years of age or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or smaller) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent
Exclusion criteria: prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis, scleromalacia; presence of other ocular conditions such as uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye
Equivalence of baseline characteristics: yes; "Baseline demographics and disease characteristics were evenly balanced among all treatment groups"</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal aflibercept 0.5 mg every 4 weeks
Intervention 2: intravitreal aflibercept 2.0 mg every 4 weeks
Intervention 3: intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial doses at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8)
Intervention 4: intravitreal ranibizumab 0.5 mg every 4 weeks
<table>
<tr><td></td><td>Intervention1</td><td>Intervention2</td><td>Intervention3</td><td>Intervention4</td></tr>
<tr><td>Agent</td><td>aflibercept</td><td>aflibercept</td><td>aflibercept</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 4 weeks</td><td>Every 8 weeks after 3 initial doses, sham injections were given at the interim 4-weeks visits after week8</td><td>Every 4 weeks</td></tr>
</table></td></tr>
</table>

	Length of follow-up: 1 year for primary end point; dosing for all groups changed to as needed (PRN) after 1 year and follow-up at 2 years from baseline
Outcomes	**Primary outcome,** as defined in study reports: "proportion of patients maintaining vision at week 52 (losing < 15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart)" **Secondary outcomes,** as defined in study reports: change in BCVA and anatomic measures, proportion gaining ≥ 15 letters, change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid as assessed by OCT, mean number of intravitreal injections, adverse events **Intervals at which outcomes assessed**: every 4 weeks through 96 weeks; week 1 after first treatment for safety assessment; weeks 12, 24, 36, and 52 for the NEI-VFQ-25 assessment
Notes	**Type of study reports:** published journal articles; clinical trial registration **Funding sources**: "Sponsored by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer HealthCare, Berlin Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript" **Disclosures of interest**: "J.S.H. is a consultant to and has received research funding from Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, and Regeneron Pharmaceuticals. He has also received travel support from Regeneron Pharmaceuticals. D.M.B. is a consultant to Alimera, Allergan, Bayer, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, and Thrombogenics and has received research funding from Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, and Thrombogenics. He has also received travel support from Regeneron Pharmaceuticals and lecture fees from Genentech. V.C. is a consultant to Alimera and Bayer and has received research funding from Alcon, Allergan, Bayer, Novartis, and Pfizer. He is an advisory board member for Allergan and Novartis and has also received travel support from Bayer. J.-F.K. is a consultant to Alcon, Bayer, and Thea and an advisory board member for Allergan, Bayer, and Novartis. He has received travel support from Regeneron Pharmaceuticals. P.K.K. is a consultant to Bayer, Genentech, Novartis, and Regeneron Pharmaceuticals. He has received research funding from Regeneron Pharmaceuticals. Q.D.N. is a consultant to Bausch & Lomb and Santen and has received research funding from Genentech, Novartis, and Pfizer. B.K. has received travel support from Bayer. A.H. is a consultant to Alcon, Allergan, Centocor, Johnson & Johnson, Neovista, Merck, Ophthotech, Oraya, Paloma, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Thrombogenics. He has received research funding and lecture fees from Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Second Sight. Y.O. is a consultant to Alcon and Bayer and has received travel support from Bayer. G.D.Y., N.S., R.V., A.J.B., and Y.S. are employees of Regeneron Pharmaceuticals. M.A., G.G., B.S., and R.S. are employees of Bayer HealthCare. C.S.'s institution has received payments from the Medical University of Vienna for data monitoring/reviewing and statistical analysis. U.S.-E. is a consultant to Alcon, Allergan, Bayer HealthCare, and Novartis, and an advisory board member for

	Alcon and Novartis. She has received travel support from Bayer HealthCare and lecture fees from Bayer HealthCare and Novartis" **Study period**: March 2008 to September 2010 **Subgroup analyses**: yes; Japanese subgroup

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was unclear. “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Allocation concealment (selection bias)	Low risk	Central randomization: “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Masking of participants and personnel (performance bias)	Low risk	“Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging”
Masking of outcome assessment (detection bias)	Low risk	“A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment”
Incomplete outcome data (attrition bias)	Low risk	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 88.1% to 91.1% of participants per treatment group completed 52 weeks of follow-up
Selective reporting (reporting bias)	Low risk	Study was registered at clinicaltrials.gov; intended outcomes were reported
Other bias	High risk	Many authors are employees of, consultants to, or have received research funding from Regeneron Pharmaceuticals, which manufactures aflibercept and participated in the design of the trial, collected and analyzed data, and prepared the study reports

<table>
<tr><td>Bibliographic reference</td><td>El-Mollayess 2012
El-Mollayess GM, Mahfoud Z, Schakal AR, Salti HI, Jaafar D, Bashshur ZF. Fixed-interval versus OCT-guided variable dosing of intravitreal bevacizumab in the management of neovascular age-related macular degeneration: A 12-month randomized prospective study. American Journal of Ophthalmology 2012;153(3):481-9.</td></tr>
<tr><td>Methods</td><td>Study design: parallel-group randomized controlled trial
Number randomized (total and per group): 120 total participants; 60 participants in each group
Exclusions after randomization: none reported
Number analyzed (total and per group): 120 participants; 60 participants in each group
Unit of analysis: individual (one study eye per participant)
Losses to follow up: none reported
Intention to treat analysis: all participants randomized were analysed
Power calculation: “detect a difference of at least 5 letters in mean visual acuity using the independent t test with 80% power and an alpha level of 5%, assuming a standard deviation of 10 letters, 60 eyes were needed in each group”
Study design comment: “If both eyes of the same patient were eligible, then the eye with the worse visual acuity was enrolled.”</td></tr>
<tr><td>Participants</td><td>Country: France and Lebanon
Mean age: 77 years
Gender (percent): 78 women and 42 men
Inclusion criteria: “1) age 50 years or older; 2) subfoveal choroidal neovascularization (CNV) attributable to AMD diagnosed by fluorescein angiography (FA); 3) presence of subretinal fluid, cystic maculopathy, or central retinal thickness >250 ?m on OCT; 4) best-corrected vision, using ETDRS charts, be- tween 20/40 and 20/400 (Snellen equivalent); 5) CNV less than 5400 µm in greatest linear dimension; and 6) ability to understand and sign a consent form."
Exclusion criteria: “1) presence of subfoveal scarring or hemorrhage; 2) media opacity that would prevent good- quality retinal imaging; 3) history of uveitis, vitrectomy, diabetic retinopathy, or other condition that may affect vision; and 4) thromboembolic event less than 6 months prior to enrollment.
Equivalence of baseline characteristics: baseline characteristics by group not reported</td></tr>
<tr><td>Interventions</td><td>Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: PRN (variable dosing)
Treatment schedule 2: every 4 to 6 weeks (lfixed-interval dosing)
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25</td><td>1.25</td></tr>
</table></td></tr>
</table>

Frequency	PRN (variable dosing)	Every 4 to 6 weeks (fixed interval dosing)	

Follow-up: 12 months
Frequency of assessments for retreatment: every 4 to 6 weeks

Outcomes

Primary outcome, as defined: improvement in BCVA and CRT at 12 months
Secondary outcomes, as defined: none reported
Adverse events: ocular and systemic adverse events
Review outcomes not reported: mean change in CRT, quality of life, cost
Intervals at which outcome assessed: every 4 to 6 weeks

Results

Visual acuity (12 months)

Agent	Bevacizumab (n=59)	Bevacizumab (n=60)	RR (95%CI)
Dose	1.25	1.25	
Frequency	PRN (variable dosing)	Every 4 to 6 weeks (fixed interval dosing)	
Gain of ≥15 letters, n(%)	24 (40)	21 (35)	1.16 (0.73, 1.85)
Mean BCVA letters	64.3	65.8	

Adverse event (12 months)

No severe ocular adverse events were noted in both groups over 12 months. Similarly no systemic adverse events were reported. However, 3 months after the completion of the study, 5 patients in the fixed-interval dosing group had major thromboembolic events.

Number of injections (12 months)

	Intervention 1	**Intervention 2**
Agent	Bevacizumab	Bevacizumab
Dose	1.25	1.25
Frequency	PRN (variable dosing)	Every 4 to 6 weeks (fixed interval dosing)
Mean number of injections	3.8	9.5

Notes

Full study name: not reported

	Trial registration: not reported **Funding sources**: Department of Ophthalmology and University Research Board of American University of Beirut Medical Center, Beirut, Lebanon **Declarations of interest**: "The authors indicate no financial interest in any product discussed in this study" **Study period**: May 2009 to October 2009 **Subgroup analyses**: none reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomization program (GraphPad StatMate, version 1.01i; GraphPad Software Inc, San Diego, California, USA) "
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	High risk	"visual acuity examiners were masked to treatment regimen and patients were instructed not to share this information with the examiner " "Treating physicians were not masked to the treatment regimen of patients under their care and no sham injections were employed."
Masking of outcome assessment (detection bias)	Low risk	"visual acuity examiners were masked to treatment regimen and patients were instructed not to share this information with the examiner" "The physician reviewing OCT images or other material to be recorded in the study was masked to that particular patient's identity and treatment regimen and in no way could be involved in the treatment of that patient."
Incomplete outcome data (attrition bias)	Low risk	"All patients completed the 12 months of the study and were able to make scheduled visits with no greater than a 7-day delay".
Selective reporting (reporting bias)	Unclear risk	Trial registry and citation to protocol not reported.
Other bias	Low risk	None identified

Bibliographic reference	**GMAN 2015** Mahmood S, Roberts SA, Aslam TM, Parkes J, Barugh K, Bishop PN. Routine versus as-needed bevacizumab with 12-weekly assessment intervals for neovascular age-related macular degeneration: 92-week results of the GMAN Trial. Ophthalmology 2015;122(7):1348-55.

<table>
<tr><td>Methods</td><td>Study design: parallel-group randomized controlled trial
Number randomized (total and per group): 331 total participants; 166 participants in PRN group, 50 participants in routine group
Exclusions after randomization: withdrew PRN -48, withdrew ROUTINE – 22
Number analyzed (total and per group): PRN-166, ROUTINE-165
Unit of analysis: individual (one study eye per participant)
Losses to follow up: PRN-26, ROUTINE-22
Compliance: completed trial – PRN-140, ROUTINE-143
Intention to treat analysis: PRN-166, ROUTINE-165
Power calculation: Yes, a noninferiority margin of 4 to 5 letters at 90% power for the sample size planned for the study
Study design comment: none</td></tr>
<tr><td>Participants</td><td>Country: UK
Median age: 80 years
Gender (percent): 61% women and 39% men
Inclusion criteria: age more than 50 years with a diagnosis of nAMD and a best-corrected visual acuity (BCVA) of logarithm of the minimum angle of resolution 0.3 to 1.2
Exclusion criteria: "lesion showed signs of >50% fibrosis, hemorrhage, or serous pigment epithelial detachment. Patients with a medical history of myocardial infarction, cardiovascular accident, or gastrointestinal perforation were excluded when the trial commenced. However, as more evidence emerged suggesting a low systemic risk from the intravitreal use of anti-VEGF drugs, the protocol was amended so that myocardial infarction and gastrointestinal perforation were not used as exclusion criteria, and only patients with a history of cerebrovascular accident within 6 months were excluded."
Equivalence of baseline characteristics: Yes, there were no substantial imbalances in the ocular or demographic characteristics between the 2 groups of the study</td></tr>
<tr><td>Interventions</td><td>Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: 3 monthly loading doses, then PRN (PRN treatment)
Treatment schedule 2: 3 monthly loading doses, then every 12 weeks (routine treatment)
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td></tr>
<tr><td>Frequency</td><td>3 monthly loading doses, then PRN</td><td>3 monthly loading doses, then every 12 weeks (routine treatment)</td></tr>
</table></td></tr>
</table>

Follow-up: 92 weeks
Frequency of assessments for retreatment: every 12 weeks

Outcomes

Primary outcome, as defined: mean BCVA at 92 weeks
Secondary outcomes, as defined: change in mean visual acuity from baseline to 92 weeks and the percentages of patients who had a change in visual acuity from baseline of ≥5, ≥10, or ≥15 letters, comparing contrast sensitivity, reading speed, and central macular thickness between the 2 arms at 92 weeks
Adverse events: Yes
Intervals at which outcome assessed: every 12 weeks for 92 weeks

Results

Visual acuity (92 weeks)

Agent	Bevacizumab (n=166)	Bevacizumab (n=165)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	3 monthly loading doses, then PRN	3 monthly loading doses, then every 12 weeks (routine treatment)	
Gain of ≥15 letters, n (%)	22(13)	40 (24)	0.55 (0.34, 0.88)
Loss of ≥15 letters, n (%)	27(16)	13 (8)	2.06 (1.10, 3.86)
Gain of ≥5 letters, n (%)	68(41)	86 (52)	0.79 (0.62, 0.99)
Loss of ≥5 letters, n (%)	63(38)	33(20)	1.90 (1.32, 2.73)
Mean change in BCVA, letters (SD)	52.8 (19.4)	57.2 (17.6)	

Adverse events (92 weeks)

Agent	Bevacizumab (n=166)	Bevacizumab (n=165)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	3 monthly loading doses, then PRN	3 monthly loading doses, then every 12 weeks (routine treatment)	
Uveitis	2	3	0.66 (0.11, 3.91)
Vitreous haemorrhage	1	1	0.99 (0.06, 15.76)

Cataract surgery	13	13	0.99 (0.48, 2.08)
Death any cause	12	10	1.19 (0.53, 2.68)
Gastrointestinal	8	6	1.33 (0.47, 3.74)
Infection	2	1	1.99 (0.18, 21.71)

Number of injections (92 weeks)

Agent	Bevacizumab	Bevacizumab
Dose	1.25mg	1.25mg
Frequency	3 monthly loading doses, then PRN	3 monthly loading doses, then every 12 weeks (routine treatment)
Mean number of injection	9.1	10.8

Notes

Full study name: The Greater Manchester Avastin for Neovascularisation Study
Trial registration: ISRCTN 34221234 and EudraCT number 2007-003853-97
Funding sources: "Supported by Greater Manchester Primary Care Trusts, National Health Service, England, and Manchester Biomedical Research Centre."
Declarations of interest: "The author(s) have made the following disclosure(s): S.M.: Advisory boards of and financial support _ Novartis and Bayer. T.M.A: Advisory boards of and financial support _ Novartis and Bayer."
Study period: February 2008 to May 2013
Subgroup analyses: none reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated allocation lists were drawn up by the trial statistician using block randomization with a variable block size."
Allocation concealment (selection bias)	Low risk	"Computer-generated allocation lists were drawn up by the trial statistician using block randomization with a variable block size."
Masking of participants (performance bias)	High risk	"patients, treating clinicians, and other staff involved in the study were not masked

Masking of outcome assessment (detection bias)	Low risk	"The optometrists who measured BCVA, reading speed, and contrast sensitivity were masked to the study arm;"
Incomplete outcome data (attrition bias)	Low risk	An intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	Compared with the trial registries, there does not appear to be selective outcome reporting
Other bias	Unclear risk	The study was not powered to investigate safety

Bibliographic reference	**HABOUR 2013** Busbee BG, Ho AC, Brown DM, Heier JS, Suner IJ, Li Z, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120(5):1046-56.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** Total: 1098 0.5 mg monthly: 276 0.5 mg PRN: 275 2.0 mg monthly: 274 2.0 mg PRN: 273 **Exclusions after randomization**: 1 patient was randomized before screen failure, and no baseline or post-baseline data were reported for this patient; therefore, the patient was excluded from analysis **Number analyzed (total and per group): Total: 1098** 0.5 mg monthly: 275 0.5 mg PRN: 275 2.0 mg monthly: 274 2.0 mg PRN: 273 **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: Discontinued study 0.5 mg monthly: 2 0.5 mg PRN: 2 2.0 mg monthly: 2 2.0 mg PRN: 2

	Discontinued treatment 0.5 mg monthly: 2 0.5 mg PRN: 2 2.0 mg monthly: 3 2.0 mg PRN: 3 **Compliance**: Not reported **Intention to treat analysis:** Yes **Reported power calculation:** Yes, 80% power in the intention-to-treat analysis for the 3 primary comparisons **Study design comment**: None
Participants	**Country**: 100 study centers across the United States **Age**: 0.5 mg monthly mean age=78.8±8.4 (range 53.0-97.0), 0.5 mg PRN mean age=78.5±8.3 (range 53.0-97.0), 2.0 mg monthly mean age=79.3±8.3 (range 50.0-96.0), 2.0 mg PRN mean age=78.3 (range=54.0-98.0) **Gender (percent):** 0.5 mg monthly 113(41.1%) men and 162 (58.9%) women, 0.5 mg PRN 112 (40.7%) men and 163 (59.3%) women, 2.0 mg monthly 104 (38.0%) men and 170 (62.0%) women, 2.0 mg PRN 117 (42.9%) men and 156 (57.1%) women **Inclusion criteria:** aged 50 years or older and fulfilled the following inclusion criteria for the study eye: (1) BCVA of 20/40 to 20/320 (Snellen equivalent), using ETDRS charts (at a distance of 4 meters); (2) active subfoveal lesions with classic CNV, some classic CNV component, or purely occult CNV; (3) total area of lesion 12 disc areas (DA) or 30.48 mm2; and (4) total CNV area constitutes 50% of total lesion area based on fluorescein angiography (FA). For the inclusion of purely occult or occult with some classic CNV, activity of the lesion had to be demonstrated by one of several criteria. This included a 10% increase in CNV lesion size on interval visits, a documented visual loss of 1 line of Snellen vision, or the presence of hemorrhage at presentation **Exclusion criteria**: a history of vitrectomy surgery; prior treatment with photodynamic therapy with verteporfin, external beam radiation therapy, or transpupillary thermotherapy; previous intravitreal drug delivery; previous subfoveal laser photocoagulation; uncontrolled blood pressure; atrial fibrillation not managed by the patient's primary care physician or cardiologist within 3 months of the screening visit; or a history of stroke within 3 months of the screening visit. **Equivalence of baseline characteristics:** Yes, "All variables were well balanced among the 4 treatment groups." **Diagnoses in participants:** approximately 46% of patients had minimally classic CNV lesions, 16% had predominantly classic lesions, and 38% had purely occult CNV

<table>
<tr><td>Interventions</td><td>Intervention 1: 0.5 mg ranibizumab monthly
Intervention 2: 0.5 mg ranibizumab PRN
Intervention 3: 2.0 mg ranibizumab monthly
Intervention 4: 2.0 mg ranibizumab PRN
<table><tr><th></th><th>Intervention1</th><th>Intervention 2</th><th>Intervention3</th><th>Intervention4</th></tr><tr><td>Agent</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Ranibizumab</td></tr><tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td></tr><tr><td>Frequency</td><td>Monthly</td><td>PRN</td><td>Monthly</td><td>PRN</td></tr></table>
Follow-up: 12 months
Frequency of assessments for retreatment: at month 3 visit and thereafter</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: mean change from baseline in BCVA at month 12
Secondary outcomes, as defined: mean number of ranibizumab injections up to, but not including, month 12; the mean change from baseline in central foveal thickness (CFT) based on SD-OCT over time to month 12; the proportion of patients who gained 15 letters from baseline in BCVA at month 12; and the proportion of patients with a Snellen
Adverse events (Y/N) Yes
Intervals at which outcome assessed: Safety and ocular parameters were assessed on day 7; subsequently, all patients had scheduled monthly visits for evaluation of safety and efficacy. Fluorescein angiography and fundus photography were per- formed at screening and at months 3, 6, and 12.</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)<table><tr><td></td><td>Ranibizumab (n=275)</td><td>Ranibizumab (n=275)</td><td>Ranibizumab (n=274)</td><td>Ranibizumab (n=273)</td></tr><tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td></tr><tr><td>Frequency</td><td>Monthly</td><td>PRN</td><td>Monthly</td><td>PRN</td></tr><tr><td>Gain of ≥15 letters, n(%)</td><td>95 (34.5)</td><td>83 (30.2)</td><td>99 (36.1)</td><td>90 (33.0)</td></tr><tr><td>Loss of ≥15 letters</td><td>6</td><td>15</td><td>18</td><td>14</td></tr><tr><td>Gain or loss between 14 letters</td><td>174</td><td>177</td><td>157</td><td>169</td></tr></table></td></tr>
</table>

Adverse events (12 months)

	Ranibizumab (n=274)	Ranibizumab (n=275)	Ranibizumab (n=274)	Ranibizumab (n=272)
Dose	0.5mg	0.5mg	2.0mg	2.0mg
Frequency	Monthly	PRN	Monthly	PRN
Any SAE	3	3	6	1
Endophthalmitis	2	0	0	0
Reduced VA	0	1	1	1
Death any cause	8	4	5	5
Nonfatal myocardial infarction	4	0	2	4
Gastrointestinal perforation	0	0	1	0

Number of injections (12 months)

Agent	Ranibizumab	Ranibizumab	Ranibizumab	Ranibizumab
Dose	0.5mg	0.5mg	2.0mg	2.0mg
Frequency	Monthly	PRN	Monthly	PRN
Mean number of injections (SD)	11.3 (1.8)	7.7 (2.7)	11.2 (2.1)	6.9 (2.4)

Notes

Full study name: Not reported
Type of study: published
Trial registration: NCT00891735
Funding sources: Genentech, Inc. (South San Francisco, CA) provided support for the study and participated in the study design; conducting the study; and data collection, management, and interpretation.
Declarations of interest: B.G.B. has served as a consultant for Alimera, Elan, Genentech, Synergetics, and Thrombogenics; has received research funding from Genentech; is a member of the speakers bureau for Genentech and Regeneron; and has received royalties from AKORN. A.C.H. has served as a consultant for Alcon, Allergan, Centocor/Johnson & Johnson, Genentech, Merck, NeoVista, Ophthotech, Oraya, Paloma, PRN, QLT, Regeneron, and Thrombogenics; has

	received research funding from Alcon, Allergan, Genentech, National Eye Institute/ National Institutes of Health, NeoVista, Ophthotech, Oraya, PRN, QLT, Regeneron, and Second Sight; and is a member of the speakers bureau for Alcon, Genentech, and Regeneron. D.M.B. has served as a consultant for Alcon, Alimera, Allergan, Genentech, Novartis, Regeneron, and Thrombogenics; has received research funding from Abbott, Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Ophthotech, Novartis, Regeneron, and Thrombogenics; and is a member of the speakers bureau for Genentech and Regeneron. J.S.H. has served as a consultant for Acucela, Allergan, Bayer, Forsight, Fovea, Genentech, Genzyme, GlaxoSmithKline, LPath, Neovista, Oraya, Paloma, QLT, Quark, and Regeneron; and has received research funding from Alcon, Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, Neurotech, Novartis, Ophthalmic Consultants of Boston, Ophthotech, Paloma, and Regeneron. I.J.S. has served as a consultant for Genentech, Eyetech, Regeneron, and Thrombogenics; has received research funding from Genentech; is a mem- ber of the speakers bureau for Genentech, Optos, and Regeneron; and is a board member of Optos. Z.L., R.G.R., and P.L. are employees of Genen- tech. Support for third-party writing assistance for this manuscript provided by Linda Merkel, PhD, and Michelle Kelly, PhD, of UBC-Envision Group, and was provided by Genentech, Inc. **Study period:** recruitment from July 2009 and August 2010 **Reported subgroup analyses:** No

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	“each patient received a computer-generated subject number on day 0, which randomly assigned patients in a 1:1:1:1 ratio to 1 of 4 ranibizumab treatment groups: 0.5 mg monthly, 0.5 mg PRN, 2.0 mg monthly, and 2.0 mg PRN"
Allocation concealment (selection bias)	Low risk	“Randomization was stratified by VA at day 0 (≤54 letters [approximate Snellen equivalent <20/80] vs. ≥55 letters [approximate Snellen equivalent ≥20/80]), CNV classification at baseline (predominantly classic, minimally classic, or purely occult), and study center.”
Masking of participants (performance bias)	Unclear risk	“All study site personnel, the designated physician(s), central reading center personnel, patients, and the sponsor and its agents were masked to treatment drug dose assignment (0.5 mg vs. 2.0 mg). Treatment frequency (ie, monthly vs. PRN dosing) was not masked to patient and site personnel”
Masking of outcome assessment (detection bias)	Unclear risk	“All study site personnel, the designated physician(s), central reading center personnel, patients, and the sponsor and its agents were masked to treatment drug dose assignment (0.5 mg vs. 2.0 mg). Treatment frequency (ie, monthly vs. PRN dosing) was not masked to patient and site personnel”

Incomplete outcome data (attrition bias)	Low risk	An intention-to-treat analysis was used.
Selective reporting (reporting bias)	Low risk	Compared with the trial registry, there does not appear to be selective outcome reporting.
Other bias	Low risk	None identified

Bibliographic reference	**CATT 2011** CATT Research Group; Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2011;364(20):1897-908.
Methods	**Number randomized (total and per group):** 1208 participants randomly assigned to study treatment; number of participants randomized per group not reported **Exclusions after randomization**: one study center (23 participants) was excluded due to protocol violations **Number analyzed (total and per group):** 1105 total participants; 265 in bevacizumab monthly group, 284 in ranibizumab monthly group, 271 in bevacizumab as needed group, and 285 in ranibizumab as needed group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 80 total participants: 21 in bevacizumab monthly group (4 died and 17 with missing data), 17 in ranibizumab monthly group (4 died and 13 with missing data), 29 in bevacizumab as needed group (11 died and 18 with missing data), 13 in ranibizumab as needed group (5 died and 8 with missing data) **Compliance**: limited information given: mean of 11.9 treatments given for bevacizumab monthly group and mean of 11.7 treatments given for ranibizumab monthly group **Intention to treat analysis**: no, 103 participants enrolled and randomized were not included in the analyses **Reported power calculation:** yes, sample of 277 participants per group for power of 90% **Study design comment:** non-inferiority design, four arms, six pairwise comparisons planned; at one year, participants in the monthly dose treatment groups were re-randomized to either continue with monthly injections or switch to as needed injections of the same treatment drug
Participants	**Country**: USA **Age**: mean was 80 years in bevacizumab monthly group, 79 years in ranibizumab monthly group, 79 years in bevacizumab as needed group, and 78 years in ranibizumab as needed group **Gender (percent):** 732/1185 (61.8%) women and 453/1185 (38.2%) men **Inclusion criteria**: age 50 years or older; one study eye per participant with untreated active CNV due to AMD (based on presence of leakage as seen by fluorescein angiography and of fluid as seen by OCT); VA of 20/25 to 20/320 on electronic visual-acuity testing

<table>
<tr><td></td><td>Exclusion criteria: fibrosis or atrophy in center of fovea in the study eye; CNV in either eye due to other causes; retinal pigment epithelial tear involving the macula; any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention or contribute to VA loss during the 3 year follow-up period; active or recent (within 4 weeks) intraocular inflammation; current vitreous hemorrhage in the study eye; history of rhegmatogenous retinal detachment or macular hole; active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis; spherical equivalent > 8 diopters; intraocular surgery (including cataract surgery) in the study eye within 2 months; uncontrolled glaucoma; participants unable to be photographed to document CNV due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV; premenopausal women not using adequate contraception; pregnancy or lactation; history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications; current treatment for active systemic infection; uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders; history of recurrent significant infections or bacterial infections; inability to comply with study or follow-up procedures
Equivalence of baseline characteristics: a slightly higher percentage of participants in bevacizumab monthly group had history of transient ischemic attack (8.7% compared with 4% in ranibizumab monthly group, 4% in ranibizumab as needed group, and 6.3% in bevacizumab as needed group)</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg bevacizumab injections on
Intervention 2: 0.5 mg intravitreal ranibizumab injections
Treatment schedule 1: PRN
Treatment schedule2: every 4 weeks for first year, then re-randomization to injections PRN or every 4 weeks

<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention3</th><th>Intervention4</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Ranibizumab</td><td>Bevacizumab</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks for 1 year, re-randomization to bevacizumab every 4 weeks or as needed</td><td>Every 4 weeks for 1 year, re-randomization to ranibizumab every 4 weeks or as needed</td><td>As needed for 2 years</td><td>As needed for 2 years</td></tr>
</table></td></tr>
</table>

	Length of follow up: **Planned: 12 months for primary analysis**; 24 months for secondary analyses, with modifications to two intervention arms as described above Actual: 12 months for primary analysis; 24 months for secondary analyses
Outcomes	**Primary outcome**, as defined: change in visual acuity from baseline at 12 months with a non-inferiority margin of 5 letters **Secondary outcomes**: proportion of eyes with 15-letter change, number of injections, OCT measured change in foveal thickness, change in lesion size on OCT and also on fluorescein angiography, incidence of ocular and systemic adverse events, and annual drug cost **Adverse events**: ocular and systematic adverse events **Review outcome not reported**: quality of life **Intervals at which outcomes were assessed**: weeks 4, 12, 24, 36, 52 during first year for visual acuity; weeks 4, 8, 12, 24, 52 for changes on OCT
Notes	**Full study name**: Comparison of Age-related macular degeneration Treatment Trials **Type of study**: published **Funding**: National Eye Institute, National Institutes of Health, US **Declarations of interest**: one investigator reported receiving consulting fees from GlaxoSmithKline and another consulting fees from Neurotech and SurModics **Study period**: accrual February 2008 through December 2009; follow up through December 2011 **Reported subgroup analyses**: none, but risk factors for 2-year VA outcomes have been reported (Ying 2015)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to 1 of 4 study groups. Randomization schedules were stratified according to clinical center with the use of a permuted-block method with randomly chosen block sizes."
Allocation concealment (selection bias)	Low risk	Web-based data entry system was used to allocate participants to treatment groups
Masking of participants (performance bias)	High risk	Initially, participants were masked to which drug they received, but not to the treatment schedule. The study investigators noted that "insurance and billing documents specified ranibizumab but not study-supplied bevacizumab. Therefore, patients may have learned or deduced their assigned drug from these financial documents."

		Physicians were masked to drug but not to injection schedule. Physicians were uninvolved in visual acuity testing and in secondary outcome assessments.
Masking of outcome assessment (detection bias)	Low risk	Electronic Visual Acuity system (computerized testing) was used for primary outcome. Retinal center personnel were masked. Adverse event reporting was unmasked, but medical monitor who evaluated serious adverse events was masked.
Incomplete outcome data (attrition bias)	Unclear	103/1208 (8.5%) participants randomized were not included in the one-year analysis. At two years, outcomes were not available for all participants by their originally assigned treatment groups.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes, specified a priori, for 1 year follow up were reported.
Other bias	Low risk	None identified

Bibliographic reference	**IVAN 2012** Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012;119(7):1399-411
Methods	**Study design:** parallel-group randomized controlled trial **Number randomized (total and per group):** **Drug randomization**: 628 total participants; 305 to bevacizumab group and 323 to ranibizumab group **Regimen randomization**: 294/305 in bevacizumab group and 312/323 in ranibizumab group completed first three injections and were randomized to continue or discontinue treatment: 149 continued bevacizumab; 145 discontinued bevacizumab; 157 continued ranibizumab; and 155 discontinued ranibizumab **Exclusions after randomization**: 18 participants did not receive treatment and were excluded after randomization to drug treatment (9 in bevacizumab group and 9 in ranibizumab group) **Number analyzed (total and per group):** at one year follow up: 561 total participants at one year; 136 in continued bevacizumab group; 138 in discontinued bevacizumab group; 141 in continued ranibizumab group; and 146 in discontinued ranibizumab group at two years follow up: 525 total participants at one year; 127 in continued bevacizumab group; 127 in discontinued bevacizumab group; 134 in continued ranibizumab group; and 137 in discontinued ranibizumab group **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**:

	at one year follow up: 49 total participants: 4 participants receiving treatment withdrew prior to completing third injection (2 in bevacizumab group and 2 in ranibizumab group); 45 participants randomized to regimen groups exited trial before one year (13 in continued bevacizumab group; 7 in discontinued bevacizumab group; 16 in continued ranibizumab group; and 9 in discontinued ranibizumab group) at two years follow up: 85 total participants: 5 participants receiving treatment withdrew prior to completing third injection (3 in bevacizumab group and 2 in ranibizumab group); 80 participants randomized to regimen groups exited trial before two years (21 in continued bevacizumab group; 18 in discontinued bevacizumab group; 23 in continued ranibizumab group; and 18 in discontinued ranibizumab group) **Compliance:** the wrong study drug was administered twice during the first year; at one year follow up: adherence was 6576/6699 (98%) scheduled injections received at two years follow up: adherence was 12761/14640 (87%) scheduled injections received **Intention to treat analysis:** no, 67 participants enrolled and randomized were not included in the analyses at one year and 103 at two years **Reported power calculation**: yes, sample of 600 participants per group for power of 90% to detect non-inferiority **Study design comment:** non-inferiority design; 2 x 2 factorial design – randomization in two stages: first randomized to drug treatment (bevacizumab or ranibizumab), then to treatment regimen (continue monthly injections or discontinue monthly injections and switch to as needed injections given in three month cycles); results reported only as bevacizumab versus ranibizumab and continuous versus discontinuous
Participants	**Country:** UK (23 study centers) **Age:** mean age for 610 participants receiving treatment was 78 years **Gender (percent):** 366/610 (60%) women and 244/610 (40%) men **Inclusion criteria**: age 50 years or older; previously untreated neovascular AMD in study eye with any component of the neovascular lesion (CNV, blood, serous pigment epithelial detachment, elevated blocked fluorescence) involving the center of the fovea, confirmed by fluorescein angiography; best-corrected VA of 25 letters or greater on the ETDRS chart (measured at 1 m) **Exclusion criteria**: neovascular lesion of 50% or more fibrosis or blood; more than 12 disc diameters; argon laser treatment in study eye within 6 months; presence of thick blood involving the center of the fovea; presence of other active ocular disease causing concurrent vision loss; myopia 8 or more diopters; previous treatment with PDT or a VEGF inhibitor in study eye; women pregnant, lactating, or of child-bearing potential; men with a spouse or partner of child-bearing potential **Equivalence of baseline characteristics**: yes

<table>
<tr><td></td><td>Diagnoses in participants: 301/610 (58%) had neovascular AMD with CNV in foveal center; 308/610 (54%) had fluid in foveal center; 90/610 (16%) had hemorrhage in foveal center; 75/610 (13%) had other foveal center involvement; and 15/610 (3%) had no CNV or not possible to grade</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg in 0.05 ml intravitreal bevacizumab injected monthly for two years
Intervention 2: 0.5 mg intravitreal ranibizumab injected monthly for two years
Intervention 3: after first 3 monthly 1.25 mg intravitreal bevacizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
Intervention 4: after first 3 monthly 0.5 mg intravitreal ranibizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
<table>
<tr><th></th><th>Intervention1</th><th>Intervention2</th><th>Intervention3</th><th>Intervention4</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td colspan="2">Monthly for 2 years
Monthly for 2 years</td><td colspan="2">Initial 3 doses monthly, then treatment was givens as needed in cycles of 3 monthly dose</td></tr>
</table>
Follow up: 2 years
Frequency of follow-up assessments: monthly</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: best-corrected distance visual acuity measured as ETDRS letters at two years
Secondary outcomes, as defined in protocol: at 1 year and 2 years follow up - frequencies of adverse effects of treatment; generic and vision-specific health-related quality of life; treatment satisfaction; cumulative resource use/cost and cost-effectiveness; clinical measures of vision (contrast sensitivity measured with Pelli-Robson charts, near visual acuity measured by Bailey-Love near reading cards, and reading speed measured with Belfast reading charts); lesion morphology (fluorescein angiography and OCT); distance visual acuity at one year; survival free from treatment failureExploratory analysis: association between serum markers and cardiovascular serious adverse eventsIntervals at which outcomes were assessed: monthly through 24 months; various data were collected at every visit depending on assessment schedule and regimen group</td></tr>
<tr><td>Notes</td><td>Full study name: alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation
Type of study: published
Funding sources: National Institute for Health Research Health Technology Assessment program, UK
Declarations of interest: various authors reported being principal investigators of trials sponsored by Novartis; attending and being remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan,</td></tr>
</table>

	and/or Bausch and Lomb; being employed by institution that has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and/or Pfizer; receiving honoraria from Novartis for lecture and/or teaching fees from Janssen-Cilag **Study period**: random enrollment 27 March 2008 to 15 October 2010 **Reported subgroup analyses**: 3 genetic polymorphisms (Lotery 2013) **Contacting study investigators**: trial authors not contacted as data were available in published reports

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomized allocations were computer generated by a third party in blocks and stratified by center." "Randomisation was stratified by centre and was blocked to ensure roughly equal numbers of participants per group within a centre."
Allocation concealment (selection bias)	Low risk	"Research teams at sites recruited participants, and accessed a password-protected website to randomize participants. Allocations were concealed until participants' eligibility and identities were confirmed." "Allocations were computer generated and concealed with an internet-based system (Sealed Envelope, London, UK). Staff in participating centres accessed the website and, on entering information to confirm a participant's identity and eligibility, were provided with the unique study number."
Masking of participants and personnel (performance bias)	Low risk	From study protocol: "Participants, clinicians and trial personnel will be masked to the VEGF inhibitor to which a participant is assigned." "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months." "We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments." From study protocol: "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Masking of outcome assessment (detection bias)	Low risk	"We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared

		ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments." "Lesion morphology was assessed by independent graders masked to drug and treatment regimen." From study protocol: "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Incomplete outcome data (attrition bias)	Unclear risk	67/628 (11%) participants randomized were not included in the one-year analysis; 111/628 (18%) participants randomized were not included in the two-year analysis.
Selective reporting (reporting bias)	Unclear risk	Differences between the protocol and published one-year and two-year results papers included: 1) two secondary outcomes in the protocol were not listed in paper: treatment satisfaction and survival free from treatment failure; and 2) exploratory (serum) analysis in protocol upgraded to a secondary outcome in paper
Other bias	Low risk	None observed

The Chan study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	**Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.**
Country/ies	USA
Study type	Open label RCT
Aim of the study	This prospective study compared the outcomes of 0.5 vs 2.0mg intravitreal ranibizumab injections (RI) for treating vascularized pigment epithelial detachment (vPED) due to age-related macular degeneration.
Study dates	Published 2015
Sources of funding	Not reported
Sample size	36 eyes (36 people)
Inclusion Criteria	Eligibility criteria included: Patients were age≥50, Patients had submacular vPED due to AMD (confirmed by fundus photography (FP), fluorescein angiography (FA), and OCT) Patients had PED measuringr12 disc areas Patients had visional acuity of ETDRS BCVA letter scores of ≥19 and ≤69 (20/400 to 20/40) Patitents hadsubmacular hemorrhage or fibrosis within 50% of entire PED.

<table>
<tr><th>Bibliographic reference</th><th>Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.</th></tr>
<tr><td>Exclusion Criteria</td><td>Patients had anti-VEGF therapy within the past 30 days;
Patients had more than one prior PDT session;
Patients had treatment of AMD in past 30 days;
Patients had any cause of CNV and PED other than AMD;
Patients had serous PED without CNV;
Patients had PED with polypoidal choroidal vasculopathy (PCV).</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Ranibizumab, 0.5mg montly (n=6)</th><th>Ranibizumab, 0.5mg PRN (n=7)</th><th>Ranibizumab, 2.0mg montly (n=12)</th><th>Ranibizumab, 2.0mg PRN (n=11)</th></tr>
<tr><td>Mean age (SD)</td><td>82.0 (6.2)</td><td>84.0 (6.0)</td><td>77.3 (6.2)</td><td>74.6 (9.4)</td></tr>
<tr><td>Male: n (%)</td><td>0</td><td>1 (14.3)</td><td>5 (41.7)</td><td>4 (36.4)</td></tr>
<tr><td>Mean BCVA, letters (SD)</td><td>54.0 (6.63)</td><td>53.3 (14.4)</td><td>61.5 ((7.2)</td><td>58.5 (8.4)</td></tr>
</table>
</td></tr>
<tr><td>Study visits and procedures</td><td>Eligible patients were randomized to receive one of four treatment protocols:
Regimen (1) RI of 0.5mg monthly for 12 months,
Regimen (2) RI of 0.5mg monthly for 4 months followed by repeat RI on a PRN basis for 8 months,
Regimen (3) RI of 2.0mg monthly for 12 months
Regimen (4) RI of 2.0mg on a monthly injection for 4 months followed by repeat RI on a PRN basis.
The PRN criteria for Regimen 2 and 4 were the following:
(a) RI was continued if the macula was not completely flat on optical coherence tomography (OCT) (sensory macula and retinal pigment epithelium (RPE)).
(b) If macular flattening occurred, retreatment was allowed for the following: (i) loss of five letters on the Early Treatment of the Diabetic Retinopathy Study (ETDRS) chart compared with a prior visit;
(ii) new or persistent subretinal fluid (SRF) or cystoid macular edema (CME) on OCT; (iii) New-onset or persistent choroidal neovascularization (CNV), and
(iv) new or persistent hemorrhage.</td></tr>
<tr><td>Intervention</td><td>intravitreal ranibizumab 2.0mg monthly/ PRN</td></tr>
<tr><td>Comparator</td><td>Intravitreal ranibizumab 0.5mg monthly/ PRN</td></tr>
<tr><td>Outcomes</td><td>Primary outcome:</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.</td></tr>
<tr><td></td><td>Change in best-corrected visual acuity
Secondary outcome:
Proportoin of people with a loss of BCVA less than 15 letters from baseline at 12 months (responders)
Proportion of patients with a loss or a gian of BCVA less than 15 letters from basedlin at 12 months (stabilizers)
Proportion of people with 15 letters loss or more BCVA from baseline at 12 months (losers)
Proportion of drpouts befire the final 12 months assessment
Proportion of switcher after the third injection
Adverse event</td></tr>
<tr><td>Analyses</td><td>Both parametric (analysis of variance (ANOVA), paired t-tests) and nonparametric statistics (w2-analysis, Mann–Whitney, Wilcoxon signed-rank, and Friedman) were utilized for comparisons.
A standardized scale
(0=none, 1+=mild, 2+=moderate, and 3+=severe) was used to assess ordinal data, that is, cataract, CME and SRF.
A P-value of ≤0.05 was considered significant.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Result</td><td>Visual acuity
<table>
<tr><td colspan="4">PRN vs monthly injection</td></tr>
<tr><td></td><td>Ranibizumab, 0.5mg PRN (n=7)</td><td>Ranibizumab, 0.5mg monthly (n=6)</td><td>Effect RR (95%CI)</td></tr>
<tr><td>N, % of people had a gain of >5 letters</td><td>6(85.7%)</td><td>3 (50%)</td><td>1.71 (0.73, 4.03)</td></tr>
<tr><td>% of people had a gain of ≥15 letters</td><td>3 (42.8%)</td><td>2(33.3%)</td><td>2.19 (0.31, 5.31)</td></tr>
<tr><td></td><td>Ranibizumab, 2.0mg PRN (n=11)</td><td>Ranibizumab, 2.0mg monthly (n=12)</td><td></td></tr>
<tr><td>N, % of people had a gain of >5 letters</td><td>7 (63.6%)</td><td>5 (41.7%)</td><td>1.53 (0.68 3.42)</td></tr>
<tr><td>% of people had a gain of ≥15 letters</td><td>2 (18.2%)</td><td>4 (33.3%)</td><td>0.55 (0.12, 2.41)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.</td></tr>
<tr><td></td><td>
<table>
<tr><td colspan="4">Monthly 2.0mg vs 0.5mg ranibizumab</td></tr>
<tr><td></td><td>Ranibizumab 2.0mg monthly (n=12)</td><td>Raibizumab 0.5monthly (n=6)</td><td></td></tr>
<tr><td>N, % of people had a gain of >5 letters</td><td>5 (41.7%)</td><td>3 (50%)</td><td>0.83 (0.29, 2.37)</td></tr>
<tr><td>% of people had a gain of ≥15 letters</td><td>4 (33.3%)</td><td>2(33.3%)</td><td>1.00 (0.25, 4.00)</td></tr>
<tr><td colspan="4">PRN 2.0mg vs 0.5mg ranibizumab</td></tr>
<tr><td></td><td>Raibizumab 2.0mg PRN (n=11)</td><td>Ranibizumab 0.5mg PRN (n=7)</td><td></td></tr>
<tr><td>N, % of people had a gain of >5 letters</td><td>7 (63.6%)</td><td>6(85.7%)</td><td>0.74 (0.43, 1.27)</td></tr>
<tr><td>% of people had a gain of ≥15 letters</td><td>2 (18.2%)</td><td>3 (42.8%)</td><td>0.42 (0.09, 1.94)</td></tr>
</table>

Visual acuity at baseline and Month 12
<table>
<tr><td></td><td>Ranibizumab 2.0mg (n=23)</td><td>Ranibizumab 0.5mg (n=13)</td><td>Effect, MD (95%CI)</td></tr>
<tr><td>Baslineline</td><td>0.52 (0.15)</td><td>0.64 (0.21)</td><td>-0.12 (-0.25, 0.01)</td></tr>
<tr><td>Month 12</td><td>0.41 (0.29)</td><td>0.53 (0.44)</td><td>-0.12 (-0.39, 0.15)</td></tr>
</table>
</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>No loss to follow-up</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Open label study</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>Open label study</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>Unclear</td></tr>
</table>

Bibliographic reference	**Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.**
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	N/A
Are reports of the study free of suggestion of selective outcome reporting?	Partially (the results were not reported all by 4 different regimen)

Treat and extend vs routinely month injection

Bibliographic reference	**TREX-AMD 2015** Wykoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology 2015;122(12):2514-22.
Methods	**Number randomized (total and per group):** 60 total participants; 40 to TREX group and 20 to monthly group **Exclusions after randomization**: none reported **Number analyzed (total and per group):** 57 total participants; 37 in the TREX group and 20 in the monthly group **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: 3 participants (all in the in the TREX group; due to temporal arteritis, lung cancer, or meningitis) **Intention to treat analysis:** no, 3 participants not included in analysis **Power calculation:** yes, "we calculated an a priori power of 42% to detect noninferiority (significance 5%, one-sided). TREX-AMD 1 year post-hoc analysis demonstrated a power of 88%" **Study design comment:** "randomized 1:2, utilizing a noninferiority limit of 5 ETDRS letters and the 12.5 ETDRS letter standard deviation reported in the LUCAS trial"
Participants	**Country**: USA (2 centers) **Mean age**: 77 years (range 59-96 years) **Gender (percent):** 38 (63%) women and 22 (37%) men **Inclusion criteria:** "treatment-naïve choroidal neovascularization secondary to exudative AMD with Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 78 and 18 (Snellen equivalent, 20/32,

<table>
<tr><td></td><td>20/500) determined by protocol trial lens refraction, and total area of subretinal hemorrhage and fibrosis comprising less than 50% of the total lesion.”
Exclusion criteria: not reported
Equivalence of baseline characteristics: can’t tell; baseline by group not reported
Diagnoses in participants: choroidal neovascularization secondary to exudative AMD</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal injection of 0.05-ml ranibizumab (0.5 mg), monthly for first 3 months, then treat-an-extend protocol (“interval between treatments was tailored based on exudative disease activity: eyes were treated at each visit, no more frequently than every 4 weeks and no less frequently than every 12 weeks”)
Intervention 2: intravitreal injection of 0.05-ml ranibizumab (0.5 mg), monthly for one year

<table>
<tr><th></th><th>Intervention1</th><th>Intervention2</th></tr>
<tr><td>Agent</td><td>Ranibizumab</td><td>ranibiumab</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months, then treat-and-extend protocol</td><td>Monthly for one year</td></tr>
</table>

Follow-up: 1 year reported, 2 years planned
Frequency of assessments for retreatment: every 1-4 weeks, based on exudative disease activity in the TREX group</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: ETDRS BCVA change from baseline
Secondary outcomes, as defined: “mean change in CRT by SD OCT, total number of intravitreal injections, percentage of patients with persistent exudative disease activity by SD OCT, percentage of patients gaining or losing 10 or 15 ETDRS letters at month 12, and the incidence and severity of ocular and systemic adverse events”
Adverse events (Y/N): yes
Intervals at which outcome assessed: every month for 12 months</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)
<table>
<tr><td></td><td>Ranibizumab (n=40)</td><td>Ranibiumab (n=20)</td><td>RR/MD (95%CI)</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td><td></td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months, then treat-an-extend protocol</td><td>Monthly for one year</td><td></td></tr>
<tr><td>Gain of ≥15 letters, n(%)</td><td>10 (25)</td><td>3 (15)</td><td>1.67 (0.52, 5.39)</td></tr>
<tr><td>Mean BCVA, (SD)</td><td>72.1 (17.08)</td><td>69.4 (10.73)</td><td>2.70 (-4.38, 9.78)</td></tr>
</table>
</td></tr>
</table>

Adverse event (12 months)

	Ranibizumab (n=40)	Ranibiumab (n=20)	RR (95%CI)
Dose	0.5mg	0.5mg	
Frequency	Monthly for 3 months, then treat-an-extend protocol	Monthly for one year	
Ocular adverse event, n(%)	10	2	2.50 (0.60, 10.34)
Systematic adverse event	5	0	5.63 (0.33, 97.10)

Number of injections (12 months)

Agent	Ranibizumab (n=40)	Ranibizumab (n=20)
Dose	0.5mg	0.5mg
Frequency	Monthly for 3 months, then treat-an-extend protocol	Monthly for one year
Mean number of injections	10.1	13.0

Notes

Full study name: The Treat-and-Extend Protocol in Patients with Wet Age-Related Macular Degeneration
Type of study: published
Trial registration (Y/N): NCT01748292
Funding sources: "Supported by Genentech, Inc., South San Francisco, California. The funding organization had no role in the design or conduct of this research."
Declarations of interest: "The author(s) have no proprietary or commercial interest in any materials discussed in this article:
C.C.W.: Research support – Alcon, Allergan, Genentech, Regeneron; Consultant – Alcon, Allergan, Bayer, Genentech, Regeneron; Lecturer – Allergan, Genentech, Regeneron.
D.M.B.: Research support – Alcon, Allergan, Genentech, Regeneron; Consultant – Alcon, Allergan, Bayer, Genentech, Regeneron; Lecturer – Bayer, Roche.
L.C.: Research support – Genentech; Consultant – Regeneron; Lecturer – Regeneron, Genentech, Bayer; Travel – Bayer, Regeneron, Genentech.
J.F.P.: Research support – Genentech. S.S.: Research support – Genentech, Carl Zeiss Meditec, Optos, Allergan; Personal fees – Genentech, Carl Zeiss Meditec, Optos, Allergan, Roche, Novartis, Alcon, Iconic."

	Study period: February 2013 to January 2014 **Reported subgroup analyses (Y/N):** none reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported. "The Treat-and-Extend Protocol in Patients with Wet Age-Related Macular Degeneration (TREX-AMD) is a phase III , multicenter, randomized, controlled clinical trial."
Allocation concealment (selection bias)	Low risk	"At enrollment, patients were randomized sequentially by a blinded study coordinator to the monthly or TREX cohort"
Masking of participants (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	3 of 60 (5%) participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Trial planned for 2 years; results at 1 year reported (study ongoing).
Other bias	Unclear risk	Funded by manufacturer of the intervention.

PRN

Without vs with loading phase

Bibliographic reference	**Barikian 2015** Barikian A, Mahfoud Z, Abdulaal M, Safar A, Bashshur ZF. Induction with intravitreal bevacizumab every two weeks in the management of neovascular age-related macular degeneration. American Journal of Ophthalmology 2014;159(1):131-7.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** 90 total participants; 30 participants in each of 3 groups **Exclusions after randomization**: none reported **Number analyzed (total and per group):** 90 participants; 30 participants in each of 3 groups **Unit of analysis**: individual (one study eye per participant)

<table>
<tr><td></td><td>Losses to follow-up: none reported
Intention to treat analysis: all participants randomized were analysed
Power calculation: none reported
Study design comment: none</td></tr>
<tr><td>Participants</td><td>Country: Lebanon
Mean age: 77 years
Gender (percent): 41 (46%) women and 49 (54%) men
Inclusion criteria: "All participants had to be older than 50 years with subfoveal choroidal neovascular membrane (CNV) attributable to AMD diagnosed by fluorescein angi- ography. Patients were required to have best-corrected visual acuity (BCVA) of 50 letters or better (20/100 Snellen equivalent or better) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Additionally, presence of subretinal fluid, cystic maculopathy, or central retinal thickness >250 mm had to be documented on optical coher- ence tomography (OCT) with CNV less than 5400 mm in greatest linear dimension. All patients had to understand and sign the study consent form."
Exclusion criteria: "prior treatment for CNV; submacular hemorrhage or scarring involving the fovea; corneal, lenticular, or vitreous opacification that prevents good-quality angiograms or OCT; history of uveitis; history of vitrectomy; proliferative diabetic retinopathy; and other ocular conditions that affect vision. Patients with cardiovascular, cerebrovascular, or peripheral vascular event less than 6 months prior to enrollment were also excluded. All CNV lesion types were included except for retinal angiomatous proliferation and polypoidal choroidal vasculopathy, since they may respond differently to treatment.
Equivalence of baseline characteristics: “there were significantly more female patients recruited to the monthly induction arm as compared to the biweekly induction arm”</td></tr>
<tr><td>Interventions</td><td>Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: first injection, then PRN
Treatment schedule 2: every 2 weeks for first 3 injections, then PRN
Treatment schedule 3: every 4 weeks for first 3 injections, then PRN
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention 3</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25</td><td>1.25</td></tr>
<tr><td>Frequency</td><td>One injection, the PRN</td><td>Every 2 weeks for 3 injections then PRN</td><td>Every 4 weeks for 3 injections, then PRN</td></tr>
</table>
Follow-up: 12 months
Frequency of assessments for retreatment: monthly</td></tr>
</table>

<table>
<tr><td>Outcomes</td><td>Primary outcome, as defined: mean initial fluid-free interval after induction period
Secondary outcomes, as defined: mean improvement in BCVA (ETDRS charts at 4 meters) and central retinal thickness
Adverse events: ocular and systemic adverse events
Review outcomes not reported: gain of 15 letters visual acuity, quality of life, number of injections, cost
Intervals at which outcome assessed: every month for 12 months</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)
<table>
<tr><td></td><td>Bevacizumab (n=30)</td><td>Bevacizumab (n=30)</td><td>Bevacizumab (n=30)</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25</td><td>1.25</td></tr>
<tr><td>Frequency</td><td>One injection, the PRN</td><td>Every 2 weeks for 3 injections then PRN</td><td>Every 4 weeks for 3 injections, then PRN</td></tr>
<tr><td>Gain of ≥ 15 letters, no.</td><td>10</td><td>6</td><td>12</td></tr>
<tr><td>Loss of ≥ 15 letters, no.</td><td>0</td><td>0</td><td>0</td></tr>
</table>
Number of injections (12 months)
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td><td>Intervention 3</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25</td><td>1.25</td></tr>
<tr><td>Mean number of injections</td><td>6.07</td><td>6.47</td><td>6.27</td></tr>
</table></td></tr>
<tr><td>Notes</td><td>Full study name: not reported
Trial registration: not reported
Funding sources: American University of Beirut Medical Center, Beirut, Lebanon
Declarations of interest: “The authors indicate no financial interest in any product discussed in this study. Z.F.B. has participated on advisory boards for Novartis and Bayer; has received honoraria from Bayer (Leverkusen, Germany) and Novartis (Basel, Switzerland) as invited speaker; and has received research grants from Novartis and Allergan (Center Valley, Pennsylvania, USA).”
Study period: September 2010 to 2012
Subgroup analyses: none reported</td></tr>
</table>

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported: “Patients were randomized in a 1:1:1 ratio to 1 of 3 groups based on the induction sequence.”
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	No missing data reported
Selective reporting (reporting bias)	Unclear risk	Trial protocol and trial registry were not reported.
Other bias	Low risk	None identified

Bibliographic reference	**BeMOc 2013** Menon G, Chandran M, Sivaprasad S, Chavan R, Narendran N, Yang Y. Is it necessary to use three mandatory loading doses when commencing therapy for neovascular age-related macular degeneration using bevacizumab? (BeMOc Trial). Eye (Basingstoke) 2013;27(8):959-63.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** 100 total participants; 49 participants in no loading group, 50 participants in loading group (unclear which group 1 participant was in) **Exclusions after randomization**: 1 participant (unclear which group) **Number analyzed (total and per group):** 99 participants; 49 participants in no loading group; 50 participants in loading group **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**: none reported **Intention to treat analysis:** participants analyzed as they are randomized, 1 participant excluded from analysis **Power calculation**: none reported; “a reasonable and pragmatic sample size of 100 patients was selected to enable the study to be carried out as a monocentric study” **Study design comment**: none
Participants	**Country**: UK

	Mean age: not reported; 13 participants ages 61 to 70; 35 participants ages 71 to 80; 51 participants ages 81+ **Gender (percent):** 72 (73%) women and 27 (27%) men **Inclusion criteria**: “Eligible criteria included treatment-naive patients with active subfoveal choroidal neovascularisation of minimally classic or occult type, secondary to age-related macular degeneration, confirmed on fluorescein angiography, and no other visually significant ocular pathology." **Exclusion criteria:** “1. Medical conditions: 1.1. Uncontrolled hypertension 1.2. Patients on more than 3 antihypertensive medications 1.3. Patients in whom a change in anti-hypertensive drug was initiated within 3 months preceding baseline visit. 1.4. Previous thrombembolic phenomenon 1.5. On Warfarin or anticoagulants 1.6. Recent Myocardial Infarction (MI) 1.7. Recent major surgery (within 28 days) 2. Ocular conditions: 2.1. Glaucoma (IntraOcular Pressure [IOP] >25, on anti-glaucoma treatment, glaucoma surgery) 2.2. Active intraocular or extraocular inflammation 2.3. Retinal vascular disease 2.4. Other sources of chorodal neovascular membrane 2.5. Previous PhotoDynamic Therapy (PDT) 2.6. Predominantly classic membranes 2.7. Previous cataract surgery (within 6 months) 2.8. Aphakia 2.9. Other retinal conditions that may effect visual outcome 3. Other: 3.1. Allergy to Fluorescein 3.2. Inability to obtain colour photographs, fluorescein angiogram, Optical Coherence Tomography (OCT) images 3.3. Allergy to anti Vascular Endothelial Growth Factor (VEGF) medications 3.4. Allergy to humanised monoclonal antibody 3.5. Inability to comply with follow-up procedures” from trial registry” **Equivalence of baseline characteristics:** “The two groups were balanced at baseline in terms of mean visual acuities and mean CMT.”

