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 under an equal or lower frequency of ranibizumab treatment.
Exclusion Criteria	Not reported
Baseline characteristics	Mean age (SD), years: 80.8 (7.6) ; Male, n(%): 15 (37.5%)
Study visits and procedures	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

<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>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
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

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
	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
Comparator	Prior conversion (ranibizumab)
Outcomes	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.
Analyses	Repeated-measures analysis of variance with Green-hous-Geisser correction was conducted to assess whether there were differences between average values.

<table>
<tr><th>Bibliographic reference</th><td>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</td></tr>
<tr><td></td><td>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>
<tr><td>Others</td><td></td></tr>
</table>

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

The following additional before and after studies were also identified looking at the issue of switching therapy. These were all single arm, non-controlled studies where the full population was switched to a given agent at baseline.

Study	Initial agent	Agent switch to	Reason for switching	Outcome	Length of follow-up
Bakall (2013)	Ranibizumab or bevacizumab	Aflibercept	Eyes with exudative AMD, resistant to the treatment of monthly injections with bevacizumab or ranibizumab	Visual acuity	6 months
Chan (2014)	Ranibizumab or bevacizumab	Aflibercept	No reason specified	Visual acuity	6 months
Gokce (2016)	Ranibizumab	Aflibercept	Complete ranibizumab resistance or tachyphylaxis	Visual acuity	3 injections
Grewal (2014)	Ranibizumab or bevacizumab	Aflibercept	Eyes recalcitrant to prior anti-VEGF treatment	Visual acuity	12 months
Hall (2014)	Ranibizumab or bevacizumab	Aflibercept	No reason specified	Visual acuity	12 months
Hariri (2015)	Ranibizumab or bevacizumab	Aflibercept	Suboptimally responsive to multiple anti-VEGF injections	Visual acuity	1 injection
Hatz (2016)	Ranibizumab	Aflibercept	Failure to extend to 6 weeks at least twice on a treat and extend regimen	Visual acuity	24 weeks
Jorstad (2017)	Ranibizumab or bevacizumab	Aflibercept	Persistent macular fluid	Visual acuity	24 months
Major (2015)	Ranibizumab or bevacizumab	Aflibercept	Persistent pigment epithelial detachment	Visual acuity	32 months
Maksys (2017)	Ranibizumab or bevacizumab	Aflibercept	Persistent subfoveal fluid	Visual acuity	3 injections
Nixon (2017)	Ranibizumab	Aflibercept	Persistent fluid on OCT	Visual acuity	12 weeks
Tiosano (2017)	Bevacizumab	Aflibercept	Incomplete response to 3-9 anti-VEGF injections	Visual acuity	28 weeks
Wykoff (2014)	Ranibizumab	Aflibercept	Incomplete response to anti-VEGF injections	Visual acuity	6 months

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 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.

Reference	Amoaku 2015
	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 Authors mention 'treat and extend', and fixed extended interval dosing but do not go in to any detail or form recommendations on this

Reference	Amoaku 2015		
	Recommencing treatment for lesions becoming 'active' again is briefly mentioned but no detail is given.		
	Response	Morphology	Functional
	Good	Absence of SRF, IRF, IRC or a reduction of CRT >75% of the baseline values	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
	Partial	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	Change in VA of 1-5 letters from the baseline
	Poor	Between 0 and <25% reduction in CRT and/or persistence of SRF, IRF, IRC and/or appearance of new IRC, IRF and SRF	Change in VA of 0-4 letters
	Non-response	Unchanging or increasing CRT, SRF, IRF and/or PED compared with the baseline	Change > -5 letters i.e. decline in VA from the baseline from 1 month after third initiation injection
	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)		

Reference	Amoaku 2015					
	Late response determined at month 12 or after					
		Morphology				
	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%					

Reference	Amoaku 2015
	Clarity of presentation: 72.2% Applicability: 8.3% Editorial independence: 58.3% Overall Guideline assessment: 33.3%
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)

Reference	**Elshout 2012**					
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
	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

Reference	Elshout 2012						
		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
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

Reference	McKibbin 2015
	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. 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:

Reference	McKibbin 2015
	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. 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

Reference	McKibbin 2015
	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% 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

Reference	Mitchell 2010
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 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.

Reference	Mitchell 2010
	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
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.

Reference	Mitchell 2010
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 Target users of the guideline: specialists (NHS/private sector), patients, carers, consumer providers.

Reference	RCOphth 2013
	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

Reference	RCOphth 2013
	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. 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.

Reference	RCOphth 2013
	(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: 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.

Reference	RCOphth 2013
	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% 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).