<table>
<tr><td>Interventions</td><td>Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: PRN (no loading)
Treatment schedule 2: every 4 weeks for first 3 injections, then PRN (loading)
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td></tr>
<tr><td>Frequency</td><td>PRN (no loading)</td><td>every 4 weeks) for first 3 injections, then PRN</td></tr>
</table>
Follow-up: 54 weeks
Frequency of assessments for retreatment: every 6 weeks</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: proportion with visual stability, defined as less than or equal to loss of 15 letters from baseline
Secondary outcomes, as defined: central macular thickness (CMT) on OCT
Adverse events: ocular and systemic adverse events
Review outcomes not reported: number of injections, cost
Intervals at which outcome assessed: every 6 weeks for 54 weeks</td></tr>
</table>

Results

Visual acuity (54 weeks)

	Bevacizumab (n=49)	Bevacizumab (n=50)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	PRN (no loading)	every 4 weeks) for first 3 injections, then PRN	
Loss of <15 letters, n(%)	33 (67)	42 (84)	0.80 (0.64, 1.01)
Gain of ≥ 10 letters	13 (26.3)	14 (28.0)	0.95 (0.50, 1.80)

Adverse events (54 weeks)

	Bevacizumab (n=49)	Bevacizumab (n=50)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	PRN (no loading)	every 4 weeks) for first 3 injections, then PRN	
Conjunctivitis	1 (2)	2 (4)	0.51 (0.05, 5.45)
Subconjunctival haemorrhage	0	1	

Number of injections (54 weeks)

Agent	Bevacizumab	Bevacizumab
Dose	1.25mg	1.25mg
Frequency	PRN (no loading)	every 4 weeks) for first 3 injections, then PRN
Mean number of injections	4.7	5.8

Notes

Full study name: not reported
Trial registration: EUDRACT No: 2006-003033-33, ISRCTN number: 12980412
Funding sources: Frimley Park Hospital NHS Trust (UK)
Declarations of interest: "The authors declare no conflict of interest."
Study period: November 2006 to November 2008
Subgroup analyses: none reported

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	1 (1%) of 100 participants excluded.
Selective reporting (reporting bias)	Unclear risk	Study protocol could not be retrieved from EUDRACT. Primary and secondary outcomes not reported in trial registry.
Other bias	Low risk	None identified

4 weeks vs 12 weeks interval loading phase

Bibliographic reference	**CLEAR-IT2 2011** Heier JS, Boyer D, Nguyen QD, Marcus D, Roth DB, Yancopoulos G, et al. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology 2011;118(6):1098-106.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group**): 159 total participants; 32 participants in 0.5 mg q4 wks group; 32 participants in 2 mg q4 wks group; 32 participants in 0.5 mg q12 wks group; 32 participants in 2 mg q12 wks group; 31 participants in 4 mg q12 wks group; Exclusions after randomization: none reported **Number analyzed (total and per group**): 159 participants in total; 32 participants in 0.5 mg q4 wks group; 32 participants in 2 mg q4 wks group; 32 participants in 0.5 mg q12 wks group; 32 participants in 2 mg q12 wks group;

	31 participants in 4 mg q12 wks group **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: none reported **Compliance**: not reported **Intention to treat analysis:** all participants analysed as randomised **Reported power calculation**: not reported **Study design comment:** none
Participants	**Country**: USA **Mean age (SD):** 78.2 (not reported) years in total; by group not reported **Gender (percent):** 38 men and 62 women in total; by group not reported **Inclusion criteria**: "Patients eligible for the study were ?50 years old, had a diagnosis of subfoveal CNV secondary to wet AMD, and met the following inclusion criteria: CR/LT ?300 um, Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA letter score of 73 to 34 letters (20/40 –20/200), loss of ≥5 ETDRS letters in BCV A over the preceding 6 months for previously treated patients with minimally classic or occult lesions, linear diameter of lesion 5400 µm by fluorescein angiography, subretinal hemorrhage (if present) sparing the fovea and comprising ≤50% of total lesion, area of scar ≤25% of total lesion, and sufficient clarity of ocular media to allow retinal photography." Exclusion criteria: "Exclusion criteria were vitreous hemorrhage in preceding 4 weeks; aphakia or pseudophakia with absence of a posterior capsule (unless as a result of a yttrium aluminum garnet capsulotomy); significant subfoveal atrophy or scarring; active ocular inflamma- tion; corneal transplant; previous uveitis in either eye; or history of macular hole of grade 3 or higher. Patients who had previously received any of the following treatments in the study eye were excluded: Subfoveal thermal laser therapy, any operative intervention for AMD, extrafoveal laser coagulation treatment or photodynamic therapy in preceding 12 weeks, pegaptanib sodium in preceding 8 weeks, systemic or intravitreal treatment with VEGF Trap-Eye, ranibizumab, or bevacizumab at any time, juxtascleral steroids, anecortave acetate, or intravitreal triamcinolone acetonide or other steroids in preceding 24 weeks. Additional reasons for exclusion were other causes of CNV in either eye; active ocular infection; congenital lid anomalies that might interfere with intravitreal administration; any retinal disease other than CNV in either eye; previous trabeculectomy or pars plana vitrectomy; cup-to-disc ratio ?0.8, intraocular pressure ≥25 or receipt of >2 agents for treatment of glaucoma; allergy to povidone iodine, fluorescein, or recombinant proteins; absolute neutrophil count 1000 cells/mm3; human immunodeficiency virus positivity, active systemic infection requiring antibiotics; proteinuria >1+ or urine protein:creati- nine ratio ≥1 on 2 repeated determinations within 1 week; New York Heart Association class III or IV; symptomatic cardiovascular or peripheral vascular disease, malignancy other than basal cell carcinoma in preceding 2 years; and any other conditions or laboratory abnormalities that could interfere with disease assessment or patient participation in the study. The use of standard agents or other anti-VEGF agents was not permitted before week 16."

<table>
<tr><td></td><td>Equivalence of baseline characteristics: can’t tell; baseline by group not reported
Diagnoses in participants: subfoveal choroidal neovascularization secondary to wet age-related macular degeneration</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal injection of VEGF Trap-Eye 0.5 mg every 4 weeks (0.5 mg q4 wks)
Intervention 2: intravitreal injection of VEGF Trap-Eye 2 mg every 4 weeks (2 mg q4 wks)
Intervention 3: intravitreal injection of VEGF Trap-Eye 0.5 mg every 12 weeks (0.5 mg q12 wks)
Intervention 4: intravitreal injection of VEGF Trap-Eye 2 mg every 12 weeks (2 mg q12 wks)
Intervention 5: intravitreal injection of VEGF Trap-Eye 4 mg every 12 weeks (4 mg q12 wks)

<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention 3</th><th>Intervention 4</th><th>Intervention 5</th></tr>
<tr><td>Agent</td><td>Aflibercept</td><td>Aflibercept</td><td>Aflibercept</td><td>Aflibercept</td><td>Aflibercept</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>2mg</td><td>0.5mg</td><td>2mg</td><td>4 mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>every 4 weeks</td><td>every 12 weeks</td><td>every 12 weeks</td><td>every 12weeks</td></tr>
</table>

Follow-up: 20 weeks and 1 year
Frequency Criteria of assessments for retreatment: “An increase in CR/LT ?100 ?m as measured by OCT; a loss of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; persistent fluid as indicated by OCT; new-onset classic neovascularization; new or persistent leak on FA; or new macular hemorrhage.”</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: change from baseline in central retinal/lesion thick ness (CR/LT) at week 12
Secondary outcomes, as defined: change in best-corrected visual acuity (BCVA), proportion of patients with a gain of ≥15 letters, proportion of patients with a loss of ≥15 letters, and safety
Adverse events (Y)
Intervals at which outcome assessed: every 4 weeks for 20 weeks</td></tr>
</table>

Results

Visual acuity (52 weeks)

Agent	Aflibercept (n=32)	Aflibercept (n=31)	Aflibercept (n=32)	Aflibercept (n=31)	Aflibercept (n=31)
Dose	0.5mg	2mg	0.5mg	2mg	4 mg
Frequency	Every 4 weeks	every 4 weeks	every 12 weeks	every 12 weeks	every 12weeks
Gain of ≥15 letters, n (%)	6 (19)	9 (29)	7 (22)	9 (29)	3(10)
Loss <15 letters	28(88)	31 (100)	28 (88)	28 (90)	30 (97)
Mean change in BCVA, letters	5.4 (12.34)	9.0 (8.50)	2.6 (10.91)	5.2 (9.81)	4.2 (6.63)

Adverse event

Number of adverse events were reported in a total group.

Number of injections ((52 weeks)

Agent	Aflibercept	Aflibercept	Aflibercept	Aflibercept	Aflibercept
Dose	0.5mg	2mg	0.5mg	2mg	4 mg
Frequency	Every 4 weeks	every 4 weeks	every 12 weeks	every 12 weeks	every 12weeks
Mean no. of injections (12-52 weeks)	2.52	1.55	1.84	2.48	1.7

Notes

Full study name: Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial [CLEAR-IT 2])
Type of study: published or unpublished
Trial registration: NCT00320788
Funding sources: Regeneron Pharmaceuticals, Inc. and Bayer HealthCare AG
Declarations of interest: "David M. Brown – Alcon Laboratories – Consultant, Grant/Financial Support; Alimera – Grant/Financial Support; Allergan – Consultant, Grant/ Financial Support; Carl Zeiss Meditec – Consultant; CoMentis – Grant/ Financial Support; Eyemaginations – Consultant; Genentech – Consultant, Grant/Financial Support, Lecturer;

	Heidelberg Engineering – Consultant, Lecturer; Jerini Ophthalmics – Consultant, Grant/Financial Support, Lec- turer; NeoVista – Consultant, Grant/Financial Support, Lecturer; Neuro- tech – Grant/Financial Support; Novartis Pharmaceuticals – Consultant, Grant/Financial Support; Oraya Therapeutics – Consultant; Othera – Grant/ Financial Support; Oxigene – Grant/Financial Support; Pfizer Ophthalmics – Consultant, Grant/Financial Support; Regeneron – Consultant, Grant/ Financial Support, Lecturer; Steba – Consultant. Jeffrey S. Heier: Acucela – Consultant; Alcon Laboratories – Consultant, Grant/Financial Support; Allergan – Consultant, Grant/Financial Support; Bausch & Lomb – Consultant; CoMentis – Grant/Financial Support; Eyemaginations – Consultant; Fovea – Consultant; Genentech – Consul- tant, Grant/Financial Support, Lecturer; Genzyme – Consultant; Heidel- berg Engineering – Consultant, Lecturer; iScience – Consultant, Grant/ Financial Support; Ista Pharmaceuticals – Consultant, Grant/Financial Support; Jerini Ophthalmics – Consultant, Grant/Financial Support, Lecturer; LPath – Consultant; NeoVista – Consultant, Grant/Financial Support, Lecturer; Neurotech – Grant/Financial Support; Notal Vision – Consultant; Novartis Pharmaceuticals – Consultant, Grant/Financial Support; Optherion – Consultant; Optimedica – Royalties; Oraya Therapeutics – Consul- tant; Oxigene – Grant/Financial Support; Paloma – Consultant, Grant/ Financial Support; Pfizer Ophthalmics – Consultant, Grant/Financial Support; Regeneron – Consultant, Grant/Financial Support, Lecturer; Resolvyx Pharmaceuticals – Consultant; Schering Plough Research Institute – Consultant; Scyfix – Consultant; Steba – Consultant; VisionCare Ophthal- mic Technologies – Consultant, Grant/Financial Support. Thomas Ciulla: Neovista – Consultant; Regeneron – Consultant; Pfizer – Consultant; Genentech – Grant/Financial Support; Regeneron – Grant/ Financial Support; Allergan – Grant/Financial Support; Alimera – Grant/ Financial Support; Othera – Grant/Financial Support; Glaxo-Smith-Kline – Grant/Financial Support; Optko – Grant/Financial Support; National Eye Institute/National Institutes of Health – Grant/Financial Support. Prema Abraham: Genentech – Consultant, Grant/Financial Support; Alcon – Consultant, Grant/Financial Support; Novartis – Consultant, Grant/Finan- cial Support; Regeneron – Grant/Financial Support; Allergan – Grant/ Financial Support; Opko Health – Grant/Financial Support; Jerini Ophthal- mic – Grant/Financial Support; Pfizer – Grant/Financial Support; Eli Lilly – Grant/Financial Support; Alimera – Grant/Financial Support; VRT – Grant/Financial Support; Schering-Plough – Grant/Financial Support. George Yancopoulous, Neil Stahl, Avner Ingerman, Robert Vitti, Alyson J. Berliner, Ke Yang: Regeneron – Employee at the time the study was conducted. Quan Dong Nguyen: Bausch & Lomb – Consultant; Genentech – Grant/ Financial Support; Regeneron – Grant/Financial Support. Supported by Regeneron Pharmaceuticals, Inc. and Bayer HealthCare AG. The sponsors participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, and the preparation, review, and approval of the manuscript. ” **Study period**: May 2006 and April 2007 **Reported subgroup analyses:** none reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported. “The CLEAR-IT 2 was a prospective, double-masked, random- ized study conducted at 33 sites in the United States.”
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Low risk	“Examiners were masked to treatment assignment and performed no other study assessments. “ “Stratus (software version 4.0 or higher) optical coherence tomography scans (Carl Zeiss Med- itec, Inc., Dublin, CA) read at a masked independent central reading center (Digital Optical Coherence Tomography Reading Center [DOCTR], Cleveland, OH).”
Incomplete outcome data (attrition bias)	Low risk	5 or 159 (3.2%) participants were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes in trial registry was reported in the full-text.
Other bias	Low risk	Funded by manufacturer of the intervention.

Wait & extend vs Treat & observe

The Eldem study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	**Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.**
Country/ies	Turkey
Study type	RCT
Aim of the study	To compare visual outcomes, number of visits and ranibizumab injections in patients treated with a Wait & Extend (W&E) or Treat & Observe (T&O) regimen.
Study dates	2010-2012
Sources of funding	Not reported
Sample size	93 ranodmised

<table>
<tr><th>Bibliographic reference</th><th>Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.</th></tr>
<tr><td>Inclusion Criteria</td><td>The study enrolled patients aged 50 years or over with primary or recurrent subfoveal CNV secondary to AMD, regardless of the lesion type, who had not previously received anti-VEGF treatment for AMD.
Inclusion criteria further required patients to have a CNV area ≥50% of the total lesion size; in patients with occult lesions with minimal or no classic component, the total lesion area had to be ≤12 disc areas, and in patients with predominantly classic lesions, the greatest linear dimension had to be ≤9 disc areas.
Patients were required to have a best corrected visual acuity (BCVA) score between 73 and 34 letters (approximately 20/40 to 20/200 Snellen equivalent).
Where both eyes were eligible, the eye with better VA was chosen for treatment unless the investigator deemed, based on medical justification, that the other eye was a more appropriate candidate for the study.</td></tr>
<tr><td>Exclusion Criteria</td><td>Key exclusion criteria included previous treatment for AMD in the study eye except juxtafoveal or extrafoveal laser photocoagulation administered at least 1 month before the study; previous participation in a clinical trial or treatment with investigational drugs within the 30 days before screening;
Previous treatment with verteporfin, external beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy or transpupillary thermotherapy before the study; previous or current intravitreal or sub-Tenon’s agent to the study eye; previous submacular surgery or any other surgical intervention.
Also excluded were patients with CNV in either eye due to other causes; subfoveal fibrosis or atrophy in the study eye; a tear in the retinal pigment epithelium of the study eye involving the macula; vitreous haemorrhage or rhegmatogenous retinal detachment or macular hole in the study eye;
presence of subretinal haemorrhage affecting the fovea centralis or if the size of the haemorrhage was ≥50% of the total lesion area or ≥1 disc area; any ocular condition that may require medical or surgical management for treatment or which, if left untreated, may result in loss of at least two lines of BCVA.</td></tr>
<tr><td>Baseline characteristics</td><td><table>
<tr><th></th><th>Wait & extend (n=48)</th><th>Treat & observe (n=45)</th></tr>
<tr><td>Median age (rang)</td><td>70.4 (53.6, 86.8)</td><td>70.3 (52.7-83.8)</td></tr>
<tr><td>Male: n (%)</td><td>25 (52%)</td><td>25 (56%)</td></tr>
<tr><td>Caucasuan: n(%)</td><td>48 (100)</td><td>45 (100)</td></tr>
<tr><td>Mean BCVA (SD)</td><td>60 (13)</td><td>60 (14)</td></tr>
</table></td></tr>
<tr><td>Study visits and procedures</td><td>All enrolled patients received three monthly loading doses of 0.5 mg ranibizumab (Lucentis;Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA, USA) via intravitreal injection administered according to the locally approved summary of product characteristics.</td></tr>
</table>

Bibliographic reference	**Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.**
	After the loading-dose period, patients were randomized (1:1) according to a blocked randomization list, which was produced by Novartis using a validated system. Upon enrolment, patients received the lowest available randomization number, which allocated them to one of two treatment arms. In the T&O arm, after the three loading doses, patients were invited for monthly visits and were re-treated if the lesion was active. In the W&E arm, after the three loading doses, patients were invited to return for a follow-up visit 1 month after the last visit. For patients with no active lesions at this visit, treatment was not administered and the interval to the next visit was extended by 2 weeks to a maximum of 8 weeks between visits. Patients whose lesions became active at any of these visits were re-treated and the follow-up schedule started over. For both groups, patients were treated according to the criteria of the Royal College of Ophthalmology (2008). Disease activity was classified as retinal, subretinal or subretinal pigment epithelium fluid or haemorrhage, as determined clinically and/or on optical coherence tomography (OCT), lesion growth on fundus fluorescein angiography (FA) and/or VA loss of >5 letters. No specific criterion values for OCT and FA findings were set and this was left to investigator discretion.
Intervention	intravitreal ranibizumab 1.25mg wait & extent (W &E)
Comparator	Intravitreal ranibizumab 0.5mg treat & observe (T&O)
Outcomes	Primary outcome: change in BCVA from baseline to Month 12 in the two treatment groups (logMAR and letter count). Secondary outcome: two treatment regimens in terms of the number of visits and injections received quality of life of ranibizumab-treated patients as measured by Visual Function Questionnaire (VFQ-25) any differences in ocular and non-ocular adverse events (AEs) and serious adverse events (SAEs)
Analyses	Descriptive statistics were used to summarize patient demographics and baseline data based on the safety population, which consisted of all patients who received at least one dose of ranibizumab. The efficacy analysis was performed in the per protocol population, which consisted of all patients evaluated at baseline and at 12 months (±2 months). The baseline and followup values, and the changes in each group, were compared using a Mann–Whitney U-test. The safety analysis was performed in the safety population with groups compared using cross-table statistics or a Mann–Whitney U-test. Longitudinal change was evaluated with a Wilcoxon test or McNemar test for variable type. Throughout, significance was set at a level of 0.05. No procedure was defined for missing values. According to the original study protocol, the data were to be analysed using parametric statistical tests; however, analysis revealed that variables showed a non-parametric distribution, and hence non-parametric tests were used in the final analysis.
Length of follow up	12 months

<table>
<tr><th>Bibliographic reference</th><td>Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.</td></tr>
<tr><td>Result</td><td>Visual acuity
<table>
<tr><td></td><td>Wait & Extend (n=38)</td><td>Treat & Observe (n=39)</td><td>Effect (MD, RR) (95%CI)</td></tr>
<tr><td>Mean change in VA, letters (SD)</td><td>7.7 (15.9)</td><td>3.2 (20.9)</td><td>4.5 (-3.78, 12.78)</td></tr>
<tr><td>N, % of people had a gain of ≥10 letters</td><td>29 (76%)</td><td>24 (62%)</td><td>1.24 (0.91, 1.68)</td></tr>
<tr><td>N, % of people had a gain of ≥15 letters</td><td>13(34%)</td><td>9(23%)</td><td>1.48 (0.72, 3.05)</td></tr>
<tr><td>% of people had a loss of >15 letters</td><td>4 (10.5%)</td><td>4 (10.3%)</td><td>1.03 (0.28, 3.81)</td></tr>
<tr><td>% of people had a loss of ≥30 letters</td><td>1 (2.6)</td><td>2 (5.1)</td><td>0.51 (0.05, 5.43)</td></tr>
<tr><td>Number of injections (range)</td><td>5.5 (3.0-12.0)</td><td>6.4 (3.0-12.0)</td><td>Cannot be estimated</td></tr>
</table>
Adverse event
<table>
<tr><td></td><td>Wait & Extend (n=38)</td><td>Treat & Observe (n=39)</td><td>Effect (RR) (95%CI)</td></tr>
<tr><td>Any ocular AEs</td><td>24</td><td>25</td><td>0.99 (0.70,1.38)</td></tr>
<tr><td>Any serious AEs</td><td>5</td><td>3</td><td>1.71 (0.44, 6.66)</td></tr>
<tr><td>Discontinued due to SAE</td><td>2</td><td>1</td><td>2.05 (0.19, 21.71)</td></tr>
</table></td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>The efficacy analysis was performed in the per protocol population. 10 people in wait & extend regimen discontinued and 6 people in treat & observe regimen.</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Open label study</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>Open label study</td></tr>
</table>

Bibliographic reference	Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.
adequately prevented during the study?	
Was the allocation sequence adequately generated?	Partially
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

E.6.2 Anti-VEGF treatment in people presenting with visual acuity better than 6/12 or worse than 6/96

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

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

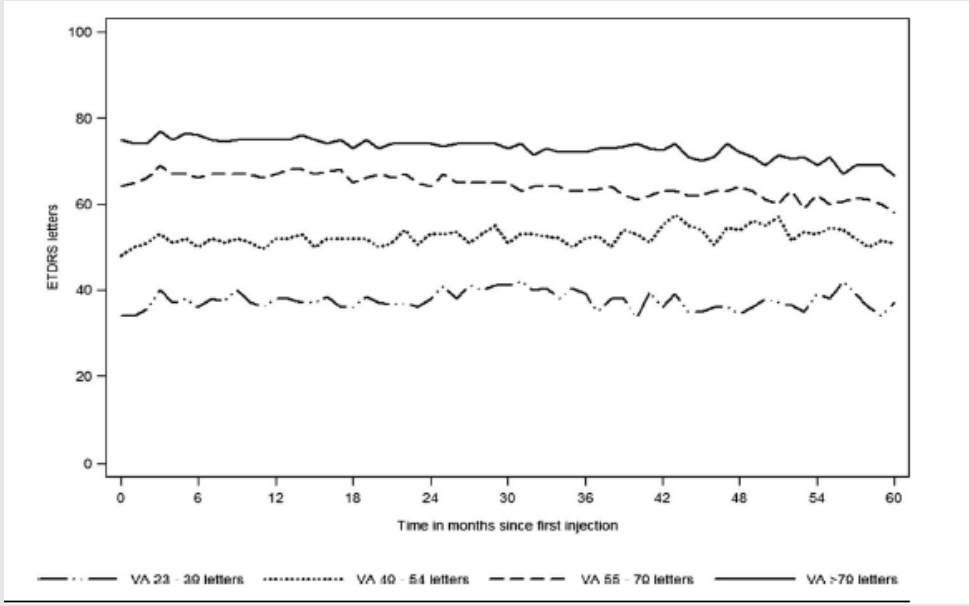
Bibliographic reference	**Buckle M; Donachie P H; Johnston R L. Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK. British Journal of Ophthalmology 100 (2): 240-5. 2014.**
Country/ies where the study was carried out	UK
Study type	Observational study
Aim of the study	To study long-term, whole population 'real world' clinical outcomes of ranibizumab therapy in treatment-navie eyes for neovascular age-related macular degeneration.
Study dates	Published 2014
Source of funding	Not reported
Sample size	1483 eyes eligible for analysis from 1278 patients.
Inclusion criteria	Treatment-navie eyes with a presenting visual acuity of 23 letters or more that were treated exclusively with ranibizumab
Exclusion criteria	Prior treatment with ranibizumab or bevacicumab privately Prior or concurrent photodynamic therapy Visual acuity <23 ETDRS letters at baseline and failure to complete the loading phrase of injections.
Patient characteristics	Age, median: 82.5 years, range: 50.2 to 100.8 years Gender, M, %: 35.1% (n=448) Visual acuity (ETDRS letters) 23-39 letters: 17.3% (n=257) 40-54 letters: 23.1% (n=343) 55-69 letters: 42.7% (n=633) >70 letters: 16.9% (n=250) Comorbidities affecting the eye (e.g. glaucoma and diabetic retinopathy) – at least one ocular co-pathology 7.3% (n=108)
Details	The study was performed at a single centre where a highly structured data set (defined before the introduction of the anti-VEGF service) is prospectively collected in an EMR system (Medisoft Ophthalmology, Leeds, UK) in the context of a paperless service.

<table>
<tr><th>Bibliographic reference</th><td>Buckle M; Donachie P H; Johnston R L. Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK. British Journal of Ophthalmology 100 (2): 240-5. 2014.</td></tr>
<tr><td></td><td>Data collected included:
Demographics,
Early Treatment Diabetic Retinopathy Study (ETDRS) VA at baseline and every visit, injection dates,
Ocular copathology, central 1 mm retinal thickness (CRT) measurements using spectral domain ocular coherence tomography (SD OCT; Heidelberg Spectralis, Hemel Hempstead, UK), and
Operative and postoperative complications.</td></tr>
<tr><td>Treatment</td><td>The department uses a pro re nata treatment posology after an initial loading phase of three injections at monthly intervals. All intravitreal injections are administered in dedicated treatment rooms with povidone iodine being used before and after injections.
After each injection the patient is asked to confirm they can still count fingers as a surrogate measure of intraocular pressure (IOP) and
if they cannot (or if the patient has glaucoma) then the IOP is checked and treated as appropriate.
Patients are followed up at monthly intervals with SD OCT and fundal examination until no injections have been required to either eye for 6 months, after which follow-up intervals are gradually extended. If no injections have been required for 1 year patients are discharged and advised to return if they notice any new symptoms of blurring or distortion of vision in either eye.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>Baseline visual acuity</td><td>>70 letters</td><td>≤70 letters</td><td>Total (%)</td><td>Effect (95%CI) RR</td></tr>
<tr><td>No. of patients at baseline</td><td>250</td><td>1233</td><td></td><td></td></tr>
<tr><td>No. of people had a gain of 15 letters or more, n(%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>End of loading phase</td><td>Not reported</td><td>227 (18.2%)</td><td>Not reported</td><td></td></tr>
<tr><td>Year 1</td><td>Not reported</td><td>184 (16.8%)</td><td>Not reported</td><td></td></tr>
<tr><td>Year 2</td><td>Not reported</td><td>137 (18.8%)</td><td>Not reported</td><td></td></tr>
<tr><td>Year 3</td><td>Not reported</td><td>70 (15.9%)</td><td>Not reported</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Buckle M; Donachie P H; Johnston R L. Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK. British Journal of Ophthalmology 100 (2): 240-5. 2014.

Year 4	Not reported	39 (15.5%)	Not reported	
Year 5	Not reported	8 (8.2%)	Not reported	
No. of people had a loss of 15 letters or more, n (%)				
End of loading phase	19 (8.5%)	56 (4.5%)	75 (5.1%)	1.93 (1.17, 3.19)
Year 1	18 (9.0%)	108 (9.8%)	126 (9.7%)	0.90 (0.56, 1.45)
Year 2	13 (10.0%)	98 (13.4%)	111 (12.9%)	0.74 (0.43, 1.27)
Year 3	12 (18.0%)	95 (21.6%)	107 (21.1%)	0.83 (0.48, 1.43)
Year 4	6 (18.5%)	58 (23.0%)	64 (22.4%)	0.77 (0.36, 1.64)
Year 5	3 (29.0%)	27 (27.4%)	30 (27.5%)	0.99 (0.36, 2.74)

Median visual acuity over time according to baseline visual acuity (n=1483 eyes at baseline)

Bibliographic reference	**Buckle M; Donachie P H; Johnston R L. Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK. British Journal of Ophthalmology 100 (2): 240-5. 2014.**
	
Others	A limitation of this study is that the sample sizes decrease with each year leading to higher SEs for the estimates in the latter years of the study period. Based on the study results, the number of eyes were as following from end of loading phase to year 5:

	>70 letters	≤70 letters1	No. of eyes
Loading phase	224	1247	1471
Year 1	203	1095	1299
Year 2	131	728	860
Year 3	67	440	507

Bibliographic reference	Buckle M; Donachie P H; Johnston R L. Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK. British Journal of Ophthalmology 100 (2): 240-5. 2014.
	<table><tr><td>Year 4</td><td>34</td><td>52</td><td>286</td></tr><tr><td>Year 5</td><td>11</td><td>98</td><td>109</td></tr></table> 1. Total number of people with visual acuity (≤70 letters) were calculated based on the percentage number of people with ≤70 letters gained 15 or more letters reported in the study.

Bibliographic reference	Fang Kai ; Tian Jun ; Qing Xueying ; Li Shuai ; Hou Jing ; Li Juan ; Yu Wenzhen ; Chen Dafang ; Hu Yonghua ; Li Xiaoxin. Predictors of visual response to intravitreal bevacizumab for treatment of neovascular age-related macular degeneration. Journal of Ophthalmology 2013.
Country/ies where the study was carried out	China
Study type	Observational study
Aim of the study	To identify the predictors of visual response to the bevacizumab treatment of neovascular age-related macular degeneration (AMD).
Study dates	Published 2013
Source of funding	Not reported
Sample size	144 patients
Inclusion criteria	People with neovascular AMD
Exclusion criteria	Not reported
Patient characteristics	Age, mean (+SD): 68.8 (8.6) years Gender, M, %: 66.0% (n=95) Mean VA score, letters (SD): 37.5 (18.4) Visual acuity (ETDRS letters) BCVA <20 letters (n=23) BCVA 20 and 39 letters (n=56)

<table>
<tr><th>Bibliographic reference</th><th>Fang Kai ; Tian Jun ; Qing Xueying ; Li Shuai ; Hou Jing ; Li Juan ; Yu Wenzhen ; Chen Dafang ; Hu Yonghua ; Li Xiaoxin. Predictors of visual response to intravitreal bevacizumab for treatment of neovascular age-related macular degeneration. Journal of Ophthalmology 2013.</th></tr>
<tr><td></td><td>BCVA 40 and 59 letters (n=45)
BCVA ≥ 60letters (n=20)

Duration of neovascular AMD
<1 month: no (%) 5 (3.8%)
1-6.9 months: 70 (53.0%)
7-12 months: 26 (19.7%)
>12 months: 31 (23.5%)</td></tr>
<tr><td>Details</td><td>All patients received comprehensive ophthalmologic examinations before each intravitreal injection, including measurements of the best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity at 2m, slit lamp biomicroscopy, fundus examination, fundus fluorescein angiography (FFA) (Topcon TRC-50EX, Tokyo, Japan), indocyanine green angiography (ICGA) (Heidelberg Spectralis
HRA, Heidelberg, Germany), and optical coherence tomography (OCT) spectral domain type, Zeiss-Humphrey, CA, USA; program, retinal mapping program version 6.2). OCT was used to measure the 1mm central retinal thickness.
A total of 185 patients (eyes) were enrolled from January 2008 to January 2010, of which baseline behaviour factors in 144 patients were available for analysis. Predictors of 3 visual response measures at the 6thmonth were evaluated, including change in VA score from baseline,
Proportion of patients that gained ≥15 letters from baseline, and change in central retinal thickness (CRT) from baseline.
For the exploratory association analysis of the NATTB data, factors were considered including patients' baseline age, gender, cigarette smoking status, VA score, CNV lesion type, duration of neovascular AMD (defined as the interval from diagnosis of neovascular AMD to participation in the study), treatment regimen, and genotype.</td></tr>
<tr><td>Treatment</td><td>Patients were randomized into 2 treatment groups each with a different regimen of administration: bevacizumab was administered every 6 weeks for a total of 8 injections (regimen A), or bevacizumab was administered every 6 weeks (3 injections) and then every 12 weeks (2 injections) (regimen B). The dose of bevacizumab was 1.25 mg (in 0.05mL of solution). Follow up of the participants was conducted at 6- or 12-week intervals for more than 6 months after the initial treatment.</td></tr>
<tr><td>Results</td><td><table>
<tr><td>Predictors</td><td>Unstandardised coefficients B (SE)</td><td>Standardised coefficients B</td><td>t (p value)</td></tr>
<tr><td>Age</td><td>-2.998 (1.347)</td><td>-0.188</td><td>-2.227 (0.028)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Fang Kai ; Tian Jun ; Qing Xueying ; Li Shuai ; Hou Jing ; Li Juan ; Yu Wenzhen ; Chen Dafang ; Hu Yonghua ; Li Xiaoxin. Predictors of visual response to intravitreal bevacizumab for treatment of neovascular age-related macular degeneration. Journal of Ophthalmology 2013.

Baseline VA score	-4.561 (1.217)	-0.303	-3.749 (<0.001)
Duration of nAMD	-3.040 (1.290)	-0.193	-2.357 (0.02)

Visual acuity change (letters), from baseline to 6 months follow-up

	VA< 20 letters	60 ≥VA≥20	Effect (95%CI)
Number	23	121	
Mean (SD) letter	13.8 (27.6)	8.3 (33.2)	5.50 (-7.24, 18.24)

Multivariate analysis of ≥15 letters gain from baseline to 6 months

Predicator	Total number of people	No. of events (%)	OR (95%CI)	Effect (95%CI) RR <20 letters vs ≥20 letters
Baseline VA				
<20 letters (G1)	23	10 (43.5)	1.000	1.46 (0.85, 2.15)
20-39 letters	56	25 (44.6)	0.688 (0.227, 2.091)	
40-59 letters	45	9 (20.0)	0.277 (0.081, 0.944)	
≥60 letters	20	2 (10.0)	0.107(0.018, 0.638)	

Bibliographic reference	Fang Kai ; Tian Jun ; Qing Xueying ; Li Shuai ; Hou Jing ; Li Juan ; Yu Wenzhen ; Chen Dafang ; Hu Yonghua ; Li Xiaoxin. Predictors of visual response to intravitreal bevacizumab for treatment of neovascular age-related macular degeneration. Journal of Ophthalmology 2013.				
	Duration of nAMD				Effect (95%CI) RR <1 month vs ≥1 month
	<1 month	5	4 (80.0)	1.000	2.75 (1.64, 4.60)
	1-6.9months	70	22 (31,4)	0.105 (0.010, 1.113)	
	7-12 months	26	10 (38.5)	0.134 (0.012, 1.542)	
	>12 months	31	5 (16.1)	0.047 (0.004, 0.571)	

Bibliographic reference	El-Mollayess G M; Mahfoud Z ; Schakal A R; Salti H I; Jaafar D ; Bashshur Z F. Intravitreal bevacizumab in the management of neovascular age-related macular degeneration: effect of baseline visual acuity. Retina 33(9): 1828-35. 2013.
Country/ies where the study was carried out	Lebanon
Study type	Observational study (prospective)
Aim of the study	To study prospectively the safety and efficacy of intravitreal bevacizumab for eyes with neovascular age-related macular degeneration with baseline visual acuity better than 70 letters (Snellen equivalent better than 20/40)
Study dates	Published 2013
Source of funding	Not reported
Sample size	90 patients, as 30 patients were enrolled to each of the 3 groups: BCVA >70 letters (n=30) BCVA 70 and 61 letters (n=30) BCVA 60 and 51 letters (n=30)
Inclusion criteria	Age 50 years and older Subfoveal CNV caused by AMD diagnosed by FA

Bibliographic reference	El-Mollayess G M; Mahfoud Z ; Schakal A R; Salti H I; Jaafar D ; Bashshur Z F. Intravitreal bevacizumab in the management of neovascular age-related macular degeneration: effect of baseline visual acuity. Retina 33(9): 1828-35. 2013.
	Presence of subretinal fluid, cystic maculopathy, or CRT>250µm on OCT Best-corrected vision, using ETDS charters, betters than 20/100 (Snellen equivalent) Ability to understand and sign consent form
Exclusion criteria	Previous treatment for CNV Submacular haemorrhage involving the fovea Submacular scarring involving the fovea Retinal angiomatour proliferation or polypoidal choroidopathy Corneal, lenticular, or vitreous opacification that prevents good quality angiograms or OCT History of uveitis History of vitrectomy Diabetic retinopathy Other ocular conditions that affect vision Cardiovascular, cerebrovascular, or peripheral vascular event < 6 months before enrollment
Patient characteristics	Age, mean (+SD): 72.9 (11.9) years Gender, M, %: 27.0% (n=30) Visual acuity (ETDRS letters) 51-60 letters: 33.3% (n=30) 61-70 letters: 33.3% (n=30) >70 letters: 33.3% (n=30)
Details	The study was conducted in the Retina clinical. Patients with neovascular AMD were enrolled if they met the eligibility criteria. Eligible eyes were enrolled into 1 of 3 groups based on the baseline BCVA. If both eyes of the same patients were eligible to enter the study, then the eye with the worse visual acuity were enrolled.
Treatment	All patients received the first and subsequent intravitreal bevacizumab injections based on a standard protocol. After initial injection, follow-up visits were carried out every 6 weeks. At each follow-up, the Early Treatment Diabetic Retinopathy Study BCVA, slit-lamp examination, dilated fundus examination, and OCT were performed. FA was repeated at the discretion of the treating physician.

Bibliographic reference	**El-Mollayess G M; Mahfoud Z ; Schakal A R; Salti H I; Jaafar D ; Bashshur Z F. Intravitreal bevacizumab in the management of neovascular age-related macular degeneration: effect of baseline visual acuity. Retina 33(9): 1828-35. 2013.**
	There was no compulsory loading phase at the initial treatment. However, intravitreal bevacizumab was administered every 6 weeks until there was no evidence of fluid on OCT. One the macular was dry on OCT, follow-up was continued every 6 weeks for all the 3 groups. However, this could be reduced to every 4 weeks if deemed necessary by the treating physician.
Results	

Baseline visual acuity	>70 letters (G1)	61-70 letters (G2)	51-60 letters (G3)	Effect (95%CI), (≥70 letters/51-70 letters)
No. of patients at baseline	30	30	30	
Mean VA at baseline letters	78	66.2	56.9	
Mean VA at 12-month, letters	78.4	70.0	61.1	
No. of people had a gain of 15 letters or more in VA, n(%)	0	4 (13.3%)	13 (36.7)	0.06 (0.00, 0.90)
No. of people had a loss of 15 letters in VA, n(%)	0	5	6	0.09 (0.01, 1.40)
No. of people had visual acuity 70 and 85 letters at 12-month, n(%)	28 (93.3%)	21 (70%)	14 (46.7%	1.60 (1.27, 2.02)
No. of people had visual acuity 80 and 85 letters at 12-month, n(%)	20 (66.7%)	6 (20.0%)	3 (30%)	4.44 (2.31, 8.54)
No. of people had visual acuity <35 letters at 12-month, n(%)	0	6 (20%)	2 (6.7%)	0.12 (0.01, 1.94)
Mean number of injections	4.4	4.6	3.2	

No severe ocular and systemic adverse events were noted in all the 3 groups over 12 months.

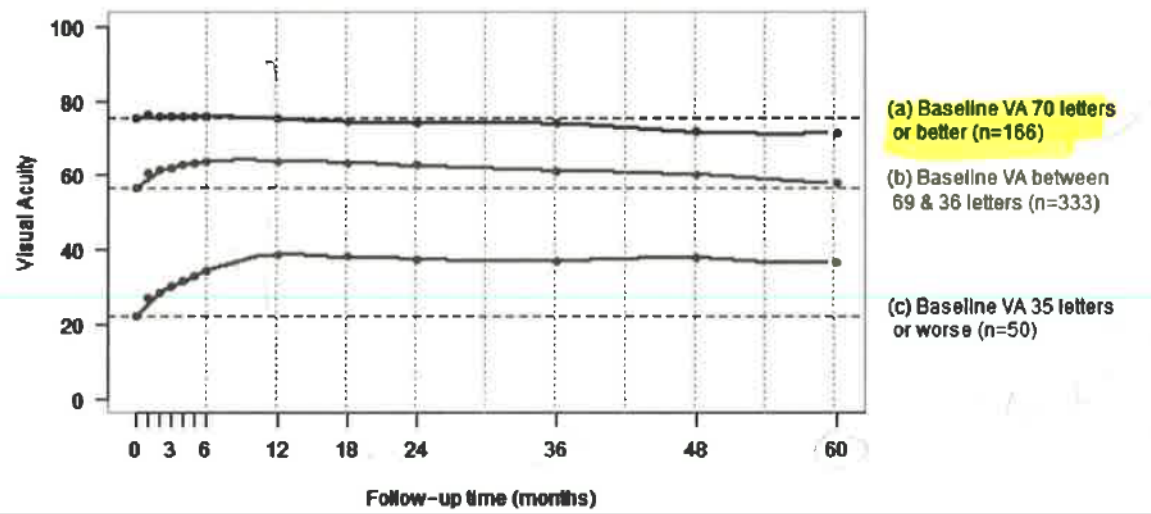
Bibliographic reference	El-Mollayess G M; Mahfoud Z ; Schakal A R; Salti H I; Jaafar D ; Bashshur Z F. Intravitreal bevacizumab in the management of neovascular age-related macular degeneration: effect of baseline visual acuity. Retina 33(9): 1828-35. 2013.
Others	The number of injections in the study was lower than trial results (CATT).

Bibliographic reference	Gillies M C; Campain A ; Barthelmes D ; Simpson J M; Arnold J J; Guymer R H; McAllister I L; Essex R W; Morlet N ; Hunyor A P; Fight Retinal Blindness Study; Group . Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 122 (9): 1837-45.2015
Country/ies where the study was carried out	The study included contributing practitioners located in Australia, New Zealand, and Switzerland.
Study type	Observational study
Aim of the study	To analyse the long-term outcomes of eyes with neovascular AMD starting treatment with anti-VEGF at least 5 years earlier.
Study dates	Published 2015
Source of funding	Supported by a grant from the Royal Australian New Zealand College of Ophthalmologist Eye Foundation and a grant from the National Health and Medical Research Council, Australia.
Sample size	1212 eyes (1043 people), and 549 eyes with data for at least 5 years
Inclusion criteria	Treatment-naive eyes, never having received any form of treatment for neovascular AMD, and were treated with intravitreal therapy at least 5 years of potential follow-up since stating treatment.
Exclusion criteria	Not reported
Patient characteristics	Age, mean: 79.1 years Gender, M, %: 39%% (n=407) Visual acuity, mean (+SD) (ETDRS letters): 55.1 (18.8) ≤ 35 letters: 17.0% (n=206) ≥70 letters: 23.0% (n=279)
Details	The study observed eye that commenced intravitreal therapy for neovascular AMD in routine practice at least 5 years and had been tracked in the Flight Retinal Blindness (FRB) database. This database collects data form each clinical visit, including the number of letters read on LogMAR VA chart, activity of choroidal neovascular membrane, treatment given, if any, ocular adverse, and whether the eye had received prior treatment for neovascular AMD.
Treatment	Most eyes were treated nonly 1 type of anti-VEGF treatment: 648 (53.5%) with ranibizumab, and

Bibliographic reference	**Gillies M C; Campain A ; Barthelmes D ; Simpson J M; Arnold J J; Guymer R H; McAllister I L; Essex R W; Morlet N ; Hunyor A P; Fight Retinal Blindness Study; Group . Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 122 (9): 1837-45.2015**
	69 (5.7%) with bevacizumab Of the 495 eyes that were treated with multiple agent, 7.8% of injections were with ranibizumab, 10.5% were with bevacizumab, and 14.7% were with aflibercept.
Results	

Baseline visual acuity	≥70 letters (G1)	36-69 letters (G2)	≤35 letters (G3)	Effect (G1 vs G2)
No. of eyes at baseline	166 eyes	333	50	
Mean VA at baseline, letters (SD)	75.2 (4.7)	56.6 (8.7)	22.6	18.60 (17.42, 19.78)
Mean VA at 5 years	70.7	58.6 (19.3)	35.2	

Regression curves over 5 years stratified by baseline visual acuity (VA)≥70 letters, between 36 and 69 letters, and ≤35 letters



Bibliographic reference	Gillies M C; Campain A ; Barthelmes D ; Simpson J M; Arnold J J; Guymer R H; McAllister I L; Essex R W; Morlet N ; Hunyor A P; Fight Retinal Blindness Study; Group . Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 122 (9): 1837-45.2015

All of visual improvement occurred in the first year of treatment.

	No. of injection (SD)	No. of visits (SD)
Year 1	6.1 (2.9)	9 (8.7)
Year 2	4.9 (3.1)	Median 7
Year 3	4.9 (3.5)	Median 7
Year 4	5.4 (3.3)	7.9 (3.7)
Year 5	4.9 (3.3)	7.4 (3.6)

Adverse event	No.	Risk rate per injection
Haemorrhage reducing BCVA by > 15 letters	28	0.11%
Infectious endophthalmitis	10	0.04%
Non-infectious endophthalmitis	3	0.01%
Intraocular surgery	82	0.33%
Retinal detachment	5	0.02%

Bibliographic reference	Gillies M C; Campain A ; Barthelmes D ; Simpson J M; Arnold J J; Guymer R H; McAllister I L; Essex R W; Morlet N ; Hunyor A P; Fight Retinal Blindness Study; Group . Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 122 (9): 1837-45.2015
	RPE tear | 9 | 0.04%
Others	Of 1212 eyes, 663 eyes from 631 people were lost to follow-up before 5 years.

Bibliographic reference	Writing committee for the UK AMD EMR user group. The neovascular age-related macular degeneration database: Multicenter study of 92 976 ranibizumab injections: Report 1: Visual acuity manuscript no. 2013-568. Ophthalmology 121 (5): 1092-1101. 2014
Country/ies where the study was carried out	UK
Study type	Observational study
Aim of the study	To study real-world ranibizumab therapy for treatment-naive eyes with neovascular age-related macular degeneration (nAMD) and to benchmark standards of care. Design Multicentre, national nAMD database study.
Study dates	Published 2014
Source of funding	Supported in part by an unrestricted grant from Novartis Pharmaceuticals UK Limited, Frimley, UK. No member or affiliate of Novartis had any input into data analysis, interpretation of the data, or writing the manuscript. This research received a proportion of its funding from the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology
Sample size	12,951 eyes of 11,135 patients who received a total of 92,976 ranibizumab injections at 14 UK hospital. 16.3% (n=1816) of these patients recruited treatment to both eyes during follow-up period.
Inclusion criteria	Treatment-naïve eyes undergoing ranibizumab therapy for nAMD.
Exclusion criteria	Eyes undergoing combined therapies or having bevacizumab in either eye during the study period were excluded.
Patient characteristics	Ethnic group – White, no. (%): 54.8% (n=6103) Mixed: 0.4% (n=41) Asian: 0.4% (n=40) Age, mean: 79 years, Gender, M, %: 36.6% (n=4071)

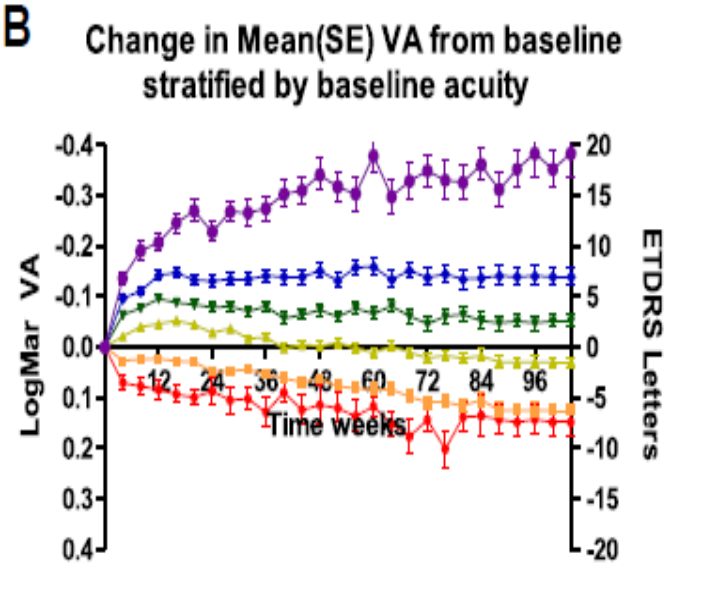
Bibliographic reference	**Writing committee for the UK AMD EMR user group. The neovascular age-related macular degeneration database: Multicenter study of 92 976 ranibizumab injections: Report 1: Visual acuity manuscript no. 2013-568. Ophthalmology 121 (5): 1092-1101. 2014**
Details	The study was performed at 14 sites where a highly structured data set (defined before the introduction of the anti-VEGF service) is prospectively collected in an EMR system (Medisoft Ophthalmology, Leeds, UK) in the context of a paperless service. Data collected included: •Demographics, •Early Treatment Diabetic Retinopathy Study (ETDRS) VA at baseline and every visit, injection dates, •Ocular copathology, central 1 mm retinal thickness (CRT) measurements using spectral domain ocular coherence tomography (SD OCT; Heidelberg Spectralis, Hemel Hempstead, UK), and •Operative and postoperative complications. Data were extracted using Medisoft Ophthalmology (Medisoft Limited, Leeds, UK) for right and left eyes of patients who had had at least 1 intravitreal injection of ranibizumab.
Treatment	Ranibizumab
Results	

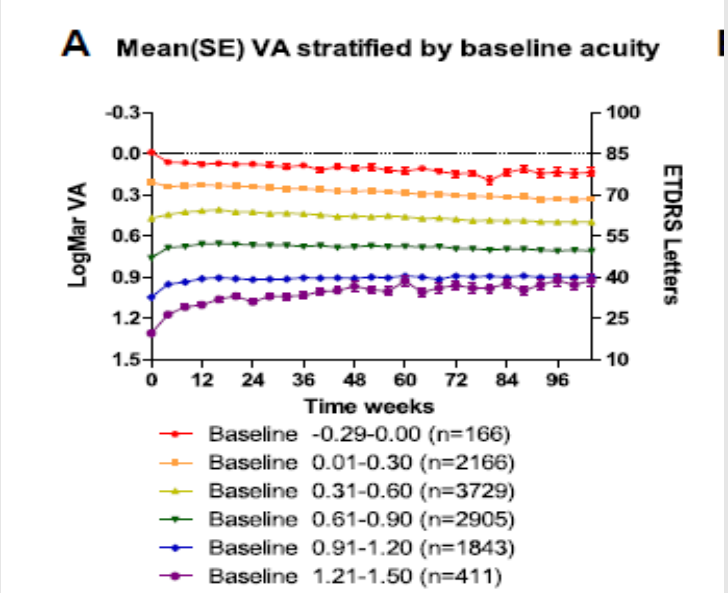
Baseline visual acuity	-0.29-0.30 (≥6/12)	<6/12 to 6/96	Effect (95%CI)	≤6/96 to 1/30	<6/12 to 6/96	Effect (95%CI)
Number of people at baseline	2332	8477		411	8477	
Visual acuity at year 1 (48 weeks) (SD)	71.83 (55.42)	53.53 (70.67)		36.5 (50.68)	53.53 (70.67)	-17.23 (-22.36, -12.10)
6 months, change in VA, letters	-2.64 (22.90)	3.54(35.74)	-6.18 (-7.38, -4.98)	11.4 (24.32)	3.54(35.74)	7.85 (5.39, 10.33)
Year 1, change in VA, letters	-3.39 (36.27)	3.11 (33.33)	-6.50 (-8.13, -4.87)	17.1 (36.49)	3.11 (33.33)	13.99 (10.39, 17.59)
Year 2,	-6.27 (36.07)	1.68 (42.92)	-7.95 (-9.68, -6.22)	19.0 (42.57)	1.68 (42.92)	17.32 (13.10, 21.54)

Bibliographic reference	Writing committee for the UK AMD EMR user group. The neovascular age-related macular degeneration database: Multicenter study of 92 976 ranibizumab injections: Report 1: Visual acuity manuscript no. 2013-568. Ophthalmology 121 (5): 1092-1101. 2014

change in VA, letters						

Change in mean(SE) visual acuity from baseline stratified by baseline acuity





Others	Lee A Y; Lee C S; Butt T ; Xing W ; Johnston R L; Chakravarthy U ; Egan C ; Akerele T ; McKibbin M ; Downey L ; Natha S ; Bailey C ; Khan R ; Antcliff R ; Varma A ; Kumar V ; Tsaloumas M ; Mandal. UK AMD EMR USERS GROUP REPORT V: benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12. British Journal of Ophthalmology 99(8): 1045-50. 2015.

To study the effectiveness and clinical relevance of eyes treated with good (better than 6/12 or 70 Early Treatment Diabetic retinopathy Study letters) visual acuity when initiating treatment with ranibizumab for neovascular AMD in the UK NHS.

	First eyes		Second eyes	

Bibliographic reference	**Writing committee for the UK AMD EMR user group. The neovascular age-related macular degeneration database: Multicenter study of 92 976 ranibizumab injections: Report 1: Visual acuity manuscript no. 2013-568. Ophthalmology 121 (5): 1092-1101. 2014**

Baseline visual acuity	>6/12 (0.3logMAR)	6/12 to >6/24 (0.6 logMAR)	>6/12 (0.3logMAR)	6/12 to >6/24 (0.6 logMAR)
Year 1	0.223 (6/10)	0.408 (6/15)	0.176 (6/9)	0.385 (6/15)
Year 2	0.306 (6/12)	0.464 (6/17)	0.197 (6/9)	0.401 (6/15)
Year 3	0.389 (6/15)	0.524 (6/20)	0.206 (6/10)	0.647 (6/27)

Bibliographic reference	**Regillo C D; Busbee B G; Ho A C; Ding B ; Haskova Z. Baseline Predictors of 12-Month Treatment Response to Ranibizumab in Patients With Wet Age-Related Macular Degeneration. American Journal of Ophthalmology 160 (5): 1014-23. 2015.**
Country/ies where the study was carried out	USA
Study type	Observational study (data from the HARBOR study) (retrospective)
Aim of the study	To identify baseline characteristics predictive of visual acuity (VA) outcomes at month 12 and treatment frequency in the first 12 months of the phase III HARBOUR study.
Study dates	Published 2015
Source of funding	GENENTECH, INC, South San Francisco, CA.
Sample size	500 people
Inclusion criteria	Treatment-naive patients aged 50 years and over with active subfoveal wet AMD.
Exclusion criteria	Not reported
Patient characteristics	Ethnic group - not reported Age, mean: 79 years Gender, M, %: not reported

Bibliographic reference	**Regillo C D; Busbee B G; Ho A C; Ding B ; Haskova Z. Baseline Predictors of 12-Month Treatment Response to Ranibizumab in Patients With Wet Age-Related Macular Degeneration. American Journal of Ophthalmology 160 (5): 1014-23. 2015.**
	Mean visual acuity (ETDRS letters): 20/80 (6/24)
Details	This retrospective, exploratory analysis of data from the HARBOR study investigated demographic and baseline characteristics predictive of VA outcomes at month 12 in the ranibizumab 0.5 mg monthly and 0.5 mg PRN groups, and treatment frequency in the first 12 months in the ranibizumab 0.5 mg PRN group. The main outcome measures that served as a basis for baseline predictors of VA outcomes at month 12 were BCVA change from baseline at month 12, the proportion of patients with a BCVA gain of >15 ETDRS letters from baseline at month 12, and the proportion of patients with a Snellen equivalent of 20/40 or better at month 12 in the ranibizumab 0.5 mg monthly and 0.5 mg PRN groups.
Treatment	HARBOR was a 24-month, phase III, randomized, multicenter, double-masked, active-treatment controlled study that evaluated the efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly or PRN after 3 monthly loading doses in treatment-naïve patients.
Results	<table><tr><td>Baseline visual acuity</td><td>>68 letters1 (Snellen 20/40)</td><td>≤68 letters (Snellen≤ 20/40)</td><td>Effect (95%CI)</td></tr><tr><td>No. of patients</td><td>62</td><td>438</td><td></td></tr><tr><td>No. of people had a gain of 15 letters or more at month 12, n(%)</td><td>7 (11%)</td><td>162 (37%)</td><td>0.31 (0.15, 0.62)</td></tr></table>

Bibliographic reference	**Vogel R N; Davis D B; Kimura B H; Rathinavelu S ; Graves G S; Szabo A ; Han D P. NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH ADVANCED VISUAL LOSS TREATED WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY: Clinical Outcome and Prognostic Indicators. Retina 2016**
Country/ies where the study was carried out	USA
Study type	Observeational study

[1] Study indicated 68 letters (Snellen >20/40)

<table>
<tr><th>Bibliographic reference</th><th>Vogel R N; Davis D B; Kimura B H; Rathinavelu S ; Graves G S; Szabo A ; Han D P. NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH ADVANCED VISUAL LOSS TREATED WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY: Clinical Outcome and Prognostic Indicators. Retina 2016</th></tr>
<tr><td>Aim of the study</td><td>To describe visual outcome and prognostic indicators in neovascular age-related macular degeneration with advanced visual loss at the initiation of anti-vascular endothelial growth factor therapy.</td></tr>
<tr><td>Study dates</td><td>Published 2016</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>A consecutive series of 1,410 patients with nAMD, 131 met study critieria</td></tr>
<tr><td>Inclusion criteria</td><td>Patients initiated on intravitreal antiVEGF therapy between January2006 and December2012 at the Medical College of Wisconsin with exudative senilemaculardegeneration.
Patients’ eyes were included if they received intravitreal injections with ranibizumab, bevacizumab or aflibercept within the study period with VA20/200 or worse at the initiation of therapy.</td></tr>
<tr><td>Exclusion criteria</td><td>Eyes were excluded from the study for visually limiting eye disease other than AMD, large submacular haemorrhage creating mass effect, follow-up period of less than six months, history of anti-VEGF therapy before the study period, and age less than 50 years.</td></tr>
<tr><td>Patient characteristics</td><td>Ethnic group - not reported

Age, mean: 82.2 (7.2) years

Gender, F, %: 78 (60.5%)

Mean visual acuity logMAR (Snellen): 1.38 (20/480) (SD 0.38)
Baseline VA≥20/400: 80 (61.5%)</td></tr>
<tr><td>Details</td><td>The change in VA at 6 months and 12 months of included patients was assessed compared with baseline. Visual improvement/worsening was defined as at least +/- 0.3 logMAR (equivalent to 15 ETDRS [Early Treatment Diabetic Retinopathy Study] letters) change. Other factors for analysis included number of injections received, drug type, and various clinical and imaging findings.</td></tr>
<tr><td>Treatment</td><td>Patients’ eyes were included if they received intravitreal injections with ranibizumab, bevacizumab or aflibercept.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>Baseline visual acuity</td><td><20 letter (Snellen 20/400)</td><td>≥20 letters (Snellen≥ 20/400)</td><td>Effect (95%CI)</td></tr>
<tr><td>No. of patients at 12 months</td><td>30</td><td>65</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Vogel R N; Davis D B; Kimura B H; Rathinavelu S ; Graves G S; Szabo A ; Han D P. NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH ADVANCED VISUAL LOSS TREATED WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY: Clinical Outcome and Prognostic Indicators. Retina 2016

Change in ETDRS letters	15.0 (SD[2]=26.32)	5.5 (SD=18.88)	9.50 (-0.98, 19.98)
No. of people had a gain of 30 letters or more at month 12, n(%)	9 (30.0)	10 (15.4)	1.95 (0.89, 4.30)
No. of people had a gain of <30 and ≥15 letters or more at month 12, n(%)	8 (26.7)	16 (24.6)	1.08 (0.52, 2.25)
No change	7 (23.3)	26 (40.0)	0.58 (0.29, 1.19)
No. of people had a loss of <30 and ≥15 letters or more at month 12, n(%)	2 (6.7)	9 (13.8)	0.48 (0.11, 2.09)
No. of people had a loss of 30 letters or more at month 12, n(%)	4 (13.3)	4 (6.2)	2.17 (0.58, 8.08)

	<20 letter (Snellen 20/400)	≥20 letters (Snellen≥ 20/400)	Effect (95%CI)
≥55 (20/80)	3 (10.0)	12 (18.5)	0.54 (0.16, 1.78)
≥35 and <55 (≥20/200 and <20/80)	6 (34.7)	27 (41.6)	0.48 (0.22, 1.04)
≥20 and <35 (≥20/400 and <20/200)	8 (26.7)	13 (20.0)	1.33 (0.62, 2.87)

[2] SD was calculated by p values reported in the study.

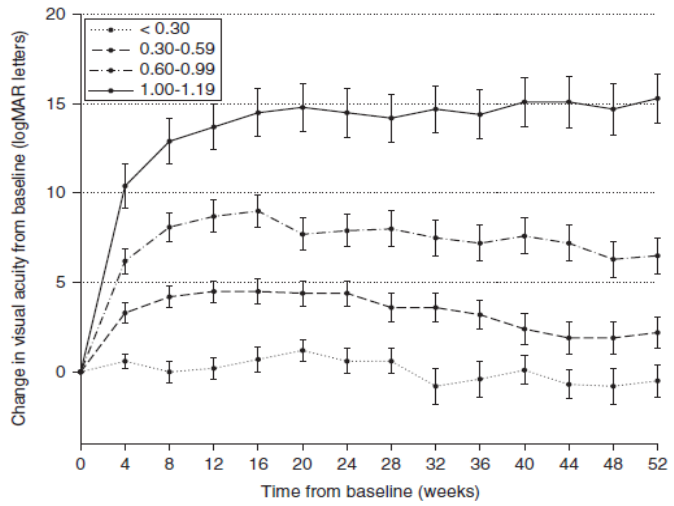
Bibliographic reference	Vogel R N; Davis D B; Kimura B H; Rathinavelu S ; Graves G S; Szabo A ; Han D P. NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH ADVANCED VISUAL LOSS TREATED WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY: Clinical Outcome and Prognostic Indicators. Retina 2016			
	<20 (<20/400)	13 (43.3)	13 (20.0)	2.17 (1.15, 4.09)

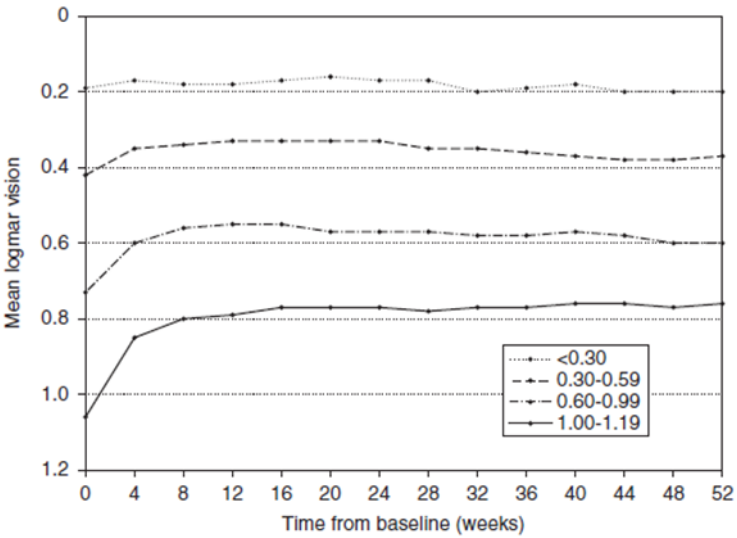
Bibliographic reference	Williams T A; Blyth C P. Outcome of ranibizumab treatment in neovascular age related macula degeneration in eyes with baseline visual acuity better than 6/12. Eye 25 (12): 1671-21. 2011
Country/ies where the study was carried out	UK
Study type	Observational study (prospectively)
Aim of the study	To assess the effect of baseline vision on outcome in ranibizumab-treated neovascular AMD.
Study dates	Published 2011
Source of funding	Not reported
Sample size	615 eyes
Inclusion criteria	Patients were managed at two centres in South East Wales (University Hospital of Wales (UHW), Cardiff and Royal Gwent Hospital (RGH), Newport) using the same management protocol. Eyes that had completed 52-week follow-up were included in the study
Exclusion criteria	CNV secondary to causes other than nAMD Previous treatment for nAMD in the affected eye (argon laser photocoagulation, photodynamic therapy or previous anti-VEGF
Patient characteristics	Ethnic group - not reported Age, mean: 79.3 years Gender, M, %: not reported Visual acuity (ETDRS letters) No. (%) (total=615) <0.30 (6/12): 88 (14.3%) 0.30-0.59 (6/12-6/24): 210 (34.1%) 0.60-0.99 (6/24-6/60: 211 (34.3%)

<table>
<tr><th>Bibliographic reference</th><th>Williams T A; Blyth C P. Outcome of ranibizumab treatment in neovascular age related macula degeneration in eyes with baseline visual acuity better than 6/12. Eye 25 (12): 1671-21. 2011</th></tr>
<tr><td></td><td>1.00-1.20 (6/60-6/96): 106 (17.2%)</td></tr>
<tr><td>Details</td><td>A complete ophthalmological examination was completed for each patient including BCVA, intraocular pressure measurement, dilated fundus biomicroscopy, optical coherence tomography (OCT) and fluorescein angiography.</td></tr>
<tr><td>Treatment</td><td>Three loading doses of intravitreal ranibizumab (0.5mg in 0.05 ml) were administered at monthly intervals followed by PRN treatment 4–6 weekly based on OCT assessment (persistent or recurrent intraretinal and/or subretinal fluid) or slit lamp examination (new subretinal
or retinal haemorrhage). Time domain OCT was in use for the first 18 months of the study (Stratus OCT, Carl Zeiss, Welwyn Garden City, UK), but later it was replaced by spectral domain 3D OCT (Cirrus HD-OCT, Carl Zeiss; Topcon 3D OCT 1000 and 2000, Topcon, Newbury, UK).</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>Baseline visual acuity</td><td><0.30 (6/12) (G1)</td><td>≥6/12 to <6/24 (G2)</td><td>≥6/24 to <6/60 (G3)</td><td>≥6/60 to ≤6/96 (G4)</td><td>Effect (95%CI) (>6/12 vs ≥6/12 to <696</td></tr>
<tr><td>No. of patients at baseline</td><td>88</td><td>210</td><td>211</td><td>106</td><td></td></tr>
<tr><td>Mean VA at week 52, logMAR</td><td>0.20</td><td>0.37</td><td>0.60</td><td>0.76</td><td></td></tr>
<tr><td>Mean change ETDRS letters at week 483</td><td>-0.5 (4.79)</td><td>2.0 (14.49)</td><td>6.5 (19.60)</td><td>15.1 (15.96)</td><td>MD -6.93 (-8.68, -5.18)</td></tr>
<tr><td>No. of people had <15 letter loss (%)</td><td>82 (93%)</td><td>185 (88%)</td><td>194 (92%)</td><td>106 (100%)</td><td>RR 1.01 (0.95, 1.08)</td></tr>
<tr><td>No. of people had >15 letter gain (%)</td><td>1 (1%)</td><td>34 (16%)</td><td>70 (33%)</td><td>49 (46%)</td><td>RR 0.04 (0.01, 0.26)</td></tr>
</table>
</td></tr>
</table>

[3] Calculation of SD based on graph reported in the study.

Bibliographic reference	Williams T A; Blyth C P. Outcome of ranibizumab treatment in neovascular age related macula degeneration in eyes with baseline visual acuity better than 6/12. Eye 25 (12): 1671-21. 2011





Bibliographic reference	**Williams T A; Blyth C P. Outcome of ranibizumab treatment in neovascular age related macula degeneration in eyes with baseline visual acuity better than 6/12. Eye 25 (12): 1671-21. 2011**
Others	Owing to capacity and service constraints of our NHS setting, the mean interval between loading visits was 35 days and not 28 days as planned. Similarly during the PRN period, the mean interval was 45 days and not 4–6 weekly. These prolonged intervals between visits and therefore treatment are likely to have had a detrimental effect on visual outcome.

Bibliographic reference	**Ying G S; Huang J ; Maguire M G; Jaffe G J; Grunwald J E; Toth C ; Daniel E ; Klein M ; Pieramici D ; Wells J ; Martin D F; Comparison of Age-related Macular Degeneration Treatments Trials; Group . Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 120 (1): 122-9. 2013**
Country/ies where the study was carried out	USA
Study type	Cohort study within the Comparison of AMR Treatment Trials
Aim of the study	To determine baseline predictors of visual acuity (VA) outcomes at 1 year after treatment with ranibizumab or bevacizumab for neovascular age-related macular degeneration (AMD).
Study dates	Published 2014
Source of funding	Supported by cooperative agreements U10 EY017823, U10 EY017825, U10 EY017826, and U10 EY017828 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services.
Sample size	1105 participants from CATT study and survived 1 year after study participation
Inclusion criteria	Treatment-naive eyes were treated exclusively with ranibizumab VA between 20/25 (6/7.5) and 20/320 (6/96)
Exclusion criteria	Not reported
Patient characteristics	Age, mean: 79 (SD=8) years Gender, M, %: 38% (n=420) Visual acuity (ETDRS letters): Study eye: 61 letters (Snellen=20/63) (SD=13) Fellow eye: 66 letter (Snellen=20/50) (SD=27)
Details	During the initial visit, participants provided information on demographic characteristics and medical history. Certified photographers followed a standard protocol for field definition and image sequencing to obtain stereoscopic, colour fundus photographs and fluoresce in angiograms. Photographs from all clinical centres were digital except photographs from one

Bibliographic reference	**Ying G S; Huang J ; Maguire M G; Jaffe G J; Grunwald J E; Toth C ; Daniel E ; Klein M ; Pieramici D ; Wells J ; Martin D F; Comparison of Age-related Macular Degeneration Treatments Trials; Group . Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 120 (1): 122-9. 2013**
	centre (film-based). Optical coherence tomography (OCT) was obtained with a Stratus (version 4.0 or higher) time domain OCT machine (Carl Zeiss Meditec, Dublin, California). At baseline and at follow-up weeks 4, 12, 24, 36 and 52, certified visual acuity examiners, masked to the treatment assignment, measured visual acuity after refraction in both eyes using the Electronic Visual Acuity Tester (EVA) following the protocol used in the Diabetic Retinopathy Clinical Research Network.6 The VA scores (the number of letters read correctly on the ETDRS chart, measured with best-corrected visual acuity) from EVA can range from 0 to 100, corresponding to Snellen equivalents of worse than 20/800 to 20/10.
Treatment	Participants were enrolled from 43 clinical centers in the United States between 2008 through 2009, and randomized to one of the four treatment groups: (1) ranibizumab monthly; (2) bevacizumab monthly; (3) ranibizumab as needed (pro re nata, PRN); (4) bevacizumab PRN.
Results	

Baseline visual acuity, study eye	68-82 letters (20-25-20/40 (G1)	53-67 letters, 20/50 to 20/80 (G2)	38-52 letters, 20/100 to 20/160 (G3)	23-37 letters, 20/200 to 20/320 (G4)	Effect (95%CI)		
					G1 vs G2	G1 vs G3	G1 vs G4
No. of people at year 1, (%)	397 (35.9%)	414 (37.5%)	223 (20.2%)	71 (6.4%)			
Mean VA at year 1, letter (SD)4	77.7 (13.9)	69.2 (14.2)	57.8 (14.9)	39.3 (14.3)	8.5 (6.6, 10.4)	19.9 (17.5, 22.3)	38.4 (34.8, 42.0)
Mean change in VA at year 1, letters (SD)	3.7 (13.9)	8.5 (14.2)	11.4 (14.9)	7.8(14.3)	-4.8 (-6.7, -2.8)	-7.7 (-10.1, -5.3)	-4.1 (-7.7. -0.5)

[4] The study reported SE, which was converted to SD (SD=SE *square root of number of people)

Bibliographic reference	Ying G S; Huang J ; Maguire M G; Jaffe G J; Grunwald J E; Toth C ; Daniel E ; Klein M ; Pieramici D ; Wells J ; Martin D F; Comparison of Age-related Macular Degeneration Treatments Trials; Group . Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 120 (1): 122-9. 2013							
	No. of people had ≥3-lines gain from baseline at year 1(%)	28 (7.1%)	150 (36.2%)	119 (53.4%)	30 (42.3%)	0.19 (0.13,0.28)	0.13 (0.09, 0.19)	0.17 (0.11, 0.26)
	Baseline visual acuity, fellow eye	83-100 letters(20/20 or betters)	68-82 letters, 20/25 to 20/40	0/67 letters , 20/50 or worse				
	No. of people at year 1, (%)	331 (30.0%)	433 (39.2%)	341 (30.9%)				
	Mean VA at year 1, letter (SD)	70.7 (18.2)	67.5 (18.7)	66.1 (18.5)	3.2 (0.56, 5.84)	4.6 (1.83 to 7.37)		
	Mean change in VA at year 1, letters (SD)	8.9 (14.6)	7.2 (14.2)	5.9 (14.8)	1.7 (-0.36, 3.76)	3.0 (0.78, 5.22)		
	No. of people had ≥3-lines gain from baseline at year 1(%)	110 (33.2%)	135 (31.2%)	82 (24.0%)				

Pooled results

Baseline visual acuity, study eye	68-82 letters (20-25-20/40)	53-67 letters, 20/50 to 20/320	Effect (95%CI)
No. of people at year 1, (%)	397 (35.9%)	708 (64.1%)	
Mean VA at year 1, letter (SD)5	77.7 (13.9)	62.6 (14.4)	MD 15.10 (13.37, 16.83)
Mean change in VA at year 1, letters (SD)	3.7 (13.9)	9.3 (14.4)	-5.60 (-7.33, -3.87)

[5] The study reported SE, which was converted to SD (SD=SE *square root of number of people)

Bibliographic reference	**Ying G S; Huang J ; Maguire M G; Jaffe G J; Grunwald J E; Toth C ; Daniel E ; Klein M ; Pieramici D ; Wells J ; Martin D F; Comparison of Age-related Macular Degeneration Treatments Trials; Group . Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 120 (1): 122-9. 2013**

No. of people had ≥3-lines gain from baseline at year 1(%)	28 (7.1%)	299 (42.2%)	0.17 (0.12,0.24)
Baseline visual acuity, fellow eye	>20/40	<20/40	
No. of people at year 1, (%)	764	341 (30.9%)	
Mean VA at year 1, letter (SD)	68.9 (18.5)	66.1 (18.5)	2.80 (0.44, 5.16)
Mean change in VA at year 1, letters (SD)	7.9 (14.4)	5.9 (14.8)	2.00 (0.13, 3.87)
No. of people had ≥3-lines gain from baseline at year 1(%)	245 (32.1%)	82 (24.0%)	1.33 (1.08, 1.65)

Bibliographic reference	**Zhu M ; Chew J K; Broadhead G K; Luo K ; Joachim N ; Hong T ; Syed A ; Chang A A. Intravitreal Ranibizumab for neovascular Age-related macular degeneration in clinical practice: five-year treatment outcomes. Graefes Archive for Clinical & Experimental Ophthalmology 253 (8): 1217-25. 2015**
Country/ies where the study was carried out	Australia
Study type	Observational study (retrospective)
Aim of the study	to assess the visual and anatomical outcomes and safety profile of intravitreal ranibizumab in treating nAMD over a period of five years
Study dates	Published 2015
Source of funding	This research is supported in part by an unrestricted grant from Novartis Pharmaceuticals Australia Pty Limited. The sponsor had no role in the design or conduct of this research

Bibliographic reference	Zhu M ; Chew J K; Broadhead G K; Luo K ; Joachim N ; Hong T ; Syed A ; Chang A A. Intravitreal Ranibizumab for neovascular Age-related macular degeneration in clinical practice: five-year treatment outcomes. Graefes Archive for Clinical & Experimental Ophthalmology 253 (8): 1217-25. 2015
Sample size	208 eyesof 208 people
Inclusion criteria	Patients treated with intravitreal ranibizumab for subfoveal nAMD
Exclusion criteria	The study eye underwent vitrectomy surgery at any time The study eye was treated with photodynamic therapy (PDT), given intravitreal bevacizumab or triamcinolone during the follow-up period, or received intravitreal ranibizumab prior to June 2007.
Patient characteristics	Ethnic group – Asian no=6 (2.9%) Age, mean: 78.4 (SD 7.2) years Gender, M, %: 31.3% (n=65) Visual acuity (ETDRS letters) 23-39 letters: 17.3% (n=257) 40-54 letters: 23.1% (n=343) 55-69 letters: 42.7% (n=633) >70 letters: 16.9% (n=250) Time history: no prior treatment (34.1%, n=71), one or more previous nAMD treatment (65.9%, n=137) Disease type: occult (72.9%, n=124), minimally classic (18.8%, n=32), predominantly (5.3%, n=9), classic (2.9%, n=5)
Details	At baseline, best corrected Snellen visual acuity (VA), intraocular pressure (IOP) measurement, and fundoscopy were conducted. Central macular thickness (CMT) was measured with Stratus time-domain optical coherence tomography (TDOCT, software version 5.0; Carl Zeiss Meditec, Dublin, CA, USA) using the fast macular thickness mapping protocol. The presence and type of choroidal neovascularisation (CNV) was determined by FFA. Patient medical history, concomitant medication, and previous treatment for nAMD were recorded. Polypoidal choroidal vasculopathy (PCV) was not screened, as indocyanine green angiography (ICGA) was performed only in cases when the clinical presentation and demographic of the patient suggested PCV. Patient follow-up intervals varied between one and six months, depending upon disease activity. At each visit, Snellen VA, OCT, ophthalmic examination, and fundoscopy were performed. OCT findings were used as a guide for treatment. At the five-

<table>
<tr><th>Bibliographic reference</th><th>Zhu M ; Chew J K; Broadhead G K; Luo K ; Joachim N ; Hong T ; Syed A ; Chang A A. Intravitreal Ranibizumab for neovascular Age-related macular degeneration in clinical practice: five-year treatment outcomes. Graefes Archive for Clinical & Experimental Ophthalmology 253 (8): 1217-25. 2015</th></tr>
<tr><td></td><td>year visit, OCT scans were performed using SD-OCT with either a Cirrus (OCT 3; Carl Zeiss Meditec, Dublin, CA, USA) or Spectralis device (Heidelberg
Engineering, Heidelberg, Germany). FFA and IOP measurement was performed at the discretion of the treating physician. The most common indication for repeat FFA was persistent fluid on OCT refractory to monthly treatment, and repeat IOP measurement was performed when patients showed signs of increased IOP after the treatment.</td></tr>
<tr><td>Treatment</td><td>The department uses a pro re nata treatment posology after an initial loading phase of three injections at monthly intervals. All intravitreal injections are administered in dedicated treatment rooms with povidone iodine being used before and after injections.
After each injection the patient is asked to confirm they can still count fingers as a surrogate measure of intraocular pressure (IOP) and if they cannot (or if the patient has glaucoma) then the IOP is checked and treated as appropriate.
Patients are followed up at monthly intervals with SD OCT and fundal examination until no injections have been required to either eye for 6 months, after which follow-up intervals are gradually extended. If no injections have been required for 1 year patients are discharged and advised to return if they notice any new symptoms of blurring or distortion of vision in either eye.

Criteria for retreatment included one or more of the following: reduction in Snellen vision of ≥1 line, persistent exudation or blood at the macula on clinical examination, presence of subretinal or intraretinal fluid on OCT, or development of new areas of CNV on FFA.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td>Baseline visual acuity</td><td>≥85 letters</td><td>≥70 and <85 letters</td><td>≥60 and <70 letters</td><td>≥35 and <60 letters</td><td><35 letters</td></tr>
<tr><td>No. of patients at baseline</td><td>6</td><td>34</td><td>46</td><td>100</td><td>22</td></tr>
<tr><td>Mean VA change 5 year, letters (95%CI)</td><td>-15.8 (-51.5, 19.9)</td><td>-12.9 (-19.2, -6.6)</td><td>-3.7 (-8.2 to 0.9)</td><td>-0.6 (-3.2 to 2.0)</td><td>11.5 (5.2 to 17.9)</td></tr>
</table>

Pooled results
<table>
<tr><td>Baseline visual acuity, study eye</td><td>≥70 letters</td><td>≥35 to <70 letters</td><td>Effect (95%CI)</td></tr>
<tr><td>No. of people at baseline</td><td>40</td><td>146</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Zhu M ; Chew J K; Broadhead G K; Luo K ; Joachim N ; Hong T ; Syed A ; Chang A A. Intravitreal Ranibizumab for neovascular Age-related macular degeneration in clinical practice: five-year treatment outcomes. Graefes Archive for Clinical & Experimental Ophthalmology 253 (8): 1217-25. 2015

Mean 5-year change in VA, letters (SD)	-13.33 (22.15)	-1.58 (14.04)	-11.75 (-18.98, -4.52)

Baseline visual acuity, study eye	<35 letters	≥35 to <70 letters	Effect (95%CI)
No. of people at baseline	22	146	
Mean 5-year change in VA, letters (SD)	11.5 (15.96)	-1.58 (14.04)	13.08 (6.04, 20.12)

Linear regression analysis of change in VA over 5 years

Baseline VA, letters	No.	Regression, coefficient* (95%CI)	P value
≥70	40	Reference	-
≥60 and <70	45	11.2 (4.9, 17.4)	<0.0005
≥35 and <60	100	16.1 (10.5, 21.6)	<0.0005
<35	12	30.7 (22.8, 38.6)	<0.005
*Adjusted for baseline age and total number of ranibizumab injection			

E.6.3 Adjunctive therapies

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

<table>
<tr><th>Bibliographic reference</th><th>Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.</th></tr>
<tr><td>Country/ies where the study carried out</td><td>University of Tehran, Iran</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Aim of the study</td><td>To determine whether combined intravitreal bevacizumab (IVB) and triamcinolone (IVT) is more effective than IVB alone in neovascular age-related macular degeneration</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>120</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients with subfoveal choroidal neovascularisation, including predominantly classic, minimally classic, occult, and retinal angiomatous proliferation secondary to age-related macular degeneration.</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients’ eye were presence of diabetic retinopathy, glaucoma, or any other type of macular disease;
Patients eye had previous history of treatment (other than photodynamic therapy)</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Combined intravitreal bevacizumab with intravitreal triamcinolone (IVB/IVT)</th><th>Intravitreal bevacizumab (IVB)</th><th>P</th></tr>
<tr><td>Number eyes</td><td>55</td><td>60</td><td></td></tr>
<tr><td>Mean age (SD)</td><td>71(8)</td><td>71 (8)</td><td>0.885</td></tr>
<tr><td>Gender (F/M)</td><td>34/21</td><td>35/25</td><td>0.703</td></tr>
<tr><td>Smoking (%)</td><td>15 (27)</td><td>13 (22)</td><td>0.484</td></tr>
<tr><td>CNV type (%)</td><td></td><td></td><td>0.971</td></tr>
<tr><td>Minimally classic</td><td>10 (18)</td><td>12 (20)</td><td></td></tr>
<tr><td>Dominantly classic</td><td>20 (36)</td><td>22 (37)</td><td></td></tr>
<tr><td>Occult</td><td>15 (27)</td><td>17 (28)</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.**
	<table><tr><td>RAP</td><td>10 (18)</td><td>9 (15)</td><td></td></tr><tr><td>PED</td><td>3 (6)</td><td>3 (5)</td><td>>0.999</td></tr><tr><td>CNV size (%)</td><td></td><td></td><td>0.084</td></tr><tr><td><2</td><td>17 (31)</td><td>18 (30)</td><td></td></tr><tr><td>2-4</td><td>29 (53)</td><td>22 (37)</td><td></td></tr><tr><td>>4</td><td>9 (16)</td><td>20 (33)</td><td></td></tr><tr><td>BCVA ETDRS (SD)</td><td>33 (18)</td><td>37 (21)</td><td>0.351</td></tr><tr><td>CMT µm (SD)</td><td>353 (119)</td><td>341 (158)</td><td>0.716</td></tr></table>
Study visits and procedures	Patients underwent a baseline evaluation; Patients were assigned randomly to IVB or IVB/IVT groups Patients in the IVB group received mandated therapy with 3 consecutive intravitreal injection of 1.25mg/0.05ml of bevacizumab with 6 weeks apart; Patients in the IVB/IVT group, intravitreal injection of 2mg/0.05mL of triamcinolone acetonide was added to bevacizumab in the first session. The second and third injections consisted of bevacizumab only; Clinical examinations and optical coherence tomography were repeated at 6-week intervals. Fluorescein angiography was repeated 6 weeks and 24 weeks after the first injection. A fourth IVB injection was given eyes with active CNV at Week 24 according to clinical findings. Intravitreal triamcinolone injection was not repeated during the follow-up period
Intervention	Combined intravitreal bevacizumab with intravitreal triamcinolone (IVT)
Comparator	Intravitreal bevacizumab (IVB)
Outcomes	Primary outcome: Change in best-corrected visual acuity Secondary outcome: Central macular thickness Need for a fourth injection Adverse events
Analyses	Chi-square, Fisher exact test and Mann-Whitney test T-test Marginal regression based on generalised estimating equation

<table>
<tr><th>Bibliographic reference</th><th>Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.</th></tr>
<tr><td>Length of follow up</td><td>24 weeks (6 months)</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Combined intravitreal bevacizumab with intravitreal triamcinolone (IVB/IVT)</td><td>Intravitreal bevacizumab (IVB)</td><td>Effect (95%CI)</td><td>P value</td></tr>
<tr><td>No. of eyes that needed for retreatment at Week 24 (%)</td><td>19 (34.5)</td><td>32 eyes (53.3)</td><td>0.65 (0.42, 1.00)</td><td>0.04</td></tr>
<tr><td>Best-corrected visual acuity changes (ETDRS letter score)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0-6 weeks</td><td>8.5 (14.4)</td><td>3.8 (8.9)</td><td>4.7 (0.2, 9.0)</td><td>0.04</td></tr>
<tr><td>0-12 weeks</td><td>11.8(16.6)</td><td>6.2 (10.8)</td><td>5.6 (0.5, 10.8)</td><td>0.03</td></tr>
<tr><td>0-18 weeks</td><td>12.9 (15.6)</td><td>8.4 (13.6)</td><td>4.5 (-1.1, 10.0)</td><td>0.11</td></tr>
<tr><td>0-24 weeks</td><td>11.3 (17.2)</td><td>8.7 (15.6)</td><td>2.6 (-3.5, 8.7)</td><td>0.40</td></tr>
<tr><td>CMT changes</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0-6 weeks</td><td>-79.6 (124.9)</td><td>-58.8 (131.3)</td><td>-20.8 (-73.6, 32.0)</td><td>0.43</td></tr>
<tr><td>0-12 weeks</td><td>-89.7 (154.9)</td><td>-85.3 (128.5)</td><td>-4.4 (-63.4, 54.6)</td><td>0.88</td></tr>
<tr><td>0-18 weeks</td><td>-114.1 (151.7)</td><td>-96.3 (156.6)</td><td>17.8 (-82.0, 46.4)</td><td>0.58</td></tr>
<tr><td>0-24 weeks</td><td>-89.1 (162.5)</td><td>-88.4 (117.1)</td><td>0.7 (-59.4, 58.0)</td><td>0.98</td></tr>
</table>
No systemic AE reported.
</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>115 eyes of 115 patients completed 6 months follow-up.</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Groups of participants were blinded to the optometrist who conducted visual acuity assessment.</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>Unclear</td></tr>
</table>

Bibliographic reference	Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.
adequately prevented during the study?	
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.
Coutry/ies where the study carried out	Beirut, Lebanon
Study type	Open label RCT
Aim of the study	To compare verteporfin photodynamic therapy combined with intravitreal ranibizumab (combination therapy) versus ranibizumab monotherapy for management of neovascular age-related macular degeneration.
Study dates	June 2007 and January 2008
Sources of funding	Novartis
Sample size	30 patients (40 eyes)
Inclusion Criteria	Age 50 years or older Subfoveal CNV secondary to AMD as determinately by fluorescein angiography Presence of fluid in the macular on OCT CNV≤5,400µm in greatest linear dimension

<table>
<tr><th>Bibliographic reference</th><td>Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.</td></tr>
<tr><td></td><td>BCVA, using ETDRS charts, of 20/50 to 20/400 in the study eye
Area of CNV at least 50% of total lesion area</td></tr>
<tr><td>Exclusion Criteria</td><td>Corneal, lenticular or vitreous opacification that prevents good quality angiograms on OCT
History of uveitis
Other ocular conditions that may affect vision
Subfoveal scarring or haemorrhage
Previous treatment for CNV
Anti-VEGF treatment less than 3 months before enrolment and or
Verteporfin PDT less than 6 months before enrolment</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Combination Therapy</td><td>Monotherapy</td><td>P values</td></tr>
<tr><td>Number of patients</td><td>13</td><td>17</td><td>-</td></tr>
<tr><td>Number of eyes</td><td>20</td><td>20</td><td>-</td></tr>
<tr><td>Mean age (SD)</td><td>71.0 (8.0)</td><td>75.6 (6.3)</td><td>0.19</td></tr>
<tr><td>Number of male</td><td>9</td><td>9</td><td></td></tr>
<tr><td>CNV type</td><td></td><td></td><td></td></tr>
<tr><td>Occult</td><td>7</td><td>9</td><td>0.49</td></tr>
<tr><td>Minimally classic</td><td>8</td><td>6</td><td>0.58</td></tr>
<tr><td>Predominantly classic</td><td>5</td><td>5</td><td>0.84</td></tr>
<tr><td>Previous treatment</td><td></td><td></td><td></td></tr>
<tr><td>None</td><td>9</td><td>10</td><td>0.71</td></tr>
<tr><td>Anti-VEGF</td><td>9</td><td>8</td><td>0.55</td></tr>
<tr><td>PDT</td><td>2</td><td>2</td><td>0.71</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were allocated to ranibizumab monotherapy or verteporfin PDT in combination with intravitreal ranibizumab in a 1:1 ratio;
Patients allocated to the monotherapy group received intravitreal ranibizumab (0.5mg);
Patients assigned to the combination therapy group were treated with PDT with verteporfin, within an hour of PDT, an intravitreal injection of ranibizumab was administrated to the treated eye;</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.</td></tr>
<tr><td></td><td>The treatment in both groups was divided into an induction phase and a follow-up phase. The introduction phase of the monotherapy group consisted of the initial ranibizumab injection followed by 2 consecutive monthly injections for a total of 3 injections. The induction phase on the combination therapy group consisted of the primary PDT session followed by the ranibizumab injection; however, no additional obligation consecutive injections were given. After the initial treatment, patients were seen at 1 week and then followed monthly.</td></tr>
<tr><td>Intervention</td><td>Combined therapy: patients were treated with PDT with verteporfin, within an hour of PDT, an intravitreal injection of ranibizumab was administrated to the treated eye.</td></tr>
<tr><td>Comparator</td><td>Monotherapy ranibizumab</td></tr>
<tr><td>Outcomes</td><td>A proportion of patients who lost < 15 letter in BCVA score at 12 months compared with baseline
Mean change in BCVA score
The proportion of patients who gain ≥15 letters in BCVA
The proportion of patients with Snellen equivalent visual acuity of 20/200 or worse compared with baseline
The effect of combination therapy vs monotherapy on the size of CNV
The effect of both treatment on the CRT
The number of intravitreal ranibizumab injections over 12 months in 2 groups</td></tr>
<tr><td>Analyses</td><td>Generalised estimation equation</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Combined therapy (PDT + ranibizumab) (n=20 eyes)</th><th>Intravitreal ranibizumab (n=20 eyes)</th><th>Effect (95%CI)</th><th>P values</th></tr>
<tr><td>Injection in 12 months</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Introduction phase</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Total number</td><td>60</td><td>119</td><td>-59</td><td></td></tr>
<tr><td>Median (range)</td><td>3 (1 to 6)</td><td>6 (3 to 10)</td><td>-3</td><td><0.001</td></tr>
<tr><td>Follow-up phase</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>2 (0 to 5)</td><td>3 (0 to 6)</td><td>-1</td><td>0.13</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.

% of patients not require injection after introduction phase	20%	15%	1.33 (0.34, 5.21)	1.0
Best-corrected visual acuity changes				
Baseline (SE)	53.4 (3.2)	53.8 (2.6)	-0.4 (-8.5, 7.7)	0.88
After 12 months	56.6 (3.3)	65.8 (2.5)	-9.2 (-17.4, -1.2)	
Letter gain by 12 months	3.2	12.0	-8.8	-
% change by 12 month	0.07 (0.04)	0.32 (0.13)	-0.25	0.03
Central macular thickness changes				
Baseline (SE)	292.5 (18.1)	283.0 (16.0)	9.5 (-37.9, 56.9)	0.52
After 12 months	219.9 (15.0)	212.3 (11.2)	7.6 (-29.1, 44.3)	0.62
Decrease by 12 months	72.6	70.7	1.9	-
% change by 12 month	-0.22 (0.04)	-0.19 (0.07)	-0.03	0.71
Safety	macular oedema (8)	retinal pigment epithelium tear (1): Cataract by Month 10 (1)	4.00 (0.97, 16.55)	

Missing data handling/loss to follow up	All patients completed the 12 month period of the study
Was allocation adequately concealed?	No (open-label), but no detail described in the study
Was knowledge of the allocated intervention	No

Bibliographic reference	Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.
adequately prevented during the study?	
Was the allocation sequence adequately generated?	Unclear (not reported)
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size (20 eyes in each group)
Were incomplete outcome data adequately addressed?	All completed follow-up
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.
Coutry/ies where the study carried out	Greece
Study type	RCT
Aim of the study	To evaluate combination treatment with reduced-fluence photodynamic therapy (RDPDT) with verteporfin and intravitreal bevacizumab, compared to bevacizumab alone, for choroidal neovascularization (CNV) in age-related macular degeneration
Study dates	Not reported
Sources of funding	Not reported
Sample size	100
Inclusion Criteria	Patients with predominantly classic and occult CNV due to AMD in one or both eyes; All eye were treatment naive Leakage documented by fluorescein angiography, intraretinal or subretinal fluid in optical coherence tomography

<table>
<tr><th>Bibliographic reference</th><th>Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.</th></tr>
<tr><td></td><td>Largest linear dimension of the lesion equal to four disk areas
Corrected distance visual acuity of 20/400 or more</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with other ocular pathologies within 2 months prior to initial assessment were excluded;
Patients' fluorescein angiography and OCT images were of inadequate quality due to significant optical media opacities;
Patients would presumably need ophthalmic surgery within the following year;</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Combined therapy (PCT + bevacizumab)</td><td>Intravitreal bevacizumab</td><td>P values</td></tr>
<tr><td>Number of patients</td><td>49</td><td>46</td><td></td></tr>
<tr><td>Male (%)</td><td>13 (27)</td><td>16 (35)</td><td></td></tr>
<tr><td>Mean age (SD)</td><td>73 (8.5)</td><td>74 (10.3)</td><td>0.543</td></tr>
<tr><td>CDVA (logMAR)</td><td>0.74 (0.32)</td><td>0.71 (0.32)</td><td>0.691</td></tr>
<tr><td>CFT</td><td>460.73 (110.68)</td><td>441.11 (122.59)</td><td>0.414</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>All patients underwent a complete ophthalmic examination before treatment;
Patients were allocated to the group with bevacizumab monotherapy were administrated intravitreal injection (1.25mg);
Patients allocated in the combination treatment group underwent one session of low-fluence PDT with verteportin, one hour later, intravitreal injection of bevacizumab (1.25mg);
Patients were assessed in a monthly basis and intravitreal bevacizumab was re-administrated at each visit if at least one of the following functional and anatomic criteria was fulfilled: a≥100μm increase in CFT; decrease in CDVA of>5 letters; presence of subretinal fluid and/or intraretinal in OCT; and presence of new haemorrhage in biomicroscopy
Data were collected 1,3,6,9 and 12 months after initiation of treatment.</td></tr>
<tr><td>Intervention</td><td>Combined therapy: PCT + bevacizumab</td></tr>
<tr><td>Comparator</td><td>Bevacizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td>Number of reinjections at the end of follow-up
CDVA (corrected-distance visual acuity)
CFT</td></tr>
<tr><td>Analyses</td><td>Independent samples t-test
Chi-square test</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.</th></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Combined therapy (PCT + bevacizumab) (n=49)</td><td>Intravitreal bevacizumab (n=46)</td><td>Effect (95%CI)</td><td>P value</td></tr>
<tr><td>Reinjections</td><td>4.45 (0.15)</td><td>6.96 (0.29)</td><td>-2.51
(-3.15, -1.87)</td><td><0.001</td></tr>
<tr><td>Corrected distance visual acuity (logMAR)</td><td>0.57 (0.04)</td><td>0.54 (0.04)</td><td>0.03
(-0.08, 0.14)</td><td>0.584</td></tr>
<tr><td>Gain in letters</td><td>8.37 (1.77)</td><td>8.64 (2.11)</td><td>-0.27
(-5.65, 5.11)</td><td>0.922</td></tr>
<tr><td>No. of patients (%) had a stable or improved vision (loss of <15 letters)</td><td>44 (89.9)</td><td>43 (93.5)</td><td>0.96
(0.85, 1.08)</td><td></td></tr>
<tr><td>No. of patients (%) gained 15 or more letter</td><td>21 (42.8)</td><td>20 (43.5)</td><td>0.99
(0.62, 1.56)</td><td></td></tr>
<tr><td>CFT, μm</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline (SE)</td><td>460.73 (15.81)</td><td>441.11(18.08)</td><td>19.62
(-58.93, 98.17)</td><td></td></tr>
<tr><td>Month 12 (SE)</td><td>290.84 (13.75)</td><td>286.00 (8.55)</td><td>4.84
(-27.37, 37.05)</td><td>0.768</td></tr>
</table>
</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>Not reported (based on results, 5 patients did not complete the 12 month follow up)</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Unclear</td></tr>
</table>

Bibliographic reference	Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Unclear
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.
Coutry/ies where the study carried out	Japan
Study type	RCT
Aim of the study	To compare the 1-year results of initial or deferred photodynamic therapy (PDT) combined with intravitreal ranibizumab (IVR) for eyes with polypoidal choroidal vasculopathy.
Study dates	January 10 2011 to October 5 2012
Sources of funding	Not reported
Sample size	72 patients (72 eyes)
Inclusion Criteria	Male patients were older than 50 years with treatment-naive PCV who met the following criteria: BCVA ranged from 01. To 0.7 using a Landolt chart The greatest lesion size was less than 12 macular photocoagulation study disk areas

<table>
<tr><th>Bibliographic reference</th><th>Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.</th></tr>
<tr><td>Exclusion Criteria</td><td>Patients' eyes had central serous chorioretinopathy, retinal vascular disease, any neovascular maculopathy, glaucoma, or a history of intraocular surgery after phacoemulsification.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Intravitreal ranibizumab</th><th>Combined therapy (PCT + ranibizumab)</th></tr>
<tr><td>Number of eyes</td><td>35</td><td>37</td></tr>
<tr><td>Mean age (SD)</td><td>73.8 (7.1)</td><td>73.6 (5.8)</td></tr>
<tr><td>Visual acuity (logMAR)</td><td>0.51 (0.24)</td><td>0.50 (0.24)</td></tr>
<tr><td>Visual acuity (ETDRS)</td><td>54.9 (13.1)</td><td>54.3 (17.9)</td></tr>
<tr><td>Central macular thickness</td><td>345.6 (118.6)</td><td>360.5 (174.4)</td></tr>
<tr><td>Bilatelal PCV (%)</td><td>5 (14.3)</td><td>7 (18.9)</td></tr>
<tr><td>Subfoveal polys (%)</td><td>19 (54.3)</td><td>16 (43.2)</td></tr>
<tr><td>Multiple polys (%)</td><td>24 (68.6)</td><td>2 (56.8)</td></tr>
<tr><td>Subretinal haemorrhage</td><td>10 (28.6)</td><td>13 (35.1)</td></tr>
<tr><td>Pigment epithelial detachment eyes (%)</td><td>10 (28.6)</td><td>12 (32.4)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised to verteporfin PDT plus intravitreal ranibizumab (IVR) combination therapy or ranibizumab alone in a 1:1 ratio;
In combination therapy group, PDT was administered within 1 week after IVR injection;
In both groups, IVR was administered once for 3 consecutive months</td></tr>
<tr><td>Intervention</td><td>Ranibizumab +PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td>Differences in the changes in BCVA at 12 months from baseline between 2 groups</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
</table>

Bibliographic reference	Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.
Results	

	Intravitreal ranibizumab	Combined therapy (ranibizumab +PDT)	Effect (95%CI)	P values
Number of eyes	31	29		
BCVA logMAR				
Baseline (SD)	0.50 (0.24)	0.52 (0.25)	0.02 (-0.10, 0.14)	
Month 12 (SD)	0.30 (0.27)	0.29 (0.27)	-0.01 (-0.11, 0.13)	
N (%) of patients had improved VA≥15 letters	15 (48.4)	13 (44.8)	0.93 (0.54, 1.60)	
CRT				
Baseline (SD)	343.6 (108.6)	360.5 (174.4)	16.9 (-57.2, 91.0)	0.63
Month 12	206.0 (67.3)	187.2 (87.5)	-18.8 (-58.5, 20.9)	0.68
Additional treatment				
No. of patients without additional treatment	6	19	3.39 (1.57, 7.28)	
Mean additional IVRs (Month 3 to 12)	3.8 (2.3)	1.5 (1.8)	-2.3 (-3.3, -1.3)	<0.001
Mean additional PDTs	0.48 (0.56)	0.14 (0.35)	-0.35 (-0.6, -0.1)	0.0134
Treatment-emergent AEs	2*	0		

*1 patients in the combined therapy group had myocardial infarction 11 days after ranibizumab injection; 1 eyes in the combined therapy group developed a new subretinal haemorrhage smaller than 3 disk areas at Month 5, which resolved spontaneously and did not affect the BCVA

Missing data handling/loss to follow up	During the study, 8 patients in the combined therapy and 4 in monotherapy group withdrew from the study.
Was allocation adequately concealed?	No (open treatment allocation)

Bibliographic reference	Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.
Was knowledge of the allocated intervention adequately prevented during the study?	No
Was the allocation sequence adequately generated?	Stratified based on BCVA
Was the study apparently free of other problems that could put it at a high risk of bias?	Only males were included in the study
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.
Coutry/ies where the study carried out	USA
Study type	Double blinded RCT
Aim of the study	To investigate the injection frequency and visual acuity (VA) outcomes with combination therapy (ranibizumab plus verteporfin photodynamic therapy, PDT) versus monotherapy (ranibizumab).
Study dates	Not reported
Sources of funding	Novartis Pharma AG
Sample size	40
Inclusion Criteria	Patients aged ≥50 years with subfoveal CNV secondary to AMD; Patients had a VA letter score of 73-24 on an ETDS chart Patients had a lesion that consisted of≥50% active CNV as shown by fluorescein angiography

<table>
<tr><th>Bibliographic reference</th><th>Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.</th></tr>
<tr><td>Exclusion Criteria</td><td>Laser photocoagulation, intravitreal steroids or verteporfin PDT in the study eye within 30 days before enrolment;
Prior external-beam radiation therapy, vitrectomy or transpupillary thermotherapy;
A history of surgery in the study eye within the past 2 months
Participation in any studies of investigational drugs within the past month;
Any trials of antiangiogenic drugs
A history of intravitreal anti VEGF treatment</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Combination therapy</td><td>Monotherapy</td></tr>
<tr><td>Number of patients</td><td>19</td><td>21</td></tr>
<tr><td>Number of female (%)</td><td>13 (68.4)</td><td>14 (66.7)</td></tr>
<tr><td>Mean age, years</td><td>79</td><td>78</td></tr>
<tr><td>Mean VA letter score (ETDRS)</td><td>52.1</td><td>52.1</td></tr>
<tr><td>Patients with prior PDT</td><td>7 (36.8)</td><td>4 (19.0)</td></tr>
<tr><td>CNV types</td><td></td><td></td></tr>
<tr><td>Occult without classic</td><td>15 (78.9)</td><td>10 (47.6)</td></tr>
<tr><td>Minimally classic</td><td>1 (5.3)</td><td>4 (19.0)</td></tr>
<tr><td>Predominantly classic</td><td>3 (15.8)</td><td>7 (33.3)</td></tr>
<tr><td>Mean CRT (SD),µm</td><td>294 (70)</td><td>324 (98)</td></tr>
<tr><td>Mean total area of lesion, mm2</td><td>8.2 (3.6)</td><td>9.4 (7.70</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised 1:1 to combination therapy or monotherapy;
Patients received standard-fluence verteportin PDT or sham PDT at baseline and intravitreal injection with ranibizumab (0.3mg) within 1 hour after PDT in the study eye, followed by 2 further ranibizumab (0.3mg) injections at monthly interval;
Patients were followed up at 30-day intervals throughout the study
At the follow-up visit at month 3-11, ranibizumab injections were administered if there was a decrease in BCVA of>5 letter compared with the highest previous BCVA values or if there was an increase in CRT on OCT≥100µm compared with the lowest previous value;
The minimum interval between ranibizumab treatment was 28 days</td></tr>
<tr><td>Intervention</td><td>Combination therapy: ranibizumab plus single standard-fluence verteporfin PDT</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.</th></tr>
<tr><td>Comparator</td><td>Monotherapy ranibizumab plus a single sham PDT</td></tr>
<tr><td>Outcomes</td><td>Best corrected visual acuity; central macular thickness</td></tr>
<tr><td>Analyses</td><td>Pearson chi square
Bonferroni-Holm stepdown test</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Combined therapy (ranibizumab +PDT)</td><td>Intravitreal ranibizumab</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>19</td><td>21</td><td></td></tr>
<tr><td>Re-treatment</td><td></td><td></td><td></td></tr>
<tr><td>Total number, Month 3-12</td><td>23</td><td>53</td><td></td></tr>
<tr><td>% of patients had no retreatment, Month12</td><td>47%</td><td>23%</td><td>1.99 (0.81, 4.89)</td></tr>
<tr><td>BCVA, Mean improvement (letters) from baseline</td><td></td><td></td><td></td></tr>
<tr><td>Month 6 (SD)</td><td>8.5 (2.5)</td><td>10.2 (1.8)</td><td>-1.70 (-3.1, -0.3)</td></tr>
<tr><td>Month 12 (SD)</td><td>9.0 (2.8)</td><td>7.5 (2.9)</td><td>1.5 (-0.3, 3.3)</td></tr>
<tr><td>% of patients gained ≥15 letters</td><td></td><td></td><td></td></tr>
<tr><td>Month 6</td><td>22.2% (n=4)</td><td>31.6% (n=7)</td><td>0.63 (0.22, 1.82)</td></tr>
<tr><td>Month 12</td><td>33.3% (n=6)</td><td>36.8% (n=8)</td><td>0.83 (0.35, 1.95)</td></tr>
<tr><td>CRT change from baseline,µm</td><td></td><td></td><td></td></tr>
<tr><td>Month 12</td><td>-89 (24)</td><td>-101 (25)</td><td>-12 (-27.2, 3.2)</td></tr>
<tr><td>Adverse events</td><td></td><td></td><td></td></tr>
<tr><td>No. of patients (%)</td><td>10 (52.6)</td><td>11 (52.4)</td><td>1.00 (0.56, 1.81)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.
Missing data handling/loss to follow up	3 patients discontinued after the initial 3 loading injection of ranibizumab (2 in monotherapy and 1 in the combination therapy group) 1 patient discontinued due to an allergy 2 were unwilling to attend monthly follow-up
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size Variation in patients' baseline characteristics (more people in combined group previously received PDT, and more patients with occult without classic CNV in the combined group)
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.
Coutry/ies where the study carried	USA
Study type	Double-blinded RCT
Aim of the study	To demonstrate non-inferiority of ranibizumab in combination with verteporfin photodynamic therapy (PDT) versus ranibizumab monotherapy in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).
Study dates	Not reported

<table>
<tr><th>Bibliographic reference</th><th>Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.</th></tr>
<tr><td>Sources of funding</td><td>Novartis Pharma AG</td></tr>
<tr><td>Sample size</td><td>321</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients were 50 years of age or older and had subfoveal CNV secondary to neovascular AMD
BCVA letter score in the study eye between 73 and 24 letters
Maximum permitted linear dimension of the total lesion was 5400µm
Total CNV area encompassed within the lesion had to be more than 50% of the total lesion area</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients received prior treatment for neovascular AMD in the study eye
Patients had uncontrolled glaucoma, angioid streaks, presumed ocular histoplasmosis syndrome, pathological myopia or CNV secondary to cause other than neovascular AMD
Patients had presence of fibrosis, haemorrhage, pigment epithelial detachments, or other hypofluorescent lesion obscuring more than 50% of the CNV lesion
Patients had presence of retinal pigment epithelial tear.</td></tr>
<tr><td>Baseline characteristics</td><td><table>
<tr><td></td><td>SF verteportin +ranibizumab</td><td>RF verteportin +ranibizumab</td><td>Sham verteportin +ranibizumab</td></tr>
<tr><td>Number of patients</td><td>104</td><td>105</td><td>112</td></tr>
<tr><td>Mean BCVA score, letters</td><td>53.8</td><td>54.6</td><td>54.5</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td>Patients were randomised 1:1:1 for receiving stand fluence verteporfin plus intravitreal ranibizumab (combination therapy), reduce fluence verteporfin plus intravitreal ranibizumab (combination therapy) or sham verteporfin plus intravitreal ranibizumab
Patients in the verteporfin PDT combination therapy groups received PDT on day 1 and PRN for months 3 through 11 within a minimum treatment interval of 90 days
Ranibizumab (0.5mg) was administrated at baseline and month 1 and 2, followed by PRN at a 30 day interval for months 3 through 11.</td></tr>
<tr><td>Intervention</td><td>Patients were randomised 1:1:1 for receiving standard fluence verteporfin plus intravitreal ranibizumab (combination therapy), reduce fluence verteporfin plus intravitreal ranibizumab (combination therapy)</td></tr>
<tr><td>Comparator</td><td>Sham verteporfin plus intravitreal ranibizumab</td></tr>
<tr><td>Outcomes</td><td>Functional (BCVA)
Treatment-emergent adverse events</td></tr>
</table>

Bibliographic reference	**Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.**
Analyses	Analysis of variance T-test Stratified and unstratified Cochran-Mantel-Haeszel tests
Length of follow up	12 months
Results	

	Combined therapy (ranibizumab +SF PDT)	Intravitreal ranibizumab	Effect (95%CI)	Combined therapy (ranibizumab +RF PDT)	Intravitreal ranibizumab	Effect (95%CI)
Number of patients	104	112		105	112	
BCVA, Mean improvement (letters) from baseline						
Month 3 (SD)	+6.3 (14.2)	+6.9 (12.1)	-0.6 (-4.1, 2.9)	+6.4(11.7)	+6.9 (12.1)	-0.5 (-3.7, 2.7)
Month 12 (SD)	+5.3 (15.7)	+8.1 (15.1)	-2.8(-6.9, 1.3)	4.4 (15.5)	+8.1 (15.1)	-3.7(-7.8, 0.4)
% of patients did not lose vision at Month 12	74.7%	78.9%	0.9 (0.8, 1.1)	70.6%	78.9%	0.9 (0.8, 1,1)
% of patients gained ≥15 letters Month 12	31.3 (n=32)	41.1 (n=46)	0.75 (0.52, 1.08)	24.7 (n=26)	41.1 (n=46)	0.6 (0.4, 0.9)
CRT change from baseline						

Bibliographic reference	Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.

Month 12	-151.7 (135.6)	-172.2 (166.7)	20.5 (-19.9, 60.9)	-140.9 (128.1)	-172.2 (166.7)	31.3 (-8.2, 70.8)
Additional treatment						
Mean number of ranibizumab retreatment (month 3-11)	2.2	7.6		2.8	7.6	
Mean number of PDT retreatment (month 3-11)	1.9	1.5		1.9	1.5	
Total ocular AEs						
No. of patients (%)	63 (60.6)	60 (54.1)	1.2 (0.89, 1.41)	56 (52.8)	60. (54.1)	0.98 (0.76, 1.25)

Missing data handling/loss to follow up	286 (89.1%) completed 12 months of the study
Was allocation adequately concealed?	Yes
Was knowledge of the allocated intervention adequately prevented during the study?	Yes
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	The trial was shortened from 24 to 12 months based on an early study's result (indicated no additional benefit of the combination treatment)
Were incomplete outcome data adequately addressed?	Unclear

Bibliographic reference	Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.
Coutry/ies where the study carried out	7 study centres in Hong Kong, Singapore, South Korean, Taiwan, Thailand
Study type	Double blinded RCT
Aim of the study	To assess the effects of verteporfin photodynamic therapy (PDT) combined with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy
Study dates	Not reported
Sources of funding	Novartis Pharma AG Switzerland
Sample size	61
Inclusion Criteria	Treatment-naïve patients aged ≥18 years with symptomatic macular PCV Patients had BCVA letter score of 73 to 24 using ETDRS chart; Patients' eyes had a greatest linear dimension of the lesion of <5400um Patients had confirmed diagnosis of PCV by Central reading center
Exclusion Criteria	Patients had received treatment previously with verteporfin PDT, focal laser photocoagulation, transpupillary thermotherapy, pneumatic displacement of subretinal blood, or any investigational treatment; Patients had a history of angioid streaks, presumed ocular histoplasmosis syndrome, or pathological myopia Patients had experienced RPE tear, retinal detachment, macular hole, or uncontrolled glaucoma Patients underwent intraocular surgery (except uncomplicated cataract extraction with intraocular lens implantation within 60 days before the screening visit)
Baseline characteristics	

	Verteportin PDT + ranibizumab	Ranibizumab
No. of patients	19	21
Mean aged (SD)	63.8 (8.3)	69.3 (8.3)

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.</td></tr>
<tr><td></td><td colspan="4"><table>
<tr><td>No. of females (%)</td><td>8 (42.1)</td><td>6 (28.6)</td></tr>
<tr><td>Mean total lesion areas, mm2(SD)</td><td>3.9 (5.5)</td><td>3.9 (2.5)</td></tr>
<tr><td>Mean polyp areas, mm2(SD)</td><td>0.3 (0.5)</td><td>0.2 (0.1)</td></tr>
<tr><td>Mean BCVA, letters (SD)</td><td>56.6 (20.9)</td><td>49.0 (18.1)</td></tr>
<tr><td>Mean CRT, µm (SD)</td><td>3347. (118.9)</td><td>268.5 (97.8)</td></tr>
<tr><td>No. patients with presence of leakage (%)</td><td>19 (100.0)</td><td>20 (95.2)</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td colspan="4">Eligible patients were randomised 1:1:1 for receiving verteporfin PDT plus intravitreal ranibizumab (0.5mg) (combination therapy), verteporfin alone or intravitreal ranibizumab (0.5mg) plus sham PDT
On day 1, patients received verteporfin PDT or sham PDT
On the same day, 1 to 24 hour after PDT, the patients were also administered a ranibizumab or sham injection
3 consecutive monthly ranibizumab intravitreal injections or sham were given starting at baseline
Re-treatments were given pro-re-nata according to the protocol specific re-treatment criteria evaluated by the investigator (mainly by ICGA assessed polyp regression)</td></tr>
<tr><td>Intervention</td><td colspan="4">verteporfin PDT plus intravitreal ranibizumab (0.5mg) (combination therapy)</td></tr>
<tr><td>Comparator</td><td colspan="4">intravitreal ranibizumab (0.5mg)</td></tr>
<tr><td>Outcomes</td><td colspan="4">Functional change: BCVA
Anatomical change: Central Foveal Thickness
Adverse events</td></tr>
<tr><td>Length of follow up</td><td colspan="4">6 months</td></tr>
<tr><td>Results</td><td colspan="4"><table>
<tr><td></td><td>Verteportin PDT + ranibizumab (n=19)</td><td>Ranibizumab (n=21)</td><td>Effect between combination and Ranibizumab (95%CI)</td></tr>
<tr><td>BCVA change</td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.**
	Month 6 | 10.9 (10.9) | 9.2 (12.4) | 1.7 (-5.5, 8.9) % of patients gaining ≥15 letters | 21% | 33.3% | 0.6 (0.2, 1.8) Central retinal thickness change | | | Month 6 | -145.6 (119.0) | -65.7 (114.3) | -79.9 (-152.4, -7.42) % patients with presence of leakage (n) | 22.2% (n=4) | 61.9% (n=13) | 0.34 (0.13, 0.86) Retreatment | | | Mean number of ranibizumab, month 3-5 | 1.1 (1.2) | 2.2 (1.2) | -1.1 (-1.8, -0.4) % of patients had ranibizumab, month3 -5 | 55.6% | 81.0% | 0.7 (0.5, 1.1) Mean number of PDT, month 3-5 | 1.4 (0.5) | 1.9 (0.3) | -0.5 (-0.8, -0.2) % of patients had PDT, month3 -5 | 44.4% | 90.5% | 0.5 (0.3, 0.8) Adverse events | | | Ocular AEs | 5 | 4 | 1.4 (0.4, 4.4) Key non-ocular AEs | 6 | 7 | 0.9 (0.4, 2.3)
Missing data handling/loss to follow up	A total of 59 of 61 randomised patients completed the study.
Was allocation adequately concealed?	Unclear (no detailed description in the study)

Bibliographic reference	Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size for each group
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Krebs I, Vecsei Marlovits, V , Bodenstorfer J, Glittenberg C, Ansari Shahrezaei, S , Ristl R, and Binder S. 2013. "Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration". Acta Opthalmologica 91:e178-83..
Coutry/ies where the study carried out	Austria
Study type	RCT
Aim of the study	Modern therapy of neovascular age-related macular degeneration consists in intravitreal injections of inhibitors of the vascular endothelial growth factor. An increasing number of these injections is required not only in monthly but also in as-needed treatment regimen. In this study, it should be examined whether an additional administered photodynamic therapy (PDT) can considerably reduce the number of injection.
Study dates	Not reported
Sources of funding	Novartis Pharma Austria
Sample size	48
Inclusion Criteria	age>50 years subfoveal CNV secondary to AMD

<table>
<tr><th>Bibliographic reference</th><th>Krebs I, Vecsei Marlovits, V , Bodenstorfer J, Glittenberg C, Ansari Shahrezaei, S , Ristl R, and Binder S. 2013. "Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration". Acta Opthalmologica 91:e178-83..</th></tr>
<tr><td></td><td>predominantly classic lesions, and occult or minimally classic lesions with evidence of recent disease progression
evidence that CNV extends under the geometric centre of the foveal avascular zone
the areas of CNV must occupy at least 50% of the total lesion</td></tr>
<tr><td>Exclusion Criteria</td><td>patients who have a BCVA <33 letters in both eyes
prior treatment in the study eye for nAMD
concomitant use of chronic non-steroidal anti-inflammatory drugs or steroids for the duration of study participation
any occult surgery within 6 months preceding day one, or a history of post-operative complications within the last 12 months preceding day one in the study eye
history of uncontrolled glaucoma in the study eyes
aphakia or absence of the posterior capsule in the study eye
spherical equivalent of the refractive error in the study eye demonstrating more than -6 dioptres or an axial length of ≥26mm of myopia
presence of a retinal pigment epithelial tear involving the macular in the study eye, angoid streaks or precursors of CNV in either eye due to other cause
active intraocular inflammation in the study eye or any active infection involving an eyeball adnexa
vitreous haemorrhage or history of rhegmatogenous retinal detachment or macular hole in the study eye</td></tr>
<tr><td>Baseline characteristics</td><td><table><tr><td></td><td>Verteportin PDT + ranibizumab (group 2)</td><td>Ranibizumab (group 1)</td></tr><tr><td>No. of patients</td><td>20</td><td>24</td></tr><tr><td>Mean age (SD)</td><td>80.3 (6.3)</td><td>77.7 (8.9)</td></tr></table></td></tr>
<tr><td>Study procedures</td><td>patients were randomised in 1:1 to one of 2 groups;
one group received 3 initial monthly ranibizumab (0.5mg) injection
the other group received an initial ranibizumab injection, a standard PDT one day thereafter and two further monthly ranibizumab injection
From month 3 to 12, patients of both groups received monthly ranibizumab injection unless BCVA worsened <5 letters compared to the BCVA at month 2 and retinal thickness at the central subfield as assessed by OCT</td></tr>
<tr><td>Intervention</td><td>Ranibizumab injection (0.5mg) plus a standard PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab injection (0.5mg)</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Krebs I, Vecsei Marlovits, V , Bodenstorfer J, Glittenberg C, Ansari Shahrezaei, S , Ristl R, and Binder S. 2013. "Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration". Acta Opthalmologica 91:e178-83..</td></tr>
<tr><td>Outcomes</td><td>The number of ranibizumab injections
Mean change BCVA at month 3,6,12</td></tr>
<tr><td>Analyses</td><td>Descriptive statistics
Regression analyses</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Verteportin PDT + ranibizumab (n=20)</td><td>Ranibizumab (n=24)</td><td>Effect (95%CI)</td></tr>
<tr><td>Distance acuity change, letter</td><td></td><td></td><td></td></tr>
<tr><td>baseline</td><td>54.0 (18.4)</td><td>52.0 (21.6)</td><td>2.0 (-9.8, 13.8)</td></tr>
<tr><td>Month12</td><td>46.9 (28.3)</td><td>57.1 (24.6)</td><td>-10.2 (-26.3, 5.6)</td></tr>
<tr><td>% of patients lost ≥3 lines</td><td>31.6% (n=6)</td><td>9.1% (n=2)</td><td>3.60 (0.81, 15.91)</td></tr>
<tr><td>Central retinal thickness change,µm</td><td></td><td></td><td></td></tr>
<tr><td>baseline</td><td>407.0 (124.5)</td><td>373.4 (91.0)</td><td>33.6 (-32.0, 99.2)</td></tr>
<tr><td>Month 12</td><td>268.8 (90.8)</td><td>291.9 (70.0)</td><td>-23.1 (-71.6, 25.6)</td></tr>
<tr><td>Ranibizumab injections</td><td></td><td></td><td></td></tr>
<tr><td>Mean number (SD)</td><td>4.7(1.8)</td><td>6.6(2.4)</td><td>-1.90 (-3.14, -0.66)</td></tr>
</table>
</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>4 patients were screening failures and 3 patients withdrew their consent, 44 eyes of 44 patients included in the study.</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Yes</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>Yes</td></tr>
</table>

Bibliographic reference	Krebs I, Vecsei Marlovits, V , Bodenstorfer J, Glittenberg C, Ansari Shahrezaei, S , Ristl R, and Binder S. 2013. "Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration". Acta Opthalmologica 91:e178-83..
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.
Coutry/ies where the study carried out	Multiple sites
Study type	Single-blinded RCT
Aim of the study	To evaluate the efficacy and safety of dexamethasone intravitreal implant 0.7 mg (DEX) as adjunctive therapy to ranibizumab in neovascular age-related macular degeneration (nvAMD).
Study dates	Not reported
Sources of funding	Allergan Inc
Sample size	310 screened and received the first protocol-mandated ranibizumab injections
Inclusion Criteria	≥50 years of age Subfoveal CNV secondary to nAMD Required ranibizumab therapy for treatment of nAMD Patients' eyes had total size of the lesion ≤12 macular photocoagulation study disc areas Patients' active CNV representing ≥50% of the areas of the lesion Patients' BCVA ≥19 and ≤69 letter using ETDRS method

<table>
<tr><th>Bibliographic reference</th><th>Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.</th></tr>
<tr><td>Exclusion Criteria</td><td>Patients were with glaucoma, diabetic retinopathy
Patients had active ocular infection at screening or the baseline visit
Patients had a history of an increased IOP in response to steroid treatment that was ≥10mm Hg and reached a level of ≥ 25mmHg or that required treatment with laser, surgery, or >1 IOP lowering medication
Patients had subfoveal scarring, fibrosis or atrophy
Patients had retinal pigment epithelium tear that included the fovea
Patients had presence of any causes of CNV other than nvAMD or any other ocular disease that could compromise intraocular lens
Patients had a history of pars plana vitrectomy
Patients currently treat with ≥2 IOP lowering medications
Screening or baseline IOP>23mmHg if untreated or >21mmHg if treated with 1 IOP-lowering medication</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Treatment-naïve cohort</td><td></td></tr>
<tr><td></td><td>DEX implant + ranibizumab</td><td>ranibizumab</td></tr>
<tr><td>Number of patients</td><td>58</td><td>57</td></tr>
<tr><td>Age, years</td><td>77.4 (9.5)</td><td>77.4 (7.1)</td></tr>
<tr><td>No. of female (%)</td><td>37 (63.8)</td><td>35 (61.4)</td></tr>
<tr><td>No. of patients had PED (%)</td><td>20 (34.5)</td><td>22 (38.6)</td></tr>
<tr><td>No. of patients had RAP (%)</td><td>4 (6.9)</td><td>3 (5.3)</td></tr>
<tr><td>Duration of CNV, months</td><td>4.9 (10.3)</td><td>4.1 (14.0)</td></tr>
<tr><td>Central retinal subfield thickness, µm</td><td>262.5 (98.9)</td><td>276.7 (133.7)</td></tr>
<tr><td>BCVA, letter</td><td>55.4 (15.5)</td><td>56.5 (13.3)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Eligible patients were treated with ranibizumab (0.5mg) in the study eye
Four week later, at the baseline study visit, the need for re-treatment of the study eye was evaluated by OCT and clinical examination
Patients who demonstrated the following criteria were eligible for re-treatment:
Macular cysts
Subreitnal fluid
Pigment epithelial detachment</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.</td></tr>
<tr><td></td><td>A ≥50um increase in the central retinal subfield mean thickness from the lowest measurement at the previous visit
New subretinal haemorrhage
Patients were randomised at the baseline visit in a 1:1 allocation to DEX implant (0.7mg) or sham procedure
At the next study visit (day 7-14), all randomised patients received a second protocol-mandated intravitreal ranibizumab injections (0.5mg)
For patients who still met the study defined retreatment criteria, up to 5 additional ranibizumab injections were administered during the outcome assessment visits at week 5,9,13,17, 21.</td></tr>
<tr><td>Intervention</td><td>Dexamethasone Intravitreal Implant (0.7mg) and Ranibizumab (0.5mg)</td></tr>
<tr><td>Comparator</td><td>Intravitreal ranibizumab injections (0.5mg)</td></tr>
<tr><td>Outcomes</td><td>ranibizumab injections free interval (time from the second protocol-mandated ranibizumab injections to determination of eligibility to receive the first as-needed ranibizumab injections)
BCVA in both eyes
Central retinal subfield thickness
Adverse events</td></tr>
<tr><td>Analyses</td><td>The analyses of efficacy variables were based on the intent-to-treat patient population;
The ranibizumab injection-free interval used Kaplan-Meier method;
Cochran-Mantel-Haenzel test
Pearson chi-square</td></tr>
<tr><td>Length of follow up</td><td>25 weeks</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Treatment-naïve cohort</td><td></td><td></td></tr>
<tr><td></td><td>DEX implant + ranibizumab</td><td>Ranibizumab</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>58</td><td>57</td><td></td></tr>
<tr><td>Median of injection free interval, days</td><td>34</td><td>29</td><td></td></tr>
<tr><td>Ranibizumab injection</td><td>4.4 (1.7)</td><td>4.9 (1.7)</td><td>-0.5 (-1.1, 0.1)</td></tr>
<tr><td>BCVA(ETDRS0 change from baseline to week 25</td><td>1.5 (10.6)</td><td>2.6 (8.4)</td><td>-1.1 (-4.6, 2.4)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.**
	Number of patients had BCVA ≥10 letter improvement: 11 (19.0%) / 9 (15.8) / 1.2 (0.5, 2.7) Number of patients had BCVA ≥15 letter improvement: 4 (6.9) / 5 (8.8) / 0.7 (0.2, 2.8) CRT changes from baseline to week 25,µm: -12.61 (96.4) / -34.7 (106.6) / 22.1 (-15.1, 59.3)
Missing data handling/loss to follow up	67 patients either failed to meet retreatment criteria (n=31) or were ineligible for the study for other reason (n=36).
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Short follow-up time
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

<table>
<tr><th>Bibliographic reference</th><th>Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.</th></tr>
<tr><td>Coutry/ies where the study carried out</td><td>12 European countries</td></tr>
<tr><td>Study type</td><td>Prospective, multicentre, double-masked, randomized, active-controlled trial</td></tr>
<tr><td>Aim of the study</td><td>To compare the efficacy and safety of same-day verteporfin photodynamic therapy (PDT) and intravitreal ranibizumab combination treatment versus ranibizumab monotherapy in neovascular age-related macular degeneration.</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>Novartis Pharma AG, Basel, Switzerland</td></tr>
<tr><td>Sample size</td><td>255</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients aged ≥50 years with a diagnosis of AMD related active subfoveal choroidal neovascularization;
The total area of CNV encompassed within the lesion had to be≥50% of the total lesion area, with the largest linear dimension of the total lesion area ≤ 5400µm
BCVA of the study eye between 73 and 24 letters</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients had prior treatment for neovascular AMD in the study eye
Patients had angioid streaks
Patients had presumed ocular histoplasmosis syndrome
Patients had pathologic myopia, CNV not from AMD, retinal pigment epithelium tear or uncontrolled glaucoma
Patients had presence of fibrosis, haemorrhage, retinal pigment epithelium detachment or other hypofluorescent areas obscuring >50% of the whole lesion</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Verteporfin PDT + ranibizumab (n=122)</td><td>Ranibizumab (n=133)</td></tr>
<tr><td>Mean age, years (SD)</td><td>76.8 (7.7)</td><td>75.5 (7.4)</td></tr>
<tr><td>N (%) male</td><td>44 (36.1)</td><td>59 (44.4)</td></tr>
<tr><td>Baseline BCVA, mean letters</td><td>54.6 (13.4)</td><td>55(12.3)</td></tr>
<tr><td>Lesion type, n(%)</td><td></td><td></td></tr>
<tr><td>Predominantly classic</td><td>50 (41.0)</td><td>57 (42.9)</td></tr>
<tr><td>Minimally classic</td><td>20 (16.4)</td><td>25 (18.8)</td></tr>
<tr><td>Occult with no classic</td><td>51 (41.8)</td><td>51 (38.3)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised in a 1:1 ratio to either combination treatment or ranibizumab monotherapy (0.5mg)</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.</td></tr>
<tr><td></td><td colspan="4">On day 1, patients received verteporfin or sham infusion followed by laser application at standard fluence PDT
On the same day, ranibizumab (0.5mg) was injected 1 hour after the start of verteporfin PDT
Ranibizumab treatment was to be repeated at month 1 and 2.
The need for re-treatment was determined by the investigator based on functional and anatomic parameter, including a≥100-µm increase in central retinal thickness from the lowest previous value, presence of subretinal fluid or haemorrhage, BCVA decrease of >5 letter, and leakage on FA.</td></tr>
<tr><td>Intervention</td><td colspan="4">Verteporfin photodynamic therapy (PDT) and intravitreal ranibizumab combination treatment</td></tr>
<tr><td>Comparator</td><td colspan="4">Ranibizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td colspan="4">Visual acuity
Central retinal thickness
Incidence of ocular and non-ocular AEs</td></tr>
<tr><td>Analyses</td><td colspan="4">Descriptive statistics</td></tr>
<tr><td>Length of follow up</td><td colspan="4">12 months</td></tr>
<tr><td>Results</td><td colspan="4"><table>
<tr><td></td><td>Verteporfin PDT + ranibizumab (n=121)</td><td>Ranibizumab (n=132)</td><td>Effect (95%CI)</td></tr>
<tr><td>BCVA, letter</td><td></td><td></td><td></td></tr>
<tr><td>Baseline (SD)</td><td>54.6 (13.5)</td><td>55.1 (12.3)</td><td>-0.5 (-3.7, 2.7)</td></tr>
<tr><td>Month12</td><td>57.1 (18.3)</td><td>59.4 (18.8)</td><td>-2.3 (-6.9, 2.3)</td></tr>
<tr><td>Change</td><td>2.5 (14.8)</td><td>4.4 (15.9)</td><td>-1.9 (-5.7, 1.9)</td></tr>
<tr><td>% of patients gained≥15 letters</td><td>18.2 (n=22)</td><td>25.8 (n=34)</td><td>0.71 (0.44, 1.14)</td></tr>
<tr><td>% of patients gained≥10 letters</td><td>37.2 (n=45)</td><td>38.6 (n=51)</td><td>0.96 (0.70, 1.32)</td></tr>
<tr><td>% of patients gained≥5 letters</td><td>50.4 (n=61)</td><td>52.3 (n=69)</td><td>0.96 (0.76, 1.23</td></tr>
<tr><td>% of patients gained≥0 letters</td><td>71.1 (n=86)</td><td>65.9 (n=87)</td><td>1.08 (0.91, 1.27)</td></tr>
<tr><td>% of patients loss< 15 letters</td><td>86.8 (n=105)</td><td>90.9 (n=120)</td><td>0.95 (0.87, 1.04)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.			
	% of patients loss< 30 letters	95.9 (n=116)	96.2 (n=127)	1.00 (0.95, 1.05)
	Central retinal thickness change, µm			
	Baseline to Month 12	-115.3 (99.0)	-10.7.7 (126.3.0)	-7.6 (-35.4, 20.3)
	Re-treatment			
	% of patients had treatment free intervals≥3 months at appoint after Month2	96 (n=116)	92 (n=121)	1.05 (0.98, 1.11)
	% of patients did not receive ranibizumab retreatment	29.5 (n=36)	24.1(n=32)	1.23 (0.82, 1.84)
	Mean number of ranibizumab injections	4.8 (2.0)	5.1 (2.0)	-0.30 (-0.79, 0.19)
	No. o4.f ranibizumab retreatment, mean (SD)	1.9 (2.0)	2.2 (2.0)	-0.3 (-0.8, 0.2)
	Mean number of PDT sessions (SD)	1.7 (0.8)	1.9 (0.9)	-0.20 (-0.41, 0.01)
	No. of verteporfin PDT retreatment, mean (SD)	0.7	0.9	
	Reported adverse events			
	No. of Ocular AEs (%)	51 (41.8)	54 (40.6)	1.0 (0.8, 1.4)
	Non-ocular AEs	66 (54.1)	70 (52.6)	1.0 (0.8, 1.3)
Missing data handling/loss to follow up	255 randomised in the study, and 240 patients (94%) completed 12 months			
Was allocation adequately concealed?	Yes			

Bibliographic reference	Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.
Was knowledge of the allocated intervention adequately prevented during the study?	Yes
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Patients in monotherapy group had slightly larger lesion size
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.
Coutry/ies where the study carried out	Saudi Arabia
Study type	Controlled, open label randomised RCT
Aim of the study	To evaluate the efficacy and safety of photodynamic therapy (PDT) with verteporfin combined with intravitreal bevacizumab in choroidal neovascularization (CNV) owing to age-related macular degeneration (AMD) in comparison with individual monotherapies used as controls.
Study dates	Feb 6 2006 to June 28 2006
Sources of funding	Not reported
Sample size	156
Inclusion Criteria	Patients aged 50 years and/or over with minimally classic or occult CNV due to AMD in 1 or both eyes; Studies eye had never been treated Patients had active leakage documented by FA and OCT, subfoveal lesion, greatest linear diameter of lesion ≤7500µm Patients had BCVA≥20/400 (ETDRS chart)

<table>
<tr><th>Bibliographic reference</th><th>Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.</th></tr>
<tr><td></td><td>Patients had a presumed evidence of disease progression defined as a deterioration of BCVA≥5 letters and increase of lesion size ≥10% within the 3 months before randomisation</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with cataract or media opacities that could significantly interfere with OCT imaging and image analysis
Patients with retinal angiomatous proliferation or polypoidal choroidal vasculopathy in studied or fellow eye
Patients had ocular surgery within the 3 months before randomisation
Patients had a history of uveitis
Patients had rise of intraocular pressure ≥25mmHg
Patients had glaucoma visual field loss in the studies eye</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>COMB</td><td>BEV</td></tr>
<tr><td>Number of patients</td><td>52</td><td>54</td></tr>
<tr><td>Age, mean (SD)</td><td>75.4 (6.3)</td><td>76.1 (5.9)</td></tr>
<tr><td>M/F</td><td>18/34</td><td>17/37</td></tr>
<tr><td>Size of lesion, µm</td><td>3982 (1927)</td><td>3784 (1387)</td></tr>
<tr><td>Fellow eye status</td><td></td><td></td></tr>
<tr><td>No. of Dry AMD (%)</td><td>24 (46)</td><td>23 (43)</td></tr>
<tr><td>Scar AMD</td><td>23 (44)</td><td>25 (46)</td></tr>
<tr><td>Wet AMD</td><td>5 (10)</td><td>6 (11)</td></tr>
<tr><td>CNV characteristics</td><td></td><td></td></tr>
<tr><td>Minimally classic</td><td>42 (81)</td><td>44 (82)</td></tr>
<tr><td>Occult</td><td>10 (19)</td><td>10 (18)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>All patients underwent a complete ophthalmatic examination at the screening visit
At the baseline visit (within 3 weeks after the screening), eligible patients were randomly allocated to treatment groups: verteporfin PDT group, intravitreal bevacizumab (BEV) group, and their combination group (COMB)
Patients who were allocated to PDT and COMB groups were administered verteporfin PDT
Patients in the BEV and COMB groups were administered bevacizumab (1.25mg), and administration of bevacizumab in the COMB group was performed immediately (within 1 hour) after verteporfin PDT
Patients were followed up 1 and 3 months after administrations of the treatments</td></tr>
<tr><td>Intervention</td><td>photodynamic therapy (PDT) with verteporfin combined with intravitreal bevacizumab</td></tr>
<tr><td>Comparator</td><td>intravitreal bevacizumab monotherapy</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.</th></tr>
<tr><td>Outcomes</td><td>Best-corrected visual acuity
Central foveal thickness</td></tr>
<tr><td>Analyses</td><td>Descriptive statistics
Mix procedure from SAS</td></tr>
<tr><td>Length of follow up</td><td>3 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Verteporfin PDT +bevacizumab (n=52)</th><th>Bevacizumab (n=54)</th></tr>
<tr><td>BCVA, logMAR</td><td></td><td></td></tr>
<tr><td>baseline</td><td>1.06 (1.02,1.10)</td><td>1.09 (1.05,1.13)</td></tr>
<tr><td>Change Month1</td><td>0.25 (0.21, 028)</td><td>0.17 (0.14, 0.20)</td></tr>
<tr><td>Change Month3</td><td>0.22 (0.20,0.25)</td><td>0.08 (0.05, 0.10)</td></tr>
<tr><td>Central foveal thickness, µm</td><td></td><td></td></tr>
<tr><td>baseline</td><td>349.1
(339.3, 358.8)</td><td>355.1
(345.5, 364.7)</td></tr>
<tr><td>Change Month1</td><td>-64.5
(-74.3, -54.7)</td><td>-54.7
(-64.3, -45.0)</td></tr>
<tr><td>Change Month3</td><td>-59.6
(-68.7, -50.4)</td><td>-34.0
(-43.0, -25.0)</td></tr>
<tr><td>Adverse events</td><td></td><td></td></tr>
<tr><td>No. of patients, pigment epithelial tear</td><td>0</td><td>3</td></tr>
<tr><td>Posterior vitreous detachments</td><td>4</td><td>8</td></tr>
<tr><td>Cataract progression</td><td>3</td><td>4</td></tr>
</table>
</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>281 were screened ,and 156 completed follow-up</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Open label (not described in the study)</td></tr>
</table>

Bibliographic reference	Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Short follow-up period
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Lim J Y, Lee S Y, Kim J G, Lee J Y, Chung H, and Yoon Y H. 2012. "Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study". Acta Opthalmologica 90:61-7.
Coutry/ies where the study carried out	Korea
Study type	RCT
Aim of the study	To compare the outcomes of treatment with intravitreal bevacizumab alone (BEVA group) or in combination with photodynamic therapy (PDT) (COMB group), in patients aged at least 50 years with neovascular maculopathy.
Study dates	July 2006
Sources of funding	Not reported
Sample size	47
Inclusion Criteria	Age 50 years or older BCVA of 0.6 or worse in the study eye
Exclusion Criteria	Intravitreal triamcinolone (IVTA) within 90 days prior to screening PDT within 30 days before screening A history of ocular surgery within 90 days prior to screening

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Lim J Y, Lee S Y, Kim J G, Lee J Y, Chung H, and Yoon Y H. 2012. "Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study". Acta Opthalmologica 90:61-7.</td></tr>
<tr><td></td><td colspan="4">A history of vitreous haemorrhage, retinal tear, retinal detachment, macular hole or retinal vein obstruction
Severe intraocular inflammation or infection within 30 days before screening
Diabetic retinopathy
Aphakia
Systemic conditions including thromboembolism, previous myocardial infarction or prior cerebral vascular accident</td></tr>
<tr><td>Baseline characteristics</td><td colspan="4"><table>
<tr><td></td><td>COMB</td><td>BEVA</td></tr>
<tr><td>Number</td><td>23</td><td>18</td></tr>
<tr><td>Mean age, years</td><td>66.3</td><td>70.9</td></tr>
<tr><td>Mean BCVA, logMAR</td><td>1.05</td><td>1.03</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td colspan="4">Patients were randomised into either an intravitreal bevacizumab monotherapy (BEVA group) or a combination therapy group (COMB group).
Intravitreal bevacizumab (1.25mg) was injected into all patients at 6 weeks intervals; a total of 3 injections were usually given.
In the combination group, PDT was performed in association with one of the 3 injections; administration of bevacizumab was performed within 7 days before or after PDT
Patients were followed-up 1 and 6 week after every bevacizumab injection during the first 18 weeks, and then at 3-month intervals.</td></tr>
<tr><td>Intervention</td><td colspan="4">PDT + bevacizumab</td></tr>
<tr><td>Comparator</td><td colspan="4">Bevacizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td colspan="4">Best-corrected visual acuity
Central foveal thickness</td></tr>
<tr><td>Analyses</td><td colspan="4">Repeated measures
Fisher’s exact test</td></tr>
<tr><td>Length of follow up</td><td colspan="4">12 months</td></tr>
<tr><td>Results</td><td colspan="4"><table>
<tr><td></td><td>COMB (n=23)</td><td>BEVA (n=18)</td></tr>
<tr><td>No. of patients had additional bevacizumab</td><td>5</td><td>4</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Lim J Y, Lee S Y, Kim J G, Lee J Y, Chung H, and Yoon Y H. 2012. "Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study". Acta Opthalmologica 90:61-7.**
	<table><tr><td>Visual acuity (lines gained)</td><td>2.43 (2.83)</td><td>3 (3.35)</td></tr><tr><td>No of bevacizumab treatments</td><td>3.25 (0.58)</td><td>3.2 (0.42)</td></tr></table>
Missing data handling/loss to follow up	6 were lost to follow up during the study
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Unclear

Bibliographic reference	**Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.**
Coutry/ies where the study carried out	Iran
Study type	RCT

Bibliographic reference	**Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.**
Aim of the study	To compare the outcomes of photodynamic therapy (PDT) combined with intravitreal bevacizumab (IVB) with versus without intravitreal triamcinolone (IVT) in neovascular age-related macular degeneration (AMD).
Study dates	Not reported
Sources of funding	Not reported
Sample size	84 patients (84 eyes)
Inclusion Criteria	Patients with subfoveal CNV of all types (predominantly classic, minimally classic, occult and retinal angiomatous proliferation) secondary to AMD and no history of prior treatment
Exclusion Criteria	Patients with presence of diabetic retinopathy, glaucoma, or any macular disease other than AMD
Baseline characteristics	

	Triple therapy (PDT+IVT+IVB)	Dual therapy (PDT+IVB)	P values
Number of patients	42	42	
Mean age, years (SD)	69.9 (9.1)	71.7 (9.0)	0.358
Male/female	25/17	23/19	0.659
CNV types, n(%)			0.503
Minimally classic	4 (9.5)	9 (21.4)	
Dominantly classic	10 (23.8)	9 (21.4)	
Occult	12 (31.0)	12 (28.6)	
RAP/RCA	15 (35.7)	12 (28.6)	
PED, n(%)	25 (59.5)	24 (57.1)	0.825
CNV size, n(%)			0.395
<2	19 (45.2)	22 (52.4)	
2-4	15 (35.7)	14 (33.3)	
>4	8 (19.1)	6 (13.3)	
Mean BCVA, logMAR	0.80 (0.40)	0.87 (0.39)	0.411
Mean CMT, µm (SD)	335 (116)	341 (140)	0.829
Mean IOP mmHg (SD)	15.2 (2.5)	15.2 (2.9)	0.992

<table>
<tr><th>Bibliographic reference</th><td>Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.</td></tr>
<tr><td>Study procedures</td><td>Eligible patients were randomly assigned to receive verteporfin PDT plus intravitreal bevacizumab (IVB) or a combination of PDT and bevacizumab/triamcinolone(IVB/IVT)
Patients in the dual treatment groups underwent standard PDT followed by intravitreal bevacizumab (1.25mg) after 48 hour;
In the triple treatment group, 2mg triamcinolone acetonide was injected intravitreally in addition to PDT and bevacizumab;
All patients were examined the 1st day after injection particularly for signs of intraocular inflammation
Need for re-treatment with IVC injection was first evaluated at week 12. Additional IVB injections were given eyes with active CNV according to clinical findings (including decrease in VA and/or haemorrhage on fundus examinations), and/or fluid on OCT, and/or persistence or reoccurrence of dye leakage on FA. Either PDT or IVT injection were not repeated during the follow-up period.</td></tr>
<tr><td>Intervention</td><td>Photodynamic therapy (PDT) combined with intravitreal bevacizumab (IVB) with intravitreal triamcinolone (IVT)</td></tr>
<tr><td>Comparator</td><td>Photodynamic therapy (PDT) combined with intravitreal bevacizumab (IVB) without intravitreal triamcinolone (IVT)</td></tr>
<tr><td>Outcomes</td><td>Change in BCVA from baseline
Change in central macular thickness
The need for additional injections
Time interval up to the first retreatment</td></tr>
<tr><td>Analyses</td><td>Intention to treat
On treatment (per-protocol) analyses
Chi-square
Fisher’s exact test
Mann-Whitney test
Analysis of covariance</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Triple therapy (PDT+IVT+IVB)</td><td>Dual therapy(PDT+IVB)</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>42</td><td>42</td><td></td></tr>
<tr><td>BCVA change from baseline, logMAR</td><td></td><td></td><td></td></tr>
<tr><td>Week 6</td><td>-0.12 (0.25)</td><td>-0.14 (0.21)</td><td>-0.02</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.

			(-0.12, 0.08)
Week12	-0.16 (0.29)	-0.16 (0.22)	0 (-0.11, 0.12)
Week 20	-0.17 (0.27)	-0.18 (0.23)	0 (-0.11, 0.11)
Week 24	-0.2 (0.3)	-0.17 (0.33)	0.03 (-0.11, 0.17)
Week 36	-0.17 (0.33)	-0.15 (0.33)	0.02 (-0.12, 0.17)
Week 54	-0.16 (0.36)	-0.15 (0.36)	0.01 (-0.15,0.17)
Central macular thickness change, µm			
Week 6	-102 (109)	-112 (128)	-11 (71,50)
Week12	-92 (107)	-114 (146)	-11 (-87,44)
Week 20	-91 (109)	-100 (143)	-9 (-75, 56)
Week 24	-82 (128)	-92 (150)	-10 (-81,61)
Week 36	-90 (133)	-91 (153)	-1 (-74, 72)
Week 54	-72 (125)	-105 (143)	-33 (-102,35)
Retreatment			
Men (SD)	0.9 (0.9)	1.3 (1.1)	-0.40

Bibliographic reference	**Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.**
	<table><tr><td></td><td></td><td></td><td>(-0.83, 0.03)</td></tr><tr><td>% eye no need of retreatment within 12 months</td><td>38.1 (n=16)</td><td>26.2 (n=11)</td><td>1.45 (0.77, 2.75)</td></tr><tr><td>Median time to first re-treatment, weeks (95%CI)</td><td>25.1 (17.1,33.2)</td><td>15.6 (14.7, 16.4)</td><td></td></tr></table> No systematic AEs were reported
Missing data handling/loss to follow up	84 patients recruited, and 63 completed 6-month follow-up, 51 completed 12 month follow-up
Was allocation adequately concealed?	Yes
Was knowledge of the allocated intervention adequately prevented during the study?	Yes
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

<table>
<tr><th>Bibliographic reference</th><th>Ranchod T M, Ray S K, Daniels S A, Leong C J, Ting T D, and Verne A Z. 2013. "LuceDex: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration". Retina 33:1600-4.</th></tr>
<tr><td>Coutry/ies where the study carried out</td><td>USA</td></tr>
<tr><td>Study type</td><td>Single-blinded RCT</td></tr>
<tr><td>Aim of the study</td><td>The LuceDex prospective randomized pilot trial compared the combination of intravitreal ranibizumab and dexamethasone with ranibizumab monotherapy for treatment of neovascular age-related macular degeneration</td></tr>
<tr><td>Study dates</td><td>Trial registered May 2011</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>40 patients</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients were aged ≥50 year, with BCVA of 20/32 to 20/400 and neovascular AMD in the study eye</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients had previous treatment for AMD in the study eye
Patients had previous intravitreal drug delivery in the study eye
Patients had previous vitrectomy in the study eye
Patients had fibrosis or atrophy involving the centre of the foveal in the study eye
Neovascular membrane from other concurrent retinal disease
Patients had history of glaucoma filtering surgery in the study eye
Patients had active co-existing macular disease
Patients had active intraocular inflammation in the study eye
Patients had history of allergy to fluorescein not amenable to treatment</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Combination group (Group 1)</th><th>Monotherapy group (Group 2)</th><th>p</th></tr>
<tr><td>Number of patients</td><td>17</td><td>20</td><td></td></tr>
<tr><td>Male, n(%)</td><td>7 (41)</td><td>6 (30)</td><td>0.72</td></tr>
<tr><td>Mean age, years</td><td>79.5</td><td>82.7</td><td>0.09</td></tr>
<tr><td>Mean BCVA (ETDRS letters)</td><td>61.9</td><td>55.6</td><td>0.10</td></tr>
<tr><td>Mean CMT, µm</td><td>342.2</td><td>291.9</td><td>0.17</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised 1:1 to combination therapy or monotherapy</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Ranchod T M, Ray S K, Daniels S A, Leong C J, Ting T D, and Verne A Z. 2013. "LuceDex: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration". Retina 33:1600-4.</td></tr>
<tr><td></td><td>Combination group received treatment comprised of intravitreal dexamethasone (500µg) followed by intravitreal ranibizumab (0.5mg)
Monotherapy group received only intravitreal ranibizumab (0.5mg)
Study eyes in both groups received the study treatment monthly for 4 months followed by treatment on indication
Retreatment criteria: any biomicroscopic/ angiographic evidence of subretinal haemorrhage, subretinal fluid, or cystoid macular oedema, appearance of new subretinal haemorrhage, or lesion activity, or any evidence by OCT of increased CFT, subretinal haemorrhage, subretinal fluid, or cystoid macular oedema. Combination group were given subsequent treatment with ranibizumab alone if IOP rose>30 mmHg.</td></tr>
<tr><td>Interventio</td><td>Combination of intravitreal ranibizumab and dexamethasone</td></tr>
<tr><td>Comparator</td><td>Ranibizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td>Best-corrected visual acuity
Central macular thickness</td></tr>
<tr><td>Analyses</td><td>Chi-square
Two sample T test</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Combination group (Group 1)</th><th>Monotherapy group (Group 2)</th><th>Effect (95%CI)</th></tr>
<tr><td>Number of patients</td><td>17</td><td>20</td><td></td></tr>
<tr><td>Visual acuity</td><td></td><td></td><td></td></tr>
<tr><td>Gain of ≥ 0 letter to Month 12, n(%)</td><td>15 (88)</td><td>14 (70)</td><td>1.26 (0.90, 1.76)</td></tr>
<tr><td>Gain ≥ 15 letters</td><td>6 (35)</td><td>4 (20)</td><td>1.76 (0.59, 5.24)</td></tr>
<tr><td>Mean visual gain, letters</td><td>11.1</td><td>5.9</td><td></td></tr>
<tr><td>Mean number of treatments</td><td>7.1</td><td>6.6</td><td></td></tr>
<tr><td>CMT changes,µm</td><td>-130.6</td><td>-90.2</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Ranchod T M, Ray S K, Daniels S A, Leong C J, Ting T D, and Verne A Z. 2013. "LuceDex: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration". Retina 33:1600-4.
Missing data handling/loss to follow up	37 out of 40 patients completed 12 month follow-up
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.
Coutry/ies where the study carried out	Not reported
Study type	Open label RCT
Aim of the study	To evaluate whether ketorolac eye drops plus intravitreal ranibizumab (IVR) or verteporfin photodynamic therapy plus IVR provides additional benefit over IVR monotherapy for treatment of choroidal neovascularization in age-related macular degeneration.
Study dates	University hospital of Brescia and Naples
Sources of funding	Not reported
Sample size	75

<table>
<tr><th>Bibliographic reference</th><th>Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.</th></tr>
<tr><td>Inclusion Criteria</td><td>Patients were older than 40 years
Presence of treatment-naïve neovascular AMD
Evidence of leakage on FA and fluid on OCT as indications of new active CNV</td></tr>
<tr><td>Exclusion Criteria</td><td>Any previous intravitreal treatment
Previous laser treatment in the study eye
Myopia more than 7 diopters in the study eye
Concurrent eye disease in the study eye that could compromise visual acuity
Concurrent corneal epithelial disruption or any condition that would affect the ability of the cornea to heal
Known sensitivity to any component of the formulation being investigated</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>PDT + ranibizumab</th><th>Ranibizumab (IVR) + off-label topical ketorolac eye drop</th><th>Ranibizumab</th></tr>
<tr><td>Number of patients</td><td>25</td><td>25</td><td>25</td></tr>
<tr><td>No. of male (%)</td><td>11 (44)</td><td>13 (48)</td><td>12(48)</td></tr>
<tr><td>Mean age (SD)</td><td>76.6 (6.2)</td><td>76.3 (9.7)</td><td>77.2 (8.3)</td></tr>
<tr><td>Visual acuity, logMAR</td><td>0.59 (0.20)</td><td>0.60 (0.24)</td><td>0.61 (0.30)</td></tr>
<tr><td>CMT, um</td><td>439 (73.5)</td><td>420 (87.2)</td><td>440 (84.0)</td></tr>
<tr><td>N (%) classic/predominantly classic</td><td>12 (48)</td><td>10 (40)</td><td>11 (44)</td></tr>
<tr><td>N (%) minimally classic/occult</td><td>13 (52)</td><td>15 (60)</td><td>14 (56)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised to 3 groups;
Group 1(RM): patients received intravitreal 0.5mg ranibizumab (IVR);
Group 2 (RK): patients received intravitreal 0.5mg ranibizumab (IVR) along with off-label topical ketorolac eye drop ;
Group 3 (RV): patients received one session verteporfin followed by intravitreal on the same day (a minimum of 1 hour after the start of verteporfin PDT)</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="5">Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.</td></tr>
<tr><td></td><td colspan="5">All patients received monthly intravitreal 0.5mg ranibizumab for 3 months, followed by monthly pro re nata IVR to treat any residual disease
Patients were evaluated on a monthly basis</td></tr>
<tr><td>Intervention</td><td colspan="5">Patients received one session verteporfin followed by intravitreal</td></tr>
<tr><td>Comparator</td><td colspan="5">Patients received intravitreal 0.5mg ranibizumab (IVR);</td></tr>
<tr><td>Outcomes</td><td colspan="5">Mean change in VA
Mean change in CRT
The number of needed ranibizumab re-treatment over 12 month period
Any adverse ocular reported at 12 months</td></tr>
<tr><td>Analyses</td><td colspan="5">Descriptive statistics
One way analysis of variance</td></tr>
<tr><td>Length of follow up</td><td colspan="5">12 months</td></tr>
<tr><td>Results</td><td colspan="5">
<table>
<tr><td></td><td>PDT + ranibizumab</td><td>Ranibizumab (IVR) + off-label topical ketorolac eye drop</td><td>Ranibizumab</td><td>Effect between combined PDT+ranibizumab and ranibizumab (95%CI)</td></tr>
<tr><td>Number of patients</td><td>25</td><td>25</td><td>25</td><td></td></tr>
<tr><td>VA, logMAR</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline</td><td>0.59 (0.20)</td><td>0.60 (0.24)</td><td>0.61 (0.30)</td><td>-0.02 (-0.16, 0.12)</td></tr>
<tr><td>Month 2</td><td>0.44 (0.16)</td><td>0.33(0.17)</td><td>0.47 (0.28)</td><td>-0.03 (-0.16, 0.10)</td></tr>
<tr><td>Month 4</td><td>0.45 (0.16)</td><td>0.32 (0.15)</td><td>0.46 (0.31)</td><td>-0.01 (-0.15, 0.13)</td></tr>
<tr><td>Month 6</td><td>0.47 (0.18)</td><td>0.30 (0.21)</td><td>0.41 (0.28)</td><td>0.06 (-0.07, 0.19)</td></tr>
<tr><td>Month 8</td><td>0.46 (0.17)</td><td>0.30(0.19)</td><td>0.44 (0.25)</td><td>0.02 (-0.10, 0.14)</td></tr>
<tr><td>Month 10</td><td>0.48 (0.17)</td><td>0.33 (0.18)</td><td>0.45 (0.23)</td><td>0.03 (-0.08, 0.14)</td></tr>
<tr><td>Month12</td><td>0.49 (0.14)</td><td>0.34(0.17)24.5</td><td>0.48 (0.28)</td><td>0.01 (-0.11, 0.13)</td></tr>
<tr><td>CRT, um (SD)</td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.
	<table><tr><td>baseline</td><td>439 (74)</td><td>420(87)</td><td>440 (84)</td><td>-1.00 (-44.88, 42.88)</td></tr><tr><td>Month 2</td><td>313 (35)</td><td>318 (43)</td><td>339 (87)</td><td>-26.00 (-62.76, 10.76)</td></tr><tr><td>Month 4</td><td>301 (20)</td><td>305(45)</td><td>340 (52)</td><td>-39.00 (-60.84, -17.16)</td></tr><tr><td>Month 6</td><td>312 (37)</td><td>293 (54)</td><td>326 (47)</td><td>-14.00 (-37.45, 9.45)</td></tr><tr><td>Month 8</td><td>318 (36)</td><td>287 (46)</td><td>329 (43)</td><td>-11.00 (-32.98, 10.98)</td></tr><tr><td>Month 10</td><td>331 (39)</td><td>282 (46)</td><td>337 (46)</td><td>-6.00 (-29.64, 17.64)</td></tr><tr><td>Month 12</td><td>309 (17)</td><td>279 (50)</td><td>315(34)</td><td></td></tr><tr><td>No. of ranibizumab treatment needed</td><td>5.8(1.3)</td><td>6.5 (1.2)</td><td>7.8 (1.0)</td><td>-2.00 (-2.64, -1.36)</td></tr></table> No serious adverse effects were observed during the study period.
Missing data handling/loss to follow up	All patients completed the study
Was allocation adequately concealed?	Unclear (not details reported in the study)
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Sample within each group were small
Were incomplete outcome data adequately addressed?	N/A

Bibliographic reference	Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.
Coutry/ies where the study carried out	UK
Study type	RCT
Aim of the study	The aim of this study is to evaluate the effect of standard-fluence verteporfin photodynamic therapy (PDT) delivered on the first day of a ranibizumab regimen for choroidal neovascularisation secondary to age-related macular degeneration compared with ranibizumab monotherapy.
Study dates	Not reported
Sources of funding	Not reported
Sample size	18
Inclusion Criteria	Patients have a BCVA logMAR visual acuity in the study eye between 24 and 73 letters Patients had a CNV of any type with the following characteristics as determined by fluorescein angiography: Evidence that CNV extends under the geometric centre of the foveal avascular zone CNV occupying liner dimension 5400um or less No subfoveal atrophic change and no subfoveal fibrosis and a total area of fibrosis 50% or less of total lesion area For occult with no classic CNV, the lesion must demonstrate presumed recent disease progression as assessed by the investigator and defined at least one the following criteria: • Blood associated with the lesion at baseline • 10% or more increase in GLD as assessed by FA in the past 3 months • Loss of visual acuity in the last 3 months defined as either 5 letter or more logMAR vision as determined by protocol refraction and protocol measurement or 2 lines or more using a Snellen chart by standard examination
Exclusion Criteria	Any previous CNV treatment in the study eye

Bibliographic reference	**Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.**
	Treatment with verteporfin in the non-study eye less than 7 days preceding enrolment Any previous participation in a clinical trial involving anti-angiogenic drugs Previous intravitreal drug delivery in the study eye History of vitrectomy, glaucoma filtration surgery, corneal transplant or submacular surgery/other interventions for AMD in the study or any intraocular surgery in the study eye within 2 months of enrolment Greater than milder non-proliferative diabetic retinopathy or any diabetic maculopathy Previous retinal vascular occlusions Subretinal haemorrhage that involves the centre of the foveal, if the size of haemorrhage is either greater than 50% of the total lesion area or more than 1 disc area in size CNV in either eye due to cause other than AMD Retinal pigment epithelial tear involving the macular in the study eye Active intraocular inflammation, or a history of uveitis History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye Infectious conjunctive, keratitis, scleritis, or endopthalmitis in either eye Aphakia or absence of the posterior capsule in the study eye, unless as a result of YAG posterior capsulotomy with previous posterior chamber intraocular lens implantation Spherical equivalent of the refractive error in the study eye of more than -8D of myopia or signs of pathologic myopia with a refraction of -4 to -8D. For patients who have undergone cataract surgery in the study eye, a preoperative myopic refractive error of more than -8D Uncontrolled glaucoma in the study eye, defined as intraocular pressure of greater than 30mmHg despite anti-glaucoma medication Any concurrent intraocular condition in the study eye that, in the opinion of the investigator, is likely to require medical or surgical least 2 Snellen lines of BCVA over the study period History of recent stroke or cardiac event, or uncontrolled angina or blood pressure
Baseline characteristics	

	Verteporfin PDT + ranibizumab	Sham PDT + ranibizumab
Number of patients	9	9
% of predominantly classic CNV	44.4	44.4
% of minimally classic CNV	55.6	55.6

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.</td></tr>
<tr><td></td><td colspan="4"><table>
<tr><td>Mean visual acuity, letter</td><td>50</td><td>55</td></tr>
<tr><td>Mean greatest linear dimension of lesion (microns)</td><td>3185</td><td>2569</td></tr>
<tr><td>Mean central retinal thickness (microns)</td><td>331</td><td>335</td></tr>
<tr><td>Mean reading speed (word per minute)</td><td>126</td><td>172</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td colspan="4">Patients were randomised to intravitreal injection of ranibizumab (0.5mg) and sham or standard-fluence verteporfin PDT at baseline (first visit)
All patients received a further 2 monthly ranibizumab treatment
Thereafter patients received monthly treatment with ranibizumab as required (if there was a loss of more than 5 letter of BCVA associated with intraretinal or subretinal fluid on OCT, or a more than 100um increase in the mean CRT when compared to the measurement obtained following 3 initial ranibizumab doses).
All patients underwent monthly visual acuity and OCT assessment and 3-monthly fluorescein angiography with follow-up to 1 year.</td></tr>
<tr><td>Intervention</td><td colspan="4">Intravitreal injection of ranibizumab and standard-fluence verteporfin PDT</td></tr>
<tr><td>Comparator</td><td colspan="4">Intravitreal injection of ranibizumab and sham verteporfin PDT</td></tr>
<tr><td>Outcomes</td><td colspan="4">Best-corrected visual acuity</td></tr>
<tr><td>Length of follow up</td><td colspan="4">12 months</td></tr>
<tr><td>Results</td><td colspan="4"><table>
<tr><td></td><td>Verteporfin PDT + ranibizumab</td><td>Sham PDT + ranibizumab</td><td>Effects (95%CI)</td></tr>
<tr><td>Number of patients</td><td>9</td><td>9</td><td></td></tr>
<tr><td>VA</td><td></td><td></td><td></td></tr>
<tr><td>Mean BCVA gain (range) at Month 12</td><td>2.2 (-8, +24)</td><td>4.4 (-11, +20)</td><td></td></tr>
<tr><td>Mean BCVA gain after initial 3 treatments</td><td>3.1 letters</td><td>6.5 letters</td><td></td></tr>
<tr><td>% of patients gaining ≥15 letters Month 12</td><td>11.1 (n=1)</td><td>11.1(n=1)</td><td>1.00 (0.07, 13.64)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.			
	% of patients gaining≥ 10 letters Month 12	11.1 (n=1)	33.3 (n=3)	0.33 (0.04, 2.63)
	% of patients gaining <15 letters Month 12	100	100	
	% of patients gaining <10 letter Month 12	100 (n=9)	88.9 (n=8)	1.12 (0.83, 1.50)
	CFT, µm			
	Mean reduction, at month 12	138	103	
	Mean reading speed at Month 12	136	171	
	Retreatment			
	Mean number (range) by Month 12	1.3 (0,3)	1.3 (0,3)	
	Mean number by Month 6	0.2	0.4	
	Mean time to first retreatment (months)	4.6	2.8	
Missing data handling/loss to follow up	None			
Was allocation adequately concealed?	Unclear			
Was knowledge of the allocated intervention adequately prevented during the study?	Yes (assessors were blinded when assessing FA imaging)			
Was the allocation sequence adequately generated?	Unclear			

Bibliographic reference	Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size
Were incomplete outcome data adequately addressed?	N/A
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Weingessel B ; Mihaltz K ; Vecsei-Marlovits P V. Predictors of 1-year visual outcome in OCT analysis comparing ranibizumab monotherapy versus combination therapy with PDT in exsudative age-related macular degeneration. The Central European Journal of Medicine128: 560-65. 2016.
Coutry/ies where the study carried out	Austria
Study type	RCT
Aim of the study	The aim of this study was to find predictive factors of 1-year visual outcome, analyzing novel optical coherence tomography (OCT) biomarkers in exsudative age-related macular degeneration (choroidal neovascularization (CNV)) in two groups of different treatment modalities.
Study dates	Published 2016
Sources of funding	Not reported
Sample size	34
Inclusion Criteria	Patients with a subfoveal CNV showing activity: presence of retinal haemorrhage, intraretinal oedema, subretinal fluid, or fibrovascular pigment epithelial detachment Patients had visual acuity as their BCVA letter score 73-24 letters Patietns had lesion size of ≤5400µm Patients were willing to return for scheduled visits for 12-month period
Exclusion Criteria	Patients with CNV which was not subfoveal or not related to AMD

<table>
<tr><th>Bibliographic reference</th><td>Weingessel B ; Mihaltz K ; Vecsei-Marlovits P V. Predictors of 1-year visual outcome in OCT analysis comparing ranibizumab monotherapy versus combination therapy with PDT in exsudative age-related macular degeneration. The Central European Journal of Medicine128: 560-65. 2016.</td></tr>
<tr><td></td><td>Patients had received any prior treatment for AMD</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>PDT +ranibizumab</td><td>ranibizumab</td></tr>
<tr><td>Number of patients</td><td>14</td><td>16</td></tr>
<tr><td>Number of patients with classic lesion</td><td>18</td><td>14</td></tr>
<tr><td>Mean age, years</td><td>83.3 (6.1)</td><td>81.1 (7.9)</td></tr>
<tr><td>BCVA (ETDRS letters)</td><td>61.3 (12.0)</td><td>53.8 (11.4)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Eligible patietns were randomised 1:1 to receive either ranibizumab monotherapy or ranibizumab combined with PDT with verteporfin.
Ranibizumab monotherapy: 0.5mg at month 0,1,2, from 3 to 12, ret-treatment with ranibizumab was performed if one of the following changes was observed between visists: new intra- or subretinal fluid, the macular as detected by OCT, an increase in OCT central retinal thickness of at least 100µm, or new macular haemorrhage.
Combined therapy: patients in the combination group received verteporfin PDT 1 day after the intravitreal injection 0.5mg of ranibizumab at baseline. At month 1 and 2, ranibizuman was injectioned without PDT; from month 3 to 12, the same rec-treatment criteroia for ranibizumab were used as in the monotherapy group.</td></tr>
<tr><td>Intervention</td><td>Ranibizumab injection combined with PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab injections</td></tr>
<tr><td>Outcomes</td><td>Changes in visual acuity
Foveal thickness
Number of injections</td></tr>
<tr><td>Analyses</td><td>Two tailed paired t test</td></tr>
<tr><td>Length of follow up</td><td>12 month</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>PDT + ranibizumab</td><td>Ranibizumab</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>14</td><td>16</td><td></td></tr>
<tr><td>Visual acuity, ETDRS letters (SD)</td><td></td><td></td><td></td></tr>
<tr><td>3-month</td><td>62.6 (19.2)</td><td>57.3 (17.6)</td><td>5.3 (-7.95, 18.55)</td></tr>
<tr><td>6-month</td><td>62.4 (19.9)</td><td>57.8 (18.4)</td><td>4.6 (-9.18, 18.38)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Weingessel B ; Mihaltz K ; Vecsei-Marlovits P V. Predictors of 1-year visual outcome in OCT analysis comparing ranibizumab monotherapy versus combination therapy with PDT in exsudative age-related macular degeneration. The Central European Journal of Medicine128: 560-65. 2016.**
	12-month: 57.2 (24.4) | 58.7 (17.6) | -1.50 (-16.82, 13.92) Number if intravitreal injections: 6.9 (1.1) | 7.4 (1.4) | -0.50 (-1.40, 0.40)
Missing data handling/loss to follow up	30 of a total of 34 patient completed 12-month follow-up
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Relative small sample size in each group
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	**Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.**
Coutry/ies where the study carried out	USA
Study type	RCT
Aim of the study	This prospective multi-centre pilot study compares the use of half-fluence photodynamic therapy combined with ranibizumab with ranibizumab monotherapy for the treatment of neovascular age-related macular degeneration.

<table>
<tr><th>Bibliographic reference</th><td>Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>Novartis Pharmaceutics</td></tr>
<tr><td>Sample size</td><td>60</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients with untreated subfoveal neovascular AMD</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with pigment epithelial detachments greater than 50% of the total lesion size</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>PDT +ranibizumab</td><td>ranibizumab</td></tr>
<tr><td>Number of patients</td><td>29</td><td>27</td></tr>
<tr><td>Number of patients with classic lesion</td><td>18</td><td>14</td></tr>
<tr><td>Mean age, years</td><td>79.3</td><td>79.1</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised to receive either 3 consecutive monthly ranibizumab injections or one ranibizumab injection combined with half-fluence PDT
Patients were monitored monthly for 12 months and re-treated PRN based on clinical discretion using standardised visual acuity testing (ETDR), clinical finings, and OCT
Patients in ranibizumab group were only re-treated with ranibizumab.
Patients in combined group were retreated with combined therapy as long as the patient had not received PDT within the previous 90 days. If the patient was within the 90 day post-PDT, the patient was only re-treated with ranibizumab.</td></tr>
<tr><td>Intervention</td><td>Ranibizumab injection combined with half-fluence PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab injections</td></tr>
<tr><td>Outcomes</td><td>Changes in visual acuity
Foveal thickness
Number of injections</td></tr>
<tr><td>Analyses</td><td>Two tailed t test</td></tr>
<tr><td>Length of follow up</td><td>12 month</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>PDT + ranibizumab</td><td>Ranibizumab</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>29</td><td>27</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.
	<table><tr><td>Visual acuity, letters (range)</td><td></td><td></td><td></td></tr><tr><td>Baseline</td><td>49.2 (5, 95)</td><td>52.9 (14, 93)</td><td></td></tr><tr><td>Month 12</td><td>51.8 (15, 82)</td><td>62.8 (20, 85)</td><td></td></tr><tr><td>N (%) patients lost ≥15 letters</td><td>4 (14)</td><td>6 (22)</td><td>0.62 (0.20, 1.96)</td></tr><tr><td>N (%) patients gained ≥15 letters</td><td>9 (31)</td><td>9 (33)</td><td>0.93 (0.44, 1.99)</td></tr><tr><td>Central foveal thickness, um (range)</td><td></td><td></td><td></td></tr><tr><td>Baseline</td><td>320.5 (212, 538)</td><td>313.6 (151, 635)</td><td></td></tr><tr><td>Month 12</td><td>213.8</td><td>221.1 (136, 275)</td><td></td></tr><tr><td>Mean number of injections</td><td>3.0</td><td>6.8</td><td></td></tr></table>
Missing data handling/loss to follow up	56 of a total of 60 patient completed 12-month follow-up
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Relative small sample size in each group
Were incomplete outcome data adequately addressed?	Unclear

Bibliographic reference	Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.
Are reports of the study free of suggestion of selective outcome reporting?	Yes

E.6.4 Switching and stopping antiangiogenic treatment for late AMD (wet)

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

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

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

The evidence tables in this section were produced by the National Guideline Centre.

Clinical evidence table for the review of the effectiveness of switching therapies

Study	**Almony 2011**
Study type	Before and after study
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in USA
Line of therapy	2nd line
Duration of study	Follow up (post intervention): Mean follow up = 6 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eyes that were unresponsive to treatment with intravitreal ranibizumab and were then switched to intravitreal bevacizumab.
Exclusion criteria	Eyes with previous vitreous surgery or any other macular disease that could have adversely influenced the visual outcomes were not included. Eyes that had received prior treatment for AMD including argon laser, photodynamic therapy, and (or) intravitreal agents were also excluded.
Recruitment/selection of patients	Retrospective chart review
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): 70% female. Ethnicity: Not stated

Further population details	1. Central serous pattern (CSR-like) AMD: Not stated; 2. Other co-morbidities affecting the eye: No other comorbidities affecting the eye; 3. Pigment epithelial detachment (PED): Mixed population (11 PED); 4. Polypoidal choroidal vasculopathy: Not stated; 5. Retinal angiomatous proliferation: Mixed population; 6. Type of late wet AMD: Mixed (24 occult, 7 minimally classic, 19 predominantly classic).
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Anti-VEGF - Bevacizumab. Mean no. of injections was 2.5 (range 1-8).. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (No improvement in subretinal fluid on fluorescein angiography and OCT, and no improvement in visual acuity after 3 injections of ranibizumab, administered every 4 weeks). (n=50) Intervention 2: Anti-VEGF - Ranibizumab. 3 injections, administered every 4 weeks. Duration 12 weeks. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Other (Supported by a Heed Foundation Fellowship)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEVACIZUMAB versus RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Visual acuity at 6 months (mean); General Summary Stats: Before (ranibizumab) = median VA 20/125 (range 20/30 to counting fingers). After (bevacizumab) = average gain of 0.3 lines; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Batioglu 2015**
Study type	Before and after study

Number of studies (number of participants)	1 (n=28 patients, 29 eyes)
Countries and setting	Conducted in Turkey; Setting: Retina unit
Line of therapy	2nd line
Duration of study	Intervention + follow up: mean follow up 4.55 (2.14 months)
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who had been on long term ranibizumab for the treatment of wet AMD and had switched to intravitreal aflibercept. Persistent intraretinal or subretinal fluid with or without PED, at least 6 consecutive monthly injections of ranibizumab, and last injection of ranibizumab within 28-35 days of switching to aflibercept.
Exclusion criteria	A history of intraocular surgery, except for uncomplicated phacoemulsification performed within the preceding 6 months; history of subfoveal laser photocoagulation; uncontrolled glaucoma or uveitis; and any other disease that could affect the BCVA in the study eye.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 73.89 (7.49). Gender (M:F): 17 males, 11 females. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not stated; 2. Other co-morbidities affecting the eye: No other comorbidities affecting the eye; 3. Pigment epithelial detachment (PED): Mixed population (24 eyes with intra/sub retinal fluid and PED); 4. Polypoidal choroidal vasculopathy: Not stated; 5. Retinal angiomatous proliferation: Not stated; 6. Type of late wet AMD: Not stated.
Indirectness of population	Serious indirectness: 2 patients received previous bevacizumab, 1 patient received previous photodynamic therapy and pegaptanib
Interventions	(n=29) Intervention 1: Anti-VEGF - Aflibercept. Three monthly alfibercept injections (2mg/0.05ml). Retreatment with a single aflibercept injections was performed according to any of the following: visual acuity loss of at least 5 letters, with optical coherence tomography evidence of fluid in the macula; persistent or recurrent intraretinal or subretinal fluid on OCT; new subretinal hemorrhage from choroidal neovascularisation. . Duration Mean 4.55 months (3.44 injections). Concurrent medication/care: Not stated

	Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Resistant to intravitreal ranibizumab - persistant intraretinal or subretinal fluid without PED). (n=29) Intervention 2: Anti-VEGF - Ranibizumab. Not stated. Duration At least 6 monthly injections. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity (logMAR) at Mean 4.55 months; General Summary Stats: Mean Before aflibercept = 0.83, after = 0.77 (no SD given); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Cho 2013**
Study type	Before and after study
Number of studies (number of participants)	1 (n=28 patients, 28 eyes)
Countries and setting	Conducted in USA; Setting: Ophthalmic Consultants of Boston
Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Eyes were included if: (1) they had persistent intraretinal or subretinal fluid 28–35 days after a minimum of six ranibizumab and/or bevacizumab injections prior to switching to aflibercept; (2) they had their last injection of ranibizumab and/or bevacizumab within 28–35 days of switching to aflibercept; (3) they had a follow-up OCT and examination 28–35 days after switching to aflibercept.
Exclusion criteria	Eyes were excluded if: (1) they received ranibizumab or bevacizumab less than 28 days or longer than 35 days prior to switching to aflibercept; (2) the OCT was dry at any time during the 3 months before switching to aflibercept (allowing inclusion of previously responsive or tachyphylactic eyes); (3) the OCT and/or fluorescein angiography suggested outer retinal tubulation without intraretinal or subretinal fluid, pigment epithelial detachment without intraretinal or subretinal fluid, or cystic degeneration, which often overlies areas of retinal pigment epithelium atrophy but does not leak on angiography; (4) they did not have 6 months of follow-up on aflibercept injections.
Recruitment/selection of patients	Medical records
Age, gender and ethnicity	Age - Mean (range): 80.68 (62-95). Gender (M:F): 14 males. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Mixed population (One patient had RAP). 6. Type of late wet AMD: Mixed (Almost all had classic or occult).
Indirectness of population	Serious indirectness: ranibizumab/bevacizumab - numbers not specified
Interventions	(n=28) Intervention 1: Anti-VEGF - Aflibercept. Intravitreal aflibercept 2.0 mg. Average of 4.4 injections (range 3-6).. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab (Rabibizumab and/or bevacizumab). 2. Reason for switching: Treatment failure (Persistent subretinal or intraretinal fluid on regular ranibizumab). (n=28) Intervention 2: Anti-VEGF - Ranibizumab. Bevacizumab and/or ranibizumab - numbers not specified. Average number of injections 20.2 (SD 7.6). . Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Visual acuity (logMAR) at 1 month; General Summary Stats: Baseline = 0.52, 6 months = 0.54 (p=0.64); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Visual acuity (logMAR) at 6 months; General Summary Stats: Baseline = 0.52, 6 months = 0.57 (p=0.49); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported
Study	Eadie 2014
Study type	Before and after study
Number of studies (number of participants)	1 (n=63 patients, 68 eyes)
Countries and setting	Conducted in USA; Setting: University of Wisconsin
Line of therapy	2nd line
Duration of study	Not clear:
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eyes were included if they were transitioned to aflibercept for treatment of persistent exudation on OCT despite regular treatment with a minimum of three injections of either ranibizumab or bevacizumab.
Exclusion criteria	Eyes with retinal thickening due to subretinal fibrosis with no signs of activity were excluded.
Recruitment/selection of patients	Review of clinical records
Age, gender and ethnicity	Age - Mean (SD): 79.9 (SD not reported). Gender (M:F): 43 women, 20 men. Ethnicity: Not stated

Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Ranibizumab and/or bevacizumab - numbers not specified
Interventions	(n=67) Intervention 1: Anti-VEGF - Aflibercept. Number of injections ranged from 2-11 (average 5.53). Treated primarily with a treat and extend approach. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab (Ranizumab and/or bevacizumab). 2. Reason for switching: Treatment failure (Persistent exudation). (n=67) Intervention 2: Anti-VEGF - Bevacizumab. Specific numbers not specified. Number of injections ranged from 3 - 38.. Duration Average 36.3 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus BEVACIZUMAB AND/OR RANIBIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (logMAR) at Final follow up; General summary Stats: Time of switch = 0.494, final follow up = 0.505, p=.84; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Eadie 2014**
Study type	Before and after study
Number of studies (number of participants)	1 (n=63 patients, 68 eyes)

Countries and setting	Conducted in USA; Setting: University of Wisconsin
Line of therapy	2nd line
Duration of study	Not clear:
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eyes were included if they were transitioned to aflibercept for treatment of persistent exudation on OCT despite regular treatment with a minimum of three injections of either ranibizumab or bevacizumab.
Exclusion criteria	Eyes with retinal thickening due to subretinal fibrosis with no signs of activity were excluded.
Recruitment/selection of patients	Review of clinical records
Age, gender and ethnicity	Age - Mean (SD): 79.9 (SD not reported). Gender (M:F): 43 women, 20 men. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Ranibizumab and/or bevacizumab - numbers not specified
Interventions	(n=67) Intervention 1: Anti-VEGF - Aflibercept. Number of injections ranged from 2-11 (average 5.53). Treated primarily with a treat and extend approach.. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab (Ranizumab and/or bevacizumab). 2. Reason for switching: Treatment failure (Persistent exudation). (n=67) Intervention 2: Anti-VEGF - Bevacizumab. Specific numbers not specified. Number of injections ranged from 3 - 38.. Duration Average 36.3 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus BEVACIZUMAB AND/OR RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Visual acuity (logMAR) at Final follow up; General summary Stats: Time of switch = 0.494, final follow up = 0.505, p=.84; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Ehlken 2014**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=138)
Countries and setting	Conducted in Germany; Setting: University Eye hospital, Freiburg.
Line of therapy	2nd line
Duration of study	Not clear: Retrospective study
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who have been treated for exudative AMD with at least three consecutive monthly intravitreal injections with an anti-VEGF agent (Bevacizumab or ranibizumab) and were unresponsive to treatment (no improvement or deterioration in visual acuity and morphology). Patients switched to three monthly injections of the other agent with the first injection within 100 days after the last injection of the first agent.
Exclusion criteria	Indication other than AMD, and other reasons for deterioration of BCVA, any pre-treatment with intravitreal injections other than anti-VEGF, photodynamic therapy, or macular surgery, macular hemorrhage involving the fovea during the study, intraocular surgery during the course of the study.

Recruitment/selection of patients	Patients identified by a database using search terms 'bevacizumab' and 'ranibizumab'
Age, gender and ethnicity	Age - Mean (SD): Group 1: 77.8 (8.2), Group 2: 77.5 (7.5). Gender (M:F): Women: 94. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Extra comments	Baseline VA (time of switch, logMAR): Group 1: 0.52 (0.3), Group 2: 0.41 (0.3)
Indirectness of population	No Indirectness
Interventions	(n=24) Intervention 1: Anti-VEGF - Bevacizumab. Patients switched from at least 3 monthly injections of ranibizumab to three monthly injections of bevacizumab within 100 days. Duration 3 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Unresponsive to treatment (no improvement or deterioration in visual acuity and morphology)). (n=114) Intervention 2: Anti-VEGF - Ranibizumab. Patients switched from at least 3 monthly injections of bevacizumab to three monthly injections of ranibizumab within 100 days. Duration 3 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (Unresponsive to treatment (no improvement or deterioration in visual acuity and morphology)).
Funding	Other author(s) funded by industry (Grant for clinical research from Novartis Pharmaceuticals Corporation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEVACIZUMAB versus RANIBIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (logMAR) at 3 months; General Summary Stats: Visual acuity significantly improves in group 1 (switch from bevacizumab to ranibizumab) (P=0.001). VA does not improve statistically significantly in group 2 (switch from R to B) (p=0.52). Other results presented as box plot; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Fassnacht-Riederle 2014**
Study type	Before and after study
Number of studies (number of participants)	1 (n=96 eyes of 88 patients)
Countries and setting	Conducted in Switzerland; Setting: Department of Ophthalmology
Line of therapy	2nd line
Duration of study	Intervention + follow up: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The affected eye had received at least three intravitreal 0.5mg ranibizumab or 1.25 bevacizumab over a period of no more than 4 months prior to switching to aflibercept. Eyes had to have evidence of insufficient anatomic response to prior therapy, defined as any persisting or increasing sub/intraretinal fluid observed in spectral domain OCT.
Exclusion criteria	Not stated
Recruitment/selection of patients	Retrospective analysis
Age, gender and ethnicity	Age - Mean (SD): 78.9 (SD not reported). Gender (M:F): 53 female. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (83 eyes had PED). 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness: 28 had tried two previous treatments prior to switch instead of just one (bev or ran only)

Interventions	(n=96) Intervention 1: Anti-VEGF - Aflibercept. Three intravitreal injections (2mg) at 4 week intervals. Duration 12 weeks. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab (Ranibizumab or bevacizumab). 2. Reason for switching: Treatment failure (Insufficiently responding - insufficient anatomic response to prior therapy, defined as any persisting or increasing sub/intraretinal fluid observed in spectral domain OCT). (n=96) Intervention 2: Anti-VEGF - Ranibizumab. Ranibizumab n = 64, bevacizumab n = 4, ranibizumab switched to bevacizumab or vice versa n = 28. At least 3 injections. Average of 26.9 injections prior to switch.. Duration Mean 35 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: 2. Reason for switching:
Funding	Academic or government funding (Werner H Spross Foundation for Opthalmology at the Triemli Hospital Zurich and a research grant of Bayer AG Switzerland)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB OR BEVACIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity (ETDRS) at 16 weeks; General Summary Stats: Mean Baseline (before aflibercept) = 61.6 letters, 16 weeks (after aflibercept) = increase of 1.9 letters (p=0.061); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported
Study	Gharbiya 2014
Study type	Before and after study
Number of studies (number of participants)	1 (n=31 eyes from 30 patients)
Countries and setting	Conducted in Italy; Setting: Multicenter private practice setting
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6 months

Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) persistent intraretinal or subretinal fluid with or without pigment epithelial detachment (PED) at the initiation of aflibercept; (2) at least six consecutive monthly injections with ranibizumab before aflibercept initiation; (3) the interval between the last ranibizumab and the first aflibercept had to be not less than 4 weeks and not exceeding 6 weeks; (4) eligible eyes could have been treated with intravitreal bevacizumab; (5) at least 6 months of follow-up on a monthly basis.
Exclusion criteria	Patients were excluded if they had (1) prior treatment with photodynamic therapy; (2) a diagnosis of retinal angiomatous proliferation or idiopathic polypoidal choroidal vasculopathy; (3) any ocular disease that could affect the best-corrected visual acuity (BCVA); (4) a history of intraocular surgery except for uncomplicated phacoemulsification performed within the preceding 6 months; and (5) any systemic condition contraindicating the use of intravitreal anti-VEGF agents.
Recruitment/selection of patients	Review of medical records
Age, gender and ethnicity	Age - Mean (SD): 70.1 (8.1). Gender (M:F): 9 male, 21 female. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness: 10 eyes received previous bevacizumab before ranibizumab
Interventions	(n=31) Intervention 1: Anti-VEGF - Aflibercept. All patients received a loading dose of three monthly aflibercept injections (2 mg/0.05 mL). Follow-up examinations were given monthly. Retreatment with a single aflibercept injection was performed according to any of the following criteria: (1) visual acuity loss of at least five letters with OCT evidence of fluid in the macula; (2) persistent or recurrent intraretinal or subretinal fluid on OCT; (3) new subretinal hemorrhage from the CNV. . Duration 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Treatment

	resistant). (n=31) Intervention 2: Anti-VEGF - Ranibizumab. Ranibizumab only n = 21, bevacizumab and then ranibizumab n = 10. Average number of injections was 34.4 (11.9). Duration Mean 41.3 (14.2) months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB WITH/WITHOUT BEVACIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Best corrected visual acuity (ETDRS) at 3 injections; Group 1: mean 42.3 (SD 10.5); n=31, Group 2: mean 42.5 (SD 12.5); n=31; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Best corrected visual acuity (ETDRS) at 6 months; Group 1: mean 42.8 (SD 10); n=31, Group 2: mean 42.5 (SD 12.5); n=21; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported
Study	Griffin 2014
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=47 eyes of 47 patients)
Countries and setting	Conducted in USA; Setting: Not stated
Line of therapy	2nd line
Duration of study	Not clear:
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Patients had to have been initially treated with either bevacizumab or ranibizumab for the treatment of neovascular AMD with a minimum of three intravitreal injections of either drug; had to be considered treatment resistant, excluding partial responders that displayed persistent choroidal exudation while receiving initial anti VEGF therapy with either bevacizumab or ranibizumab; had to have received a baseline visit that was recorded, being the visit immediately prior to conversion to aflibercept therapy.
Exclusion criteria	Patients were excluded if the OCT was dry at the time during the three injections prior to conversion; elapsed time between prior treatment and the switch exceeded 63 days; following conversion the patient interrupted consecutive aflibercept treatment with an alternative anti VEGF therapy or any other intervention for the treatment of AMD; they did not have at least 3 aflibercept injections after conversion.
Recruitment/selection of patients	Retrospective study
Age, gender and ethnicity	Age - Mean (SD): 80.5 (8.02). Gender (M:F): 20 men. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: 18 patients previously recieved ranibizumab and bevacizumab
Interventions	(n=47) Intervention 1: Anti-VEGF - Aflibercept. Injections were given using a 1mL tuberculin syringe with a 30 gauge needle. The dose was 2mg. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab (ranibizumab or bevacizumab). 2. Reason for switching: Treatment failure (Treatment resistant - persistent macular exudation). (n=47) Intervention 2: Anti-VEGF - Ranibizumab. Ranibizumab only n = 14, bevacizumab only n = 15, both n = 18. Mean number of injections was 11.3 (1.9). All injection doses for bevacizumab 1.25 mg and ranibizumab was 0.5mg. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB AND/OR BEVACIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best correced visual acuity (logMAR) at After 3 injections; General Summary Stats: Mean Baseline (before aflibercept) = 0.56 (IQR = 0.29-0.99), after 3 injections = 0.53 (IQR = 0.24-0.71); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Bibliographic reference	**Gerding H. Funcational and anatomic efficacy of a conversion to aflibercept in eyes with age-related macular degeneration after long-term ranibizumab treatment. Klinische Monatsblatter fur Augenheilkunde 232 (4): 560-3. 2015.**
Country/ies	Switzerland
Study type	Observational study (retrospective before-after study, reviewed all patients with excudative AMD in whom ranibizumab to aflibercept between study period at Department of retinology, Olten Switzerland).
Aim of the study	the aim of this study to analyse the functional and anatomic efficacy of a conversion from ranibizumab to aflibercept treatment in eyes with exsudative age-related macular degeneration (AMD) with recently unsatisfactory response to a ranibizumab treatment
Study dates	1st Jan 2013 and 1st July 2013
Sources of funding	Not reported
Sample size	37 patients with excudative AMD in whom ranibizumab to aflibercept (40 eyes)
Inclusion Criteria	Eyes were selected for definite analysis when meeting the following criteria: 1.At least nine injections of ranibizumab had previously been applied, 2.no other treatment of AMD had been used, 3.within the last 3 months at least two ranibizumab injections had been given, 4.follow-up indicated continuity of are sponse to ranibizumab according to OCT and/or visual acuity data within the last 6months, 5.complete follow-up until month 6 after the conversion to aflibercept was available, 6.OCT presented persisten to rrecurrent intra-and/or subretinal fluid at the time of conversion, 7.clinical response towards ranibizumab was classified as poor,which was defined by: a) the necessity of monthly ranibizumab injections, or b)OCT findings were worse within the last 6months than previously

<table>
<tr><th>Bibliographic reference</th><th>Gerding H. Funcational and anatomic efficacy of a conversion to aflibercept in eyes with age-related macular degeneration after long-term ranibizumab treatment. Klinische Monatsblatter fur Augenheilkunde 232 (4): 560-3. 2015.</th></tr>
<tr><td></td><td>under an equal or lower frequency of ranibizumab treatment.</td></tr>
<tr><td>Exclusion Criteria</td><td>Not reported</td></tr>
<tr><td>Baseline characteristics</td><td>Mean age (SD), years: 80.8 (7.6) ; Male, n(%): 15 (37.5%)</td></tr>
<tr><td>Study visits and procedures</td><td>Al lintravitreal injections were performed as previously reported(Gerdingetal.20110.Regular monthly visits included the determination of best corrected visual acuity using standardized logarithmic Snellen charts and spectral domain OCTimaging(Spectralis,HeidelbergEngineering,Heidelberg, Germany).OCTdata represent total retinal thickness values including the retinal pigment epithelium layerand, if present, the detachment of the retinal pigment epithelium at the central foveal point</td></tr>
<tr><td>Intervention</td><td>Converstion to aflibercept</td></tr>
<tr><td>Comparator</td><td>Prior conversion (ranibizumab)</td></tr>
<tr><td>Outcomes</td><td>Primary outcome:
change in BCVA before and after the conversion</td></tr>
<tr><td>Analyses</td><td>Excel implemented software (Version 2003, Microsoft) was used for the calculation of descriptive statistics.
Comparison of distribution was performed with the 2-tailed Wilcoxon signed-rank test for two related samples,using the SPSS Statistic software package (Version12.0). Differences were considered as statisticallysignificant when the calculated p-values were less than 0.05.</td></tr>
<tr><td>Length of follow up</td><td>6 months</td></tr>
<tr><td>Result</td><td>Visual acuity
<table>
<tr><td></td><td>Prio to the 1st aflibercept injection (n=40 eyes)</td><td>After conversion, at Month 6 (n=40 eyes)</td><td>Effect (MD) (95%CI)</td></tr>
<tr><td>Mean change in VA, logMAR(SE)</td><td>0.56 (SE=0.33) (SD=2.09)</td><td>0.64 (SD1.77)</td><td>-0.08 (-3.61, 3.45)</td></tr>
</table></td></tr>
<tr><td>Others</td><td>All eyes in this series presented persistent orrecurrent fluid at the time of switching to aflibercept.</td></tr>
</table>

Study	Heussen 2014

Study type	Before and after study
Number of studies (number of participants)	1 (n=65 (71 eyes))
Countries and setting	Conducted in Germany; Setting: Not stated
Line of therapy	2nd line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: by fluorescein angiography and spectral-domain optical coherence tomography (SD-OCT)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	A diagnosis of exudative AMD confirmed by fluorescein angiography and spectral-domain optical coherence tomography (SD-OCT), previous injections with ranibizumab and subsequent injections with aflibercept in the same eye.
Exclusion criteria	Patients with a diagnosis of polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferations (RAP) were not included for the purpose of this study.
Recruitment/selection of patients	Retrospective consecutive case series
Age, gender and ethnicity	Age - Mean (range): 77 (43–95). Gender (M:F): 24 men, 41 women. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: 2. Other co-morbidities affecting the eye: 3. Pigment epithelial detachment (PED): 4. Polypoidal choroidal vasculopathy : 5. Retinal angiomatous proliferation: 6. Type of late wet AMD:
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: Anti-VEGF - Aflibercept. All 71 eyes received at least one aflibercept injection. Sixty-six eyes received at least two aflibercept injections, 45 eyes had three aflibercept injections, and 12 eyes had four aflibercept injections. The average number of aflibercept injections was 2.73 (range 1–4). . Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Insufficient or diminishing treatment effects under ranibizumab). (n=71) Intervention 2: Anti-VEGF - Ranibizumab. All eyes received nine ranibizumab injections (range 3–43) or

	3.25 injections per year before switching to aflibercept therapy. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Other (Research support from Novartis and Heidelberg Engineering)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Visual acuity (logMAR) at After 1 injection; Group 1: mean 0.65 (SD 0.48); n=71, Group 2: mean 0.67 (SD 0.46); n=71; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Visual acuity (logMAR) at After 2 injections; Group 1: mean 0.60 (SD 0.43); n=66, Group 2: mean 0.59 (SD 0.42); n=66; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Visual acuity (logMAR) at After 3 injections; Group 1: mean 0.43 (SD 0.2); n=45, Group 2: mean 0.56 (SD 0.21); n=45; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Visual acuity (logMAR) at After 4 injections; Group 1: mean 0.25 (SD 0.47); n=12, Group 2: mean 0.47 (SD 0.43); n=12; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Homer 2015**
Study type	Before and after study
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in USA; Setting: Not stated
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 24 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with nAMD treated with at least 6 intravitreal ranibizumab or bevicizumab injections in the previous 12 months, who required treatment on a 4-8week interval to remain exudation free and were switched to aflibercept.
Exclusion criteria	Eyes with idiopathic polypoidal choroidal vasculopathy, central serous retinopathy, anti-VEGF therapy < 28 days prior, prior photodynamic therapy, significant subfoveal fibrosis or large subretinal hemorrhage, prior triamcinolone (<6 months), intraocular surgery (<2 months), prior vitrectomy, active intraocular inflammation, vitreous haemorrhage, retinal pigment epithelium tear, or best corrected vision <20/40
Recruitment/selection of patients	Retrospective review
Age, gender and ethnicity	Age - Mean (SD): 83.6 (7.1). Gender (M:F): 15 female. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: No CSR-like AMD 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear (CVD in 2). 3. Pigment epithelial detachment (PED): No PED 4. Polypoidal choroidal vasculopathy: No polypoidal choroidal vasculopathy 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Anti-VEGF - Aflibercept. 2.0 mg, 3 monthly injections followed by treatment at a generally fixed interval of 8 weeks, further extended by 2 week intervals at the discretion of the treating physician. (21 eyes of 18 patients). Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab (Ranibizumab OR Bevacizumab). 2. Reason for switching: Treatment failure (Required treatment on a 4-8week interval to remain exudation free). (n=21) Intervention 2: Anti-VEGF - Bevacizumab. 0.5mg/0.05ml ranibizumab or 1.25mg/0.05ml bevacizumab. At least 6 injections in past 12 months. . Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab (Bevacizumab or Ranibizumab). 2. Reason for switching: Treatment failure
Funding	Academic or government funding (Supported in part by a unrestricted grant from Research to Prevent Blindness)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus BEVACIZUMAB OR RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported	

- Actual outcome: Best corrected visual acuity (logMAR) at 24 months; Group 1: mean 0.42 (SD 0.23); n=21, Group 2: mean 0.42 (SD 0.31); n=21; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Kaiser 2012**
Study type	Before and after study
Number of studies (number of participants)	1 (n=19 patients)
Countries and setting	Conducted in USA; Setting: Single site study
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: PED or no PED
Inclusion criteria	Patients had to be 50 years of age or older; had active CNV lesions secondary to AMD in the study eye; best corrected visual acuity of 20/40 to 20/320 in the study eye; and had inadequate clinical response to pegaptanib or bevacizumab.
Exclusion criteria	If they were unable to undergo flourescein angiography or fundus photography because of uncontrolled allergies, or had previous treatment with verteporfin in the non-study eye less than 7 days preceding day 0; previous treatment with bevacizumab for anything other than AMD with PED; previous participation in a clinical trial involving antiangiogenic therapy; previous intravitreal drug deliver in the study eye; laser photocoagulation in the study eye within 1 month preceding day 0; history of submacular surgery or other surgery for AMD in the study eye; previous participation in any study of the investigational drug within 1 month of day 0; or lesion characteristics of CNV due to causes other than AMD
Recruitment/selection of patients	Not stated

Age, gender and ethnicity	Age - Mean (range): 77.1 (63-85). Gender (M:F): Female 13%. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Systematic review: mixed 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (6 with PED). 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Mixed (17 occult, 1 classic (1 missing data)).
Indirectness of population	Serious indirectness: 1 patient previously received pegaptanib before switch and 5 received pegaptanib and bevacizumab, the rest had bevacizumab only (13)
Interventions	(n=19) Intervention 1: Anti-VEGF - Ranibizumab. A fixed 12 month dosing regimen of 0.5mg of intravitreal ranibizumab, receiving ranibizumab at day 0 and monthly for 12 months. . Duration 12 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab (Bevacizumab and/or pegaptnib). 2. Reason for switching: Treatment failure (No clinical response - inadequate clinical response (a gain of less than 1 line of visual acuity or persistence of 300um or greater central retinal thickness on OCT) to anti VEGF treatment following at least two consecutive intravitreal injections.). (n=19) Intervention 2: Anti-VEGF - Bevacizumab. Bevacizumab n = 13, pegaptanib n = 1, both n = 5. Duration Mean 5 (SE 0.6). Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RANIBIZUMAB versus BEVACIZUMAB AND/OR PEGAPTANIB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (ETDRS) at 12 months; Mean Change in VA from day 0 (switch) to 12 months = 0.67 (SE 0.57) ETDRS; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Visual acuity (ETDRS)[with PED] at 12 months; Mean change in VS (ETDRS) -0.6 (0.68); Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome: Visual acuity (ETDRS)[no PED] at 12 months; Mean Change in VA 1.67 (0.94); Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 2: Safety and adverse events at As reported

- Actual outcome: Adverse events at 12 months; General Summary Stats: No serious adverse events ;Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Kawashima 2015**
Study type	Before and after study
Number of studies (number of participants)	1 (n=41 eyes of 41 patients)
Countries and setting	Conducted in Japan; Setting: Not stated
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: AMD and PCV
Inclusion criteria	Consecutive patients with AMD or PCV who were treated at our institution from 1 December 2012 to 31 August 2013 with ranibizumab for longer than 6 months, and showed recurrent or residual exudative changes after the last three injections.
Exclusion criteria	Patients were excluded when photodynamic therapy had been performed within 6 months of the conversion, or if they dropped out within 6 months after conversion.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 75.6 (8). Gender (M:F): 36 male, 5 female. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : Mixed population (26 with PCV). 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear

Indirectness of population	Serious indirectness: 8 patients received previous bevacizumab or pegaptanib prior to the ranibizumab
Interventions	(n=41) Intervention 1: Anti-VEGF - Aflibercept. Aflibercept (2.0 mg) injections administered once a month for 3 months and then administered bi-monthly. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Treatment resistent - recurrent or residual exudative changes after the last 3 injections). (n=41) Intervention 2: Anti-VEGF - Ranibizumab. Eight patients also received previous bevacizumab or pegaptanib before ranibizumab. Average number of previous injections was 10.3 (7.8). Duration Mean 39.5 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Academic or government funding (Supported by the Japan Society for the Promotion of Science and the Innovative Techno-Hub for Integrated Medical Bio-Imaging of the Project for Developing Innovation Systems, from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (logMAR) at 6 months; Group 1: mean 0.35 (SD 0.4); n=41, Group 2: mean 0.4 (SD 0.37); n=41; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Visual acuity (logMAR) [PCV] at 6 months; General Summary Stats: Mean Baseline 0.4 (0.37), change in VA -0.09 (0.14); Risk of bias:Very high ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Kucukerdonmez 2015**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=87)

Countries and setting	Conducted in Germany; Setting: Department of Ophthalmology
Line of therapy	2nd line
Duration of study	Not clear: Retrospective study
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Underwent full ophthalmologic examination at each visit
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Poor responders and non-responders
Inclusion criteria	Subfoveal choridal neovascularization, poor treatment effect under anti-VEGF treatment, a minimum of 3 anti-VEGF injections (bevacizumab or ranibizumab) before being switched, follow up of at least 12 months after switch.
Exclusion criteria	Follow up of less than 6 months after the last injection of the first drug, extrafoveal and juxtafoveal CNV, retinal angiomatous proliferation, polupoidal choroidal vasculopathy, retinal pigment epithelial rupture, subfoveal fibrosis or subfoveal hemorrhage, other eye diseases that could interfere with the visual outcome, history of vitreoretinal or glaucoma surgery, patients who previously or additionally received other treatment for CNV such as thermal laser photocogulation, photodynamic therapy, intravitreal pegaptanib, triamcinolone, intravitreal tissue plasminogen activator injection or macular surgery.
Recruitment/selection of patients	Chart review of patients with nAMD
Age, gender and ethnicity	Age - Mean (SD): group 1: 78.8 (6.5), group 2: 77.3 (7.2). Gender (M:F): 56 women. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : No polypoidal choroidal vasculopathy 5. Retinal angiomatous proliferation: No retinal angiomatous proliferation 6. Type of late wet AMD: Mixed (11 predominant classic, 4 minimal classic, 72 occult).
Extra comments	Baseline BCVA (logMAR, mean, median, range) (initial)- Group 1: 0.55 (0.5, 0.1-1.1), Group 2: 0.51 (0.5, 0-1.3). Baseline (switch) - Group 1: 0.67 (0.6, 0.1-1.3), Group 2: 0.56 (0.5, 0-1.3)
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Anti-VEGF - Ranibizumab. Ranibizumab in every 4 weeks for 3 injections (upload period), and then the intervals for re-examination were 4 weeks. Retreatment was performed on an as

	needed basis. The dosage was 5mg/0.05mL.. Duration 3 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (Poor treatment effect). (n=43) Intervention 2: Anti-VEGF - Bevacizumab. Bevacizumab in every 6 weeks for 3 injections (upload period), and then the intervals for re-examination were 6 weeks. Retreatment was performed on an as needed basis. The dosage was 1.25mg/0.05mL.. Duration 3 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Poor treatment response).
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RANIBIZUMAB versus BEVACIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity at 1 year; Mean Group 1 (bev to ran): mean = 0.71, median = 0.7, range = 0.2-1.6, p = 0.573 (compared to switch scores). Group 2 (ran to bev): mean = 0.66, median = 0.6, range = 0-2, p = 0.401 (compared to switch); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity at >1 year; Mean Group 1: mean = 0.88, median = 0.9, range = 0.2-1.7, p = 0.015 (compared to switch). Group 2: mean = 0.72, median = 0.7, range = 0-2, p = 0.081 (compared to switch); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Kumar 2013**
Study type	Before and after study
Number of studies (number of participants)	1 (n=33 patients, 34 eyes)
Countries and setting	Conducted in USA; Setting: Retina Practice

Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 79 (8). Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (33 had subfoveal PED). 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Mean number of previous ranibizumab was 26.5 (18.4), mean number of previous bevacizumab was 1.8 (2.8), mean number of PDT treatments was 0.4 (1.1), last three treatments before the switch had to be with ranibizumab.
Interventions	(n=34) Intervention 1: Anti-VEGF - Aflibercept. Three consecutive intravitreal injections of 2mg, maximum treatment interval of 56 days.. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Persistent foveal subretinal and/or intraretinal fluid despite previous treatment with 0.5mg of ranibizumab). (n=34) Intervention 2: Anti-VEGF - Ranibizumab. 0.5 mg ranibizumab, at least 3 injections. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Best corrected visual acuity (LogMAR) at After 3 injections; Group 1: mean 0.52 (SD 0.34); n=34, Group 2: mean 0.57 (SD 0.36); n=34; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Best corrected visual acuity (LogMAR) at 6 months; Group 1: mean 0.47 (SD 0.32); n=34, Group 2: mean 0.57 (SD 0.36); n=34; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Safety and adverse events at As reported
- Actual outcome: Adverse events at 6 months; General Summary Stats: No significant ocular safety events (e.g. endophtalmitis, retinal tears); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Mantel 2016**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in Switzerland; Setting: Tertiary referral centre
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients from a clinical trial who still needed monthly retreatment with ranibizumab after 24 months of treatment. Previously treatment naive. Neovascular AMD and active subfoveal choroidal neovascularisation.

Exclusion criteria	Not stated
Recruitment/selection of patients	Patients were recruit from a previous prospective clinical trial to evaluate the clinical value of an observe and plan treatment regimen for nAMD using intravitreal ranibizumab. Those who still needed monthly retreatment with ranibizumab were eligible for this study.
Age, gender and ethnicity	Age - Mean (SD): 76.0 (23.5). Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (9 patients (43%) had PEDs). 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Mixed population (1 patient had RAP). 6. Type of late wet AMD: Mixed (4 predominantly classic, 4 minimally classic, 12 occult).
Extra comments	Baseline BCVA before any treatment (ETDRS letters, SD): Group A - 62.5 (11.5), Group R - 63.6 (17.9). Baseline change in BCVA between therapy initiation and baseline (ETDRS letters, SD): Group A - 5.6 (15.8), Group R - 7.5 (15.1)
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Anti-VEGF - Ranibizumab. Group R (control group) - patients started with 3 monthly injections and then treatment intervals were extended according to optical coherence tomography criteria under an on-going Observe and Plan regimen for 12 months. Patients had previously had 24 months of ranibizumab. . Duration 12 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab (Treated with ranibizumab for 24 months). 2. Reason for switching: Treatment failure (Those still needing monthly retreatment based on the presence of refractory fluid when treatment was performed monthly, or the recurrent fluid when the treatment interval was extended to 1.5 months.). (n=10) Intervention 2: Anti-VEGF - Aflibercept. Group A - patients started with 3 monthly injections and then treatment intervals were extended according to optical coherence tomography criteria under an on-going Observe and Plan regimen for 12 months. Patients had previously had 24 months of ranibizumab. . Duration 12 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Aflibercept 2. Reason for switching: Treatment failure (Those still needing monthly retreatment based on the presence of refractory fluid when treatment was performed monthly, or the recurrent fluid when the treatment interval was extended to 1.5 months).

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RANIBIZUMAB versus AFLIBERCEPT Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: BCVA (ETDRS letters) at 12 months; Group 1: mean 0.5 (SD 2.5); n=11, Group 2: mean -2 (SD 3); n=10; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Moisseiev 2015**
Study type	Before and after study
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Israel; Setting: Assuta clinic
Line of therapy	2nd line
Duration of study	Follow up (post intervention): Mean follow up 14.2 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: Eyes with at least 10% reduction in CRT after the switch and eyes without anatomical improvement after the switch
Inclusion criteria	NVAMD initially treated with at least 3 intravitreal bevacizumab injections and later with at least 3 ranibizumab intravitreal injections with at least 4 months of follow up after the 3rd ranibizumab injection. Visual acuity at least 20/1200

Exclusion criteria	Previous photodynamic therapy or laser photocoagulation, additional ocular morbidity that significantly affected the visual acuity, history of ocular trauma or surgery other than uncomplicated cataract extraction, cataract surgery within 3 months before or after the anti-vascular endothelial growth factor switch, and large submacular hemorrhages secondary to NVMD.
Recruitment/selection of patients	Retrospective review of Maccabi Health care Services patients
Age, gender and ethnicity	Age - Mean (SD): 78.6 (8.1). Gender (M:F): 60 men, 50 women. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: No other comorbidities affecting the eye 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Extra comments	Baseline (before the last 3 monthly bevacizumab injections) = 0.51 (0.33)
Indirectness of population	No indirectness
Interventions	(n=110) Intervention 1: Anti-VEGF - Bevacizumab. Mean no. of injections = 9.2 (5.0) (range 3-27). Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (n=110) Intervention 2: Anti-VEGF - Ranibizumab. Mean no. of injections after switch = 8.9 (4.9) (range 3-29). Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (Persistent intraretinal or subretinal fluid on spectral domain optical coherence tomography and/or absence of visual improvement. (One patient changed after a transient ischemic event).).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEVACIZUMAB versus RANIBIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (LogMAR) at At least 4 months (end of follow up); Group 1: mean 0.52 (SD 0.32); n=110, Group 2: mean 0.56 (SD 0.4); n=110; Risk of bias: Very high; Indirectness of outcome: No indirectness

- Actual outcome: Visual acuity (LogMAR) at 3 months; Group 1: mean 0.52 (SD 0.32); n=110, Group 2: mean 0.5 (SD 0.37); n=110; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Narayan 2015**
Study type	Before and after study
Number of studies (number of participants)	1 (n=192)
Countries and setting	Conducted in Australia; Setting: Retinal practice in Adelaide, South Australia
Line of therapy	2nd line
Duration of study	Intervention + follow up: Mean 16 months
Method of assessment of guideline condition	--: The diagnosis of AMD was based on clinical findings and confirmed using fluorescein angiography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with CNV secondary to neovascular AMD were treated with 0.5 mg intravitreal ranibizumab in one or both eyes.
Exclusion criteria	Patients were excluded if they received prior verteporfin photodynamic therapy.
Recruitment/selection of patients	Data collected from patient records
Age, gender and ethnicity	Age - --: Gender (M:F): 81 men. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (2 PED). 4. Polypoidal choroidal vasculopathy: Not applicable / Not stated / Unclear 5. Retinal

	angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Extra comments	Mean VA before R treatment = 0.652 ± 0.430 (SD).
Indirectness of population	--
Interventions	(n=80) Intervention 1: Anti-VEGF - Aflibercept. After more than 12 months of ranibizumab treatment, eyes that required ranibizumab injections at 4-week or 6-week intervals were changed to aflibercept therapy. Eyes were injected with 2 mg intravitreal aflibercept at the same intervals as their ranibizumab injections. Injections were extended to 6-week then 8-week intervals if there were no signs of active CNV. Patients were continued on aflibercept for at least 12 months. . Duration Mean 16 months ± 1 month. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Either had persistent macular fluid and were being treated at 4-week intervals or required 4-week or 6-week injection intervals to maintain a fluid-free macula.). (n=160) Intervention 2: Anti-VEGF - Ranibizumab. All eyes were treated with a fixed regimen of three 0.5 mg intravitreal ranibizumab injections given at 4-week intervals and were given a follow-up appointment 6 weeks after the third ranibizumab injection. Retreatment was offered in the presence of persistent intraretinal and/or submacular fluid. Eyes that required retreatment were given another course of three injections at 4-week intervals followed by an appointment 6 weeks after the third injection. Following the second course of three ranibizumab injections, these eyes received maintenance injections at 4-week, 6-week, 8-week, 10-week, or 12-week intervals depending on the time to recurrence from the last assessment that showed no signs of active CNV. Duration Mean 42 months ± 18 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (logMAR) at 12 months; Group 1: mean 0.615 (SD 0.305); n=80, Group 2: mean 0.642 (SD 0.318); n=80; Risk of bias: Very

high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported
Study	Nomura 2015
Study type	Before and after study
Number of studies (number of participants)	1 (n=25)
Countries and setting	Conducted in Japan; Setting: Outpatient clinic
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: AMD with CVH and AMD without CVH
Inclusion criteria	Patients who started intravitreal afilbercept between March and June 2013 and were followed up for 12 months after the first treatment. Only those whose best corrected visual acuity data and SD-OCT images were available at baseline and 3, 6 and 12 months after initial treatment were included.
Exclusion criteria	Previous history of laser photocoagulation, verteporfin photodynamic therapy, or virectomy, or with any other pathologic conditions such as diabetic retinopathy.
Recruitment/selection of patients	Retrospective study
Age, gender and ethnicity	Age - Mean (SD): AMD = 73.6 (6.5), AMD+CVH = 77.1 (9.2). Gender (M:F): 16 male. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: No other comorbidities affecting the eye 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : Mixed population (17 PCV). 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear

Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Anti-VEGF - Aflibercept. 2mg/0.05ml. Three injections administered at months 0, 1 and 2, and then additional injections were administered as a modified treat and extend regime until no signs of macular hemorrhage and no intraretinal/subretinal fluid were observed. Then treatment lengthened by 2 weeks to a maximum of 8 weeks. . Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Persistant subretinal fluid, frequent reoccurence). (n=9) Intervention 2: Anti-VEGF - Ranibizumab. Not stated. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (n=16) Intervention 3: Anti-VEGF - Ranibizumab. Not stated. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (n=16) Intervention 4: Anti-VEGF - Aflibercept. 2mg/0.05ml. Three injections administered at months 0, 1 and 2, and then additional injections were administered as a modified treat and extend regime until no signs of macular hemorrhage and no intraretinal/subretinal fluid were observed. Then treatment lengthened by 2 weeks to a maximum of 8 weeks. . Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Persistent subretinal fluid/cystoid macular edema/subretinal hemorrhage/progression of CNV/frequent reoccurrence).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT (AMD+ CVH POPULATION) versus RANIBIZUMAB (AMD+CVH POPULATION)

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Best corrected visual acuity at 3 months; Group 2: mean 0.13; n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Best corrected visual acuity at 6 months; Group 2: mean 0.13 ; n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness

- Actual outcome: Best corrected visual acuity at 12 months; Group 2: mean 0.19; n=9; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RANIBIZUMAB (AMD ONLY POPULATION) versus AFLIBERCEPT (AMD ONLY POPULATION) Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity at 3 months; Group 1: mean 0.17; n=16, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity at 6 months; Group 1: mean 0.14; n=16, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity at 12 months; Group 1: mean 0.14; n=16, Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Pinheiro-Costa 2015**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=85 eyes of 69 patients)
Countries and setting	Conducted in Portugal; Setting: Tertiary health care center
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The presence of neovascular AMD prevously treated with intravitreal bevacizumab or ranibizumab that was switched to intravitreal aflibercept; a minimum of 3 injections of bevacizumab or ranibizumab before the switch and 1 year of follow up after the switch.

Exclusion criteria	CNV lesions secondary to causes other than AMD, myopia greater than -6 D; concomitant retinal vascular disorders in the studied eye, and cataract surgery or YAG capsulotomy performed during the folow up period.
Recruitment/selection of patients	Retrospective chart review
Age, gender and ethnicity	Age - Mean (range): 76.6 (61-92). Gender (M:F): 38 women. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : Mixed population (2 PCV). 5. Retinal angiomatous proliferation: Mixed population (3 RAP). 6. Type of late wet AMD: Mixed (59 occult, 6 predominantly classic, 10 minimally classic).
Indirectness of population	Serious indirectness: 3 patients received previous photodynamic therapy
Interventions	(n=39) Intervention 1: Anti-VEGF - Aflibercept. 2mg aflibercept. Duration Mean 14.1 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (Patients with persistent exudation after 3 or more consecutive monthly injections). (n=39) Intervention 2: Anti-VEGF - Bevacizumab. 3 patients with previous PDT. 1.25mg. Duration Mean 22.5 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus BEVACIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Best corrected visual acuity (ETDRS) at 1 year; Group 1: mean 55.8 (SD 18.1); n=39, Group 2: mean 58.2 (SD 16.8); n=39; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Saito 2014**
Study type	Before and after study
Number of studies (number of participants)	1 (n=42 patients, 43 eyes)
Countries and setting	Conducted in Japan; Setting: University hospital
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients had a treatment history of 3 consecutive monthly intravitreal injections of ranibizumab. All patients had at least 15 months of follow up with ranibizumab. All patients were treated with 3 consecutive monthly intravitreal injections of aflibercept and followed for at least 3 months.
Exclusion criteria	Previous treatment for AMD such as laser photcoagulation, submacular surgery, and transpupillary thermotherapy; glaucoma; retinal pigment epithelial tears; and maculopathies such as diabetic maculopathy, retinal vascular occlusion, or idiopathic macular telangiectasia; photodynamic therapy with verteporfin within the last 12 months.
Recruitment/selection of patients	Retrospective review
Age, gender and ethnicity	Age - Mean (SD): 76.5 (6.1). Gender (M:F): 9 women, 33 men. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (13 PED (30%)). 4. Polypoidal choroidal vasculopathy : Polypoidal choroidal vasculopathy present (100%). 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Occult late wet AMD
Indirectness of population	No indirectness: 23 patients received ranibizumab only (9 also received additional treatment with ran + PDT), 8 patients received ranibizumab and PDT, 12 patients had PDT monotherapy

Interventions	(n=43) Intervention 1: Anti-VEGF - Aflibercept. Three consecutive montly intravitreal injections 2mg/0.05 mL). Duration 3 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Refractory - the presence of persistent subretinal or intraretinal fluid seen on OCT images and unchanged or decreased visual acuity compared with baseline despite the patients having received the last 2 consecutive monthly intravitreal injections of ranibizumab after 12 months from the initial injection). (n=43) Intervention 2: Anti-VEGF - Ranibizumab. Not stated. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity (logMAR) at 1 month; Mean Ran = 0.38, Aflib = 0.33; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity (logMAR) at 2 months; Mean Ran = 0.38, Aflib = 0.32; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity (logMAR) at 3 months; Mean Ran = 0.38, aflib = 0.34; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Saito 2016**
Study type	Before and after study
Number of studies (number of participants)	1 (n=65 patients, 66 eyes)

Countries and setting	Conducted in Japan; Setting: Not stated
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	PCV treated with intravitreal aflibercept who were refractory to ranibizumab.
Exclusion criteria	Previous treatmend for AMD such as laser coagulation, submacular surgery, and transpupillary thermotherapy; glaucoma; retinal pigment epithelium tears; and maculopathies such as diabetic maculopathy, retinal vascular occlusion, or idiopathic macular telangiectasia; photodynamic therapy with veteporfin within the last 12 months.
Recruitment/selection of patients	Retrospective review
Age, gender and ethnicity	Age - Mean (SD): 75.7 (5.8). Gender (M:F): 51 men, 14 women. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (20 eyes with PED). 4. Polypoidal choroidal vasculopathy : Polypoidal choroidal vasculopathy present 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Occult late wet AMD
Indirectness of population	Serious indirectness: Ranibizumab monotherapy in 35 eyes (12 received additional treatment with combined ran and PDT), combined ranibizumab and PDT in 9 eyes, PDT monotherapy in 22 eyes.
Interventions	(n=66) Intervention 1: Anti-VEGF - Aflibercept. 2mg/0.05 mL, bimonthly injections after three consecutive monthly intravitreal injections. . Duration 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Refractory - presence of persistent subretinal or inraretinal fluid seen on OCT imaged and unchanged/decreased VA without relation to progressions of cataract or massive hemorrhage compared with baseline). (n=66) Intervention 2: Anti-VEGF - Ranibizumab. Average 32.7 (11.2) months, 12.9 (6.4) injections. Duration

	Mean 32.7 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity (logMAR) at 1 month; Mean Ran = 0.40, aflibercept = 0.35; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity (logMAR) at 2 months; Mean Ran = 0.40, aflib = 0.33; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity (logMAR) at 3 months; Mean Ran = 0.40, aflib = 0.35; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity (logMAR) at 4 months; Mean Ran = 0.40, aflib = 0.34; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity (logMAR) at 6 months; Mean Ran = 0.40, aflib = 0.33; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Bibliographic reference	**Sarao V ; Parravano M ; Veritti D ; Arias L ; Varano M ; Lanzetta P. Intravitreal Aflibercept for Choroidal Neovascularization Due to Age-Related Macular Degeneration Unresponsive to Ranibizumab Therapy. Retina 36 (4): 770-77. 2016**
Country/ies	Italy and Spain
Study type	Prospective before-after study

Bibliographic reference	**Sarao V ; Parravano M ; Veritti D ; Arias L ; Varano M ; Lanzetta P. Intravitreal Aflibercept for Choroidal Neovascularization Due to Age-Related Macular Degeneration Unresponsive to Ranibizumab Therapy. Retina 36 (4): 770-77. 2016**
Aim of the study	To assess the efficacy of intravitreal injection of aflibercept for treating choroidal neovascularization due to age-related macular degeneration unresponsive to ranibizumab.
Study dates	1st April 2012 and 30th December 2013
Sources of funding	Not reported
Sample size	92 eyes
Inclusion Criteria	Patients were included in the study if they were: 1.Age older than 50 years 2.angiographically documented CNV secondary to AMD 3.A failed response to ranibizumab monotherapy defined as persistent or recurrent subretinal and/or intraretinal fluid on SD-OCT after at least 4 ranibizumab injections during the previous 6 months and 1 month after the last injection 4.BCVA of 70 ETDRS letter score or wrse (≤20/40 Snellen)
Exclusion Criteria	1.Presence of RAP and PCV 2.RPE tear inovling the macular 3.History of systemic or ocular corticosteroid medication within 6 months before the baseline evaluation 4.Active intraocular inflammation or systemic infection 5.Refractuve error of> -8D 6.Loss of vision as a result of other causes
Baseline characteristics	Mean age (SD), years: 78.3 (8.2) Male, n(%): 31 (34%) BCVA, letters (SD): 52.8 (17.8) No. of ranibizumab injection in the 6 months before enrolment: 5.2 (1.6) Total number of preivous ranibizumab injections: 15.2 (1.9)
Study visits and procedures	Patients received 1 aflibercept injection (2mg) at baseline and then were scheduled for monthly follow-up exminations. All injection procedure were performed bt 3 experienced retnal physicians. At each follow-up tome, patients underwent a complete ophthalmic evaluation and SD-OCT examination. FA and ICG were performed based on investigator judgement using the same procedures at baseline. Retreatments were considered at investigators' discretion based on SD-OCT, BCVA, FA findings. Patients were followed-up for potential systemic and ocular side effects.
Intervention	Converstion to aflibercept

<table>
<tr><th>Bibliographic reference</th><th>Sarao V ; Parravano M ; Veritti D ; Arias L ; Varano M ; Lanzetta P. Intravitreal Aflibercept for Choroidal Neovascularization Due to Age-Related Macular Degeneration Unresponsive to Ranibizumab Therapy. Retina 36 (4): 770-77. 2016</th></tr>
<tr><td>Comparator</td><td>Prior conversion (ranibizumab)</td></tr>
<tr><td>Outcomes</td><td>Primary outcome:
change in BCVA
Seconadary outcome
The reduction in central retinal thickness and retreatment rate during the follow-up.
The incidence of ocular and non-ocular AEs as recorded.</td></tr>
<tr><td>Analyses</td><td>Repeated-measures analysis of variance with Green-hous-Geisser correction was conducted to assess whether there were differences between average values.
Serial comparisons of pre-treatment and post-treatment outcomes were performed with Dunnett multiple comparison or Wilcoxon matched-paired non-parametric tests.
Prognistic parameters were analysed by Pearson’s correction coefficient or Spearman’rho.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Result</td><td>Visual acuity: pre-treatment
<table>
<tr><td></td><td>Pre 6 months</td><td>Pre 3 months</td><td>Pre 1month</td><td>baseline</td></tr>
<tr><td>BCVA change from baseline, letter (SD)</td><td>+6.1 (12.1)</td><td>+3.4 (9.8)</td><td>+1.9 (7.4)</td><td>0</td></tr>
</table>
Visual acuity: post-treatment
<table>
<tr><td></td><td>Month 1</td><td>Month 3</td><td>Month 6</td><td>Month 9</td><td>Month 12</td></tr>
<tr><td>BCVA change from baseline, letter (SD)</td><td>+5.2 (8.9)</td><td>+3.9 (9.2)</td><td>+3.6 (9.3)</td><td>+2.6 (10.6)</td><td>+1.8 (10.7)</td></tr>
</table>
Estimated effect (from baseline to month 12):
<table>
<tr><td></td><td>Month 1</td><td>Month 3</td><td>Month 6</td><td>Month 9</td><td>Month 12</td></tr>
<tr><td>Estimated effect (from baseline), letter (SD)</td><td>+5.2
(3.38, 7.02)</td><td>+3.9
(2.02, 5.78)</td><td>+3.6
(1.70, 5.50)</td><td>+2.6
(0.43, 4.77)</td><td>+1.8
(-0.39, 3.99)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Sarao V ; Parravano M ; Veritti D ; Arias L ; Varano M ; Lanzetta P. Intravitreal Aflibercept for Choroidal Neovascularization Due to Age-Related Macular Degeneration Unresponsive to Ranibizumab Therapy. Retina 36 (4): 770-77. 2016
Others	

Study	Shaikh 2015
Study type	Before and after study
Number of studies (number of participants)	1 (n=30 patients, 33 eyes)
Countries and setting	Conducted in USA; Setting: Cincinnati Eye Institute
Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients receiving regular IVB or IVR for at least 6 months who were changed to IVA for persistently active wet AMD and had at least a 6 month follow up after this change.
Exclusion criteria	Eyes with recent photodynamic treatment and exudation from retinovascular disease or choroidal neovascularization from causes other than wet AMD.
Recruitment/selection of patients	Retrospective review of records
Age, gender and ethnicity	Age - Mean (range): Bevac group: 80 (68-93), Ranib group: 79 (78-87). Gender (M:F): 15 male, 15 female. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear

	5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Anti-VEGF - Bevacizumab. Not stated. Duration At least 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (n=8) Intervention 2: Anti-VEGF - Ranibizumab. Not stated. Duration At least 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (n=33) Intervention 3: Anti-VEGF - Aflibercept. Patients were observed approximantely montholy according to the PRONTO or treat and extend protocols. Injection was administered in an out patient office setting. The eye was prepped with topical proparacaine drops and 5% betadine solution. . Duration 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab (Bevacizumab or ranibizumab). 2. Reason for switching: Treatment failure (Persistently active AMD).
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEVACIZUMAB versus AFLIBERCEPT

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (logMAR) at 6 months; General Summary Stats: A mean loss of 0.06 logMAR vision (p=.16) after aflibercept. Score at switch not stated.; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RANIBIZUMAB versus AFLIBERCEPT

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Visual acuity (logMAR) at 6 months; General Summary Stats: A mean loss of 0.06 logMAR vision (p=.16) after aflibercept. Score at switch

not stated; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Shiragami 2014**
Study type	Before and after study
Number of studies (number of participants)	1 (n=50 patients, 50 eyes)
Countries and setting	Conducted in Japan; Setting: Not stated
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: PVC, RAP
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 77.7 (6.06). Gender (M:F): 37 men, 13 women. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : Mixed population (23 PCV). 5. Retinal angiomatous proliferation: Mixed population (6 RAP). 6. Type of late wet AMD: Mixed (Occult in 7 eyes, minimally classic in 27 eyes, predominantly classic in 16 eyes).

Indirectness of population	Serious indirectness: Previous treatment was ranibizumab or combined ranibizumab plus PDT (on average 0.68 (0.65) PDT sessions)
Interventions	(n=50) Intervention 1: Anti-VEGF - Pegaptanib Sodium. Over a 12 month period, intravitreal pegaptanib 0.3mg was administered at 6 week intervals. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Treatment resistent - thickening of the macular exudate, deterioration of visual function). (n=50) Intervention 2: Anti-VEGF - Ranibizumab. Three initial consecutive monthly IVR injections followed by pro re nata. PDT-combined therapy with 3 monthly loading doses was performed for most of the PCV and RAP patients.. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PEGAPTANIB SODIUM versus RANIBIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Best corrected visual acuity (logMAR) [total] at 12 months; Group 1: mean 0.56 (SD 0.42); n=50, Group 2: mean 0.63 (SD 0.41); n=50; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Best corrected visual acuity (logMAR) [PCV] at 12 months; Group 1: mean 0.5 (SD 0.34); n=23, Group 2: mean 0.57 (SD 0.35); n=23; Risk of bias: Very high ; Indirectness of outcome: No indirectness
- Actual outcome: Best corrected visual acuity (logMAR) [RAP] at 12 months; Group 1: mean 0.6 (SD 0.29); n=6, Group 2: mean 0.81 (SD 0.39); n=6; Risk of bias: Very high ; Indirectness of outcome: No indirectness

Protocol outcome 2: Safety and adverse events at As reported
- Actual outcome: Adverse events at 12 months; General Summary Stats: No serious adverse events and no complications; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	Tao 2010
Study type	Before and after study
Number of studies (number of participants)	1 (n=29)
Countries and setting	Conducted in Unknown; Setting: Not stated
Line of therapy	2nd line
Duration of study	Intervention + follow up: 7 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ophthalmologic assessment
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	After preceding (at least 3) injections of bevacizumab given in intervals of 6 weeks to 2 months, the visual acuity had not increased, and that the subretinal or intraretinal fluid persisted, as examined by optical coherence tomography.
Exclusion criteria	Existence of other retinal diseases such as diabethic retinopathy or retinal vascular occulsion
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 75 (7.3). Gender (M:F): 14 women. Ethnicity: 100% white
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: No other comorbidities affecting the eye 3. Pigment epithelial detachment (PED): Mixed population (PEDs in 9 eyes). 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Mixed (occult in 3 eyes, classic/predominantly classic in 3 eyes).
Extra comments	baseline (before initial treatment): 0.57 (0.39), (time of switch): 0.7 (0.37)
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: Anti-VEGF drug in combination treatment - Anti-VEGF + intravitreal steroids (dexamethasone, fluocinolone acetonide, triamcinolone acetonide). Bevacizumab (1.5mg in 0.06mL) + triamcinolone acetonide (20-25mg) - 4 injections in total. Duration 7 months. Concurrent medication/care: Not stated

	Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (Visual acuity had not increased and the subretinal/intraretinal fluid persisted after at least 3 injections of bevacizumab monotherapy). (n=29) Intervention 2: Anti-VEGF - Bevacizumab. At least 3 injections. Duration Not stated. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Not applicable / Not stated / Unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEVACIZUMAB + INTRAVITREAL STEROIDS (TRIAMCINOLONE ACETONIDE) versus BEVACIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity at 4 months; Group 1: mean 0.63 (SD 0.41); n=29, Group 2: mean 0.7 (SD 0.37); n=29; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity at 7 months; Group 1: mean 0.68 (SD 0.41); n=29, Group 2: mean 0.7 (SD 0.37); n=29; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Best corrected visual acuity at 2 months; Group 1: mean 0.59 (SD 0.38); n=29, Group 2: mean 0.7 (SD 0.37); n=29; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Thorell 2014**
Study type	Before and after study
Number of studies (number of participants)	1 (n=65 patients, 73 eyes)
Countries and setting	Conducted in USA; Setting: Bascom Palmer Eye Institute

Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patiented needed to have been treated for at least 12 months with bevacizumab or ranibizumab due to persistent or recurrent intraretinal or subretinal macular fluid as visualised using OCT imaging.
Exclusion criteria	Patients were excluded if their follow up visits were performed outside the institute, if clinic visits were missed, or if there was any concomitant retinal pathology that could interfere with the interpretation of outcomes such as a history of vitreoretinal surgery or laser.
Recruitment/selection of patients	Retrospective review
Age, gender and ethnicity	Age - Mean (SD): 76.2 (8.7). Gender (M:F): 43 female. Ethnicity: Not stated
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: Not applicable / Not stated / Unclear 3. Pigment epithelial detachment (PED): Mixed population (70 PED eyes). 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: 15 patients had received bevacizumab monotherapy, 47 had received ranibizumab monotherapy, 11 had received both.
Interventions	(n=73) Intervention 1: Anti-VEGF - Aflibercept. 2mg. Average number of injections was 4.5 (1.0).. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Bevacizumab 2. Reason for switching: Treatment failure (Required frequent re-treatment, persistent or recurrent intaretinal or subretinal macular fluid). (n=73) Intervention 2: Anti-VEGF - Ranibizumab. 15 bevacizumab only, 27 ranibizumab, 11 both. Had to have at least 12 months of treatment. . Duration Average 44.9 months. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure

Funding	Academic or government funding (Supported by a grant from Carl Zeiss Meditec, Maucla vision research foundation, an unrestricted grant from Research to Prevent Blindness)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus BEVACIZUMAB AND/OR RANIBIZUMAB Protocol outcome 1: Visual acuity (LogMAR) at As reported - Actual outcome: Best corrected visual acuity (ETDRS) at 6 months; Group 1: mean 69.5 (SD 11.3); n=73, Group 2: mean 69 (SD 10.9); n=73; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Safety and adverse events at As reported; Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Study	**Yonekawa 2013**
Study type	Before and after study
Number of studies (number of participants)	1 (n=94 patients, 102 eyes)
Countries and setting	Conducted in USA; Setting: Eye and Ear Infirmary and Havard Vangaurd Medical Associates
Line of therapy	2nd line
Duration of study	Follow up (post intervention): Mean 18 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Neovascular AMD who were previously treated with ranibizumab and/or bevacizumab and then converted to aflibercept.
Exclusion criteria	Concomitant visually significant ocular pathology, insufficient clinical records, fewer than 3 previous anti VEGF inections and lack of follow up after conversion to aflibercept.

Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 79.6 (57-93). Gender (M:F): Women 61.1%. Ethnicity: White, n = 90
Further population details	1. Central serous pattern (CSR-like) AMD: Not applicable / Not stated / Unclear 2. Other co-morbidities affecting the eye: No other comorbidities affecting the eye 3. Pigment epithelial detachment (PED): Not applicable / Not stated / Unclear 4. Polypoidal choroidal vasculopathy : Not applicable / Not stated / Unclear 5. Retinal angiomatous proliferation: Not applicable / Not stated / Unclear 6. Type of late wet AMD: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: 48 ranibizumab only, 26 bevacizumab only, 28 both. In addition, 6 eyes had received previous PDT, 1 had received thermal laser, and 2 had received pegaptanib.
Interventions	(n=102) Intervention 1: Anti-VEGF - Aflibercept. Treatment schedules, retreatment schedules and injection methods were at the discretion of individual retina specialists. . Duration Mean 18.4 weeks. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure (Refractory or recurrent (persistent intraretinal and/or subretinal fluid, or responded well but required frequent repeated injections to maintain a dry macular)). (n=102) Intervention 2: Anti-VEGF - Ranibizumab. 48 ranibizumab only, 26 bevacizumab only, 28 both. In addition, 6 eyes had received previous PDT, 1 had received thermal laser, and 2 had received pegaptanib.. Duration Average 141.7 weeks. Concurrent medication/care: Not stated Further details: 1. First choice agent: Ranibizumab 2. Reason for switching: Treatment failure
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AFLIBERCEPT versus RANIBIZUMAB AND/OR BEVACIZUMAB

Protocol outcome 1: Visual acuity (LogMAR) at As reported
- Actual outcome: Best corrected visual acuity (logMAR) at After 1 injection; Group 1: mean 0.44 (SD 0.36); n=102, Group 2: mean 0.42 (SD 0.3); n=102; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Best corrected visual acuity (logMAR) at 18 weeks; Group 1: mean 0.38 (SD 0.27); n=102, Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Safety and adverse events at As reported - Actual outcome: Adverse events at 18 weeks; General Summary Stats: 1 patient had a tear of the retinal pigment epithelium, one patient developed trace subretinal hemorrhage. No other complications of deaths; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Functional capacity, participation, independence and ability to carry out activities of daily living. at As reported; Health related quality of life at As reported; Impact on carers at As reported

Clinical evidence tables for the review of factors for treatment switching or stopping

Reference	Amoaku 2015
Study type	Guideline
Scope and purpose:	Objectives: Define the parameters that determine the response to anti-VEGF therapy in n-AMD Categorise the types of response of n-AMD to anti-VEGF therapy Define at what point in the course of treatment response should be determined Help link individual responses to that in clinical cohorts and the interpretation of clinical trials and their translation Population: Neovascular age-related macular degeneration being treated with anti-VEGFs. No age specified or definitions given.
Study methodology	Stakeholder involvement: Development group: 16 retinal specialists from the UK. No other professional groups or patients were involved. Unclear if any of the clinicians is a methodology expert Target users of the guideline: not clearly defined No external review of the guideline Rigour of development: Systematic approach: Medline search. No further information given Criteria for selecting the evidence: not described Critical appraisal: Not described. Formulating recommendations: consensus. No further information given. Health benefits/adverse events/risks considered: Some discussion of risk factors, risk of under treatment, ceiling effect, tachyphylaxis. Link between recommendations and supporting evidence: not explicitly written, but flows to form the recommendations. External review prior to publication: No

Reference	Amoaku 2015
	Guideline update procedure: not described. Clarity of presentation: Recommendations are specific and unambiguous: Not written explicitly. To follow a diagram. Imaging and treatment options not clearly described in which the algorithm. Different options clearly presented: Different options are given. What drug/treatment to switch to are not discussed fully. Recommendations easily identifiable: in a 4 x 4 diagram. Definitions on different page. Timing of review not listed on the diagram. Could do with improvement to ensure that they are easy to follow. Some recommendations hidden in the text. Supported with tools for application: no Applicability: Facilitators and barriers to application: less frequent treatment, poor access to services, appointment delays, system failures discussed. Advice/tools for putting recommendations into practice: Not described. Resource implications: Not discussed. Monitoring and auditing criteria: Not described.
Recommendations:	Definitions proposed by the committee (followed by a more detailed explanation): Primary response: best determined at 1 month following the last initiation dose, while maintained treatment (secondary) response is determined any time after the 4th visit Optimal (good response): Resolution of fluid (intraretinal fluid; IRF, subretinal fuid; SRF and retinal thickening), and/or improvement of >5 letters, subject to the ceiling effect of good starting VA Poor response: <25% reduction from the baseline in the central retinal thickness (CRT), with persistent or new IRF, SRF or minimal or change in VA (that is, change in VA of 0+4 letters) Non-response: increase in fluid (IRF, SRF and CRT), or increasing haemorrhage compared with the baseline and/or loss of >5 letters compared with the baseline or best corrected vision subsequently Primary failures: determined by the 4th visit (1 month following the third initiation dose) Secondary failures: poor or no response to treatment, show a morphological response during the initiation phase but later demonstrate decreasing responsiveness to anti-VEGF treatment Recalcitrant CNV: persistence of IRF or SRF on SD-OCT at <30 days after the last of 6 intravitreal injections of an anti VEGF agent at monthly intervals Tachyphylaxis: decreasing therapeutic response to a pharmacological agent following repeated administration over time ‘Late responders’: treatment should not be discontinued before five consecutive injections have been administered at the optimum recommended interval for the specific anti-VEGF agent unless there is an obvious deterioration of lesion morphology (poor response) within this period. Hypersensitivity to anti-VEGF: discontinuation of therapy and switch to another product

<table>
<tr><td>Reference</td><td colspan="3">Amoaku 2015</td></tr>
<tr><td></td><td colspan="3">Authors mention ‘treat and extend’, and fixed extended interval dosing but do not go in to any detail or form recommendations on this
Recommencing treatment for lesions becoming ‘active’ again is briefly mentioned but no detail is given.</td></tr>
<tr><td></td><td>Response</td><td>Morphology</td><td>Functional</td></tr>
<tr><td></td><td>Good</td><td>Absence of SRF, IRF, IRC or a reduction of CRT >75% of the baseline values</td><td>Improvement in VA >5 letters from the baseline (ceiling effect in eyes with good starting VA defined as ETDRS 70 letters or above). Pay more attention to morphological features if VA is good esp >70</td></tr>
<tr><td></td><td>Partial</td><td>Reduction of CRT of between 25 and 75% of the baseline values, and/or persistence of SRF, IRF, IRC and/or appearance of new IRC, IRF and SRF</td><td>Change in VA of 1-5 letters from the baseline</td></tr>
<tr><td></td><td>Poor</td><td>Between 0 and <25% reduction in CRT and/or persistence of SRF, IRF, IRC and/or appearance of new IRC, IRF and SRF</td><td>Change in VA of 0-4 letters</td></tr>
<tr><td></td><td>Non-response</td><td>Unchanging or increasing CRT, SRF, IRF and/or PED compared with the baseline</td><td>Change > -5 letters i.e. decline in VA from the baseline from 1 month after third initiation injection</td></tr>
<tr><td></td><td colspan="3">CRT: central retinal thickness in the central 1000μm subfield, IRC: intraretinal cysts, SRF: subretinal fluid.
Notes given by the author to go with the definitions given in the table above:
Retinal atrophy/thinning and/or subretinal fibrosis do not imply poor response but confound VA. Similarly, minimal change of fluid over scar tissue etc. may not imply poor response. These may result from longstanding disease, rather than treatment outcomes.
Outer retinal tabulation (ORT) do not represent active fluid leakage
PED presence- evidence to date does not indicate that flattening of PED determines outcomes; however, PED progression indicates active disease and requires ICGA to exclude IPCV and/or consideration of treatment change
Morphological and functional features (responses) may not correlate.
Primary response determined after initiation phase i.e. at first visit after the 3rd initiation injection.
Secondary response determined any time from 1 month after the 3rd initiation injection (months 4-11)
Late response determined at month 12 or after</td></tr>
<tr><td></td><td></td><td colspan="2">Morphology</td></tr>
</table>

Reference	Amoaku 2015					
	Visual acuity		No response	Poor response	Partial response	Good response
		Good response	Continue current therapy or undertake more imaging and consider switch/combination	Continue current therapy or undertake more imaging and consider switch/combination	Continue current therapy	Continue current therapy
		Partial response	More imaging and consider switch/ combination	More imaging and consider switch/ combination	Continue current therapy or undertake more imaging and consider other treatment	Continue current therapy
		Poor response	Discontinue. Consider review with further imaging or change therapy	More imaging and consider switch/ combination unless poor visual potential	More imaging and consider switch/ combination unless poor visual potential	Continue current therapy unless poor visual potential
		No response	Discontinue. Consider review with further imaging or change therapy	Discontinue. Consider review with further imaging or change therapy	More imaging and consider switch/ combination unless poor visual potential	Continue current therapy unless poor visual potential
Source of funding	Editorial independence: Views of the funding body have not influenced the content of the guideline: No funding described. Doesn't explicitly say no funding. Recording and addressing of conflicts of interest: Yes.					
Limitations	Domain scores (2 assessors, final scaled domain % overall rating): Scope and purpose: 41.7% Stakeholder involvement: 22.2% Rigour of development: 16.7% Clarity of presentation: 72.2% Applicability: 8.3% Editorial independence: 58.3% Overall Guideline assessment: 33.3%					

Reference	Amoaku 2015
Comments	Poor methods for a systematic review of the literature, it is based more on consensus/experience from the retinal specialists. Lack of involvement of the wider stakeholders (no patient involvement, nurse practitioners, GPs etc.) Financial implications and auditing tools were not considered.

Reference	Elshout 2012				
Study type	RCT data				
Study methodology	Objectives: To present a new epidemiological method relying on randomized controlled clinical trial (RCT) data to assess whether a treatment was effective, aiding in the decision to continue or stop the treatment in clinical patients Population: Patients had AMD with either minimally classic or occult (with no classic lesions) choroidal neovascularization (CNV) treated with ranibizumab or sham monthly injections				
Number of patients	Data from the MARINA trial (Rosenfeld et al. 2006) Ranibizumab group: n=238 Sham group: n=238				
Patient characteristics	Not described- see results section for results by subgroup				
Statistical measures	Defined normal distributions using results of RCTs to calculate the cutoff point above which it is certain that a proportion of treated patients achieve their change in VA due to the treatment's effect Intersections of the two curves: probability densities in both the treated group and non-treated group are equal Applied the calculations to the change in Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity Looked at cut offs by follow up and effect modifiers (2 year data) (REF of 2 year follow up data BOYER 2007)				
Results	Results by follow up in the MARINA trial:				
		Change in ETDRS VA, Means (SD- calculated from SE published in the paper)			
	Follow up (months)	Ranibizumab group (n=238)	Sham group (n=238)	Cutoff point (%)	Treated patients who ended above cutoff point (%)	Treated patients who ended above cutoff point due to treatment (%)
	1	3.9 (10.2)	-0.2 (8.6)	4.9	46	40

Reference	Elshout 2012						
	3	5.9 (10.5)	-3.7 (11.3)	0.4	70	49	
	6	6.5 (11.8)	-6.6 (13.0)	-0.9	73	55	
	12	7.2 (14.6)	-10.4 (15.1)	-1.9	73	61	
	24	6.6 (17.2)	-14.9 (18.8)	-5.0	75	60	
	Results by Effect Modifier:						
				Change in VA at 24 months, Mean (SD- calculated from 95% CI from the trial report)			
	Effect Modifier	Subgroup	No. in Treated/Reference group	Ranibizumab Group	Sham Group	Cutoff point	Treated patients who ended above cutoff point due to treatment (%)
	Age, years	50-64	16/11	6.1 (21.2)	-13.7 (23.9)	-6.2	48
		65-74	64/67	7.2 (15.8)	-11.9 (19.7)	-4.8	54
		75-84	124/132	7.6 (16.4)	-16.0 (19.0)	-5.3	64
		≥ 85	36/28	1.9 (16.4)	-16.8 (19.3)	-9.4	54
	Initial VA	20/160 or worse	48/51	10.6 (17.5)	-0.8 (13.3)	9.1	57
		20/100 to 20/125	59/50	9.3 (15.4)	-13.6 (16.1)	-2.4	69
		20/63 to 20/80	68/72	5.4 (16.2)	-20.0 (17.6)	-7.7	69
		20/50 or better	65/65	1.8 (15.8)	-21.3 (19.8)	-11.4	61
	CNV lesion size, (no. disc areas)	≤2	39/46	10.2 (14.2)	-13.4 (18.2)	-2.9	66
		>2 ≤ 4	86/77	9.7 (14.4)	-15.5 (18.7)	-4.0	68
		>4 ≤6	63/60	3.8 (20.0)	-15.0 (18.3)	-4.3	57
		>6	52/55	2.1 (16.7)	-15.5 (20.7)	-9.8	49
	CNV lesion type	Minimally classic	91/87	6.4 (20.0)	-14.7 (17.3)	-2.6	64
		Occult	149/150	6.2 (14.7)	-15.3 (19.5)	-6.6	59

Reference	Elshout 2012
Source of funding	None described.
Limitations	Risk of Bias Assessment Selection bias – low risk of bias Performance bias – low risk of bias Attrition bias – high risk of bias (although ITT analysis, crossover and dropout gives rise to bias) Detection/measurement bias – low risk of bias Outcome bias – low risk of bias Other source of bias – no detected Overall risk of bias – Low.
Comments	Rosenfeld 2006, the original trial was assessed for quality assessment.

Reference	McKibbin 2015
Study type	Recommendations from a roundtable discussion
Scope and purpose:	Objectives: To discuss the UK experience with aflibercept to date Use the experience with expert opinion to develop recommendations on the practical application of aflibercept in wet AMD after Year 1 Discuss maintaining VA gains from Year 1 and reducing treatment burden where possible Review the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) study with aflibercept in wet AMD Population: Neovascular age-related macular degeneration being treated with aflibercept. No age specified or definitions given.
Study methodology	Stakeholder involvement: Development group: 11 retinal specialists from the UK. No other professional groups or patients were involved. Unclear if any of the clinicians is a methodology expert Target users of the guideline: not clearly defined External review of the guideline: NA as not a guideline. No external review of the recommendations. Rigour of development: Systematic approach: Does not follow a systematic approach. Reviewed VIEW study and audit data.

Reference	McKibbin 2015
	Criteria for selecting the evidence: NA Critical appraisal: Not described. Formulating recommendations: consensus. No further information given. Health benefits/adverse events/risks considered: Some discussion of adverse events in the trial data and the risk benefit profile of patients having more injections. Link between recommendations and supporting evidence: yes for some recommendations (re-treatment). Others did not have supporting evidence. External review prior to publication: No Guideline update procedure: not described. Clarity of presentation: Recommendations are specific and unambiguous: Yes Different options clearly presented: Different options are given. What drug/treatment to switch to is not discussed. Recommendations easily identifiable: Yes in a table and flow diagram. Re-treatment recommendations are given separately. Supported with tools for application: no Applicability: Facilitators and barriers to application: Clinic capacity, NHS funding, use of virtual clinics is discussed. Advice/tools for putting recommendations into practice: No tools described Resource implications: Discussed cost effectiveness, delivering treatment within the local service framework and the NICE commissioning guidance. Recommendations are made for clinics based on capacity limitations. Monitoring and auditing criteria: Not described.
Recommendations:	Treatment goals The goals of treatment after Year 1 are to maintain the visual and anatomical gains These goals should be achieved while minimising the treatment burden and using resources cost-effectively Patient groups and their treatment approaches (monitoring with OCT and VA examination should be performed at every visit) Approach 1: Eyes with active disease but stable VA at the end of Year 1 should continue with fixed 8-weekly dosing. The patient is injected and the next injection is scheduled for 8 weeks time Approach 2: Eyes with inactive disease and stable VA are eligible for individualised T & E. The patient is injected and the interval to the next injection is extended, by 2-week intervals, up to a maximum of 12 weeks. In eyes that develop active disease during T & E, the patient is injected and the interval to the next injection is reduced by 2-weekly intervals. Approach 3: Eyes that have had inactive disease and stable VA for at least three consecutive visits may be considered for a trial of monitoring without treatment and with extended follow-up intervals. This could be initiated at the end of Year 1 or during Year 2. The patients undergoes monitoring and the interval to the next monitoring visit may be extended, by 2-week intervals, up to a maximum of 12 weeks.

Reference	McKibbin 2015
	Discharge strategy Patients who may be suitable for discharge should be seen by an ophthalmologist in person to allow for a full-informed discussion. As an alternative to discharge, patients can be followed up at regular intervals in a community setting to check for changes in visual function in either eye. If active disease develops during this time, the patient should return tot the clinic for treatment Fellow eye involvement Both eyes should be monitored using OCT, to ensure that fellow eye involvement is captured early If a patient is having bilateral therapy, treatment intervals should be tailored to patient visits in order to synchronise treatment of both eyes The better-seeing eye should drive the re-treatment interval for the worse-seeing eye. If the VA is similar between eyes (difference in VA between eyes ≤5 letters), the eye with the most active disease should drive the re-treatment interval Safety The risk-benefit profile should be discussed with the patient before initiating therapy and each time the treatment regimene is altered Comorbidities Comorbidities that affect a patient's ability to get to the clinic may influence the treatment approach An informed discussion with the patient is vital Revised re-treatment criteria Patients should be retreated if, in the opinion of the treating physician, there is new or persistent disease activity, as indicated by one or more of the following (this list provides examples but is not exhaustive): New or persistent fluid as indicated by OCT, or increase in central retinal thickness compared with the lowest previous value as measure by OCT, or Loss of vision from the best previous VA if, in the opinion of the treating physician, this is because of disease activity, or New choroidal neovascularisation or new or persistent leakage on fluorescein angiography, or New macular haemorrhage
Source of funding	Editorial independence: Views of the funding body have not influenced the content of the guideline: Sponsored by Bayer HealthCare (produces some VEGFs). Authors were said to have final control of the content and editorial decisions. Recording and addressing of conflicts of interest: Yes.
Limitations	Domain scores (2 assessors, final scaled domain % overall rating): Scope and purpose: 38.9% Stakeholder involvement: 36.1% Rigour of development: 12.5% Clarity of presentation: 72.2%

Reference	McKibbin 2015
	Applicability: 27.1% Editorial independence: 50.0% Overall Guideline assessment: 41.7%
Comments	Poor methods for a systematic review of the literature, it is based more on consensus/experience from the retinal specialists. Lack of involvement of the wider stakeholders (no patient involvement, nurse practitioners, GPs etc.).

Reference	Mitchell 2010
Study type	Consensus recommendations
Scope and purpose:	Objectives: Not clearly described To generate evidence based and consensus recommendations for treatment indication and assessment, retreatment and monitoring Population: Neovascular age-related macular degeneration being treated with ranibizumab. No age specified or definitions given.
Study methodology	Stakeholder involvement: Development group: Unclear. Assume it is the 7 authors; all of which are from their Department of Ophthalmology (no other information except that is was an expert panel). Authors are from Australia, France, Italy, Germany, Austria (2 authors), Japan and Switzerland. Unclear if any of the clinicians is a methodology expert Target users of the guideline: not clearly defined. To help guide ophthalmologists. External review of the guideline: stated to be externally peer reviewed. Rigour of development: Systematic approach: PubMed search, 31 October 2008 (restricted to English literature, no date restriction), MeSH term macular degeneration (multi) and the words vascular endothelial growth factor, ranibizumab or Lucentis gave 187 papers. The Cochrane Register of Controlled Trials, Cochrane Database of Systematic Reviews (16 and 4 references respectively). Abstract data which was relevant was included. Criteria for selecting the evidence: Doesn’t describe study design, comparisons or outcomes in the inclusion criteria. Critical appraisal: Assessed against Level I-III quality criteria. Unclear ratings, if done by consensus etc. Formulating recommendations: consensus. No further information given. Health benefits/adverse events/risks considered: Safety data was reviewed. Doesn’t exclusively report the balance/trade off but describes that the benefit/risk profile should be discussed with the patient

Reference	Mitchell 2010
	Link between recommendations and supporting evidence: The recommendations follow straight after the evidence. No description how the panel linked the evidence to inform the recommendations External review prior to publication: Unclear when the recommendations were externally peer reviewed. No description given. Guideline update procedure: not described. Clarity of presentation: Recommendations are specific and unambiguous: Some of the recommendations are unclear e.g. additional treatment should be started, but they don't specify what treatment. No intent or purpose of the recommended action are described. Different options clearly presented: Different options are given. What drug/treatment to switch to is not discussed. Not v clear. Recommendations easily identifiable: Yes listed in a table. Supported with tools for application: no Applicability: Facilitators and barriers to application: Not discussed Advice/tools for putting recommendations into practice: No tools described Resource implications: Not discussed. Monitoring and auditing criteria: Two auditing criteria proposed: proportion of patients losing (15 letters, gaining ≥15 letters or maintain ≥ 20/40 vision and the maintenance of functional vision and maintain independence (read/drive/ go out shopping). Quality assessment: Level I: strong evidence e.g. well designed, randomised, controlled clinical trials that address the issue in question Level II: substantial evidence that lacks some qualities e.g. derived from RCTs but with flaws such as absent control group or sufficiently long follow up Level III: relatively weak evidence e.g. Derived from non-comparative studies without controls, descriptive studies, panel consensus or expert opinion
Recommendations:	Level I evidence: monthly ranibizumab intravitreal injection demonstrated the best VA outcomes in the clinical trials Level III evidence: when a monthly regimen is not possible, a flexible strategy with monthly monitoring is feasible; benefits could be lower than with monthly treatment Monthly follow up (particularly in the first 12 months) aims to detect active disease from: history, VA assessments, slit-lamp examinations and OCT; FA is mostly not needed at this stage If active disease is present or recurs, additional treatment should be initiated quickly to improve functional outcomes If the disease is inactive, retreatment can be deferred In both cases, patients would be reviewed at each following month using the same assessments, with treatment re-administered only if active disease is present If the clinical signs remain quiescent for longer than the first 12 months, extending the follow up intervals may then be justified

Reference	Mitchell 2010
Source of funding	Editorial independence: Views of the funding body have not influenced the content of the guideline: stated to not have been commissioned. Funded unconditionally by Novartis Pharma AG. Recording and addressing of conflicts of interest: Yes.
Limitations	Domain scores (2 assessors, final scaled domain % overall rating): Scope and purpose: 51.6% Stakeholder involvement: 22.2% Rigour of development: 44.8% Clarity of presentation: 80.6% Applicability: 12.5% Editorial independence: 79.2% Overall Guideline assessment: 50.0%
Comments	Poor methods for a systematic review of the literature, it is based more on consensus/experience from the retinal specialists. Lack of involvement of the wider stakeholders (no patient involvement, nurse practitioners, GPs etc.).

Reference	RCOphth 2013
Study type	Guideline
Scope and purpose:	Objectives: Need for guideline discussed, purpose and, intended users. To set the standards for best practice in the NHS and in the private sector Education of ophthalmic trainees and those in other disciplines Give patients, carers and consumer organisations a resource with improved current information Benchmark for service planning by providers Guide purchasers in the commissioning of services and set national standards for audit Population: Neovascular age-related macular degeneration (AMD- ageing changes without any other obvious precipitating cause that occur in the central area of the retina (macula) in people aged 55 years and above). Exudative disease is also termed neovascular AMD (any or all of the following when seen in the macular area of the fundus; intraretinal, subretinal or sub-RPE haemorrhages and/or fluid with or without peri-retinal fibrosis in the absence of other retinal (vascular disorders).
Study methodology	Stakeholder involvement: Development group: 11 panellists; 7 retinal specialists, 1 college scientific advisor, 2 vison scientists, 1 patient representative. Unclear if any of the clinicians is a methodology expert

Reference	RCOphth 2013
	Target users of the guideline: specialists (NHS/private sector), patients, carers, consumer providers. No external review of the guideline Rigour of development: Systematic approach: Sources of information – Pubmed, the Cochrane Library, Current Contents and their own personal collections. No other information provided. A systematic approach was not demonstrated, however SR from Cochrane were used in the guideline. Criteria for selecting the evidence: not described; search strategy available online. Critical appraisal: Was not carried out. Formulating recommendations: Unclear, presume consensus. No further information given. Health benefits/adverse events/risks considered: Yes Link between recommendations and supporting evidence: Not explicitly written for all recommendations. There is some supporting evidence. External review prior to publication: No Guideline update procedure: not described only a date of 2015 given. Clarity of presentation: Recommendations are specific and unambiguous: Recommendations are within the guideline, not in a particular section. No algorithm/ diagram. There are 'Practical Points' in bold within the guideline which appear to be key points the clinician should be aware of. Different options clearly presented: Different options are given. What drug/treatment to switch to are not discussed fully. Recommendations easily identifiable: They are within the text. They are not clearly marked out. Supported with tools for application: no Applicability: Facilitators and barriers to application: No Advice/tools for putting recommendations into practice: No Resource implications: follow NICE cost effectiveness recommendations. No other financial/resource implications described. Monitoring and auditing criteria: the referral pathway, number and frequency of injections, complications and visual outcomes.
Recommendations:	Follow up intervals Ranibizumab and aflibercept are initiated with a 'loading' phase of three injections given monthly for three consecutive doses, followed by a maintenance phase in which patients are monitored with BCVA, history, examination, OCT and/or angiographic examination. The interval between two doses should not be shorter than 4 weeks normally for ranibizumab or 8 weeks for aflibercept. However, there are instances where the occasional patient with hyperactive lesions may for a short time require more intensive therapy. It is expected that all patients will receive 3 loading doses of ranibizumab, or aflibercept unless there are particular contraindications. Pegaptanib (Macugen) is given by 6 weekly injections. However current recommendations from NICE are that it is not cost-effective as a first line therapy in the treatment of wet macular degeneration.

Reference	RCOphth 2013
	9.6 Re-treatment decision making It is recommended that only ophthalmologists experienced in the management of patients with age related macular degeneration should decide on initiating treatment and permanent cessation of treatment. Criteria for Continuation of treatment: After the three initial doses, ranibizumab should be continued at 4 weekly intervals, aflibercept at 8 weekly intervals and pegaptanib at 6 weekly intervals if: a) There is persistent evidence of lesion activity b) The lesion continues to respond to repeated treatment c) There are no contra-indications (see below) to continuing treatment. Disease activity is denoted by retinal, subretinal, or sub-RPE fluid or haemorrhage, as determined clinically and/or on OCT, lesion growth on FFA (morphological), and/or deterioration of vision (functional). Where there is recurrence of CNV activity, treatment is reinstated until lesion stabilisation is achieved as indicated by BCVA and or lesion morphology. 9.7 Drug Holding and Cessation of therapy Consider temporarily discontinuing treatment if: (1) There is no disease activity The disease should be considered to have become inactive when there is: a) Absence of FFA leakage or other evidence of disease activity in the form of increasing lesion size, or new haemorrhage or exudates (i.e. no increase in lesion size, new haemorrhage or exudates) even if there is persistent fluid (intraretinal cysts or tubulation denoting chronic changes) on OCT. b) No re-appearance or further worsening of OCT indicators of CNV disease activity on subsequent follow up following recent discontinuation of treatment. b) No additional lesion growth or other new signs of disease activity on subsequent follow up following recent discontinuation of treatment. c) No deterioration in vision that can be attributed to CNV activity. (2) There has been one or more adverse events related to drug or injection procedure including: a) endophthalmitis b) retinal detachment c) severe uncontrolled uveitis d) ongoing periocular infections e) other serious ocular complications attributable to an anti-VEGF agent or injection procedure f) thrombo-embolic phenomena, including MI or CVA in the preceding 3 months, or recurrent thrombo-embolic phenomena which are thought to be related to treatment with an anti-VEGF agent g) other serious adverse events (SAE) e.g. hospitalisation Consider discontinuing treatment permanently if there is:

Reference	RCOphth 2013
	1. A hypersensitivity reaction to a licensed anti-VEGF agent is established or suspected. A change to pegaptanib, if not previously used, or PDT is recommended. 2. Reduction of BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributable to AMD in the absence of other pathology. 3. Reduction in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline as this may indicate lack of responsiveness to treatment, or adverse event or both 4. There is evidence of deterioration of the lesion morphology despite optimum treatment. Such evidence includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNV disease activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over a 3 consecutive visits. 9.8 Consider discharging the patient from long term hospital follow up if: Discharging patient from Hospital eye clinic follow up 1. The decision to discontinue a licensed anti-VEGF agent permanently has been made 2. There is no evidence of other ocular pathology requiring investigation or treatment 3. There is low risk of further worsening or reactivation of nvAMD that could benefit from restarting treatment e.g. very poor central vision and a large, non-progressive, macular scar. Practical Points Patients should be advised of the need for frequent monitoring when commencing a course of intravitreal drug treatment for AMD. This will be every 4-8 weeks depending on the licensed anti-VEGF used. Treatment and follow-up may need to be continued for up to and beyond 2 years. Further research is required into appropriate duration and optimal regimen in terms of frequency of injections. It still remains to be seen whether less frequent dosing of ranibizumab or aflibercept than that used in the pivotal trials will achieve the same visual benefit. Licensed anti-VEGF treatment will only improve vision in a third of patients. The majority will maintain vision and some 10% will not respond to therapy. Evidence suggests aflibercept treatment outcomes are similar to those of ranibizumab. Pegaptanib treatment will reduce the risk of moderate and severe visual loss but most patients will still lose some vision over 2 years. Patients should understand the risk associated with intravitreal injections and be instructed to report symptoms suggestive of endophthalmitis without delay.
Source of funding	Editorial independence: Views of the funding body have not influenced the content of the guideline: No funding described. Doesn't explicitly say no funding. Recording and addressing of conflicts of interest: No
Limitations	Domain scores (2 assessors, final scaled domain % overall rating): Scope and purpose: 47.2%

Reference	RCOphth 2013
	Stakeholder involvement: 86.1% Rigour of development: 40.6% Clarity of presentation: 83.3% Applicability: 47.9% Editorial independence: 41.7% Overall Guideline assessment: 58.3%
Comments	External systematic reviewer was employed, and search strategy available online: http://evslarchive.moorfields.nhs.uk/amd_docs_0607/ref3.pdf (link broken).

E.6.4.1 Agree II critical appraisal for the review of factors for treatment switching or stopping

Score	1 Strongly disagree	2	3	4	5	6	7 Strongly agree

Assessor 1 in black script, Assessor 2 in red script.

Amoaku 2015 AGREE II score

Domain	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
Scope and Purpose	5 5	1 3	5 2						11 10

Domain	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
Stakeholder involvement	3 / 3	1 / 1	2 / 4						6 / 8
Rigour of development	2 / 1	1 / 1	2 / 1	1 / 4	4 / 4	4 / 3	1 / 1	1 / 1	16 / 16
Clarity of presentation	5 / 5	5 / 6	5 / 6						15 / 17
Applicability	5 / 1	1 / 1	1 / 1	1 / 1					8 / 4
Editorial independence	6 / 1	7 / 4							13 / 5
Overall Guideline Assessment	4 / 2	I would recommend this guideline for use (yes/ yes with modifications/no):						No / No	

Amoaku 2015 Scaled domain score calculations

Domain	Maximum score	Minimum score	Observed score	Scaled domain score
Scope and purpose	42	6	21	41.7%
Stakeholder involvement	21	6	14	22.2%
Rigour of development	112	16	32	16.7%
Clarity or presentation	42	6	32	72.2%
Applicability	56	8	12	8.3%
Editorial independence	28	4	18	58.3%

Domain	Maximum score	Minimum score	Observed score	Scaled domain score
Overall Guideline assessment	14	2	6	33.3%

McKibbin 2015 AGREE II score

Domain	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
Scope and Purpose	3 / 5	1 / 1	5 / 5						9 / 11
Stakeholder involvement	3 / 7	1 / 1	2 / 5						6 / 13
Rigour of development	1 / 1	1 / 1	1 / 1	1 / 6	5 / 4	1 / 1	1 / 1	1 / 1	12 / 16
Clarity of presentation	6 / 5	5 / 5	6 / 5						17 / 15
Applicability	6 / 3	5 / 3	1 / 1	1 / 1					13 / 8
Editorial independence	4 / 1	7 / 4							11 / 5
Overall Guideline Assessment	4 / 3	I would recommend this guideline for use (yes/ yes with modifications/no):						YWM / NO	
N.B. YWM is an abbreviation for ‘yes with modifications’									

McKibbin 2015 Scaled domain score calculations

Domain	Maximum score	Minimum score	Observed score	Scaled domain score
Scope and purpose	42	6	20	38.9%
Stakeholder involvement	21	6	19	36.1%
Rigour of development	112	16	28	12.5%
Clarity of presentation	42	6	32	72.2%
Applicability	56	8	21	27.1%
Editorial independence	28	4	16	50%
Overall Guideline assessment	14	2	7	41.7%

Mitchell 2010 AGREE II score

Domain	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
Scope and Purpose	2 / 6	1 / 5	5 / 4						11 / 15
Stakeholder involvement	3 / 4	1 / 1	2 / 3						6 / 8
Rigour of development	6 / 6	3 / 2	4 / 4	1 / 1	5 / 5	5 / 5	5 / 5	1 / 1	30 / 29
Clarity of presentation	5 / 6	4 / 6	7 / 7						16 / 19
Applicability	1 / 4	1 / 1	4 / 1	1 / 1					7 / 7

Domain	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
Editorial independence	7 4	7 5							14 9
Overall Guideline Assessment	4 4	I would recommend this guideline for use (yes/ yes with modifications/no):						YWM YWM	
N.B. YWM is an abbreviation for 'yes with modifications'									

Mitchell 2010 Scaled domain score calculations

Domain	Maximum score	Minimum score	Observed score	Scaled domain score
Scope and purpose	42	6	26	55.6%
Stakeholder involvement	21	6	14	22.2%
Rigour of development	112	16	59	44.8%
Clarity of presentation	42	6	35	80.6%
Applicability	56	8	14	12.5%
Editorial independence	28	4	23	79.2%
Overall Guideline assessment	14	2	8	50.0%

RCOphth 2013 AGREE II score

Domain	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
Scope and Purpose	7 2	1 1	7 5						15 8

Domain	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
Stakeholder involvement	7 6	5 6	7 6						19 18
Rigour of development	6 2	1 1	5 1	2 1	5 5	5 5	6 5	4 1	34 21
Clarity of presentation	7 5	7 6	7 4						21 15
Applicability	6 1	6 4	2 5	6 1					20 11
Editorial independence	4 4	5 1							9 5
Overall Guideline Assessment	4 5	I would recommend this guideline for use (yes/ yes with modifications/no):						YWM YWM	
N.B. YWM is an abbreviation for 'yes with modifications'									

RCOphth 2013 Scaled domain score calculations

Domain	Maximum score	Minimum score	Observed score	Scaled domain score
Scope and purpose	42	6	23	47.2%
Stakeholder involvement	21	6	37	86.1%
Rigour of development	112	16	55	40.6%
Clarity of presentation	42	6	36	83.3%
Applicability	56	8	31	47.9%

Domain	Maximum score	Minimum score	Observed score	Scaled domain score
Editorial independence	28	4	14	41.7%
Overall Guideline assessment	14	2	9	58.3%

E.7 Monitoring

E.7.1 Frequency of monitoring

Frequency of review

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

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

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

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

No studies were identified for these review questions.

E.7.2 Self monitoring

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

<table>
<tr><th>Bibliographic reference</th><th>Randomised Trial of a Home Monitoring System for Early Detection of Choroidal Neovascularization Home Monitoring of the Eye (HOME) Study. Chew E Y; Clemons T E; Bressler S B; Elman M J; Danis R P; Domalpally A ; Heier J S; Kim J E; Garfinkel R , Ophthalmology, 121, 535-533, 2014</th></tr>
<tr><td>Country/ies where the study carried out</td><td>USA</td></tr>
<tr><td>Study type</td><td>Randomised Controlled Trial</td></tr>
<tr><td>Aim of the study</td><td>To determine whether home monitoring with the ForeseeHome device, using macular visual field testing with hyperacuity technique and telemonitoring, results in earlier detection of age-related macular degeneration-associated choroidal neovascularization, reflected in better visual acuity, when compared with standard care.</td></tr>
<tr><td>Study dates</td><td>Published 2014
Enrolled between 30/07/2010 and 16/11/2012</td></tr>
<tr><td>Sources of funding</td><td>Supported by the National Institutes of Health.</td></tr>
<tr><td>Sample size</td><td>1520</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients were at risk for developing CNV, with either bilateral large drusen (potentially 2 study eyes) or large drusen in 1 eye (study eye) and advanced AMD in the fellow (nonstudy eye) and best-corrected visual acuity (BCVA) of 20/60 or better in the study eyes.</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with pre-existing significant visual field defect
Patients with reliable qualification test
Patient did not meet study ocular criteria
Patients were seen more frequently than 4 months
Patients did not take online device tutorial
Patients’ media opacities were not sufficient for fundus photographs
Patients’ study eye did not have BCVA 20/60 or better
Evidence of macular or retinal disorder in study eye
Patients with no computer experience
Patients did not consent to examination by ophthalmologist</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>Baseline characteristics</td><td>Devise monitoring</td><td>Standard care</td><td>Total</td></tr>
<tr><td>Number</td><td>763</td><td>757</td><td>1520</td></tr>
<tr><td>Female (%)</td><td>444 (58.2)</td><td>451 (59.6)</td><td>895 (58.9)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Randomised Trial of a Home Monitoring System for Early Detection of Choroidal Neovascularization Home Monitoring of the Eye (HOME) Study. Chew E Y; Clemons T E; Bressler S B; Elman M J; Danis R P; Domalpally A ; Heier J S; Kim J E; Garfinkel R , Ophthalmology, 121, 535-533, 2014**

Mean age (SD)	72.6 (7.7)	72.3 (7.7)	72.5 (7.7)
White race (%)	733 (96.1)	730 (96.4)	1463 (96.3)
AREDS2 participant	295 (38.7)	269 (35.5)	564 (37.1)
Bilateral large drusen	642 (84.1)	608 (80.3)	1250 (82.2)
Large druse, advanced AMD	111 (14.5)	132 (17.4)	243 (16.0)
Mean visual acuity (SD)	81.5 (7.5)	81.9 (7.1)	81.7 (7.3)

Study visits and procedures	At baseline, all participants underwent best corrected visual acuity (BCVA) testing and colour fundus photography of 3 stereoscopic field in both eyes. Certified examined used a standardized protocol to obtain visual acuity using the electronic version of the Early Treatment Diabetic Retinopathy Study visual acuity charts.
Intervention	Home monitoring device. In addition to receiving the same standard care instructions, the participants received a home monitoring device, with instructions for installation and use.
Comparator	Standard care. The participants randomised to the standard care only group received instruction that were investigator specific for self-monitoring of vision at home to detect progression of AMD.
Outcomes	Detection of progression to CNV Vision function at the time of CNV detection
Analyses	The Mann-Whitbney U test T-test Fisher exact test was used to compare proportions between 2 groups 2 interim analyses were planned at appropriately 50% and 75% of the total number of CNV events.
Length of follow up	Planned follow-up until 31/05/2014
Results	Progression to Choroidal neovascularization 82 participants (intention to treat cohort) have progressed to CNV in at least 1 of their study eyes based on investigators' determination including 51 in the device group and 31 in the control group. Visual acuity at the time of choroidal neovascularization detection Primary visual acuity outcome at diagnosis of choroidal neovascularization by treatment group

Population	Treatment	

Bibliographic reference	Randomised Trial of a Home Monitoring System for Early Detection of Choroidal Neovascularization Home Monitoring of the Eye (HOME) Study. Chew E Y; Clemons T E; Bressler S B; Elman M J; Danis R P; Domalpally A ; Heier J S; Kim J E; Garfinkel R , Ophthalmology, 121, 535-533, 2014

	Device monitoring	Standard care	Total	P value
Intent to treat population				
No. of patients	51	30	81	
VA score at baseline				
Mean (SD)	79.7 (8.0)	80.7 (5.7)	80.1 (7.2)	
Median (IQR)	81.0 (73.0 to 86.0)	82.0 (77.0, 85.0)	81.0 (75.0, 85.0)	
VA score at CNV event				
Mean (SD)	72.3 (13.8)	68.1 (16.1)	70.8 (14.8)	
Median (IQR)	75.0 (70.0, 82.0)	72.0 (64.0, 77.0)	73.0 (67.0, 80.0)	
VA score change from baseline at event				
Mean (SD)	-7.4 (11.4)	-12.6(16.5)	-9.3(13.7)	
Median(IQR)	-4.0(-11.0, -1.0)	-9.0 (-14.0, -4.0)	-7.0 (-12.0, -2.0)	0.021

Secondary visual acuity outcomes at diagnosis of choroidal neovascularization by treatment group

Population	Treatment, no (%)			
	Device monitoring	Standard care	Total	P value
Intent to treat population				
No. of patients	51	30	81	
Maintained 20/40 or better	40 (87)	18 (62)	58 (77)	0.014
Maintained vision (loss of no more than 5 letters)	27 (53)	12(40)	39(48)	0.185

Bibliographic reference	**Randomised Trial of a Home Monitoring System for Early Detection of Choroidal Neovascularization Home Monitoring of the Eye (HOME) Study. Chew E Y; Clemons T E; Bressler S B; Elman M J; Danis R P; Domalpally A ; Heier J S; Kim J E; Garfinkel R , Ophthalmology, 121, 535-533, 2014**
	<table><tr><td>15+ letter loss from baseline</td><td>6 (12)</td><td>7(23)</td><td>13(16)</td><td>0.146</td></tr><tr><td>Declined to 20/200 or worse</td><td>1 (2)</td><td>1 (3)</td><td>2 (2)</td><td>0.607</td></tr></table>
Missing data handling/loss to follow up	24 out of a total of 763 participants in device group discontinued in the study 20 out of a total of 757 participants in control group (standard care group) discontinued in the study
Was allocation adequately concealed?	The study was unmasked (participants, investigator, and clinical co-ordinator were aware of the random assignment of the device and control groups)
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes
Other information	All comparison were made in the ITT cohort, which included all participants who had an investigator-confirmed CNV event assigned to the 2 groups regardless of the adherence to the use of the device. Additionally analysis was conducted on the initial per protocol (PPI) population, in which the device group was restricted to those participants who were using the device at the time of CNV detection, regardless of adherence to minimal recommended frequency of monitoring, and on a second per protocol (PP2) population, which further restricted the device group to only those population who met minimum use criteria of 2 tests per week in their study eye(s) before the CNV event.

<table>
<tr><th>Bibliographic reference</th><th>Improved Adherence to Vision Self-monitoring with the Vision and Memory Stimulating (VMS) Journal for Non-neovascular Age-related Macular Degeneration during a Randomized Controlled Trial. Bittner AK ; Torr-Brown S ; Arnold E ; Nwankwo A ; Beaton P ; Rampat R ; Dagnelie G ; Roser M , Journal of clinical & experimental ophthalmology 5: 320, 2014</th></tr>
<tr><td>Coutry/ies where the study carried out</td><td>USA</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim of the study</td><td>To determine whether vision self-monitoring frequency and confidence were greater amongst intermediate stage, non-neovascular AMD patients who received the VMS journal compared to those receiving usual care (e.g..Amsler grid or instructions from their eye care provider)
To determine whether the VMS journal could help promote adhere to weekly vision self-monitoring over the course of a year.</td></tr>
<tr><td>Study dates</td><td>Published 2014
Recruitment between Jan and December 2011.</td></tr>
<tr><td>Sources of funding</td><td>Supported by National Institutes of Health Grants</td></tr>
<tr><td>Sample size</td><td>198</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients with intermediate stage, non-neovascular AMD</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with vision loss due to ocular pathology other than AMD or cataract were excluded.
Patients had cataract in the last 3 months or capsulotomy in the last 24 hours in either eye
Patients were unable to give informed consent, non-English speaking or unable to complete the required procedures.</td></tr>
<tr><td>Baseline characteristics</td><td>The characteristics of participants in VMS journal and control groups who completed at least one follow-up.
<table>
<tr><td></td><td>VMS journal</td><td>Standard care</td><td>Total</td></tr>
<tr><td>Number</td><td></td><td></td><td>157</td></tr>
<tr><td>Female (%)</td><td>48 (65.8)</td><td>44 (52.4)</td><td>92 (58.6)</td></tr>
<tr><td>Mean age (SD)</td><td>74.0 (8.9)</td><td>76.8 (8.7)</td><td>75.5 (8.9)</td></tr>
<tr><td>Previous NV AMD one eye (%)</td><td>9 (12.3)</td><td>11 (13.1)</td><td>20 (12.7)</td></tr>
<tr><td>Intermediate AMD one eye (%)</td><td>21 (28.8)</td><td>24 (28.6)</td><td>45 (28.7)</td></tr>
<tr><td>Intermediate AMD both eye (%)</td><td>43 (58.9)</td><td>49 (58.3)</td><td>92 (58.6)</td></tr>
<tr><td>Mean VA better eye (logMAR)</td><td>0.15 (0.12)</td><td>0.21 (0.21)</td><td>0.18 (0.18)</td></tr>
<tr><td>Mean VA worse eye (logMAR)</td><td>0.32 (0.30)</td><td>0.45(0.38)</td><td>0.39 (0.35)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Improved Adherence to Vision Self-monitoring with the Vision and Memory Stimulating (VMS) Journal for Non-neovascular Age-related Macular Degeneration during a Randomized Controlled Trial. Bittner AK ; Torr-Brown S ; Arnold E ; Nwankwo A ; Beaton P ; Rampat R ; Dagnelie G ; Roser M , Journal of clinical & experimental ophthalmology 5: 320, 2014**
Study procedures	Participant's ocular disease status and corrected disease visual acuity (VA) were measured by retinal specialists using standard clinical tests. Participants were randomly allocated to experimental and control groups. There were 2 follow-up questionnaires which were either completed by phone interviews by researchers or self-completed by the participants via paper questionnaires.
Intervention	VMS journals were mailed to participants in the experimental group, with no training or education provided by the eye care provider. A <5 minute duration follow-up call occurred 2 weeks after the study materials were mailed to participants to confirm receipt of journal and address questions.
Comparator	Usual care
Outcomes	Vision self-monitoring frequency Confidence in vision self-monitoring Adherence to weekly vision self-monitoring over the course of a year
Analyses	The relationship between dichotomous variables was assessed by Pearson's chi-square tests. Differences in continuous variables among groups were examined by two sample t-tests. Multiple logistic regression models were used to explore factors that were predicators of weekly vision self-monitoring behaviour and non-confidence in their vision monitoring. Multiple logistic regression models were used to explore factors that were predicators of weekly vision self-monitoring behaviour and non-confidence in their vision monitoring.
Length of follow up	12 months
Results	Vision self-monitoring frequency At 6 and 12 months, respectively, 29% and 25% of the control subjects (n=22 and 17) indicated that they had not checked their vision in the past 6 months, while 1.5% and 5% (n=1 and 3) of the subjects with the VMS journal reported that they did not check their vision. There was a statistically significant difference in the proportion of subjects in each group who reported vision monitoring at least weekly at 6 and 12 months, respectively 85% and 80% of the subjects with the VMS journal vs 50% of the control group at both follow-up times (p<0.001). After adjusting for all other characteristic variable, participants with the VMS journal had statistically significant 7.1 and 4.2 times greater odds of reporting they self-monitor their vision weekly at 6 and 12 month s respectively.

	6 month follow up	12 month follow up

Bibliographic reference	**Improved Adherence to Vision Self-monitoring with the Vision and Memory Stimulating (VMS) Journal for Non-neovascular Age-related Macular Degeneration during a Randomized Controlled Trial. Bittner AK ; Torr-Brown S ; Arnold E ; Nwankwo A ; Beaton P ; Rampat R ; Dagnelie G ; Roser M , Journal of clinical & experimental ophthalmology 5: 320, 2014**

Weekly vision self-monitoring	OR	95%CI	P values	OR	95%CI	P values
VMS group vs Control group	7.12	2.68, 18.9	<0.001	4.18	1.68, 10.4	0.002

Confidence in vision self-monitoring

There was a highly statistically significant difference in the portion of patients who reported that they were not confident that monitoring their vision was helping to take care of their sight when comparing the VMS journal group to the usual care control group: 15% vs 53% at 6 months, and 13% vs 44% a6t 12 months (p<0.001).

After adjusting for all other characteristic variables, participants in the usual care group had statistically significant 6.7 and 5.0 times greater odds of reporting non-confidence at 6 and 12 months respectively.

	6 month follow up			12 month follow up		
Weekly vision self-monitoring	OR	95%CI	P values	OR	95%CI	P values
VMS group vs Control group	0.15	0.06, 0.38	<0.001	0.20	0.07, 0.56	0.002

Adherence to weekly vision self-monitoring over the course of a year

72% of patients (N=113, n=53 in VMS group and n=60 controls) completed both the 6 and 12-month questionnaires. The analyses of these 113 patients to evaluate changes in response over time from 6 to 12 months. There was no statistically change in weekly vs less frequent self-monitoring between the groups (p=0.68), with 82% and 80% of the VMS group and control subjects, respectively reporting no change in their frequency between 6 and 12 months.

Missing data handling/loss to follow up	21 out of a total of 94 who received the VMS journal and 20 out of a total of 104 who were in the control group were lost to follow-up or developed neovascular AMD. A small proportion of patients in each groups completed the 12-month follow up after missing the 6-month follow-up.
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear

Bibliographic reference	Improved Adherence to Vision Self-monitoring with the Vision and Memory Stimulating (VMS) Journal for Non-neovascular Age-related Macular Degeneration during a Randomized Controlled Trial. Bittner AK ; Torr-Brown S ; Arnold E ; Nwankwo A ; Beaton P ; Rampat R ; Dagnelie G ; Roser M , Journal of clinical & experimental ophthalmology 5: 320, 2014
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

E.7.3 Monitoring strategies and tools for people with late age-related macular degeneration (wet active)

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

Bibliographic reference	**Coscas Gabriel J; Lupidi Marco ; Coscas Florence ; Cagini Carlo ; Souied Eric H; Optical coherence tomography angiography versus traditional multimodal imaging in assessing the activity of exudative age-related macular degeneration: A New Diagnostic Challenge. Retina 35 (11): 2219-28. 2015**
Country/ies where the study carried out	Paris, France
Study type	Retrospective cross sectional study
Aim of the study	To compare optical coherence tomography angiography (OCTA) with traditional multimodal imaging in patients with exudative age-related macular degeneration in terms of guiding the treatment decision.
Study dates	Patient enrolment between November 2014 and January 2015
Sources of funding	Not stated
Number of patients	80 eyes (73 patients)
Inclusion criteria	Patients were older than 50 years of age with the presence of drusen, CNV established on FA and ICGA and associated with the presence of typical OCT findings (sub/intraretinal fluid, sub-RPE fluid, or pigmented epithelium detachment (PED) and evidence of neovascular network on OCTA.
Exclusion criteria	Patients were any associated, previous or concomitant ophthalmological condition, such as media opacities that could confound the interpretation of traditional multimodal image or OCTA
Eligible participants characteristics	80 eyes (73 consecutive patients) were enrolled in the study. Mean age (SD): 74.1 years (8.5) No. of men: 34(46%)
Type of test	Optical coherence tomography angiography (OCT-A)
Reference standard	Fluorescein angiography Indocyanine green angiography (ICG) SD- Optical coherence tomography (OCT)
Prevalence	Presence of leakage

		Multimodal imaging		
OCT-A		Positive	Negative	Total
	Positive	56	3	59
	Negative	2	19	21

Bibliographic reference	**Coscas Gabriel J; Lupidi Marco ; Coscas Florence ; Cagini Carlo ; Souied Eric H; Optical coherence tomography angiography versus traditional multimodal imaging in assessing the activity of exudative age-related macular degeneration: A New Diagnostic Challenge. Retina 35 (11): 2219-28. 2015**
	Total 58 22 80
Sensitivity	OCT-A (multimodal imaging as reference standard): 96.6% (95%CI 90.6-99.6%)
Specificity	OCT-A (multimodal imaging as reference standard): 86.4% (95%CI 69.6-97.0%)
Positive predictive values	OCT-A (multimodal imaging as reference standard): 94.9% (95%CI 88.1-98.9%)
Negative predictive values	OCT-A (multimodal imaging as reference standard): 90.5% (95%CI 75.1-98.8%)
Comments	In the traditional multimodal imaging approach, need for treatment was assessed using the presence of at least 2 of the 3 following features: The presence of leakage on FA, evidence of CNV network on ICGA, and presence of subretinal, intraretinal or sub-RPE fluid on SD-OCT Patient selection: a retrospective study with a selection of consecutive patients with a clinical diagnosis of exudative AMD; Index test: evaluations were performed by 2 retinal specialists who were masked to each other and independently graded the imaged obtained both from the index test and reference standards at different time points and in different orders; Reference standard: Traditional multimodal imaging were used as reference standard, including FA, ICGA and SD-OCT; Flow and timing: each patient underwent a complete bilateral clinical examination and multimodal imaging protocol including FA, ICGA and SD-OCT to establish the treatment decision; on the same day as the traditional multimodal imaging evaluation, each patient was subjected to a spectralis OCTA prototype treatment;

Bibliographic reference	**Eter N ; Spaide R F; Comparison of fluorescein angiography and optical coherence tomography for patients with choroidal neovascularization after photodynamic therapy. Retina 25 (6): 691-6. 2005**
Country/ies where the study carried out	USA
Study type	Retrospective, non-randomised study
Aim of the study	To investigate retinal morphology by means of fluorescein angiography (FA) and optical coherence tomography (OCT) in patients who had undergone photodynamic therapy (PDT) with verteporfin at their 3-month-interval examination
Study dates	Not stated
Sources of funding	Not stated
Number of patients	60 eyes (60 patients)

<table>
<tr><th>Bibliographic reference</th><th>Eter N ; Spaide R F; Comparison of fluorescein angiography and optical coherence tomography for patients with choroidal neovascularization after photodynamic therapy. Retina 25 (6): 691-6. 2005</th></tr>
<tr><td>Inclusion criteria</td><td>Patients were with predominantly classic CNV secondary to age-related macular degeneration received PDT with verteporfin according to TAP study protocol</td></tr>
<tr><td>Exclusion criteria</td><td>Not stated</td></tr>
<tr><td>Eligible participants characteristics</td><td>60 eyes (60 patients, 30 consecutively evaluated patients) were enrolled in the study.

PDT treatment history:
<table>
<tr><td>No. of PDT</td><td>No. of participants</td></tr>
<tr><td>1</td><td>29</td></tr>
<tr><td>2</td><td>18</td></tr>
<tr><td>3</td><td>7</td></tr>
<tr><td>4</td><td>2</td></tr>
<tr><td>6</td><td>1</td></tr>
<tr><td>9</td><td>1</td></tr>
</table>
Median age: 78 years
No. of men: 31(51.7%)</td></tr>
<tr><td>Type of test</td><td>Optical coherence tomography (OCT)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography (FA)</td></tr>
<tr><td>Prevalence</td><td>Presence of leakage on FA and cystoid spaces on OCT
<table>
<tr><td></td><td></td><td>FA</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive (leakage)</td><td>Negative (no leakage)</td><td>Total</td></tr>
<tr><td></td><td>Positive (cystoid spaces)</td><td>40</td><td>2</td><td>42</td></tr>
<tr><td></td><td>Negative (no cystoid spaces</td><td>10</td><td>8</td><td>18</td></tr>
<tr><td></td><td>Total</td><td>50</td><td>10</td><td>60</td></tr>
</table>
Presence of cystoid spaces on FA and OCT</td></tr>
</table>

Bibliographic reference	Eter N ; Spaide R F; Comparison of fluorescein angiography and optical coherence tomography for patients with choroidal neovascularization after photodynamic therapy. Retina 25 (6): 691-6. 2005
	<table><tr><td></td><td></td><td>FA</td><td></td><td></td></tr><tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr><tr><td></td><td>Positive</td><td>20</td><td>22</td><td>42</td></tr><tr><td></td><td>Negative</td><td>2</td><td>16</td><td>18</td></tr><tr><td></td><td>Total</td><td>22</td><td>38</td><td>60</td></tr></table>
Sensitivity	Presence of leakage on FA and cystoid spaces on OCT, OCT (FA as reference standard): 80% (95%CI 68.0-89.9%) Presence of cystoid spaces on FA and OCT, OCT (FA as reference standard): 90.9% (95%CI 76.2-98.8%)
Specificity	Presence of leakage on FA and cystoid spaces on OCT, OCT (FA as reference standard): 80% (95%CI 51.8-97.2%) Presence of cystoid spaces on FA and OCT, OCT (FA as reference standard): 42.1% (95%CI 27.1-57.9%)
Positive predictive values	Presence of leakage on FA and cystoid spaces on OCT, OCT (FA as reference standard): 95.2% (95%CI 87.1-99.4%) Presence of cystoid spaces on FA and OCT, OCT (FA as reference standard): 47.6% (95%CI 32.9-62.6%)
Negative predictive values	Presence of leakage on FA and cystoid spaces on OCT, OCT (FA as reference standard): 44.4% (95%CI 23.0-67.1%) Presence of cystoid spaces on FA and OCT, OCT (FA as reference standard): 88.9% (95%CI 71.3-98.5%)
Comments	FA imagines were evaluated for staining of and leakage from the lesion and also for the presence of loculated fluid in cystoid spaces in the macular. OCT evaluated the presence of subretinal fluid or cystoid spaces within the retina. Patient selection: a retrospective study with a selection of consecutive patients with predominantly classic CNV secondary to AMD received PDT. Index test: OCT images were independently reviewed in a masked fashion, but it is unclear whether OCT results were masked to results of reference standard. Reference standard: FA results were reviewed in a masked fashion, but iIt is unclear whether FA results were masked to results of OCT Flow and timing: Patients were examined 3 months after PDT, and had both OCT and FA, but time intervals were unclear. All patients included in the analysis.

<table>
<tr><th>Bibliographic reference</th><th>Giani A ; Luiselli C ; Esmaili D D; Salvetti P ; Cigada M ; Miller J W; Staurenghi G ; Spectral-domain optical coherence tomography as an indicator of fluorescein angiography leakage from choroidal neovascularization. Investigative Ophthalmology & Visual Science 52(8): 5579-86. 2011</th></tr>
<tr><td>Country/ies where the study carried out</td><td>Milan, Italy</td></tr>
<tr><td>Study type</td><td>Retrospective cross sectional study</td></tr>
<tr><td>Aim of the study</td><td>To evaluate spectral-domain optical coherence tomography (SD-OCT) findings that predict angiographic leakage in choroidal neovascularization (CNV)</td></tr>
<tr><td>Study dates</td><td>Not stated</td></tr>
<tr><td>Sources of funding</td><td>Not stated</td></tr>
<tr><td>Number of patients</td><td>93 eyes (93 patients) with CNV from neovascular AMD</td></tr>
<tr><td>Inclusion criteria</td><td>Clinical history of AMD and FA diagnosis of subfoveal CNV, FA and SD-OCT were performed;
Previous treatment with anti-VEGF (ranibizumab or bevacizumab) for CNV
FA and SD-OCT acquired 1 month after any anti-VEGF agent injection, and every 3 months thereafter</td></tr>
<tr><td>Exclusion criteria</td><td>Previous laser treatment, photodynamic therapy, or vitreoretinal surgery on the study eye; significant macular haemorrhage that obscured the lesion, and a spherical refractive error >6diopters.</td></tr>
<tr><td>Eligible participants characteristics</td><td>93 eyes (93 patients) were enrolled in the study.

Mean age (SD): 77.0 years (11.4)
No. of men: 41(44.1%)
Mean no. of anti-VEFG (SD): 6.7 (3.5)</td></tr>
<tr><td>Type of test</td><td>SD-Optical coherence tomography (OCT)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography (FA)</td></tr>
<tr><td>Prevalence</td><td>Parameter: fluid (associated with FA presence of leakage)
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>49</td><td>30</td><td>79</td></tr>
<tr><td></td><td>Negative</td><td>3</td><td>11</td><td>14</td></tr>
<tr><td></td><td>Total</td><td>52</td><td>41</td><td>93</td></tr>
</table>
Parameter: PED (pigment epithelium detachment)</td></tr>
</table>

Bibliographic reference	Giani A ; Luiselli C ; Esmaili D D; Salvetti P ; Cigada M ; Miller J W; Staurenghi G ; Spectral-domain optical coherence tomography as an indicator of fluorescein angiography leakage from choroidal neovascularization. Investigative Ophthalmology & Visual Science 52(8): 5579-86. 2011

		FA leakage		
OCT		Positive	Negative	Total
	Positive	20	13	33
	Negative	32	28	60
	Total	52	41	93

Parameter: NSD (neurosensory retinal detachment)

		FA leakage		
OCT		Positive	Negative	Total
	Positive	35	5	40
	Negative	17	36	53
	Total	52	41	93

Parameter: ICS (intraretinal cystic spaces)

		FA leakage		
OCT		Positive	Negative	Total
	Positive	27	23	50
	Negative	25	18	43
	Total	52	41	93

Parameter: Flecks

		FA leakage		
OCT		Positive	Negative	Total
	Positive	42	7	49
	Negative	10	34	44
	Total	52	41	93

Sensitivity		Sensitivity (95%CI)

Bibliographic reference	Giani A ; Luiselli C ; Esmaili D D; Salvetti P ; Cigada M ; Miller J W; Staurenghi G ; Spectral-domain optical coherence tomography as an indicator of fluorescein angiography leakage from choroidal neovascularization. Investigative Ophthalmology & Visual Science 52(8): 5579-86. 2011	
	Fluid	94.2% (86.5-98.8%)
	Pigment epithelium detachment (PED)	38.5% (25.8-51.9%)
	Neurosensory retinal detachment (NSD)	67.3% (54.1-79.2%)
	Intraretinal cystic spaces (ICS)	51.9% (38.5-65.2%)
	Flecks	80.8% (69.1-90.2%)
Specificity		Specificity (95%CI)
	Fluid	26.8% (14.6-41.2%)
	Pigment epithelium detachment (PED)	68.3% (53.5-81.4%)
	Neurosensory retinal detachment (NDS)	87.8% (76.3-95.8%)
	Intraretinal cystic spaces (ICS)	43.9% (29.3-59.1%)
	Flecks	82.9% (70.2-92.7%)
Positive predictive values		PPV (95%CI)
	Fluid	62.0% (51.1-72.3%)
	Pigment epithelium detachment (PED)	60.6% (43.7-76.3%)
	Neurosensory retinal detachment (NDS)	87.6% (75.8-95.7%)
	Intraretinal cystic spaces (ICS)	54.0% (40.2-67.5%)
	Flecks	85.7% (74.8-93.9%)
Negative predictive values		NPV (95%CI)
	Fluid	78.6% (54.6-95.0%)
	Pigment epithelium detachment (PED)	46.7% (34.3-59.2%)

Bibliographic reference	**Giani A ; Luiselli C ; Esmaili D D; Salvetti P ; Cigada M ; Miller J W; Staurenghi G ; Spectral-domain optical coherence tomography as an indicator of fluorescein angiography leakage from choroidal neovascularization. Investigative Ophthalmology & Visual Science 52(8): 5579-86. 2011**
	Neurosensory retinal detachment (NDS): 67.9% (54.9-79.7%) Intraretinal cystic spaces (ICS): 41.9% (27.7-56.7%) Flecks: 77.3% (64.0-88.2%)
Comments	The study examined specific patterns of fluid accumulation, which can affect the specificity of SD-OCT evaluation with regard to having an FA leakage, including PED, NSD, ICS, and flecks. Fluid was considered present if NSD, PED, or ICS were presented. Patient selection: a retrospective study with a selection of consecutive patients with CNV secondary to AMD from neovascular AMD. Patients had previous laser treatment, PDT or vitreoretinal surgery on the study eye were excluded. Index test: Examiner were masked from all other patient data including FA images when evaluating SD-OCT. Reference standard: Examiner were masked from all other patient data including SD-OCT images when evaluating FA. Flow and timing: All SD-OCT and FA were routinely acquired 1 month after any anti-VEGD injection, and every 3 months thereafter, but time intervals were unclear. All patients included in the analysis.

Bibliographic reference	**Henschel A ; Spital G ; Lommatzsch A ; Pauleikhoff D ; Optical coherence tomography in neovascular age related macular degeneration compared to fluorescein angiography and visual acuity. European Journal of Ophthalmology 19(5): 831-5. 2009.**
Country/ies where the study carried out	Germany
Study type	Prospective cross sectional study
Aim of the study	To assess the sensitivity and specificity of optical coherence tomography (OCT) for monitoring patients with choroidal neovascularization (CNV) after photodynamic therapy (PDT) in comparison to fluorescein angiography (FA).
Study dates	Not stated
Sources of funding	Not stated
Number of patients	14 patients
Inclusion criteria	Patients with different types of CNV
Exclusion criteria	Not stated

<table>
<tr><th>Bibliographic reference</th><th>Henschel A ; Spital G ; Lommatzsch A ; Pauleikhoff D ; Optical coherence tomography in neovascular age related macular degeneration compared to fluorescein angiography and visual acuity. European Journal of Ophthalmology 19(5): 831-5. 2009.</th></tr>
<tr><td>Eligible participants characteristics</td><td>14 patients. Of 13 patients, OCT and FA were carried out prior to PDT and at 2,6, and 12 weeks after treatment. One patient only completed the 6 week visit.

Mean follow-up time per patient was 14.1 weeks</td></tr>
<tr><td>Type of test</td><td>Optical coherence tomography (OCT)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography (FA)</td></tr>
<tr><td>Prevalence</td><td>Parameter: intraretinal fluid
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>28</td><td>18</td><td>46</td></tr>
<tr><td></td><td>Negative</td><td>3</td><td>12</td><td>15</td></tr>
<tr><td></td><td>Total</td><td>31</td><td>30</td><td>61</td></tr>
</table>
Parameter: subretinal fluid
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>22</td><td>8</td><td>30</td></tr>
<tr><td></td><td>Negative</td><td>9</td><td>22</td><td>31</td></tr>
<tr><td></td><td>Total</td><td>31</td><td>30</td><td>61</td></tr>
</table>
Parameter: intraretinal or subretinal fluid
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>30</td><td>19</td><td>49</td></tr>
<tr><td></td><td>Negative</td><td>1</td><td>11</td><td>12</td></tr>
<tr><td></td><td>Total</td><td>31</td><td>30</td><td>61</td></tr>
</table></td></tr>
<tr><td>Sensitivity</td><td><table><tr><td></td><td>Sensitivity (95%CI)</td></tr></table></td></tr>
</table>

Bibliographic reference	**Henschel A ; Spital G ; Lommatzsch A ; Pauleikhoff D ; Optical coherence tomography in neovascular age related macular degeneration compared to fluorescein angiography and visual acuity. European Journal of Ophthalmology 19(5): 831-5. 2009.**
	Intraretinal fluid: 90.3% (77.9-97.9%) Subretinal fluid: 71.0% (54.1-85.3%) Intraretinal or subretinal fluid: 96.8% (88.4-99.9%)
Specificity	Specificity (95%CI) Intraretinal fluid: 40.0% (23.5-57.7%) Subretinal fluid: 73.3% (56.5-87.3%) Intraretinal or subretinal fluid: 36.7% (20.7-54.3%)
Positive predictive values	PPV (95%CI) Intraretinal fluid: 60.9% (46.5-74.3%) Subretinal fluid: 73.3% (56.5-87.3%) Intraretinal or subretinal fluid: 61.2% (47.4-74.2%)
Negative predictive values	NPV (95%CI) Intraretinal fluid: 80.0% (57.2-95.3%) Subretinal fluid: 71.0% (54.1-85.3%) Intraretinal or subretinal fluid: 91.7% (71.5-99.8%)
Comments	In FA, leakage was rated as positive if extravasation of the dye was visible outside the initial lesion boundaries 3 minutes after dye injection. All OCT were assessed for presence or absence of intraretinal or subretinal fluid. Intraretinal fluid was considered to be present if loculated hyporeflective cystoid spaces were visible in one of the acquired OCT. Subretinal fluid was rated as present if a hyporeflective space was definable between the outer retinal surface and the hyperreflective retinal pigement epithelium/choriocapilary complex in one of the OCT scans. A total of 14 patients with CNV. 13 patients had OCT and FA prior to PDT and at 2,6 and 12 weeks after treatment. One patient only completed the 6-week visit. In 3 patients images could be obtained at 24 weeks after treatment additionally. Patient selection: a prospective study with a selection of patients with CNV (n=14). In 13 patients, OCT and FA were carried out prior to PDT and at 2, 6, and 12 weeks after treatment. Once patient only completed the 6-week visit. In 3 patients, images could be obtained at 24 weeks after treatment additionally.

Bibliographic reference	**Henschel A ; Spital G ; Lommatzsch A ; Pauleikhoff D ; Optical coherence tomography in neovascular age related macular degeneration compared to fluorescein angiography and visual acuity. European Journal of Ophthalmology 19(5): 831-5. 2009.**
	Index test: All acquired OCT were assessed for the presences or absence of intraretinal or subretinal fluid. Images were reviewed in masked fashion. Reference standard: In FA, leakage was rated as positive if extravasation of the dye was visible outside the initial lesion boundaries 3 minutes after dye injection. All acquired images were reviewed in a masked fashion. Leakage activities on FA was defined as the gold standard. Flow and timing: time intervals were unclear. All patients included in the analysis, but results were not presented at different time points of study follow-up.

Bibliographic reference	**Khurana R N; Dupas B ; Bressler N M; Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. Ophthalmology 117(7): 1376-80. 2010.**
Country/ies where the study carried out	USA
Study type	Retrospective consecutive case series study
Aim of the study	To compare fluorescein leakage from choroidal neovascularization (CNV) with signs of intraretinal or subretinal fluid on time-domain optical coherence tomography (TD-OCT) and spectral-domain optical coherence tomography (SD-OCT) in patients receiving anti-vascular endothelial growth factor (anti-VEGF) therapy for CNV caused by age-related macular degeneration (AMD).
Study dates	All patients with CNV secondary to AMD who were imaged on the same day with FA and TD-OCT and SD-OCT over an 8-month period (November 2007 to June 2008) were reviewed.
Sources of funding	Ronald G Michels Foundation; Foundation Odette et Jean Duranton de Magny, Foundation de France; James P Gills Professionorship and a Wilmer Retina Division Research Fund.
Number of patients	93 eyes (93 patients) with CNV from neovascular AMD
Inclusion criteria	All patients with CNV secondary to AMD who were imaged on the same day with FA and TD-OCT and SD-OCT
Exclusion criteria	Not stated
Eligible participants characteristics	59 eyes (56 patients) were enrolled in the study. Mean age (SD): 78.0 years (7.8) Median no. of previous anti-VEFG (SD): 4
Type of test	Optical coherence tomography (OCT) (both TD-OCT and SD-OCT)

Bibliographic reference	**Khurana R N; Dupas B ; Bressler N M; Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. Ophthalmology 117(7): 1376-80. 2010.**
Reference standard	Fluorescein angiography (FA)
Prevalence	Parameter: interstitial fluid

		FA leakage		
TD-OCT		Positive	Negative	Total
	Positive	11	8	19
	Negative	18	22	40
	Total	29	30	59
SD-OCT	Positive	19	11	30
	Negative	10	19	29
	Total	29	30	59

Parameter: retinal cystoid abnormalities

		FA leakage		
TD-OCT		Positive	Negative	Total
	Positive	10	8	18
	Negative	19	22	41
	Total	29	30	59
SD-OCT	Positive	17	13	30
	Negative	12	17	29
	Total	29	30	59

Parameter: subretinal fluid

		FA leakage		
TD-OCT		Positive	Negative	Total
	Positive	14	5	19
	Negative	15	25	40
	Total	29	30	59
SD-OCT	Positive	20	7	27

Bibliographic reference	Khurana R N; Dupas B ; Bressler N M; Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. Ophthalmology 117(7): 1376-80. 2010.

	Negative	9	23	32
	Total	29	30	59

Parameter: interstitial fluid, cystoid abnormalities or subretinal fluid

		FA leakage		
TD-OCT		Positive	Negative	Total
	Positive	17	11	28
	Negative	12	19	31
	Total	29	30	59
SD-OCT	Positive	26	16	42
	Negative	3	14	17
	Total	29	30	59

Sensitivity

TD-OCT (vs FA)

	Sensitivity (95%CI)
interstitial fluid	37.9% (21.5-55.9%)
retinal cystoid abnormalities	34.5% (18.6-52.4%)
subretinal fluid	48.3% (30.6-66.1%)
interstitial fluid, cystoid abnormalities or subretinal fluid	58.6% (40.6-75.5%)

SD-OCT (vs FA)

	Sensitivity (95%CI)
interstitial fluid	65.5% (47.6-81.4%)
retinal cystoid abnormalities	58.6% (40.6-75.5%)
subretinal fluid	69.0% (51.3-84.1%)
	PPV (95%CI)

Specificity

TD-OCT (vs FA)

	Specificity (95%CI)

<table>
<tr><th>Bibliographic reference</th><th>Khurana R N; Dupas B ; Bressler N M; Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. Ophthalmology 117(7): 1376-80. 2010.</th></tr>
<tr><td></td><td>
<table>
<tr><td>interstitial fluid</td><td>73.3% (56.5-87.3%)</td></tr>
<tr><td>retinal cystoid abnormalities</td><td>73.3% (56.5-87.3%)</td></tr>
<tr><td>subretinal fluid</td><td>83.3% (68.3-94.2%)</td></tr>
<tr><td>interstitial fluid, cystoid abnormalities or subretinal fluid</td><td>63.3% (45.7-79.3%)</td></tr>
</table>
SD-OCT
<table>
<tr><td></td><td>Specificity (95%CI)</td></tr>
<tr><td>interstitial fluid</td><td>63.3% (45.7-79.3%)</td></tr>
<tr><td>retinal cystoid abnormalities</td><td>56.7% (38.9-73.6%)</td></tr>
<tr><td>subretinal fluid</td><td>76.7% (60.3-89.7%)</td></tr>
<tr><td>interstitial fluid, cystoid abnormalities or subretinal fluid</td><td>46.7% (29.4-64.3%)</td></tr>
</table>
</td></tr>
<tr><td>Positive predictive values</td><td>TD-OCT
<table>
<tr><td></td><td></td></tr>
<tr><td>interstitial fluid</td><td>57.9% (35.7-78.5%)</td></tr>
<tr><td>retinal cystoid abnormalities</td><td>55.6% (32.9-77.0%)</td></tr>
<tr><td>subretinal fluid</td><td>73.7% (52.4-90.3%)</td></tr>
<tr><td>interstitial fluid, cystoid abnormalities or subretinal fluid</td><td>60.7% (42.4-77.6%)</td></tr>
</table>
SD-OCT
<table>
<tr><td></td><td>PPV (95%CI)</td></tr>
<tr><td>interstitial fluid</td><td>63.3% (45.7-79.3%)</td></tr>
<tr><td>retinal cystoid abnormalities</td><td>56.7% (38.9-73.6%)</td></tr>
<tr><td>subretinal fluid</td><td>74.1 (56.4-88.4%)</td></tr>
<tr><td>interstitial fluid, cystoid abnormalities or subretinal fluid</td><td>61.9% (46.9-75.8%)</td></tr>
</table>
</td></tr>
<tr><td>Negative predictive values</td><td>TD-OCT</td></tr>
</table>

Bibliographic reference	**Khurana R N; Dupas B ; Bressler N M; Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. Ophthalmology 117(7): 1376-80. 2010.**

	NPV (95%CI)
interstitial fluid	55.0% (39.6-69.9%)
retinal cystoid abnormalities	53.7% (38.5-68.5%)
subretinal fluid	62.5% (47.2-76.6%)
interstitial fluid, cystoid abnormalities or subretinal fluid	61.3% (43.9-77.3%)

SD-OCT

	NPV (95%CI)
interstitial fluid	65.5% (47.6-81.4%)
retinal cystoid abnormalities	58.6% (40.6-75.5%)
subretinal fluid	71.9% (55.4-85.8%)
interstitial fluid, cystoid abnormalities or subretinal fluid	82.4% (61.7-96.0%)

COmments

OCT abnormalities were defined as the presences of interstitial fluid, retinal cystoid abnormalities, or subretinal fluid.

Patient selection: a retrospective study reviewing the records of all patients with CNV who were imaged on the same day with FA, TD-OCT and SD-OCT.

Index test: All images were analysed by a trained grader but it was unclear whether the interpretation of results were masked to results of reference standard.

Reference standard: All images were analysed by a trained grader but it was unclear whether the interpretation of results were masked to results of index test.

Flow and timing: inclusion of participants had images on the same day. All participants included in the analysis.

Bibliographic reference	**Salinas-Alaman A ; Garcia-Layana A ; Maldonado M J; Sainz-Gomez C ; Alvarez-Vidal A ; Using optical coherence tomography to monitor photodynamic therapy in age related macular degeneration. American Journal of Ophthalmology 140 (1): 23-8. 2005.**
Country/ies where the study carried out	Spain

<table>
<tr><th>Bibliographic reference</th><th>Salinas-Alaman A ; Garcia-Layana A ; Maldonado M J; Sainz-Gomez C ; Alvarez-Vidal A ; Using optical coherence tomography to monitor photodynamic therapy in age related macular degeneration. American Journal of Ophthalmology 140 (1): 23-8. 2005.</th></tr>
<tr><td>Study type</td><td>Prospective observational case study</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the role of optical coherence tomography (OCT) in determining choroidal neovascularization (CNV) activity before and after photodynamic therapy (PDT) in patients with age-related macular degeneration (ARMD).</td></tr>
<tr><td>Study dates</td><td>Not stated</td></tr>
<tr><td>Sources of funding</td><td>Not stated</td></tr>
<tr><td>Number of patients</td><td>62 eyes (53 consecutive patients)</td></tr>
<tr><td>Inclusion criteria</td><td>All patients with exudative AMD with predominantly classic CNV</td></tr>
<tr><td>Exclusion criteria</td><td>Not stated</td></tr>
<tr><td>Eligible participants characteristics</td><td>53 patients were included in the study.

Mean age (SD): 76.5 years (7.5)
Mean no. of PDT treatment: 2.5 (SD 1.2) followed for 6 months; 2.9 (SD 1.1) followed for 12 months</td></tr>
<tr><td>Type of test</td><td>Optical coherence tomography (OCT)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography (FA)</td></tr>
<tr><td>Prevalence</td><td>Parameter: interstitial fluid or subretinal fluid
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>110</td><td>25</td><td>135</td></tr>
<tr><td></td><td>Negative</td><td>5</td><td>36</td><td>41</td></tr>
<tr><td></td><td>Total</td><td>115</td><td>61</td><td>176</td></tr>
</table></td></tr>
<tr><td>Sensitivity</td><td>Presence of leakage on FA and intraretinal or subretinal fluid on OCT, OCT (FA as reference standard): 95.7% (95%CI 91.7-98.6%)</td></tr>
<tr><td>Specificity</td><td>Presence of leakage on FA and intraretinal or subretinal fluid on OCT, OCT (FA as reference standard): 59.0% (95%CI 46.5-70.9%)</td></tr>
<tr><td>Positive predictive values</td><td>Presence of leakage on FA and intraretinal or subretinal fluid on OCT, OCT (FA as reference standard): 81.5% (95%CI 74.5-87.5%)</td></tr>
<tr><td>Negative predictive values</td><td>Presence of leakage on FA and intraretinal or subretinal fluid on OCT, OCT (FA as reference standard): 87.8% (95%CI 76.3-95.8%)</td></tr>
</table>

Bibliographic reference	**Salinas-Alaman A ; Garcia-Layana A ; Maldonado M J; Sainz-Gomez C ; Alvarez-Vidal A ; Using optical coherence tomography to monitor photodynamic therapy in age related macular degeneration. American Journal of Ophthalmology 140 (1): 23-8. 2005.**
Comments	A total of 62 eyes included in the study. After the treatment, 42 eyes were reviewed every 3 months for 12 months (n=168 pair of OCT and FA), and the other 20 eye were reviewed 3-monthly for 6 months (n=40 pairs of OCT and FA). Therefore, by the end of 12 month follow-up, there were a total of 208 sets of FA and OCT were expected, 176 were obtained. Patient selection: a prospective study with a selection of consecutive patients with exudative AMD with predominantly classic CNV. Index test: experienced technician performed OCT examinations, another independent observer who was masked to the patient status evaluated the OCT on each occasion, but it was unclear whether the results of OCT were masked to results of FA. Reference standard: Two independent observers determined the presence or absence of leakage on FA in each case, but it was unclear whether results were masked to OCT results. Flow and timing: Time intervals of OCT and FA were unclear. Sets of OCT and FA results were included but sets of OCT and FA results were not presented at different time points of study follow-up.

Bibliographic reference	**Van de Moere ; A ; Sandhu S S; Talks S J; Correlation of optical coherence tomography and fundus fluorescein angiography following photodynamic therapy for choroidal neovascular membranes. British Journal of Ophthalmology 90 (3): 304-6. 2006**
Country/ies where the study carried out	UK
Study type	Retrospective comparative observational case series
Aim of the study	To assess the correlation between optical coherence tomography (OCT) and leakage on fundus fluorescein angiography (FFA) following photodynamic therapy (PDT) with verteporfin for choroidal neovascularisation (CNV)
Study dates	A review of patients who had received initial PDT with verteporfin between July 2001 and October 2004
Sources of funding	Not stated
Number of patients	121 eyes
Inclusion criteria	All patients who had received initial PDT with verteporfin for a classic or predominantly subfoveal CNV secondary to AMD, to allow at least 3 months of follow-up
Exclusion criteria	Not stated
Eligible participants characteristics	121 eyes were included in the study.

<table>
<tr><th>Bibliographic reference</th><td>Van de Moere ; A ; Sandhu S S; Talks S J; Correlation of optical coherence tomography and fundus fluorescein angiography following photodynamic therapy for choroidal neovascular membranes. British Journal of Ophthalmology 90 (3): 304-6. 2006</td></tr>
<tr><td></td><td>No. of female: 66 (51.2%)
Mean age (range): 73.9years (30-94)</td></tr>
<tr><td>Type of test</td><td>Optical coherence tomography (OCT)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography (FA)</td></tr>
<tr><td>Prevalence</td><td>Parameter: pigment epithelial detachment
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>4</td><td>0</td><td>4</td></tr>
<tr><td></td><td>Negative</td><td>66</td><td>51</td><td>117</td></tr>
<tr><td></td><td>Total</td><td>70</td><td>51</td><td>121</td></tr>
</table>
Parameter: subretinal fluid
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>33</td><td>8</td><td>41</td></tr>
<tr><td></td><td>Negative</td><td>37</td><td>43</td><td>80</td></tr>
<tr><td></td><td>Total</td><td>70</td><td>51</td><td>121</td></tr>
</table>
Parameter: intraretinal fluid
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>58</td><td>24</td><td>82</td></tr>
<tr><td></td><td>Negative</td><td>11</td><td>27</td><td>39</td></tr>
<tr><td></td><td>Total</td><td>70</td><td>51</td><td>121</td></tr>
</table>
Parameter: gross cystoid macular oedema
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	Van de Moere ; A ; Sandhu S S; Talks S J; Correlation of optical coherence tomography and fundus fluorescein angiography following photodynamic therapy for choroidal neovascular membranes. British Journal of Ophthalmology 90 (3): 304-6. 2006

OCT		Positive	Negative	Total
	Positive	16	1	17
	Negative	54	50	104
	Total	70	51	121

Parameter: sponge-like retinal thickening

		FA leakage		
OCT		Positive	Negative	Total
	Positive	33	10	43
	Negative	37	41	78
	Total	70	51	121

Parameter: solitary foveal cyst

		FA leakage		
OCT		Positive	Negative	Total
	Positive	9	13	22
	Negative	61	38	99
	Total	70	51	121

Parameter: absence of foveal depression

		FA leakage		
OCT		Positive	Negative	Total
	Positive	38	18	56
	Negative	32	33	65
	Total	70	51	121

Parameter: retinal thickness>350µm

Bibliographic reference	Van de Moere ; A ; Sandhu S S; Talks S J; Correlation of optical coherence tomography and fundus fluorescein angiography following photodynamic therapy for choroidal neovascular membranes. British Journal of Ophthalmology 90 (3): 304-6. 2006

		FA leakage		
OCT		Positive	Negative	Total
	Positive	44	9	53
	Negative	26	42	68
	Total	70	51	121

Sensitivity	
	Sensitivity (95%CI)
Subretinal fluid	47.1% (35.6-58.8%)
Intraretinal fluid	82.9% (73.3-90.7%)
Gross cystoid macular oedema	22.9% (13.9-33.3%)
Sponge-like retinal thickening	47.1% (35.6-58.8%)
Solitary foveal cyst	12.9% (6.0-21.6%)
Retinal thickness>350µm	62.9% (51.3-73.7%)
Absence of foveal depression	54.3% (42.6-65.7%)

Specificity	
	Specificity (95%CI)
Subretinal fluid	84.3% (73.3-92.8%)
Intraretinal fluid	52.9% (39.3-66.3%)
Gross cystoid macular oedema	98.0% (92.9-99.9%)
Sponge-like retinal thickening	80.4% (68.6-90.0%)
Solitary foveal cyst	74.5% (61.8-85.4%)
Retinal thickness>350µm	82.4% (70.9-91.4%)
Absence of foveal depression	64.7% (51.2-77.1%)

Positive predictive values	
	Positive predictive value(95%CI)
Subretinal fluid	80.5% (62.7-90.9%)
Intraretinal fluid	70.7% (60.5-80.0%)
Gross cystoid macular oedema	94.1% (79.4-99.8%)
Sponge-like retinal thickening	76.7% (63.2-87.9%)

Bibliographic reference	**Van de Moere ; A ; Sandhu S S; Talks S J; Correlation of optical coherence tomography and fundus fluorescein angiography following photodynamic therapy for choroidal neovascular membranes. British Journal of Ophthalmology 90 (3): 304-6. 2006**
	Solitary foveal cyst: 40.9% (21.8-61.6%) Retinal thickness>350µm: 83.0% (71.9-91.8%) Absence of foveal depression: 67.9% (55.2-79.3%)
Negative predictive values	Negative predictive value(95%CI) Subretinal fluid: 53.8% (42.8-64.5%) Intraretinal fluid: 69.2% (54.1-82.5%) Gross cystoid macular oedema: 48.1% (38.6-57.6%) Sponge-like retinal thickening: 52.6% (41.5-63.5%) Solitary foveal cyst: 38.4% (29.1-48.1%) Retinal thickness>350µm: 61.8% (50.0-72.9%) Absence of foveal depression: 50.8% (38.7-62.8%)
Comments	Patient selection: a retrospective study with a selection of patients who all had received PDT for a classic or predominantly classic subfoveal CNV secondary to AMD. Index test: The accredited ophthalmic photographer performed OCT. Each OCT image was evaluated independently by one of investigators, who were masked to the treatment course, number of treatment, and whether treatment was given or not at that visit. It was unclear whether results of OCT were masked to FA results. Reference standard: The same accredited ophthalmic photographer performed FFA. Each FFA image was evaluated independently by one of investigators, who were masked to the treatment course, number of treatment, and whether treatment was given or not at that visit. It was unclear whether results of OCT were masked to FA results. (different investigators evaluated FFA and OCT) Flow and timing: The OCT and FA from the same visit were analysed. All patients included in the analysis.

Bibliographic reference	**van Velthoven ; M E ; de Smet ; M D ; Schlingemann R O; Magnani M ; Verbraak F D; Added value of OCT in evaluating the presence of leakage in patients with age-related macular degeneration treated with PDT. Graefes Archive for Clinical & Experimental Ophthalmology 244 (9): 1119-23. 2006.**
Country/ies where the study carried out	Amsterdam, Netherlands
Study type	Prospective observational case series

<table>
<tr><th>Bibliographic reference</th><th>van Velthoven ; M E ; de Smet ; M D ; Schlingemann R O; Magnani M ; Verbraak F D; Added value of OCT in evaluating the presence of leakage in patients with age-related macular degeneration treated with PDT. Graefes Archive for Clinical & Experimental Ophthalmology 244 (9): 1119-23. 2006.</th></tr>
<tr><td>Aim of the study</td><td>To evaluate the presence of leakage on fluorescein angiography (FA) in patients with age-related macular degeneration (AMD) retreated with photodynamic therapy (PDT) can be difficult. New diagnostic tools such as optical coherence tomography (OCT) might help to optimize PDT management.</td></tr>
<tr><td>Study dates</td><td>Patient recruitment between July and October 2003</td></tr>
<tr><td>Sources of funding</td><td>There was no financial support for this study</td></tr>
<tr><td>Number of patients</td><td>30 eyes (30 consecutive patients)</td></tr>
<tr><td>Inclusion criteria</td><td>All patients who had received at least one prior PDT treatment, and were scheduled for their regular 3-monthly FA.</td></tr>
<tr><td>Exclusion criteria</td><td>Not stated</td></tr>
<tr><td>Eligible participants characteristics</td><td>30 patients were included in the study.
Mean age (MD): 75.5years (9.0)
No. of prior PDT treatment range from 1 to 12 (median 2.5)</td></tr>
<tr><td>Type of test</td><td>Time domain optical coherence tomography (OCT) (stratus OCT)</td></tr>
<tr><td>Reference standard</td><td>Fluorescein angiography (FA)</td></tr>
<tr><td>Prevalence</td><td>Parameter: leakage
<table>
<tr><td></td><td></td><td>FA leakage</td><td></td><td></td></tr>
<tr><td>OCT</td><td></td><td>Positive</td><td>Negative</td><td>Total</td></tr>
<tr><td></td><td>Positive</td><td>15</td><td>4</td><td>19</td></tr>
<tr><td></td><td>Negative</td><td>8</td><td>3</td><td>11</td></tr>
<tr><td></td><td>Total</td><td>23</td><td>7</td><td>30</td></tr>
</table></td></tr>
<tr><td>Sensitivity</td><td>OCT (FA as reference standard): 65.2% (95%CI 45.1-82.8%)</td></tr>
<tr><td>Specificity</td><td>OCT (FA as reference standard): 42.9% (95%CI 11.8-77.7%)</td></tr>
<tr><td>Positive predictive values</td><td>OCT (FA as reference standard): 78.9% (95%CI 58.6-93.6%)</td></tr>
<tr><td>Negative predictive values</td><td>OCT (FA as reference standard): 27.3% (95%CI 6.7-55.6%)</td></tr>
<tr><td>Comments</td><td>Patient selection: a prospective study with a selection of consecutive patients with AMD and subfoveal CNV who had received at least one prior PDT treatment and were scheduled for regular 3-monthly FA.
Index test: The OCT from all patients were evaluated by two different investigator for the presence of signs of leakage but it was unclear whether OCT results were masked to FA results.</td></tr>
</table>

Bibliographic reference	van Velthoven ; M E ; de Smet ; M D ; Schlingemann R O; Magnani M ; Verbraak F D; Added value of OCT in evaluating the presence of leakage in patients with age-related macular degeneration treated with PDT. Graefes Archive for Clinical & Experimental Ophthalmology 244 (9): 1119-23. 2006.
	Reference standard: The FA results were evaluated by two experienced investigator independently for the presence of signs of leakage, and the observers were masked for any relevant clinical data such as VA, number of prior treatment or previous FAs but it was unclear whether FA results were masked to OCT results. Flow and timing: All patients had their regular 3-monthly FA, and were also had OCT but time intervals were unclear. All patients were included in the analysis.

E.8 Information

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

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

Bibliographic reference	**Boulanger-Scemama E, Querques G, About F, Puche N, Srour M, Mane V, Massamba N, Canoui-Poitrine F, and Souied E H. 2015. "Ranibizumab for exudative age-related macular degeneration: A five year study of adherence to follow-up in a real-life setting". Journal Francais d Opthalmologie 38:620-7.**
Country/ies where the study was carried out	Creteil University, France
Study type:	Retrospective review the charts of all consecutive patients with exudative AMD who underwent their first ranibizumab injection, and a 7-item multiple-choice questionnaire was to be completed by patients who had not attended a follow-up visit for more than 6 months
Aim of the study:	To analyse adherence to follow-up over 5 years in patients treated with intravitreal ranibizumab for exudative age-related macular degeneration (AMD) in a tertiary health care centre.
Study dates:	1st October 2006 and 31st March 2012
Source of funding	Not reported
Sample size	58
Inclusion criteria	Patients with exudative age-related macular degeneration who underwent their first ranibizumab.
Exclusion criteria	Patients with choroidal neovascularisation resulting from conditions other than AMD were excluded.
Participants chacteristics	Baseline characteristics: the following characteristics were recorded for each patient: gender, previous treatment, opposite eye involvement, best corrected visual acuity at baseline and follow-up visit, number of visits and number of ranibizumab injection over the follow-up and distance from home to hospital
Methods	All eligible patients were followed up and those who had not attended a follow-up visit for more than 6 months at the final observation were considered to be lost to follow-up. A phone surgery then was conducted to establish patients' actual follow-up status and reasons for discontinuation. Those who were contactable were asked to complete a 7- item multiple-choice questionnaire. The questionnaire was also sent by mail to each patient. When no response was obtained either by phone or by mail, follow-up status was considered as unknown. Questionnaire: which of the following reasons for dropping out of follow-up applies to you? Answer items: General comorbidities Social isolation

<table>
<tr><th>Bibliographic reference</th><th>Boulanger-Scemama E, Querques G, About F, Puche N, Srour M, Mane V, Massamba N, Canoui-Poitrine F, and Souied E H. 2015. "Ranibizumab for exudative age-related macular degeneration: A five year study of adherence to follow-up in a real-life setting". Journal Francais d Opthalmologie 38:620-7.</th></tr>
<tr><td></td><td>Financial burden
Burden of periodic follow-up visit
Subjective dissatisfaction with IVT benefit
IVT intolerance
Long distance from home to hospital
“Yes” or “no” were possible for each item</td></tr>
<tr><td>Results: barriers to adherence appointment attendance and uptake of treatment</td><td>A total of 58 patients completed the 7-item questionnaire either by phone or by mail, and the mail reasons for follow-up discontinuation were:
<table>
<tr><td>Reasons for discontinuation</td><td>Percentage of patients reported</td></tr>
<tr><td>Long distance from home to hospital</td><td>51.7% (n=30)</td></tr>
<tr><td>Subjective dissatisfaction with IVT benefit</td><td>34.5% (n=20)</td></tr>
<tr><td>Burden of periodic follow-up visits</td><td>24.1% (n=14)</td></tr>
<tr><td>Financial burden</td><td>8.6%</td></tr>
<tr><td>Social isolation</td><td>5.2%</td></tr>
<tr><td>General comorbidities</td><td>1.7%</td></tr>
<tr><td>IVT intolerance</td><td>0.0%</td></tr>
</table></td></tr>
<tr><td>Results:
facilitators to adherence appointment attendance and uptake of treatment</td><td>None given</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Burton Amy E, Shaw Rachel, and Gibson Jonathan. 2013. "Experiences of patients with age-related macular degeneration receiving anti-vascular endothelial growth factor therapy: A qualitative study". British Journal of Visual Impairment 31:178-188.</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>UK</td></tr>
<tr><td>Study type</td><td>Interpretative phenomenological study</td></tr>
<tr><td>Aim of the study:</td><td>To investigate the subjective experiences of patients with anti-VEGF injections.</td></tr>
</table>

Bibliographic reference	Burton Amy E, Shaw Rachel, and Gibson Jonathan. 2013. "Experiences of patients with age-related macular degeneration receiving anti-vascular endothelial growth factor therapy: A qualitative study". British Journal of Visual Impairment 31:178-188.
Study dates	Recruitment May and July 2010, and interviews were conducted over 18 months.
Source of funding	The Aston Research centre for healthy ageing, Aston University
Sample size	7
Inclusion criteria	Patients with wet age-related macular degeneration amenable to treatment
Exclusion criteria	Not reported
Participants chacteristics	Sample characteristics: Average age of participants was 82 years older, ranging from 75 to 89 years. 2 were male. 2 participants had wet AMD in both of their eyes; 3 participants had wet AMD in one eye and dry AMD in other eye; and the other 2 participants had wet AMD in one eye and no AMD in the other eye.
Methods	Face to face interviews which lasted between 1 and 2.5 hours, were completed at 3 time points over 18 months. The first interview was completed as soon after recruitment as possible, the second at 9 months post-recruitment, and the third at 18 months post recruitment. Initial interviews were based on a semi-structured schedule, which included questions about experience of diagnosis, impacts on daily activities, relationships with family and friends, and thoughts about the future. Later interviews began with the open question “how have things been since the last time we met” in order to expand upon previous accounts and ensure that interviews were led by participant experience. A thematic account of the participants’ experience was produced using interpretive phenomenological analysis.
Thematic analysis: barriers to adherence appointment attendance and uptake of treatment	Imagination of treatment could be more distressing than the reality is an important issue that patients may decline treatment due to fear. Communication: 1. Hospital appointments involving multiple tests and interactions with a variety of health-care professionals could be confusing; “I didn’t see the reason why there were so many different people that I had to go and see individually, I mean the same nurse could have come and done, put…the injection in my arm, she could have come and took it out, you were going from one place to another, and you waited, another place to another, then you waited, another place to another you waited…when I asked, for someone to come and take this [needle] out at the end, one young lady came and she took my blood pressure. I’d finished the, and I said ‘are you going to take this?’ ‘no you’ll have to wait for a nurse’. 2. Not having enough information to provide informed consent for treatment; “It seemed like they were photographing my eyes, there was a flash, I presume that was it. Because jokingly, I said what was that and I said well you could have said smile like you know and she looked at me as if I’m barmy…But then I went to, I think it was about 4 or 5 different places, which , well they know what they’re doing. It’s no use me arguing about it is it?” 3. Problems with hospital appointment letters, which give little information about what each appointment was for and what the patients should expect;

Bibliographic reference	**Burton Amy E, Shaw Rachel, and Gibson Jonathan. 2013. "Experiences of patients with age-related macular degeneration receiving anti-vascular endothelial growth factor therapy: A qualitative study". British Journal of Visual Impairment 31:178-188.**
	"When I read all this (in the letters)…I thought they've sent me all these {appointments) all at once, having they slipped up? Which one am I supposed to have? Because I know they do slip up at hospitals because at the orthopaedic hospital, they sent me a, the follow up of what the scans going to be before I had and appointment for the scan!" Participants were unsure about when their treatment cycle would end, and there were examples of patient attempting to make their own judgement about the need for treatment.
Thematic analysis: facilitators to adherence appointment attendance and uptake of treatment	Prior knowledge and experience to ease anxiety, fear and uncertainty during treatment. "On the last treatment…there was (an) older lady…there was her husband and she was… (nervous) like you know, obviously…they said, 'what's it like', and I said, 'your first one?'…I'd had two or three, and I said, 'no, there is no pain' I said, and 'I said there's no need to worry, no pain, definitely no pain'…she went in before me and when she come out her husband went, 'thanks', I said 'it's alright, it's no problem', and you know, I'm glad I could have put someone at ease," Relationship with service providers as a way to manage the distress treatment caused. "It is scary going in to hospital, it is, so when you get to know all the staff and the staff know you, and it is, and they are all, I don't know how many people who's hand I've held, because they all do that, I might tell you, it is very very good, because when the initial thing goes, the needle is there, you do, and you grip you know? And so it mightn't sound much when the nurses do it but it is very important, very important, because you do grab the hand, I mean, it doesn't last for long but it's quite scary." Patients preferred appointment that exemplified balanced relationship, mutual respect, and professional friendship and that left them feeling empowered about decision they could make regarding treatment management of their condition.

Bibliographic reference	**Burton A E, Shaw R L, and Gibson J M. 2013. "'I'd like to know what causes it, you know, anything I've done?' Are we meeting the information and support needs of patients with macular degeneration? A qualitative study". BMJ Open 3:e003306.**
Country/ies where the study was carried out	UK NHS
Study type:	Interpretative phenomenological study
Aim of the study:	To examine patients' experience of information and support for age-related macular degeneration.
Study dates	2010
Source of funding:	The Aston Research centre for healthy ageing, Aston University
Sample size	13
Inclusion criteria:	patients with age-related macular degeneration and were capable of taking part in in-depth interviews

Bibliographic reference	Burton A E, Shaw R L, and Gibson J M. 2013. "'I'd like to know what causes it, you know, anything I've done?' Are we meeting the information and support needs of patients with macular degeneration? A qualitative study". BMJ Open 3:e003306.
Exclusion criteria:	Not reported
Participants characteristics	Sample characteristics: participant ages ranged from 75 to 89 with a mean age of 81.5. Best eye visual acuity ranged from 6/6 to 6/30 while worse eye visual acuity ranged from 6/9.5 to hand movement only. Seven of the participants were eligible for treatment and six were unable to be treated (two due to having dry AMD and three had wet AMD which was too advanced for treatment).
Methods	In-depth semi-structured interviews were used to explore issues which were important to participants in their own words. The interview schedule included questions focusing on experience of diagnosis and other eye care consultations, the impact of AMD and related vision impairment on daily activities, relationships with and/or support needs from family and friends, and thoughts about the future. Perceptions and experience can change over time and interviews were therefore carried out with each participant on up to three occasions over 18 months to explore perceptions of on-going encounters with healthcare professionals during this time. Analysis was conducted guided by the thematic analyses.
Thematic analysis: barriers to adherence appointment attendance and uptake of treatment	Source of information: For those being treated for AMD the number of appointment, letters sent were overwhelming and confusing. In addition, the wait for information through letters could be frustrating time for patients. “I’ve got to go next month. So, whether they’ll [treat] the one eye today and then do the other one next month, I don’t know.” Some leaflets given by the hospital were unread and forgotten about; A wide variety of information deficits following diagnosis was evident in the accounts: the cause of AMD, reasons for medical process and procedures, vitamins, registering as partially sighted, impact of smoking, foods for eye health and activities they should or should not pursue. A lack of knowledge about the purpose of medical process and procedures. For example, letters were often unclear about the purpose of appointments. In addition during long3-4hour appointment patients were not made aware of the purpose of scan and other procedures. Few participants were aware of the support services available to them.
Thematic analysis: facilitators to adherence appointment attendance and uptake of treatment	Half of participants expressed a desire for regular monitoring by healthcare professionals (a sense of security knowing that they were under the care of the hospital) Self-advocacy: 8 participants highlighted the need to self-advocacy (they were expected to identify advancing vision loss and seek the appropriate support as and when it was necessary. Most did not feel they were adequately informed to identify any ‘big changes’ in vision that warranted a return to the hospital.

<table>
<tr><th>Bibliographic reference</th><th>Droege K M, Muether P S, Hermann M M, Caramoy A, Viebahn U, Kirchhof B, and Fauser S. 2013. "Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life". Graefes Archive for Clinical & Experimental Ophthalmology 251:1281-4.</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Cologne University hospital, German</td></tr>
<tr><td>Study type</td><td>A survey of patients' adherence to ranibizumab treatment</td></tr>
<tr><td>Aim of the study</td><td>To identify factors and problems influencing treatment adherence in patients undergoing anti-VEGF therapy for neovascular age-related macular degeneration (AMD) under real-life conditions.</td></tr>
<tr><td>Study dates</td><td>Published 2013</td></tr>
<tr><td>Source of funding</td><td>Not specified</td></tr>
<tr><td>Sample size</td><td>95</td></tr>
<tr><td>Inclusion criteria</td><td>patients treated with rainbizumab for exudative age-related macular degeneration with full cover of health insurance for ranibizumab treatment</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Participants characteristics</td><td>Baseline characteristics: 42 men and 53 women were included in the study.
<table>
<tr><th></th><th>Adherent</th><th>Dropout (loss of motivation)</th><th>Dropout (other reasons)</th></tr>
<tr><td>Number of patients (%)</td><td>77 (81.1)</td><td>7 (7.3)</td><td>11 (11.6)</td></tr>
<tr><td>Number of male</td><td>37</td><td>1</td><td>4</td></tr>
<tr><td>Mean age (SD), years</td><td>77.8 (7.4)</td><td>83.7 (10.0)</td><td>82.6 (8.6)</td></tr>
<tr><td>Follow-up time (days) (SD)</td><td>753 (128)</td><td>263 (83)</td><td>392 (287)</td></tr>
<tr><td>Number of ranibizumab injections (SD)</td><td>11.4 (5.1)</td><td>5.0 (1.4)</td><td>7.0 (4.6)</td></tr>
<tr><td>Number of visits (SD)</td><td>21.4 (4.1)</td><td>7.6 (2.1)</td><td>11.1 (7.3)</td></tr>
<tr><td>BCVA change at last visit, letter (SD)</td><td>-5.1 (17.6)</td><td>-12.1 (21.2)</td><td>-6.6 (19.0)</td></tr>
</table></td></tr>
<tr><td>Methods</td><td>Patients treated with rainbizumab for exudative age-related macular degeneration were followed up and asked to respond to a 16-item questionnaire regarding anxiety, benefit and administrative factors of treatment. The questionnaire was pretested in 5 AMD patients for internal validation. The questionnaire was administrated by 2 study nurses.</td></tr>
<tr><td>Results: barriers to adherence appointment attendance and uptake of treatment</td><td>18 patients stopped visits for the following reasons
<table>
<tr><th>Reasons for discontinuation</th><th>Details</th><th>No. of patients</th></tr>
<tr><td>Loss motivation</td><td>Withdrew from further treatment due to subjective dissatisfaction</td><td>7</td></tr>
<tr><td>Other reasons</td><td>Serious general disease</td><td>3</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="2">Droege K M, Muether P S, Hermann M M, Caramoy A, Viebahn U, Kirchhof B, and Fauser S. 2013. "Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life". Graefes Archive for Clinical & Experimental Ophthalmology 251:1281-4.</td></tr>
<tr><td></td><td colspan="2"><table>
<tr><td></td><td>Chosen treatment option closer to home</td><td>5</td></tr>
<tr><td></td><td>No further anti-VEGF due to fibrosis</td><td>2</td></tr>
<tr><td></td><td>Death</td><td>2</td></tr>
</table></td></tr>
<tr><td>Results:
facilitators to adherence appointment attendance and uptake of treatment</td><td colspan="2">None given</td></tr>
<tr><td>Problems associated with treatment</td><td colspan="2">Most patients were anxious about examination results regarding disease activities (62.1%), whereas only 19.0% of patients were afraid of IVIs<table>
<tr><td>Anxiety and pain</td><td>% of participants reported</td></tr>
<tr><td>I was afraid of the first intravitreal injection</td><td>32.6% mostly true</td></tr>
<tr><td>I was afraid of subsequent intravitreal injection</td><td>63.2% definitely false</td></tr>
<tr><td>My fear of intravitreal injection decreased in the further course of treatment</td><td>41.1% definitely true</td></tr>
<tr><td>I was afraid of examination results regarding disease activity</td><td>34.7% mostly true</td></tr>
<tr><td>I experienced intravitreal injection as painful</td><td>48.4% definitely false</td></tr>
<tr><td>Benefit</td><td></td></tr>
<tr><td>I have benefit from treatment</td><td>53.7% definitely true</td></tr>
<tr><td>My visual acuity would probably be worse without treatment today</td><td>70.5% definitely true</td></tr>
<tr><td>My expectations regarding treatment have generally been met</td><td>43.2% mostly true</td></tr>
<tr><td>I would undergo treatment again if I had to choose again</td><td>93.7% mostly true</td></tr>
<tr><td>Insurance</td><td></td></tr>
<tr><td>Cost of treatment was reimbursed by health insurance</td><td>74.7% definitely true</td></tr>
<tr><td>Advance payment for treatment was a financial burden</td><td>52.6% definitely false</td></tr>
<tr><td>I have general problem with my health insurance regarding treatment approval and refunds</td><td>85.3% definitely false</td></tr>
<tr><td>Other factors</td><td></td></tr>
<tr><td>The frequency of monthly visit was arduous</td><td>64.2% definitely false</td></tr>
<tr><td>Examinations and treatment were impeded by my general health</td><td>69.5% definitely false</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Droege K M, Muether P S, Hermann M M, Caramoy A, Viebahn U, Kirchhof B, and Fauser S. 2013. "Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life". Graefes Archive for Clinical & Experimental Ophthalmology 251:1281-4.
	Travel to/from the hospital was generally a problem: 43.2% definitely false I required an accompanying person for travel to/from the clinic: 61.5% mostly true

Bibliographic reference	McCloud C, Khadka J, Gilhotra J S, and Pesudovs K. 2014. "Divergence in the lived experience of people with macular degeneration". Optometry & Vision Science 91:966-74.
Country/ies where the study was carried out	Australia
Study type	Interpretative phenomenological study
Aim of the study	To explore and understand the lived experiences of people diagnosed with aged-related macular degeneration including people whose treatment was successful and those whose treatment had failed to maintain vision.
Study dates:	July 2012-May 2013
Source of funding	National Health and Medical Research Council
Sample size	34
Inclusion criteria	Patients with a diagnosis of age-related macular degeneration.
Exclusion criteria	Not reported
Sample characteristics	Median age of participants was 81 years (range: 56-102). 56% were female. The majority of participants (n-28) had exudative macular degeneration and were undergoing (n=24) intravitreal injection of anti-VEGF treatment.
Methods	Participants were recruited into either a focus group (60-90 minutes) of 3 to 5 participants or to single in-depth interviews. A semi-structured interview guide was developed based on evidence from the literature and expert knowledge. Data collection ceased when conceptual saturation was achieved. Consistent with an editing analysis style of qualitative data analysis and to enable development of a sense of the whole data set, data analysis began when data collection was complete and all transcriptions were read and re-read. After this initial immersion within the data, line-by-line coding occurred with subsequent conceptual coding and theme development through an iterative movement from coding to theme using the NVivo.
Thematic analysis: barriers to adherence appointment attendance and uptake of treatment	Much of the anxiety participants felt could be attributed to the relative newness of the treatment and experience of participants where disease progressed. Participants worried about the cost of treatment relative to the improvement achieved and wondered whether they may be a criteria for withdrawal.

Bibliographic reference	McCloud C, Khadka J, Gilhotra J S, and Pesudovs K. 2014. "Divergence in the lived experience of people with macular degeneration". Optometry & Vision Science 91:966-74.
	The invasiveness of the treatment and often painful recovery were significant issue. “Even though I’ve getting injection for three years now you still get very apprehensive when you go there for you next injection. It’s not the actual fear, it’s just you’re apprehensive because you know what’s coming”. “I had the two injections and they were extremely painful… quite frankly I was a bit traumatised. I was in shock” “Two days with a lot of rubbish in your eye. Must be a shovel full of gravel in my eye I think for two days afterwards” The physical difficulties participants experienced with frequent and on-going treatment were often compounded by psychological issues of anxiety and fear. When treatment failed or was not an option as occurred with participants diagnosed with exudative AMD that progressed to geographic AMD, the stopping of treatment or inability to treat was felt as a major loss. “I kept going back and having these injection and now they’ve given up on them…I think I’d rather die [than go blind]”. “With the dry[AMD], they can’t do nothing for me, and that is what I’m upset that with wet they give you help, with dry, nothing”.
Thematic analysis: facilitators to adherence appointment attendance and uptake of treatment	Optimism: a level of optimism that was felt when treatment was effective and can be further seen in the participants who responded well to treatment, and participants whose vision had not improved with treatment but had remained stable also expressed a degree of optimism. “It isn’t treating it, it’s slowing it down, it’s slowing the deterioration down…” Despite the visual and psychological difficulties, participants expressed a clear willingness to endure the injections if they continued to gain or maintain their vision. “If I didn’t have treatment I’d go blind, clinically blind, therefore the only thing to do was to have the injections”.

Bibliographic reference	Mitchell J, Bradley P, Anderson S J, Ffytche T, and Bradley C. 2002. "Perceived quality of health care in macular disease: a survey of members of the Macular Disease Society". British Journal of Ophthalmology 86:777-81.
Country/ies where the study was carried out:	UK NHS
Study type	a survey of experience of people with macular disease
Aim of the study	To investigate the experiences of people with macular disease within the British healthcare system
Study dates	1999
Source of funding	Macular disease society and Alcon laboratories
Sample size	1421 completed questionnaires
Inclusion criteria	18 year old or over, diagnosed with macular disease for at least 6 months, and resident in the UK
Exclusion criteria	Not reported

<table>
<tr><th>Bibliographic reference</th><th>Mitchell J, Bradley P, Anderson S J, Ffytche T, and Bradley C. 2002. "Perceived quality of health care in macular disease: a survey of members of the Macular Disease Society". British Journal of Ophthalmology 86:777-81.</th></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>A questionnaire was randomly sent to 2,000 Macular Disease Society members.</td></tr>
<tr><td>Results: barriers to adherence appointment attendance and uptake of treatment</td><td>Experience at the diagnostic consultation
Reasons for dissatisfaction with diagnostic consultation as below:
<table>
<tr><th>Reasons for dissatisfaction</th><th>Number of patients (%)</th></tr>
<tr><td>Specialist’s attitude
(dismissive, patronising, brusque, unfeeling, uninterested in patient/condition, use of jargon, talking to colleagues while ignoring patients, making patients fee of no consequence because of their age)</td><td>263 (43.5)</td></tr>
<tr><td>Lack of information or advice (about condition, prognosis, adjustment, low vision aids, self-help groups, counselling), lack of written information</td><td>262 (43.4)</td></tr>
<tr><td>Told nothing could be done</td><td>80 (13.1)</td></tr>
<tr><td>Problems with management (delay in getting appointment, paperwork, correspondence lost, seeing different doctors)</td><td>71 (11.7)</td></tr>
<tr><td>Shocked by what they were told</td><td>47 (7.1)</td></tr>
<tr><td>Lack of time with consultant</td><td>41 (6.9)</td></tr>
<tr><td>Discharged after consultation</td><td>34 (5.6)</td></tr>
<tr><td>Condition not named</td><td>32 (5.4)</td></tr>
<tr><td>No opportunity for questions</td><td>21 (3.5)</td></tr>
<tr><td>Wanted second opinion</td><td>11 (1.8)</td></tr>
</table>
Experience with general practitioners (GPs) around the time of diagnosis*
<table>
<tr><th></th><th>Participants’ response</th></tr>
<tr><td>To what extent was your general practitioner will informed about macular disease</td><td>185 reported that their GP was very well informed;
379 reported their GP was not at all well informed;</td></tr>
<tr><td>To what extent has your GP been helpful and supportive</td><td>About equal number reported their GP was either very supportive (383) or not at all supportive (379)</td></tr>
</table>
*a high proportion of non-responders to these 2 questions.</td></tr>
</table>

Bibliographic reference	Mitchell J, Bradley P, Anderson S J, Ffytche T, and Bradley C. 2002. "Perceived quality of health care in macular disease: a survey of members of the Macular Disease Society". British Journal of Ophthalmology 86:777-81.
Results: facilitators to adherence appointment attendance and uptake of treatment	None given

Bibliographic reference	Nunes R P, Nobrega M J, De Novelli , F J, Coral S A, Berti T B, Missen M M, and Correa M C. 2010. Causes of interruption of bevacizumab therapy in age-related macular degeneration. Arquivos Brasileiros de Oftalmologia 73:146-9.
Country/ies where the study was carried out:	Brazi
Study type	Retrospective case series
Aim of the study	To evaluate the rate and the causes of interruption of bevacizumab intravitreal therapy in patients with exudative age-related macular degeneration (AMD).
Study dates	Published 2010
Source of funding	Not specified
Sample size	19 answered to telephone questionnaire
Inclusion criteria	Patients with exudative age-related macular degeneration who were treated with one or more bevacizumab intravitreal injection.
Exclusion criteria	Not reported
Baseline characteristics	Not specified amongst participants
Methods	The causes of cessation of therapy were obtained through telephone interview. The criteria of interruption of treatment was the absence of patient follow-up after a minimum of 3 months from the last ophthalmic examination.
Results: barriers to adherence appointment attendance and uptake of treatment	82 patients were treated, and 19 answered to telephone questionnaire

Reasons for discontinuity	Number of patients reported (%)
Unexpected poor visual results	8 (42.1)
Lack of information about follow-up visits	5 (26.3)
Comorbidities	3 (15.8)
Difficulties in booking new appointment	2 (10.5)

Bibliographic reference	**Nunes R P, Nobrega M J, De Novelli , F J, Coral S A, Berti T B, Missen M M, and Correa M C. 2010. Causes of interruption of bevacizumab therapy in age-related macular degeneration. Arquivos Brasileiros de Oftalmologia 73:146-9.**
	Travelling problem: 1 (5.3)
Results: facilitators to adherence appointment attendance and uptake of treatment	None given

Bibliographic reference	**Thompson A C, Thompson M O, Young D L, Lin R C, Sanislo S R, Moshfeghi D M, and Singh K. 2015. "Barriers to Follow-Up and Strategies to Improve Adherence to Appointments for Care of Chronic Eye Diseases". Investigative Ophthalmology & Visual Science 56:4324-31.**
Country/ies where the study was carried out	USA
Study type	A cross sectional of survey of individuals attending follow-up ophthalmology appointments
Aim of the study	To understand factors associated with poor attendance of follow-up appointments for care of glaucoma (GL), age-related macular degeneration (AMD), and diabetic retinopathy (DR) in a tertiary referral centre, and to identify strategies to improve adherence.
Study dates	2009
Source of funding	The Stanford Medical Scholars Programme
Sample size	240 participants (84 were with age-related macular degeneration)
Inclusion criteria	Individuals aged 18 years or over and a medical record that documented treatment for a diagnosis of GL, AMD or DR at least 12 months.
Exclusion criteria	Individuals were excluded if they were a new referral or had more than one of the aforementioned diseases
Participants characteristics	

	Follow-up, n(%)		Un adjusted odd ratios (95%CI) for poor follow-up
	Poor 102 (42.5)	Good 138 (57.5)	
AMD	29 (28.4)	57 (41.3)	1.17 (0.50, 2.87)
DR	10 (9.8)	23 (16.7)	1 (reference)
Duration of eye disease, median year (range)	6 (1-50)	6 (1-55)	
Mean age (SD)	70.5 (14.3)	72.2 (14.7)	

Bibliographic reference	Thompson A C, Thompson M O, Young D L, Lin R C, Sanislo S R, Moshfeghi D M, and Singh K. 2015. "Barriers to Follow-Up and Strategies to Improve Adherence to Appointments for Care of Chronic Eye Diseases". Investigative Ophthalmology & Visual Science 56:4324-31.

Male	47 (46.1)	63 (45.7)	
Education level			
High school or less	24 (23.3)	32 (23.2)	1.02 (0.55, 1.86)
College/graduate degree	78 (76.5)	106 (76.8)	1 (reference)
Employment			
Working	18 (17.65)	33 (23.9)	0.68 (0.35, 1.28)
Not working	84 (82.25)	105(76.1)	1 (reference)

Methods

A cross sectional study of 240 individual's follow-up ophthalmology appointment. Upon arrival for their eye appointment, eligible subjects were invited for a private oral interview by one or two trained study investigator.

Participants were categorised as cases of poor follow-up if at any time in the 12 months proceeding their oral interview, they had failed to reschedule a missed or patient-cancelled appointment within 1 month of the desired follow-up.

Data were collected form patients interviews and chart review using a validated questionnaire on barriers to follow-up, strategies to improve follow-up, disease knowledge, and perceptions that may impact follow-up patterns.

Results: barriers to adherence appointment attendance and uptake of treatment

	Follow-up, n (%)		Unadjusted Odd ratios for poor follow-up(95%CI)
Self-reported barriers to follow-up	Poor 102 (42.5)	Good 138 (57.5)	
Long wait time			
Yes	53 (52.0)	51 (37.0)	1.85 (1.1, 3.1)
No	49 (48.0)	87 (63.0)	1 (reference)
Difficulty rescheduling			
Yes	38 (37.3)	37 (26.8)	1.62 (0.93, 2.81)
No	64 (62.8)	101 (73.2)	1 (reference)
Financial barriers			
Yes	26 (25.5)	21 (15.2)	1.91 (1.00, 3.66)
No	76 (74.5)	117 (84.8)	1 (reference)
Work responsibilities			
Yes	12 (11.8)	9 (6.5)	1.91 (0.78, 4.9)

Bibliographic reference	**Thompson A C, Thompson M O, Young D L, Lin R C, Sanislo S R, Moshfeghi D M, and Singh K. 2015. "Barriers to Follow-Up and Strategies to Improve Adherence to Appointments for Care of Chronic Eye Diseases". Investigative Ophthalmology & Visual Science 56:4324-31.**

No	90 (88.2)	129 (93.4)	1 (reference)
Other medical/physical illness			
Yes	24 (23.5)	25 (19.6)	1.39 (0.74, 2.6)
No	78 (76.5)	113 (81.9)	1 (reference)
Lack of an escort			
Yes	22 (21.6)	27 (19.6)	1.13 (0.60, 2.12)
No	80 (78.4)	111 (80.4)	1 (reference)

Results:
facilitators to adherence appointment attendance and uptake of treatment

Patient reported potential strategies to improve attendance of follow-up appointments

	N (%), 240 (100)
Pre-appointment reminder (by phone, text, email)	196 (81.7)
Parking vouchers	115 (47.9)
Transportation service to and from the clinic	107 (44.6)
Mobile eye care van	77 (32.1)
Networking with other patients with the same eye disease	99 (41.3)
More education on one's eye disease	98 (40.8)
More education on the importance of follow-up	72 (30.0)

Bibliographic reference	**Varano Monica, Eter Nicole, Winyard Steve, Wittrup-Jensen Kim U, Navarro Rafael, and Heraghty Julie. 2015. Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey. Clinical Ophthalmology 9:2243-50.**
Country/ies where the study was carried out	9 countries (Australia, Brazil, Canada, France, Germany, Italy, Japan, Spain, and UK)
Study type	Cross-sectional survey
Aim of the study	To evaluate the current management of wet age-related macular degeneration (wAMD) and to identify barriers to treatment from a patient/caregiver perspective.
Study dates	June 2012 and September 2012

Bibliographic reference	**Varano Monica, Eter Nicole, Winyard Steve, Wittrup-Jensen Kim U, Navarro Rafael, and Heraghty Julie. 2015. Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey. Clinical Ophthalmology 9:2243-50.**
Source of funding	Bayer HealthCare Pharmaceuticals
Sample size	910 patients with AMD completed survey
Inclusion criteria	patients with wet age-related macular degeneration
Exclusion criteria	Not reported
Participant characteristics	Not specified
Methods	The survey was performed using a questionnaire. The self-administered 15-minute questionnaire was conducted online. The survey link was soft-launched, allowing a small number of responders to complete the questionnaire so that the data could be checked to ensure accurate capture. The questionnaire was divided into patient and caregiver section. Patients and caregivers were asked to provide yes/no/not sure answers based on a number of variable option or to rate question using impact scale, dependency scale or convenience scale.
Results: barriers to adherence appointment attendance and uptake of treatment	Most patients (65.4%, n=585) and caregivers (77.0%, n=685) reported a number of obstacles in managing wAMD, including: Treatment itself: having injection, frequency of injection, possible injection related side effects Treatment cost Finding the right treatment option: anti-VEGF (type, laser and related to information on choosing the best option Missing appointment: caregivers was unable to take them to the appointment; fear about receiving injection; patient illness. Other obstacles included: tired of treatment regimen; lack of understanding about disease; given inadequate disease information; getting access to/affording technology; other priorities. Obstacles to difficulty attending every appointment were reported by patients: Caregivers unable to take me to appointment Unwell or in hospital Scared about receiving an injection Sometimes forget the appointment Cannot afford to attend every appointment Appointments are too frequent/inconvenient
Results: facilitators to adherence appointment attendance and uptake of treatment	None given

<table>
<tr><th>Bibliographic reference</th><th>Vaze A, Fraser-Bell S, and Gillies M. 2014. Reasons for discontinuation of intravitreal vascular endothelial growth factor inhibitors in neovascular age-related macular degeneration. Retina 34:1774-1778.</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Sydney, Australia</td></tr>
<tr><td>Study type</td><td>Retrospective case series</td></tr>
<tr><td>Aim of the study</td><td>To identify the reasons for discontinuing intravitreal anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration.</td></tr>
<tr><td>Study dates</td><td>Published 2014</td></tr>
<tr><td>Source of funding</td><td>RANZCO eye foundation, Sydney and the National Health and Medical Research Council</td></tr>
<tr><td>Sample size</td><td>105 had discontinued treatment</td></tr>
<tr><td>Inclusion criteria</td><td>Patients with neovascular age-related macular degeneration began anti-VEGF treatment over the 6 years from March 2006 to June 2012</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Participants characteristics:</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>The Fight Retinal Blindness project data tracking system was used to identify accurately all patients who discontinued treatment.
The reasons for discontinuation of the intravitreal anti-VEGF treatment for neovascular AMD during the study period were ascertained.
The Fight Retinal Blindness data fields for treatment discontinuation include the following possibilities:
Treatment being successful
Further treatment being futile
Patient goes to another doctor
Patient declines
Medically contraindicated
Deceased</td></tr>
<tr><td>Results: barriers to adherence appointment attendance and uptake of treatment</td><td>A total of 105 patients discontinued treatment
<table>
<tr><th>Reasons for discontinuity</th><th>Number of patients reported</th></tr>
<tr><td>Treatment stopped by the doctor because of inactive lesion</td><td>9</td></tr>
<tr><td>Treatment stopped by the doctor as further treatment futile</td><td>27</td></tr>
<tr><td>Treatment declined by the patient:</td><td>26</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Vaze A, Fraser-Bell S, and Gillies M. 2014. Reasons for discontinuation of intravitreal vascular endothelial growth factor inhibitors in neovascular age-related macular degeneration. Retina 34:1774-1778.	
		Pain/discomfort (3) Too frequent visits (2) Difficulty in attending the practice (2) Treatment not being perceived to be beneficial (6) Treatment perceived to be too expensive (2) Other medical condition that were more severe (11)
	Other reasons	40 Patients were referred to another doctor locally or on-going management (27) Death (11) Complication about treatment (2)
	Missing (patients lost to follow-up)	3
Results: facilitators to adherence appointment attendance and uptake of treatment	None given	

E.8.2 Informational needs of people with suspected or confirmed AMD and their family members/carers

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

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

Bibliographic reference	**Burton AE, Shaw RL, and Gibson JM. 2013. "'I'd like to know what causes it, you know, anything I've done?' Are we meeting the information and support needs of patients with macular degeneration? A qualitative study". BMJ Open 3:e003306.**
Country/ies where the study was carried out	UK NHS
Study type	Interpretative phenomenological study
Aim of the study	To examine patients' experience of information and support for age-related macular degeneration
Study date	2010
Source of funding	The Aston Research centre for healthy ageing, Aston University
Sample size	13
Inclusion criteria	Patients with age-related macular degeneration who could take part in in-depth interviews.
Exclusion criteria	Not specified
Sample characteristics	Participant ages ranged from 75 to 89 with a mean age of 81.5. Best eye visual acuity ranged from 6/6 to 6/30 while worse eye visual acuity ranged from 6/9.5 to hand movement only. Seven of the participants were eligible for treatment and six were unable to be treated (two due to having dry AMD and three had wet AMD which was too advanced for treatment).
Methods	The interviews were carried out in the patients' homes. In-depth semi-structured interviews were used to explore issues which were important to participants in their own words. The interview schedule included questions focusing on experience of diagnosis and other eye care consultations, the impact of AMD and related vision impairment on daily activities, relationships with and/or support needs from family and friends, and thoughts about the future. Perceptions and experience can change over time and interviews were therefore carried out with each participant on up to three occasions over 18 months to explore perceptions of on-going encounters with healthcare professionals during this time. A thematic analysis was used to examine the data.
Thematic analysis	Four Themes were identified: Sources of information; Equipment and information from support services; Self-advocacy; Future expectations. Theme 1: Sources of information These included books, leaflets, flyers; appointment letters; public events, meetings; verbal information in the clinic or from opticians; information from other people.

Bibliographic reference	Burton AE, Shaw RL, and Gibson JM. 2013. "'I'd like to know what causes it, you know, anything I've done?' Are we meeting the information and support needs of patients with macular degeneration? A qualitative study". BMJ Open 3:e003306.
	These sources are not always accurate, which can result in people waiting when they should seek help or having unrealistic expectations of recovery based on anecdotal evidence from friends. "[I see] a black cloud. My neighbour's husband had it and they said it was nothing to worry about at the hospital anyway, you know. But it doesn't last and I've heard a lot of people who say they've had it but it but it went off after years." "Well, [name] had something done to his eye at the hospital, didn't he? Now he can see better…… he had an operation and he can see perfect" Inaccurate information can cause unnecessary distress and fear about going completely blind. "It is really frightening, because I know somebody at one of my groups [….] who says she's got dry macular but….. she's virtually blind" Verbal information provided at hospital was the most common source, but was associated with problems with understanding and retention, which may not be helped by hearing problems or difficulty in understanding the doctor's accent. Written sources could be problematic -patients were confused and overwhelmed by multiple appointment letters/written documents and could/did not always read them. "I have got some leaflets, I haven't read them in ages" 'When I read all [these letters] I thought, err [date] [date] [date]….have they slipped up? Which one am I supposed to have?" Group meetings and speeches could be a positive source of information regarding things like attendance allowance that participants may otherwise be unaware of. Conversations with the AMD patients revealed a lack of understanding of the causes of AMD, reasons for processes associated with treatment and unrealistic expectations for the future. The way information was delivered (or not) at the opticians had a big effect on patient perception of their eye problems and emotions surrounding their appointments. Theme 2: Equipment and information from support services Shortages of information were felt prior to diagnosis, following diagnosis and during the course of the disease. The lack of prior awareness of AMD was raised as a factor that made diagnosis more stressful for 9 of the 13 patients and prevented them from having a context to refer to regarding their diagnosis. "one morning that the lampposts were all curly and that really frightened me, but I wasn't sure what it was" "I didn't realise it was so common" Following diagnosis: there was a lack of information and understanding about the causes of AMD, the importance of the use of vitamins and foods to promote eye health, the impact of smoking and how to register as partially sighted. "we don't really know what caused it"

Bibliographic reference	Burton AE, Shaw RL, and Gibson JM. 2013. "'I'd like to know what causes it, you know, anything I've done?' Are we meeting the information and support needs of patients with macular degeneration? A qualitative study". BMJ Open 3:e003306.
	"I'd like to know what causes it, you know, anything I've done" 'I was advised to take those [I-caps] and that's supposed to help it not get any worse" The lack of understanding of the purpose of medical procedures was also raised with people spending many hours at the hospital without understanding what the procedures and tests were trying to achieve. Letters often failed to clearly explain the purpose of an appointment. 'I'm going, as I say I'm going up there next month. I don't know what the procedure is going to be, but they don't tell you do they? They don't tell you." "I have to go next month, I'm supposed to have the other eye done. Well, this is what I could assume, it might be about today I don't know." People were reported to have given up favourite pastimes in order to preserve their remaining vision, suggesting a fundamental communication problem regarding the nature of the disease that is not helped by some medical practitioners referring to AMD as "wear and tear and your age". "I keep sort of thinking oh I will [do some painting] and I think no, I sort of put a limit on how much I use my eyes a lot, does this make sense to you?" People were either unaware of support groups or worried that these groups were for people who were overwhelmed by having AMD and thus would be depressing to attend. "Interviewer: Is there any support you'd like to receive that you are not receiving and that would help you? Rick: I don't know what that would be, support there is." During the disease course: different information was needed at different points in the disease course and needed to be tailored to the person's disease stage. Early AMD patients needed information about monitoring their condition and spotting changes; wet AMD patients needed to know about available treatments and outcomes; patients with advanced disease needed to hear about support services and equipment. "He said that you could be registered as part-sighted. Well what does that mean? What does it do? Does it open the door for different things?" Theme 3: Self-advocacy Patients with early or advanced dry AMD or untreatable wet AMD who were not being monitored regularly by medical staff had been told to seek help at the Emergency department (ED) if any further vision problems occurred, but they were mainly uncertain of what sort of changes to look out for and what constituted a serious enough change to necessitate a visit to the ED. In addition, they associated the ED with accidents and were reluctant to attend it for a change in vision, highlighting the need to explain the expanded role of the modern ED to them. Patients felt unable to identify advancing vison loss and unqualified to determine when a change was severe enough to merit them seeking help. The language used by the clinician to describe vision changes was not accessible to the patients and did not fit with their understanding of the condition.

Bibliographic reference	**Burton AE, Shaw RL, and Gibson JM. 2013. "'I'd like to know what causes it, you know, anything I've done?' Are we meeting the information and support needs of patients with macular degeneration? A qualitative study". BMJ Open 3:e003306.**
	"I'm not sure what I'm looking for." "I mean it's fine isn't it, for someone to say to you, well you would notice a change because…. But you can't be sure…I'm not sure what I'm looking for! I mean obviously if I suddenly couldn't see or some dramatic change, but would it be as dramatic as that?" Some patients worried about seeking help unnecessarily and wasting scarce NHS resources. Theme 4: Future expectations- fear and uncertainty, and hope. The approach to the future taken by a patient was dependent on the type of AMD they had and the level of uncertainty surrounding their future. This fear could be reduced by the availability of accessible, accurate information.
Author's comments	Patients with early and intermediate AMD may benefit from advice regarding smoking cessation and the use of vitamins/nutritional advice, but if patients are unaware of the purpose of these recommendations they may be less likely to adhere to them. Changes due to AMD may be attributed to ageing and wear and tear leading to confusion. Patients were not adequately informed about the course of disease progression and would have benefited from support and advice from health care professionals with a better understanding of what it is like to live with AMD. Patients often lack the ability to self-advocate and the lack of continuity between the NHS and support services complicates matters. The authors recommend a more structured pathway to ensure patient access to relevant services (including counselling and support services) at the correct times. The way information was provided was also problematic as patients often forgot the verbal information delivered at diagnosis and written documents could be hard for them to access. Conclusion: AMD patients have a range of information needs that change over the course of the condition.
Quality Assessment	Was there a clear statement of the aims of the research? Yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Was the recruitment strategy appropriate to the aims of the research? Yes Was the data collected in a way that addressed the research issue? Yes Has the relationship between researcher and participants been adequately considered? Unclear Have ethical issues been taken into consideration? Yes Was the data analysis sufficiently rigorous? Unclear - Sufficient primary data was provided to support analysis so not downgraded Is there a clear statement of findings? Yes How valuable is the research? High value

Bibliographic reference	Burton AE, Shaw RL, and Gibson JM. 2013. "'I'd like to know what causes it, you know, anything I've done?' Are we meeting the information and support needs of patients with macular degeneration? A qualitative study". BMJ Open 3:e003306.
	Overall quality: High

Bibliographic reference	Crossland MD, Helman CG, Feely MP, Gould ES, Rubin GS. 2007. Why did I lose vision? A qualitative study of patient perceptions of the causes of age-related macular degeneration. Visual Impairment Research, 9: 39-43.
Country/ies where the study was carried out	UK
Study type	Interpretative phenomenological study
Aim of the study	To determine what reasons people with AMD give for their vision loss
Study dates	Not stated
Source of funding	Not stated
Sample size	15
Inclusion criteria	Patients diagnosed with bilateral age-related macular degeneration with a visual acuity of 6/12 or worse in their better eye. Patients that had attended the Moorfields Medical Retina clinic once and were going for their first ever low-vision clinic appointment later that day. Patients were selected based on having equal exposure to ophthalmological interventions within that episode of vision loss.
Exclusion criteria	other eye conditions in addition to AMD
Sample characteristics	Participant ages ranged from 73 to 91 years and just under half were male. Patients lived in London or Essex. Visual acuity ranged from 6/12 to 6/120. AMD subtype was not described. Patients were at an early stage of contact with clinics
Methods	A semi-structured interview was carried out in a non-clinical room by a research psychologist wearing informal clothing. This research was carried out as part of a larger interview investigating patients' expectations of the low vision clinic. All participants were asked "Can you describe your eyesight at the moment?" "Why do you think this has happened?" Follow-up questions were along the lines of "Can you tell me more about this?" "What exactly do you mean by that?" The interviews were recorded, transcribed and independently assessed by two senior optometrists to identify key themes. Any discrepancies were resolved by discussion.
Thematic analysis	Themes for reason of vision loss identified by participants: Old age– identified by the majority of study participants " ….. doesn't matter if you go to your dentist, doctor, optician- it's your age" [Male, 85 years] Reading/close work/ "using eyes" – the idea that you can "use your vision up" came up several times.

Bibliographic reference	Crossland MD, Helman CG, Feely MP, Gould ES, Rubin GS. 2007. Why did I lose vision? A qualitative study of patient perceptions of the causes of age-related macular degeneration. Visual Impairment Research, 9: 39-43.
	Smoking- mentioned as a potential cause by 2 participants, but not necessarily believed. "They say that smoking does it- I've been smoking now since 1941, 42. .....I've got arthritis in both knees, they say that's due to smoking, high blood pressure, that's due to smoking…. [I] Just think they're all wrong, I don't know what to say. [Male, 76 years] Medical/surgical intervention Chance- "apparently these things just happen" [Male, 76 years] No idea/refused to speculate Trauma to eye Stress Diet
Authors' comments	The authors were surprised that relatively few people thought of old age as the cause of AMD and that no-one raised genetic susceptibility as a potential cause. Of concern that some participants attributed vision loss to other medical treatments (e.g. cataract surgery) and misunderstood the use of photodynamic therapy and laser photocoagulation, expecting an improvement in symptoms rather than a reduced risk of disease progression. Despite counselling, patients may continue to hold incorrect beliefs about the causes of their vision loss. Of particular concern was the idea of "using their vision up" as this may have implications for peoples' quality of life if they avoid certain activities as a result. It was thought to be important to tell people more than once that they would not make things worse by using their eyes. To note- patients were at an early stage of contact with medical services for their AMD. Conclusion: patients attribute their vison loss to many, often incorrect, causes. Patients need access to more accurate education regarding AMD.
Quality Assessment	Was there a clear statement of the aims of the research? Yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Was the recruitment strategy appropriate to the aims of the research? Yes Was the data collected in a way that addressed the research issue? Yes Has the relationship between researcher and participants been adequately considered? Unclear Have ethical issues been taken into consideration? Yes Was the data analysis sufficiently rigorous? Unclear Is there a clear statement of findings? Yes

Bibliographic reference	Crossland MD, Helman CG, Feely MP, Gould ES, Rubin GS. 2007. Why did I lose vision? A qualitative study of patient perceptions of the causes of age-related macular degeneration. Visual Impairment Research, 9: 39-43.
	How valuable is the research? High value Overall quality: Moderate

Bibliographic reference	Dahlin Ivanoff S, Sjöstrand J, Kleep KI, Axelsson L, Lundgren Lindqvist B. 1996. Planning a health education programme for the elderly visually impaired person- a focus group study. Disability and rehabilitation, 18: 515-522.
Country/ies where the study was carried out	Sweden.
Study type	Interpretative phenomenological study
Aim of the study	To determine how people with a diagnosis of AMD perceived and described their disease and how it affected their activities of daily living in order to design a health education programme.
Study dates	Not stated
Source of funding	Not stated
Sample size	25
Inclusion criteria	Patients with a diagnosis of AMD referred by an ophthalmologist and attending the low-vison clinic for the first time during the study period. ≥ 65 years with AMD as the primary diagnosis and a visual acuity of the better eye with correction of no less than 0.1. Still living in their own homes and able to take part in a focus group discussion.
Exclusion criteria	Not stated
Sample characteristics	10 men and 15 women of 80.5 years on average. 12 people lived with a spouse. Visual acuity ranged from 0.1 to 0.6 (median 0.3) for the better eye.
Methods	A focus group methodology was employed whereby a group of participants meet to discuss different aspects of a topic. A moderator was used to facilitate the discussion and encourage everyone to contribute. The number of groups depends on the amount of information available and data collection continues until nothing new emerges, usually after 3-4 groups. This study consisted of 5 focus groups of 3-6 participants. The groups had the same moderator and assistant moderator. Each session began by clarifying the purpose of the focus group and then asking patients in turn to describe how their problems started. The moderator was not allowed to answer questions from the participants during the discussion and could only ask for statements to be explained further. Each group met twice, a week apart, and all sessions were recorded and transcribed verbatim. Themes were identified within each of the 4 research questions. These included one regarding the information required by people with AMD and how they wanted to receive it.

Bibliographic reference	**Dahlin Ivanoff S, Sjöstrand J, Kleep KI, Axelsson L, Lundgren Lindqvist B. 1996. Planning a health education programme for the elderly visually impaired person- a focus group study. Disability and rehabilitation, 18: 515-522.**
Thematic analysis	Limited to data pertaining to patients' informational needs. Perceptions of the disease: Uncertainty regarding the names of other eye diseases and whether they are alternative names for AMD. AMD as part of the normal ageing process and that, as a result, nothing can be done. Problems related to the lack of public awareness of the disease. There is the perception that no research is being carried out and that the disease cannot be as common as they have been told as they were unaware of it before diagnosis. They believe that there is no fund-raising to help prevent the disease. Potential causes discussed include: work that could cause eye strain (for example working with computers); other diseases and medication; chemicals; violent sports; reading and watching TV a lot; looking at eclipses. Questions concerning treatment alternatives covered laser surgery; vitamin supplements; transplantation of the eye, cornea or lens. A lack of understanding exists as to why spectacles seldom improve the vison of AMD sufferers. Information required: More information is desired about the disease and its consequences, with an emphasis on disease prognosis and the expected speed of decline in their vision. They discussed a wish to have all available information to allow them to prepare for the future and to have straight answers about the disease. Patients discussed a need for more time to be allocated to giving them information and the problems of being intimidated/ feeling ignorant/ feeling like time wasters at the doctors that meant that it was hard for them to ask questions and fully process the information provided. Patients were worried that they might go blind.
Author's comments	Conclusion: That these patients need a health education programme based on their own perceptions.
Quality Assessment	Was there a clear statement of the aims of the research? Yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Was the recruitment strategy appropriate to the aims of the research? Yes Was the data collected in a way that addressed the research issue? Yes Has the relationship between researcher and participants been adequately considered? Unclear Have ethical issues been taken into consideration? Unclear Was the data analysis sufficiently rigorous? Yes

Bibliographic reference	**Dahlin Ivanoff S, Sjöstrand J, Kleep KI, Axelsson L, Lundgren Lindqvist B. 1996. Planning a health education programme for the elderly visually impaired person- a focus group study. Disability and rehabilitation, 18: 515-522.**
	Is there a clear statement of findings? Yes How valuable is the research? High value Overall quality: Moderate

Bibliographic reference	**McCloud C, Lake L. 2015. Understanding the patient's lived experience of neovascular age-related macular degeneration: a qualitative study.. Eye, 29: 1561-1569.**
Country/ies where the study was carried out	Australia
Study type	Interpretative phenomenological study
Aim of the study	To understand the experiences of neovascular AMD patients, including ongoing treatment with anti-vascular endothelial growth factor (VEGF) with the intention of informing clinical practice.
Study dates	Not stated
Source of funding	Flinders University Faculty start up grant 2013-14
Sample size	25
Inclusion criteria	Patients with a diagnosis of neovascular AMD and receiving treatment with anti-VEGF in at least one eye on a regular basis. Patients did not make co-payments for their treatment and were identified from the clinical records of a South Australian Tertiary Public Hospital.
Exclusion criteria	Not stated
Sample characteristics	12 male participants; ages ranging from 67-90 years. Visual acuity was varied from 6/6 to 6/120 and count fingers. Treatment with anti-VEGF ranged from 9 months to >10 years.
Methods	Data was collected using the recording of individual participant experiences using in-depth, unstructured interviews. Patients were interviewed individually. Interviews started with the statement "tell me of your experience of AMD and the treatment you are receiving" and ended when the participant had nothing else to say. Data was recorded and sorted into themes, Data was also collected from medical records and a focus group session with nursing staff carrying out the anti-VEGF injections.
Thematic analysis	The research identified two major themes: 'A life negotiated by neovascular AMD' and 'uncertainty'. The information presented in this summary relates only to AMD patient or carer/family member informational needs.

Bibliographic reference	McCloud C, Lake L. 2015. Understanding the patient's lived experience of neovascular age-related macular degeneration: a qualitative study.. Eye, 29: 1561-1569.
	Theme 1: A life negotiated by neovascular AMD Following diagnosis and information about treatment options patients expressed relief that the condition was treatable. Patient familiarity with the process of injections and treatment in general helped with anxiety, but anxiety remained and was increased when treatment was given by an unfamiliar doctor. "I tootle along, and I know exactly what's going to happen and it doesn't bother me at all." "I feel a bit uptight because someone is going to stick a needle in my eye and you don't get the same doctor each time." Small unexpected or larger planned changes in the procedure or staff involved were linked to recovery difficulties, but if the reasons for the changes were communicated well, once they were used to the changes, participants felt that the new methods improved the experience. 'there's been some improvements here, that they've made' Once patients were aware of the visual disturbances and discomfort following treatment they developed coping strategies while they waited for vison to return. "If I go there, I know I'm going to get an anaesthetic in the eye, and I'm going to get the injection, and…… and I'm going to be unable to see clearly for a number of hours. I can come back home, I can put ….just relax and when it comes back, then I'm back to normal. " Patients did not usually seek help or advice when unfamiliar symptoms occurred after injection. Patients acceptance of invasive treatment was associated with an underlying fear of blindness "I'd just want to lay down and die if that happened to me." Theme 2: Uncertainty Many patients felt that vison problems were a part of the aging process. "And I thought it was age, everybody's eyesight deteriorates with age.." Patients lived with a sense of uncertainty and fear for their future linked to the continued effectiveness of the anti-VEGF treatment. They knew that anti-VEGF was a way of managing AMD, not a cure. Patient experiences were more positive if they received reassurance, support and caring communication from medical staff.
Author's comments	Conclusion: Anxieties and uncertainties about the future emerged, coupled with thankfulness for treatment, along with the importance of familiar processes and guarded optimism. The information provided by this study could be used to help provide better patient-centred care.
Quality Assessment	Was there a clear statement of the aims of the research? Yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Was the recruitment strategy appropriate to the aims of the research? Yes

Bibliographic reference	McCloud C, Lake L. 2015. Understanding the patient's lived experience of neovascular age-related macular degeneration: a qualitative study.. Eye, 29: 1561-1569.
	Was the data collected in a way that addressed the research issue? Yes Has the relationship between researcher and participants been adequately considered? Unclear Have ethical issues been taken into consideration? Yes Was the data analysis sufficiently rigorous? Yes Is there a clear statement of findings? Yes How valuable is the research? High value Overall quality: High

Bibliographic reference	Vukicevic M, Heraghty J, Cummins R, Gopinath B, Mitchell P. 2016. Caregiver perceptions about the impact of caring for patients with wet age-related macular degeneration. Eye, 30: 413-421.
Country/ies where the study was carried out	Australia
Study type	Survey study (with open questions)
Aim of the study	To explore the perceptions of caregivers of person with neovascular AMD in relation to the most important aspects of caring.
Study dates	Not stated
Source of funding	Bayer Australia, Macular Disease Foundation Australia and Orthoptics Australia.
Sample size	643
Inclusion criteria	Caregivers of people with neovascular AMD, which included the spouse or partner, family members, friends and paid care workers.
Exclusion criteria	Not stated
Sample characteristics	Caregivers ranged from 35-39 years to >85 years and were predominantly female, as were the AMD patients they cared for
Methods	A cross-sectional, self-administered survey with 27 closed responses (not detailed in this paper) and 2 open ended questions: 1. Do you have any other comments about caring for someone with wet AMD that you believe are important for other people to know and understand? 2. What are the three most important aspects of caring for someone with AMD for you? Extended responses were coded using NVivo, analysed using an inductive approach and sorted into thematic networks.
Thematic analysis	Three overarching themes arose: The Impact of Caring; Injections and Information; and Activities of Daily Living. The information presented in this summary relates only to AMD patient or carer/family member informational needs.

Bibliographic reference	Vukicevic M, Heraghty J, Cummins R, Gopinath B, Mitchell P. 2016. Caregiver perceptions about the impact of caring for patients with wet age-related macular degeneration. Eye, 30: 413-421.
	Theme 1: The Impact of caring To care for someone with wet AMD well they need to understand the condition and the physical/emotional effects on the person's wellbeing. This is considered important to help them be compassionate and empathetic in their dealings with the AMD sufferer. Caregiver's needs are not focused on by the respondents, but they do mention the importance of respite care. Theme 2: Injections and information Caregivers raised the point that since AMD has a genetic component it is important that all family members of AMD sufferers are aware of their increased risk and have regular eye tests. "Important to be monitored and diagnosed early to access treatment to stop if possible progress of disease. Important to be educated and be aware of risk and contributing factors." Information is seen to be lacking about wet AMD and how carers can help the patient manage their condition. There is also a shortage of information for carers about support services. There is the perception that other people (including the public and notably medical staff in eye clinics) did not understand the impact that AMD has on a person's life and were insensitive to patients' needs. "There is little understanding by health professionals, especially ophthalmologists of difficulties faced by patients." "It is surprising that staff, including administration, have very little idea on many simple things that make mobility difficult e.g. small occasional tables placed in the centre of a room below vision level and in the way of where he walks etc." Note: there is mention of the difficulty of paying for the costs of treatment in Australia and this is not relevant for patients in the UK.
Author's comments	Conclusion: Most caregivers were family members who experienced distress due to their additional responsibilities and the subjugation of their own needs. This can have a negative impact on their relationship with the AMD sufferer and is compounded by the limited numbers seeking or being able to use respite care.
Quality Assessment	Was there a clear statement of the aims of the research? Yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Was the recruitment strategy appropriate to the aims of the research? Yes Was the data collected in a way that addressed the research issue? Yes Has the relationship between researcher and participants been adequately considered? Unclear Have ethical issues been taken into consideration? Yes Was the data analysis sufficiently rigorous? Yes Is there a clear statement of findings? Yes

Bibliographic reference	Vukicevic M, Heraghty J, Cummins R, Gopinath B, Mitchell P. 2016. Caregiver perceptions about the impact of caring for patients with wet age-related macular degeneration. Eye, 30: 413-421.
	How valuable is the research? High value Overall quality: High